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 improve bioavailability

Drug bioavailability is a well known issue in the pharmaceutical sector,[3] 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.[4] 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 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 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 series of non-covalent supramolecular adducts named “Phytosome”. Phytosome formulations show better pharmacokinetic profile than their non-formulated herbal extract, and their implementation markedly enhances the bioavailability of selected phytochemicals.
**General Phytosome overview**[^5]

Although similar, fundamental differences exist between a Phytosome and a liposome. In liposomes, the active principles 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 principle 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.

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[^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] thus making Phytosomes different from liposomes. By embedding the active principle 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 delivery forms have been developed by Indena starting from the late eighties. In the table below are reported current commercially available products.

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>ACTIVE PRINCIPLE FORMULATED WITH PHYTOSOME TECHNOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOSWELLIA EXTRACT</td>
<td>boswellic acids from <em>Boswellia serrata</em>’s resin</td>
</tr>
<tr>
<td>CENTELLA ASIATICA SELECTED TRITERPENES</td>
<td>selected triterpenes from <em>Centella asiatica</em>’s leaf</td>
</tr>
<tr>
<td>ESCIN β-SITOSTEROL</td>
<td>escin and β-sitosterol from <em>Centella asiatica</em>’s seed</td>
</tr>
<tr>
<td>GINKGOSELECT®</td>
<td>ginkgoflavonglucosides, ginkgoterpenes, bilobalide and ginkgolides from <em>Ginkgo biloba</em>’s leaf</td>
</tr>
<tr>
<td>VIRTIVA®</td>
<td>ginkgoflavonglucosides, ginkgoterpenes and phosphatidyleseine from <em>Ginkgo biloba</em>’s leaf</td>
</tr>
<tr>
<td>GINKGO BILOBA DIMERIC FLAVONOIDS</td>
<td>biflavones from <em>Ginkgo biloba</em>’s leaf</td>
</tr>
<tr>
<td>GINKGO BILOBA TERPENES</td>
<td>ginkgoterpenes, bilobalide and ginkgolides from <em>Ginkgo biloba</em>’s leaf</td>
</tr>
<tr>
<td>GINSELECT®</td>
<td>ginseng typical constituents from <em>Panax ginseng</em>’s root</td>
</tr>
<tr>
<td>18β-GLYCETYRRHETIC ACID</td>
<td>18β-glycyrrhetinic acid from <em>Glycyrrhiza glabra</em>’s root</td>
</tr>
<tr>
<td>GREENSELECT®</td>
<td>polyphenols from <em>Camellia sinensis</em>’ young leaf</td>
</tr>
<tr>
<td>HAWTHORN</td>
<td>vitexin-2’-O-rhamnoside from <em>Crategus</em>’ flowering top</td>
</tr>
<tr>
<td>LEUCOSELECT®</td>
<td>proanthocyanidins from <em>Vitis vinifera</em>’s seed</td>
</tr>
<tr>
<td>PROANTHOCYANIDIN A2</td>
<td>proanthocyanidin A2 from <em>Aesculus hippocastanum</em>’s bark</td>
</tr>
<tr>
<td>RESVERATROL</td>
<td>resveratrol from <em>Polygonum cuspidatum</em>’s rhizome</td>
</tr>
<tr>
<td>SERICOSIDE</td>
<td>sericoside from <em>Terminalia sericea</em>’s root</td>
</tr>
<tr>
<td>SILYMARIN</td>
<td>silybin-like substances from <em>Silybum marianum</em>’s fruit</td>
</tr>
<tr>
<td>SILPHOS®</td>
<td>silybin from <em>Silybum marianum</em>’s fruit</td>
</tr>
<tr>
<td>MERIVA®</td>
<td>curcuminooids from <em>Curcuma longa</em>’s seed</td>
</tr>
<tr>
<td>VISNADEX®</td>
<td>visnadin from <em>Ammi visnaga</em>’s umbel without fruit</td>
</tr>
</tbody>
</table>
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,[12-14] dogs[15] and in humans[16-23] have shown instead substantial increases in bioavailability by oral administration of Silipide® (IdB 1016) or Siliphos®, the pharmacokinetically equivalent[24] of Silipide®. As an exemplification of these studies, after oral administration of 200 mg/kg of silybin in rats,[12] 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).

In a new comparative study in humans,[25] 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.

Similar results have been also seen comparing the absorption (-)-epigallocatechin 3-O-gallate (EGCG), the main constituent of Greenselect® Phytosome.[26] 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[27] 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 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.

Finally as an example, an activity comparison between the Phytosome and non Phytosome form by topical application is reported as well.[28] The inflammatory response 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.

18-ß Glycyrrhetic acid Phytosome vs 18-ß Glycyrrhetic acid

What is a Phytosome?
A Phytosome is a delivery system composed by a natural active ingredient and a soy lecithin.

Why use Phytosome formulation?
The Phytosomes 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 absorption 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?
The Phytosome adducts are structures in which 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.
References


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