

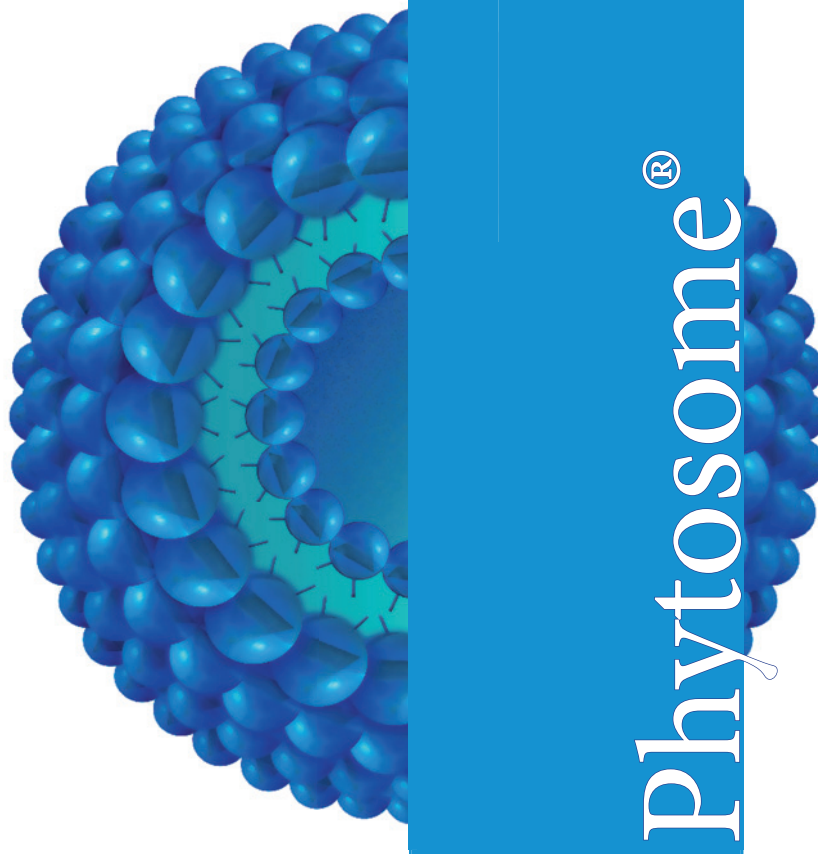
**PHYTOSOME** <sup>®</sup>  
MORE  
BIOAVAILABLE

New and proprietary technology to enhance the bioavailability of selected phytochemicals

.....  
Clinical and pharmacological data support its efficacy

.....  
Pharmacokinetic data show absorption benefits

.....  
Improved oral absorption and stability



**F**or good bioavailability, natural products must have a good balance between hydrophilicity (for dissolving into the gastro-intestinal fluids) and lipophilicity (to cross lipidic biomembranes).

Many phytoconstituents like glycosilated polyphenolics have good water solubility, but are, nevertheless, poorly absorbed<sup>[1]</sup> because of their large size, incompatible with a process of passive diffusion and/or their poor miscibility with oils and other lipids. As a result, the ability of flavonoids to cross the lipid-rich outer membrane of small intestine enterocytes is severely limited.<sup>[2]</sup>

### *Multiple approaches to improve bioavailability*

Drug bioavailability is a well known issue in the pharmaceutical sector,<sup>[3]</sup> and different strategies have been developed to ameliorate the absorption.

Also in case of poorly absorbed natural derived ingredients, various strategies are being followed in the nutraceutical sector to achieve this goal. The first one might also seem the most complex and drug-like one which refers to the medicinal chemistry approach: by the chemical derivatization of the chemical product, the aim is to obtain compounds showing an improved bioavailability.

This approach, however, generates a number of chemical analogues that need to be appropriately screened.

An alternative strategy that is also being pursued is the combination of the active molecules with other compounds as adjuvants promoting the active molecule's absorption.<sup>[4]</sup> A third approach involves extensive formulation research of structures capable of both stabilizing natural molecules and promoting their intestinal absorption.

The formulative research comprises the formation of liposomes, micelles, nanoparticles, nanoemulsions, microsphere or other complexes.

With the Phytosome<sup>®</sup> approach the improved pharmacokinetic profile is obtained without resorting to pharmacological adjuvants or structural modification of the ingredients, but by formulating them with a dietary ingredient (soy lecithin).

