indena®

PHYTOSOME®
MORE BIOAVAILABLE

Proprietary technology to optimize the bioavailability of selected phytochemicals

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Unique pharmacological and human data are available

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Pharmacokinetic data show absorption benefits

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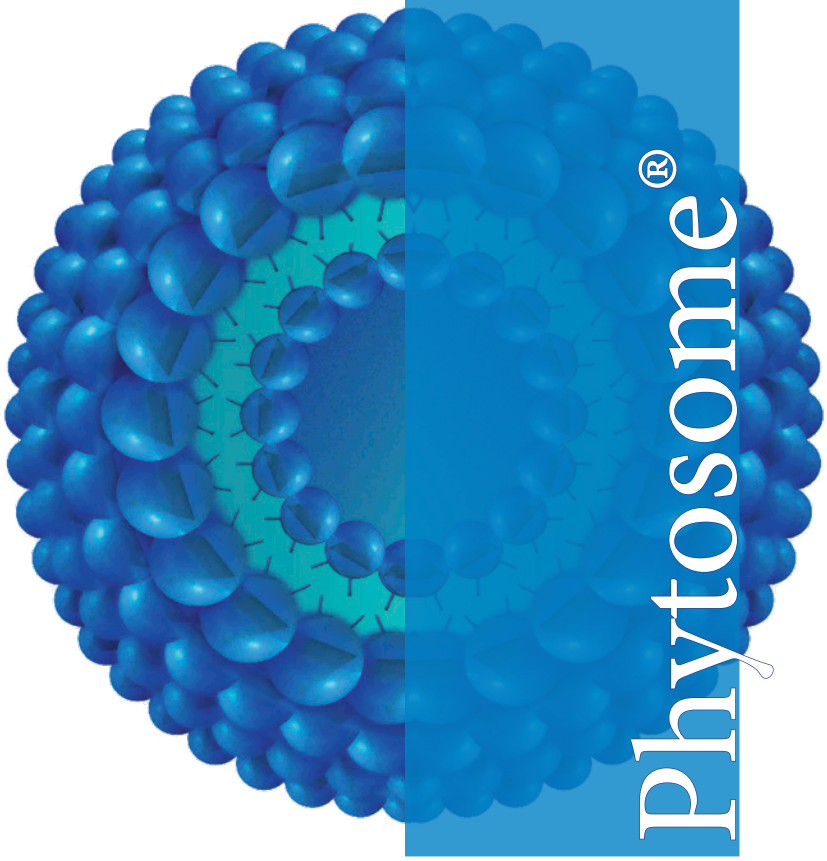
Optimized oral absorption and stability



For 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[1] 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.[2]

Multiple approaches to optimize bioavailability

Natural ingredients bioavailability is a well known issue[3] and different strategies have been developed to ameliorate the absorption. The first one, chemical derivatization, is applied 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.[4]
A third approach involves extensive formulation research of structures capable of both stabilizing natural molecules and promoting their intestinal absorption.
The formulative reasearch comprises the formation of liposomes, micelles, nanoparticles, nanoemulsions, microsphere or other complexes.
With the Phytosome® approach the pharmacokinetic profile is guaranteed without resorting to pharmacological adjuvants or structural modification of the ingredients, but by formulating them with a dietary ingredient (lecithin).

