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phytosome™
THE BIOMIMETIC DELIVERY SYSTEM

PHYTOSOME®
at a glance

PROBLEM STATEMENT

Botanical nutraceuticals and natural compounds are often provided with poor water solubility and limited intestinal absorption which usually hamper from addressing significant oral bioavailability.

WORK ASSUMPTION

For optimal bioabsorption, natural extracts must have a good balance between hydrophilicity for dissolving into the gastro-intestinal fluids and lipophilicity to cross cell's lipidic biomembranes.

SOLUTION

Indena has developed Phytosome®, a proprietary 100% food-grade biomimetic delivery system that optimizes bioabsorption and pharmacokinetic profile of botanical extracts by formulating them with a dietary ingredient (lecithin).

THE TOUCH OF INDENA

With nearly a century of experience and deep knowledge of unique industrial equipment and processes, Indena pioneered and developed Phytosome® technology to optimize the bioabsorption of selected botanicals, assuring batch to batch reproducibility of the natural compound matrix.

Background

Natural products represent the basis of the traditional medicine and were widely used since ancient time. Nowadays they still uphold and consolidate their unique role in protection and maintenance of healthy conditions enabling beneficial effects to convey from Nature to human wellbeing.

Despite their promising health-promoting potential, botanical extracts and natural compounds are often provided with poor water solubility and limited intestinal absorption which usually hinder significant oral bioavailability.

For effective bioabsorption, natural products must have a good balance between hydrophilicity (for dissolving into the gastro-intestinal fluids) and lipophilicity (to cross lipidic biomembranes).

For example, 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, for instance, to cross the lipid-rich outer membrane of small intestine enterocytes is severely limited[2].

At the same time, botanical compounds are naturally available in complex forms and matrixes that are responsible of their beneficial effects but may need to be optimized in order to enhance physiological uptake levels.

PHYTOSOME®
and the biomimetic approach

The search for a bio-mimetic (bios=life; mimesis=imitation) approach[3] to improve actives bioabsorption in the full respect of their natural profile has been pioneered by Indena with the development of Phytosome®.

Phytosome® is a proprietary 100% food-grade delivery system to optimize bioavailability and pharmacokinetic profile of natural actives by formulating them with a dietary ingredient (lecithin).

Lecithins are natural surfactants which take part, together with bile salts, to the physiological absorption process of lipophilic compounds and form the lipid bilayer structure of cell membranes being readily absorbed, e.g. from the intestine, even if poorly soluble in water.

As amphipathic molecule consisting of a positively charged head group and two neutral tail acyl moieties, lecithin acts as inhibitor of self-aggregation, leaving sparingly soluble compounds into a dispersed state more readily absorbed.

Phytosome® represents a natural approach to obtain a solid dispersion of poorly oral bioavailable compounds that can promote phytochemicals solubility and bioabsorption through improved wetting, reduced agglomeration and changes in the physical state of the active ingredients (such as modifications in the crystalline status or production of either partially or totally amorphous stable forms).

The new scientific paradigm: CHAOS IS THE NEW ORDER

In its genuine inspiration by Nature, **Phytosome® food-grade matrix allows to maintain the original Chaos of natural products according to the biomimetic principle Nature as Measure™**, without involving chemical derivatives or new chemical entities, pharmacological adjuvants or structural modification of the ingredients.

In this biomimetic approach nothing is left to chance. In a continuous evolution and innovation of R&D value chain, **every Phytosome® is specifically designed to optimize the bioabsorption of a selected botanical extract.**

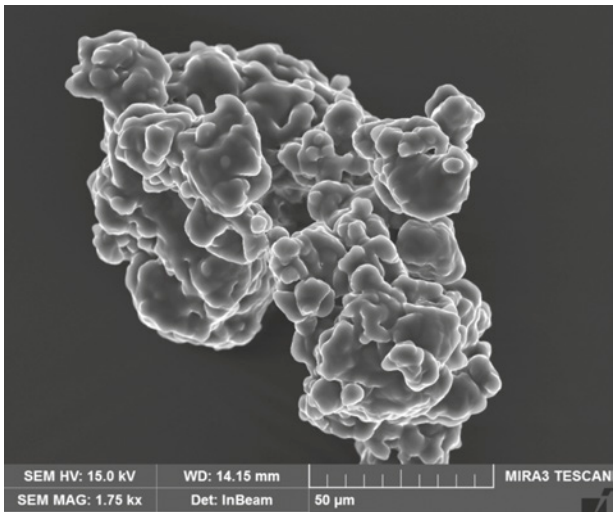
Strict scientific studies demonstrate that Phytosome® formulations show better solubility in gastrointestinal simulated fluids, pharmacokinetic and efficacy profile than their non-formulated herbal extracts.