### *The Phytosome<sup>®</sup> solution*

Polyphenolics exhibit a marked affinity for phospholipids via hydrogen bondings and dipolar interactions with the charged phosphates groups of phospholipids.

By formulating the polyphenolic phytoconstituents in a definite ratio with soy lecithin, Indena has developed a new solution, branded as "Phytosome<sup>®</sup>", mimicking the natural intake of polyphenols.

Phytosome<sup>®</sup> formulations show better pharmacokinetic profile than their non-formulated herbal extract, and their implementation markedly enhances the bioavailability of selected phytochemicals.

Please note that this documentation is available for various countries all over the world and hence it may contain statements not applicable to your country. The marketer of any finished product containing any ingredient is responsible for assuring that the destination of the product and the claims made for the finished product are lawful and comply with all applicable laws and regulations of the country or countries in which the product is to be sold.

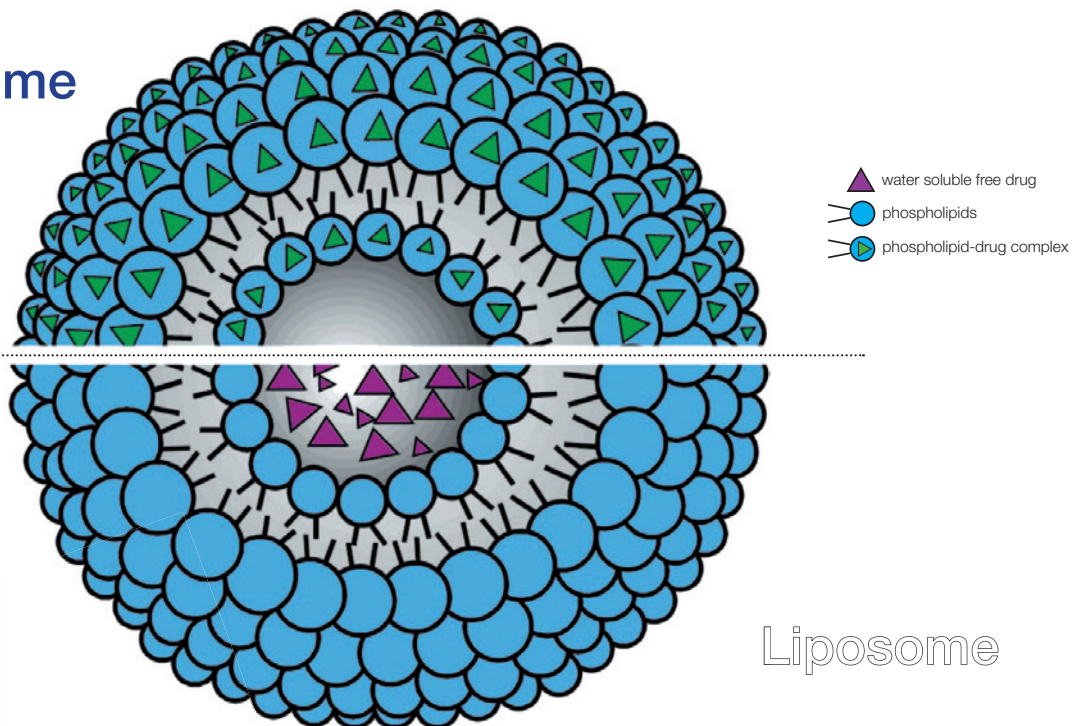
## Characteristics

### General Phytosome® overview<sup>[5]</sup>

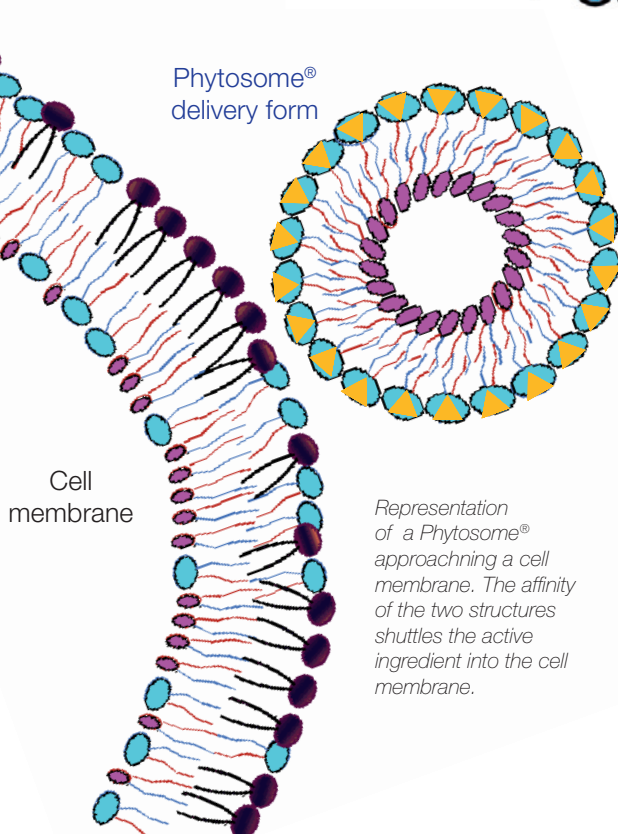
Although similar, fundamental differences exist between a Phytosome® and a liposome.