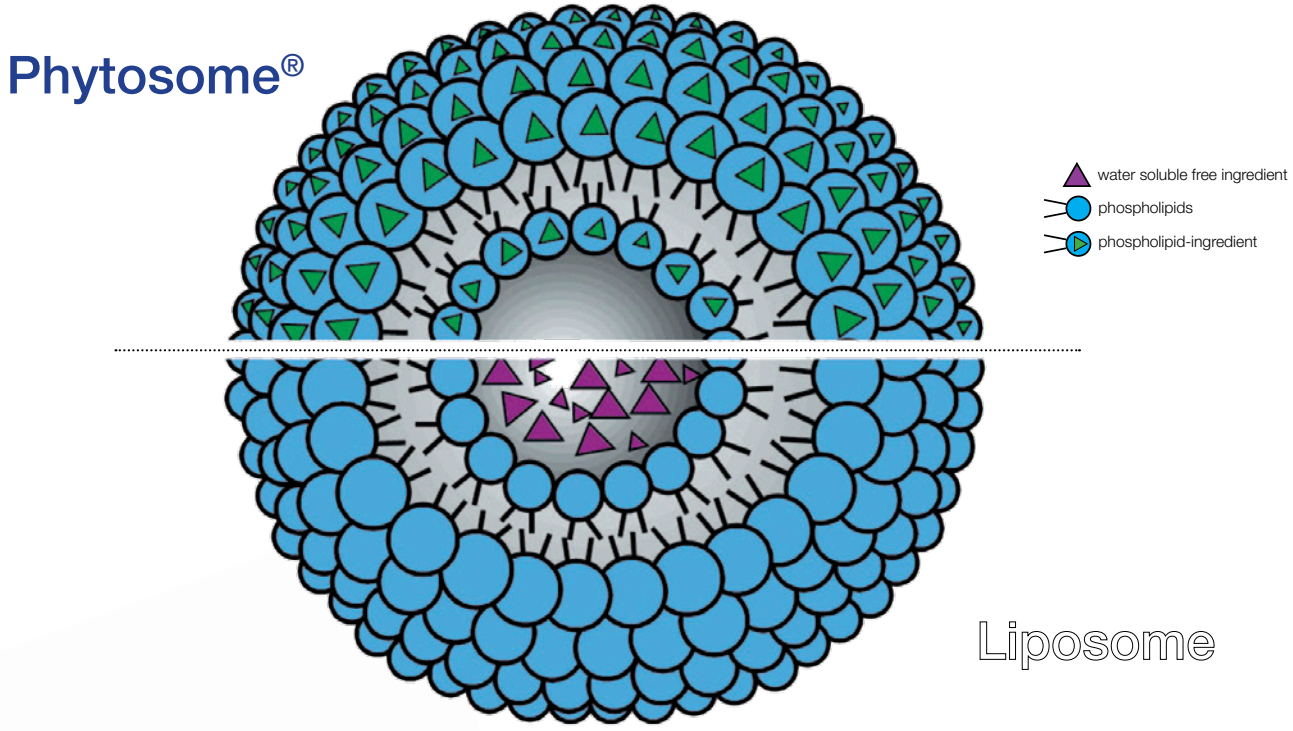
The Phytosome® solution

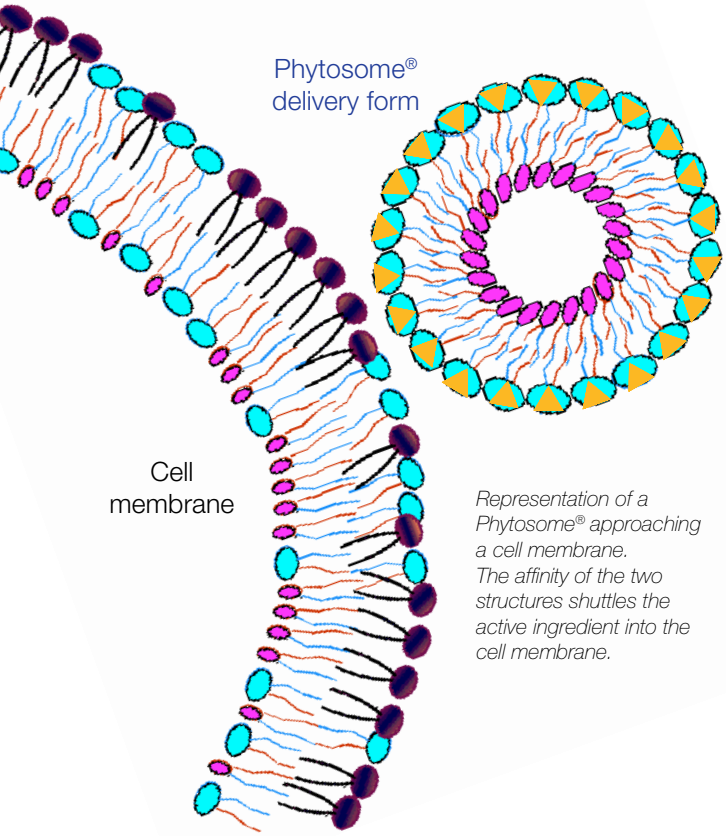
Polyphenolics exhibit a marked affinity for phospholipids via hydrogen bondings and dipolar interactions with the charged phosphates groups of phospholipids.
By formulating the polyphenolic phytoconstituents in a definite ratio with lecithin, Indena has developed a new solution, branded as "Phytosome®", mimiking the natural intake of polyphenols.
Phytosome® formulations show better bioavailability than the non-formulated herbal extract, optimizing the biological activities while preserving the natural safety profile.

