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 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.

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”, mimicking 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.
Phytosomes are delivery forms of phytoconstituents (mainly polyphenolics and triterpenes) that can be formulated into Phytosomes. 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.

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>ACTIVE COMPOUNDS FORMULATED WITH Phytosome TECHNOLOGY</th>
<th>BIOLOGICAL ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASPEROME® BOSWELLI PHYTOSOME</td>
<td>boswellic acids from <em>Boswellia serrata</em>’s resin</td>
<td>Joint health, Soothing, Healthy digestion</td>
</tr>
<tr>
<td>CENTELLA ASIATICA SELECTED TRITERPENES PHYTOSOME</td>
<td>selected triterpenes from <em>Centella asiatica</em>’s leaf</td>
<td>Collagen restructurant, Antiwrinkles agent</td>
</tr>
<tr>
<td>GINKGOSELECT® PHYTOSOME GINKGO BILOBA PHYTOSOME</td>
<td>ginkgoflavoglucosides, ginkgoterpenes, bilobalide and ginkgolides from <em>Ginkgo biloba</em>’s leaf</td>
<td>Cognitive and circulatory system health, Antioxidant activity</td>
</tr>
<tr>
<td>VIRTIVA® - GINKGO BILOBA PHOSPHATIDYL SERINE PHYTOSOME</td>
<td>ginkgoflavoglucosides, ginkgoterpenes and phosphatidyleseine from <em>Ginkgo biloba</em>’s leaf</td>
<td>Cognitive system health</td>
</tr>
<tr>
<td>GINSELECT® PHYTOSOME GINSENG IDB PHYTOSOME</td>
<td>ginseng typical constituents from <em>Panax ginseng</em>’s root</td>
<td>Adaptogen, Tonic, Skin health</td>
</tr>
<tr>
<td>GREENSELECT® PHYTOSOME GREEN TEA PHYTOSOME</td>
<td>polyphenols from <em>Camelia sinensis</em>’ young leaf</td>
<td>Antioxidant activity, Weight loss agent</td>
</tr>
<tr>
<td>HAWTHORN PHYTOSOME</td>
<td>vitexin-2”-O-rhamnoside from <em>Crategus</em>’ flowering top</td>
<td>Cardiovascular health, Antioxidant activity</td>
</tr>
<tr>
<td>LEUCOSELECT® PHYTOSOME GRAPE SEED PHYTOSOME</td>
<td>proanthocyanidins from <em>Vitis vinifera</em>’s seed</td>
<td>Healthy cardiovascular function, UV protectant, Antioxidant activity</td>
</tr>
<tr>
<td>SILYMARIN PHYTOSOME</td>
<td>silybin-like substances from <em>Silybum marianum</em>’s fruit</td>
<td>Healthy liver function, Antioxidant activity, Healthy skin</td>
</tr>
<tr>
<td>SILIPHOS® SILYBIN PHYTOSOME</td>
<td>silybin from <em>Silybum marianum</em>’s fruit</td>
<td>Healthy liver function</td>
</tr>
<tr>
<td>MERIVA® TURMERIC PHYTOSOME</td>
<td>curcuminoids from <em>Curcuma longa</em>’s seed</td>
<td>Joint health</td>
</tr>
</tbody>
</table>
In a new comparative study in humans, 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. 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 and in human volunteers. 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.
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 Phytosomes are used to optimize bioavailability of natural ingredients. 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 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.

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 (ABEA), α-boswellic acid (αBA), and acetyl-α-boswellic acid (AaBA)] was evaluated in the plasma and in a series of rats tissues when administered in the Phytosome (as Casperome®) and not Phytosome form.

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

References