In liposomes, the active constituents are dissolved in the central part of the cavity, with limited possibility of molecular interaction between the surrounding lipid and a hydrophilic substance. On the contrary, in a Phytosome®, the active compounds can somehow be compared to an integral part of the lipid membrane. Furthermore, in liposomes the content of phospholipids is much higher, about five times the one in Phytosome®, making this delivery form not suitable for oral clinical realistic dosages for natural compounds.

## Phytosome



## Liposome



Water-soluble phytoconstituents (mainly polyphenolics) can be converted into Phytosomes.

A Phytosome is generally more bioavailable than a simple herbal extract due to its enhanced capacity to cross the lipid-rich biomembranes and reach circulation.<sup>[6-9]</sup>

Phospholipids are small lipid molecules where glycerol is bonded to two fatty acids, while the third, hydroxyl, normally one of the two primary methylenes, bears a phosphate group bound to a biogenic amino or to an amino acid<sup>[10]</sup> thus making Phytosomes different from liposomes.

By embedding the active compounds into the environment of phospholipids, these are shielded from water-triggered degradation while, at the same time, the rapid exchange of phospholipids between biological membranes and the extracellular fluids can shuttle them into biological membranes, boosting its cellular captation.<sup>[11]</sup>

# Phytosome® products

Phytosome® delivery forms have been developed by Indena starting from the late eighties. In the table below are reported current commercially available products.

TRADE NAME	ACTIVE COMPOUNDS FORMULATED WITH PHYTOSOME® TECHNOLOGY	BIOLOGICAL ACTIVITY	
BOSWELLIA PHYTOSOME®	boswellic acids from <i>Boswellia serrata</i> 's resin	Healthy inflammatory response, Soothing, Lenitive	
CENTELLA ASIATICA SELECTED TRITERPENES PHYTOSOME®	selected triterpenes from <i>Centella asiatica</i> 's leaf	Collagen restructurant, Antiwrinkles agent	
ESCIN β-SITOSTEROL PHYTOSOME®	escin and β-sitosterol from <i>Centella asiatica</i> 's seed	Antioedema, Capillartropic	
GINKGOSELECT® PHYTOSOME®	ginkgoflavonglucosides, ginkgoterpenes, bilobalide and ginkgolides from <i>Ginkgo biloba</i> 's leaf	Cognition and circulation improver, Antioxidant, Vasokinetic	
VIRTIVA®	ginkgoflavonglucosides, ginkgoterpenes and phosphatidyleseine from <i>Ginkgo biloba</i> 's leaf	Cognitive enhancer	
GINKGO BILOBA DIMERIC FLAVONOIDS PHYTOSOME®	biflavones from <i>Ginkgo biloba</i> 's leaf	Lipolytic, Vasokinetic, Phosphodiesterase inhibitor	
GINKGO BILOBA TERPENES PHYTOSOME®	ginkgoterpenes, bilobalide and ginkgolides from <i>Ginkgo biloba</i> 's leaf	Soothing, Lenitive, Antiallergic agent	
GINSELECT® PHYTOSOME®	ginseng typical constituents from <i>Panax ginseng</i> 's root	Adaptogen, Tonic, Skin elasticity improver	
18β-GLYCYRRHETINIC ACID PHYTOSOME®	18β-glycyrrhetic acid from <i>Glycyrrhiza glabra</i> 's root	Soothing, Lenitive	
GREENSELECT® PHYTOSOME®	polyphenols from <i>Camelia sinensis</i> ' young leaf	Weight loss agent, Antioxidant	
HAWTHORN PHYTOSOME®	vitexin-2"-O-rhamnoside from <i>Crataegus</i> ' flowering top	Cardiovascular health, Antioxidant	
LEUCOSELECT® PHYTOSOME®	proanthocyanidins from <i>Vitis vinifera</i> 's seed	Healthy cardiovascular function, UV protectant, Antioxidant	
PROANTHOCYANIDIN A2 PHYTOSOME®	proanthocyanidin A2 from <i>Aesculus hippocastanum</i> 's bark	UV protector, Cicatrizing-trophodermic, Firming and oval reshaping agent	
REXATROL™	resveratrol from <i>Polygonum cuspidatum</i> 's rhizome	Antioxidant, Antiageing, Sirt 1 modulator	
SERICOSIDE PHYTOSOME®	sericoside from <i>Terminalia sericea</i> 's root bark	Antioxidant, UV protectant, Antiwrinkles, Soothing, Redensifier	
SILYMARIN PHYTOSOME®	silybin-like substances from <i>Silybum marianum</i> 's fruit	Healthy liver, Antioxidant, UV protectant	
SILIPHOS®	silybin from <i>Silybum marianum</i> 's fruit	Healthy Liver, Retinoic acid-like compound	
MERIVA®	curcuminoids from <i>Curcuma longa</i> 's seed	Joint health, Healthy inflammatory response	
VISNADEX®	visnadin from <i>Ammi visnaga</i> 's umbel without fruit	Vasokinetic	