Characteristics

General Phytosome® overview[5]

Although similar, fundamental differences exist between a Phytosome® and a liposome.
In liposomes, the ingredients 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®, which is a solid dispersion of an extract in a dietary phospholipid matrix, the ingredient 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.





Representation of a Phytosome® approaching a cell membrane. The affinity of the two structures shuttles the active ingredient into the cell membrane.

Phytoconstituents (mainly polyphenolics and triterpenes) can be formulated into Phytosome®s.
A Phytosome® is generally bioavailable due to its enhanced capacity to cross the lipid-rich biomembranes and reach circulation.[6-9]
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.[10]
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.[11]

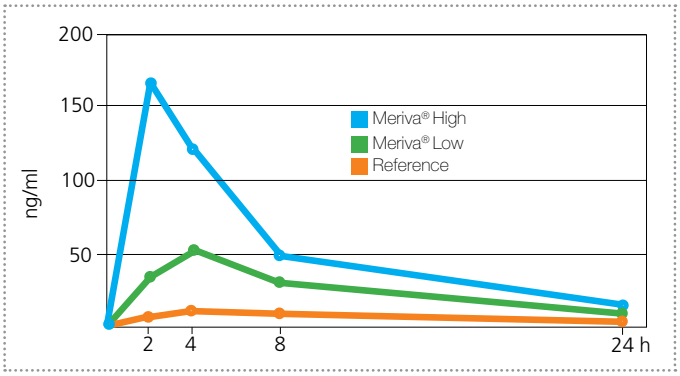
Phytosome® products

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
CASPEROME® BOSWELLIA PHYTOSOME®	boswellic acids from *Boswellia serrata*'s resin	Healthy inflammatory response
CENTELLA ASIATICA SELECTED TRITERPENES PHYTOSOME®	selected triterpenes from *Centella asiatica*'s leaf	Collagen restructurant
GINKGOSELECT® PHYTOSOME® GINKGO BILOBA PHYTOSOME®	ginkgoflavonglucosides, ginkgoterpenes, bilobalide and ginkgolides from *Ginkgo biloba*'s leaf	Cognition and circulation improver, Antioxidant
VIRTIVA® - GINKGO BILOBA PHOSPHATIDYLSERINE PHYTOSOME®	ginkgoflavonglucosides, ginkgoterpenes and phosphatidyleseine from *Ginkgo biloba*'s leaf	Cognitive enhancer
GINSELECT® PHYTOSOME® GINSENG IDB PHYTOSOME®	ginseng typical constituents from *Panax ginseng*'s root	Adaptogen, Tonic
GREENSELECT® PHYTOSOME® GREEN TEA PHYTOSOME®	polyphenols from *Camelia sinensis*' young leaf	Antioxidant, Weight loss agent
HAWTHORN PHYTOSOME®	vitexin-2"-O-rhamnoside from *Crategus*' flowering top	Cardiovascular health, Antioxidant
LEUCOSELECT® PHYTOSOME® GRAPE SEED PHYTOSOME®	proanthocyanidins from *Vitis vinifera*'s seed	Healthy cardiovascular function, Antioxidant
SILYMARIN PHYTOSOME®	silybin-like substances from *Silybum marianum*'s fruit	Healthy Liver, Antioxidant
SILIPHOS® SILYBIN PHYTOSOME®	silybin from *Silybum marianum*'s fruit	Healthy Liver, Antioxidant
MERIVA® TURMERIC PHYTOSOME®	curcuminoids from *Curcuma longa*'s seed	Joint health, Healthy inflammatory response