HEALTH - FOOD

COSMETICS

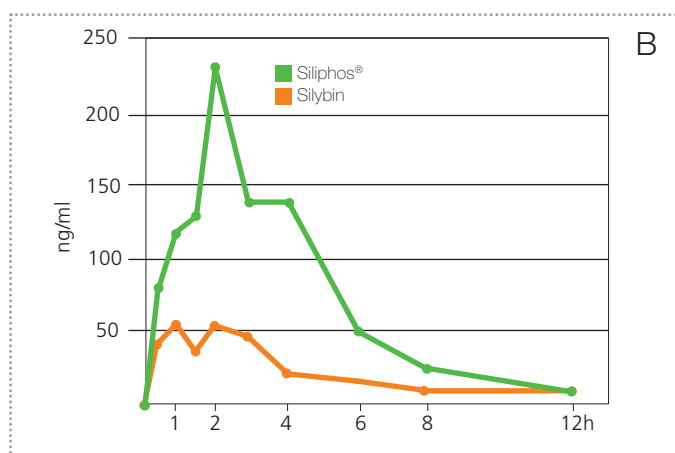
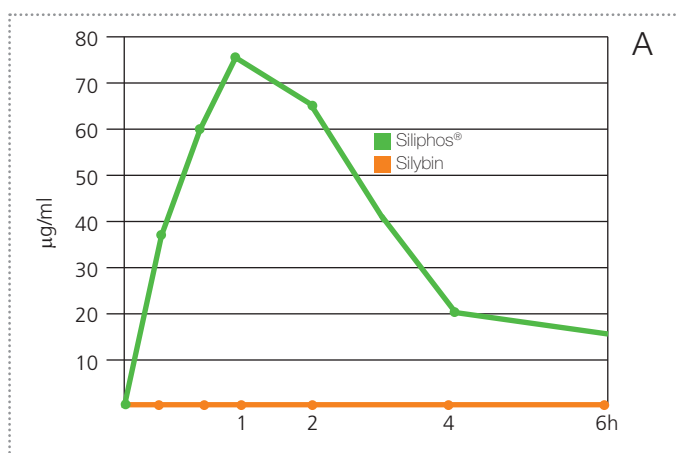
[www.phytosomes.info](http://www.phytosomes.info)

## Siliphos® vs Silymarin and Silybin

Silymarin is poorly soluble in water, and both in vivo and humans studies have shown that only nanogram per milliliter concentrations in plasma following oral administration of silymarin extracts can be found.

Pharmacokinetic studies in rats,<sup>[12-14]</sup> dogs<sup>[15]</sup> and in humans<sup>[16-23]</sup> have shown instead substantial increases in bioavailability by oral administration of Silipide® (IdB 1016) or Siliphos®, the pharmacokinetically equivalent<sup>[24]</sup> of Silipide®. As an esemplification of these studies, after oral administration of 200 mg/kg of silybin in rats,<sup>[12]</sup> the plasma

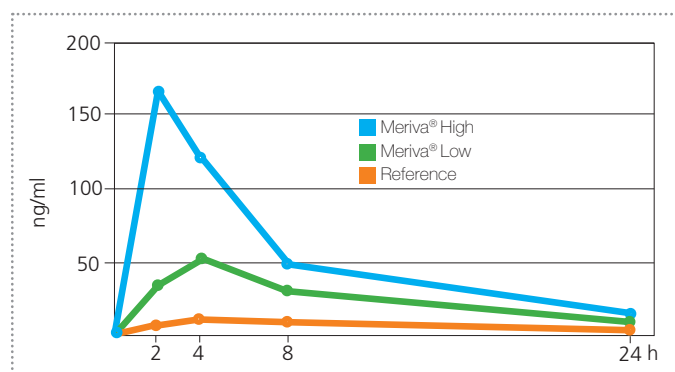
levels of silybin and its conjugated metabolites were below the analytical detection limit, while, after oral administration of Siliphos® (200 mg/kg as silybin) the plasma levels of silybin (free and total) were easily measurable (Chart A). Furthermore, in another study on humans, comparing the administrations of 360 mg of silybin delivered as Silipide® and silymarin, it has been reported a 4.6 higher bioavailability of silybin, when administered as Silipide® (Chart B).



## Meriva® vs Curcumin

In a new comparative study in humans,<sup>[25]</sup> the overall curcuminoid absorption was about 29-fold higher for Meriva® (27.2 for the low dosage, 31.5 for the high dosage), compared to the unformulated curcuminoid mixture, while a 50 to 60 fold higher absorption has been shown for demethoxycurcumin and bisdemethoxycurcumin.

The improved absorption, and possibly also a better plasma curcuminoid profile, might underlie the clinical efficacy of Meriva® at doses significantly lower than the unformulated curcuminoid mixtures.

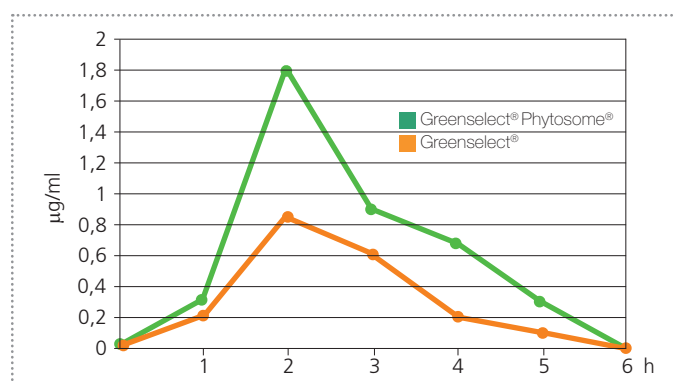


## Greenselect® Phytosome vs green tea extract

Similar results have been also seen comparing the absorption (-)-epigallocatechin 3-O-gallate (EGCG), the main constituent of Greenselect® Phytosome.<sup>[26]</sup> Twelve healthy male volunteers were randomly divided in two groups. One received a single dose of Greenselect® (containing 240 mg of tea catechins by HPLC).

The second group received 1,200 mg of Greenselect® Phytosome (containing 240 mg of tea catechins by HPLC). EGCG was chosen as the biomarker for absorption. The peak concentration at 2 hours is more than doubled with Greenselect® Phytosome in comparison to the simple Greenselect®.

Further, the plasma levels of EGCG remain considerably higher with Greenselect® Phytosome.



## Ginkgoselect® Phytosome® vs Ginkgo biloba extract

The pharmacokinetic profile of Ginkgoselect® Phytosome® has been defined in experimental animals<sup>[27]</sup> and in human volunteers.<sup>[7]</sup> Its bioavailability has been compared to GBE. Fifteen healthy volunteers were randomly divided into two groups and administered respectively with Ginkgoselect® and Ginkgoselect® Phytosome®, providing both 9.6 mg of total terpene lactones.