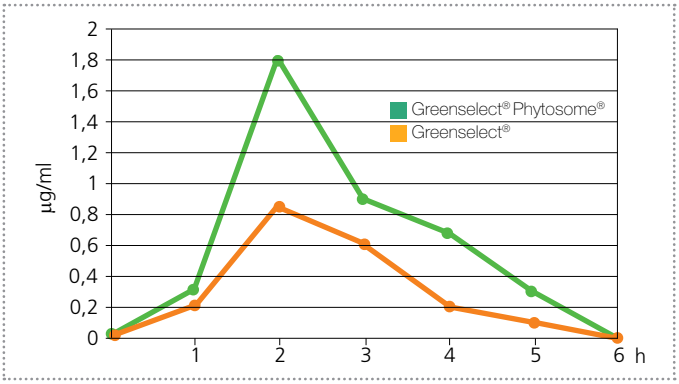
Meriva® vs Curcumin

In a new comparative study in humans,[12] 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.



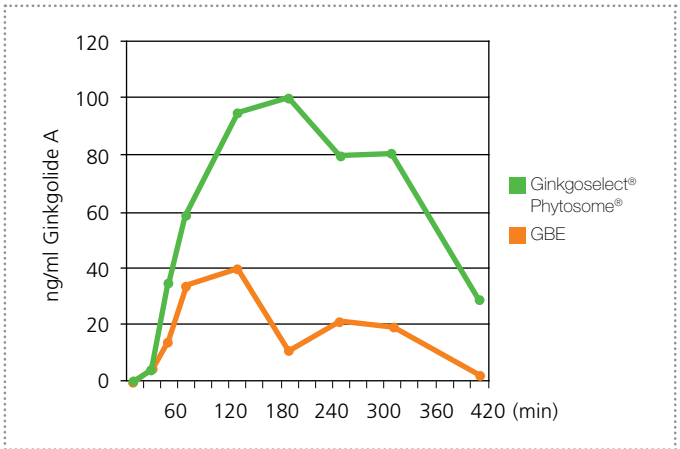
Greenselect® Phytosome® vs green tea extract

Similar results have been also seen comparing the absorption (-)-epigallocatechin 3-O-gallate (EGCG), the main constituent of Greenselect® Phytosome®.[13] 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[14] and in human volunteers.[7] 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 cromatography/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®.



Casperome® vs Boswellia serrata extract

Finally as a further example, the concentration of the six major BAs [11-keto-β-boswellic acid (KBA), acetyl-11-keto-β-boswellic acid (AKBA), β-boswellic acid (βBA), acetyl-β-boswellic acid (AβBA), α-boswellic acid (αBA), and acetyl-α-boswellic acid (AαBA)] was evaluated in the plasma and in a series of rats tissues when administered in the Phytosome® (as Casperome®) and not Phytosome® form.[15]

Weight equivalent and equimolar oral administration of Casperome® provided significantly higher plasma levels (up to 7-fold for KBA, and 3-fold for βBA quantified as area under the plasma concentration time curve, AUClast) compared to the non-formulated extract and this was accompanied by remarkably higher tissue levels providing a further confirmation of this delivery system also for low polar compounds.

Concluding remarks

What is a Phytosome®?

A Phytosome® is a solid dispersion of an extract in a dietary phospholipid matrix (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 optimize bioavailability of natural ingredients. Components with too high polarity cannot overcome the lipidic barrier of the skin or the gastro-intestinal system, and, therefore, cannot be absorbed. The Phytosome® helps to reduce the polarity of natural substances, thus making them more easily absorbable. In other words, the Phytosome® is an innovative transportation system for poorly bioavailable natural ingredients.

What are the advantages of the Phytosome®?

It optimize 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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