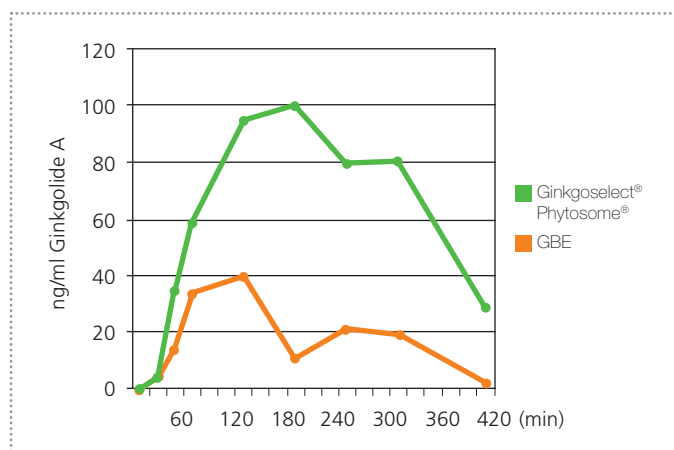
The subjects switched formulations after a week of wash out. Blood samples were collected at 30, 60, 120, 180, 240, 300 and 400 min after ingestion.

Terpene lactones detection was performed by means of liquid chromatography/atmospheric pressure chemical ionization mass spectrometry (LC/APCI-ITMS).

Ginkgolides A, B and bilobalide were absorbed to a higher extent (about three-fold) after administration of Ginkgoselect® Phytosome®.

As an example, the chart below reports plasma

concentrations of ginkgolide A which, according to AUC, shows a 3.5 fold higher absorption of the Ginkgoselect® Phytosome®.

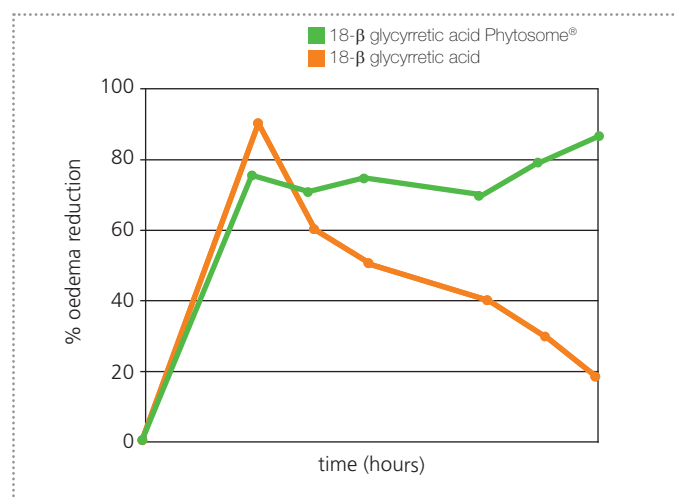


## 18-β Glycyrrhetic acid Phytosome® vs 18-β Glycyrrhetic acid

Finally as an example, an activity comparison between the Phytosome® and non Phytosome® form by topical application is reported as well.<sup>[28]</sup>

The anti-inflammatory and anti-oedemigenous effects of the 18β-Glycyrrhetic Acid Phytosome® were assessed in the experimental model of Croton oil-induced oedema reduction.

At the same dose (0.16 μM), the action of the 18β-Glycyrrhetic Acid Phytosome® was found to be greater and to last longer than that of 18β-glycyrrhetic acid alone. This means that the Phytosome® not only increases the active ingredient tolerability and absorption, but also improves its efficacy.



## Concluding remarks

### What is a Phytosome®?

A Phytosome® is a solid dispersion of an extract in a dietary phospholipid matrix (soy lecithin). Incorporation of the considered extract into an amphiphilic milieu prevents its self-aggregation, and these formulations have the specific aim to improve the absorption of poorly available active ingredients, mimicking the effect of a fatty meal.

### Why use Phytosome® formulation?

The Phytosome®s are used to improve bioavailability of active ingredients. Active components with too high polarity cannot overcome the lipidic barrier of the skin or the gastrointestinal system, and, therefore, cannot be absorbed. The Phytosome® helps to reduce the polarity of active substances, thus making them more easily absorbable. In other words, the Phytosome® is an innovative transportation system for poorly bioavailable active ingredients.

### What are the advantages of the Phytosome®?

It improves absorption and, consequently, bioavailability of active ingredients.

In both oral and topical tests, Phytosome® has demonstrated a higher biological activity compared to an equal amount of the active ingredient or extract not made in the Phytosome® form.

### What is the difference between Phytosome® and liposome?

In a Phytosome®, a poorly water soluble or polar active ingredient is anchored to the polar head of the phospholipid and becomes an integral part of the micellar membrane, unlike liposomes, in which the active ingredient is generally contained inside the micelle structure consisting of phospholipids.

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