PHYTOSOME® formulations

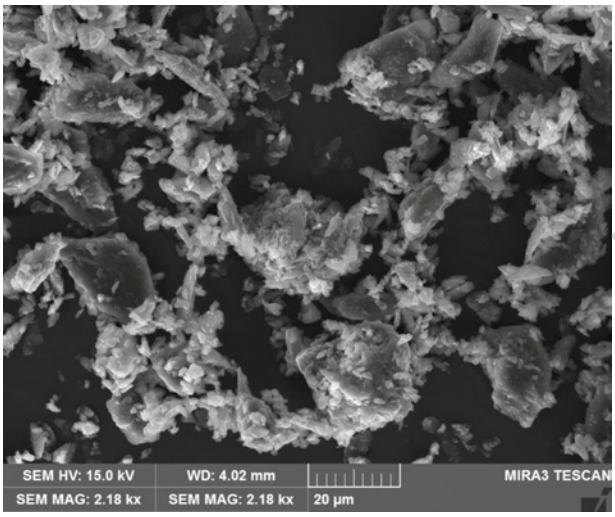
Phytosome®s are 100% food-grade delivery systems of selected botanical extracts, formulated as solid dispersion in a lecithin-based matrix.

Functional and technological properties of the final product are optimized by modulating and controlling several factors such as manufacturing process parameters and addition of selected food-grade additives.

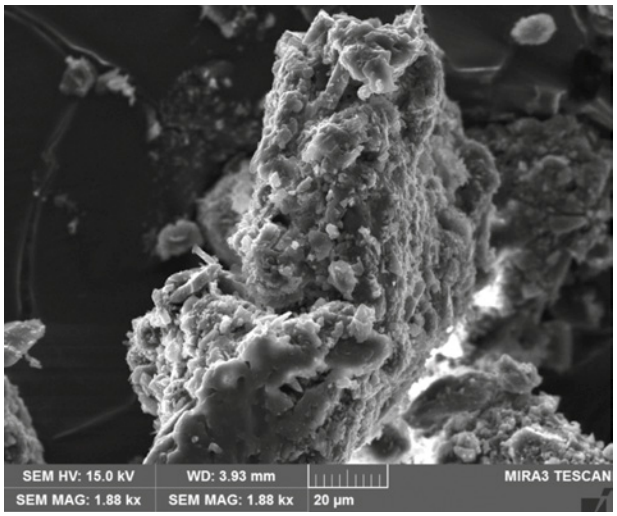
Good physical and technological properties are important to optimize dissolution profile of the natural active and, consequently, its bioabsorption;



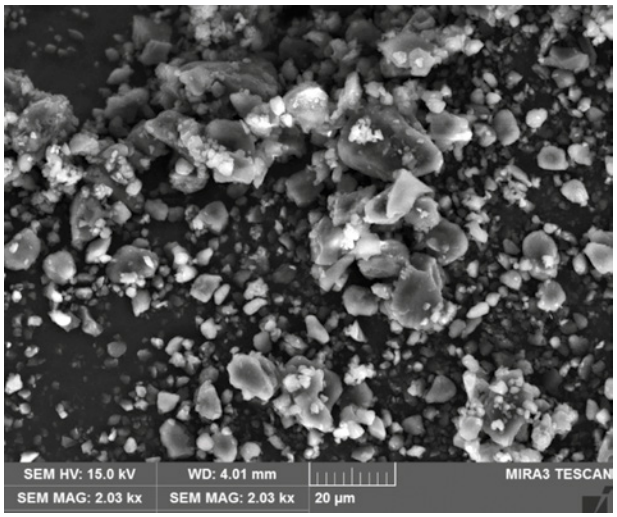
Pic. 1 - Lecithin. A shapless soft mass. (SEM microscopy)



Pic. 2 - A crystalline natural compund. The particles are regularly shaped with crystal habitus. (SEM microscopy)



Pic. 3 - A mechanical mixture of crystalline natural product and lecithin. The crystals of Pic. 2 are still evident although incorporated in the lecithin soft mass. (SEM microscopy)



Pic. 4 - The Phytosome® with the same composition of the mechanical mixture of Pic. 3. The solid is constituted by well defined particles homogeneous in size and shape. (SEM microscopy)

at the same time, they facilitate the formulation process, allowing Phytosome® to be easy incorporated in a variety of dosage forms.

Solid oral dosage forms represent the ideal solution to formulate Phytosome®: tablets, capsules, softgels and granulates can be obtained by means of standard manufacturing procedures.

Main Phytosome®s

- SILIPHOS®
- GREENSELECT® PHYTOSOME®
- MERIVA®
- CASPEROME®
- QUERCEFIT™
- VAZGUARD™
- UBIQSOME®

SILIPHOS®

Silybin is a crystalline solid characterized by intense X-ray powder diffraction and well-shaped crystal particles; once formulated as Phytosome® (namely Siliphos®) the resulting solid is amorphous with absence of X-ray diffraction and particles homogeneous in size and shape (SEM microscopy, fig. 1). Consequently, Siliphos® is an amorphous solid dispersion with a particulate specific by shape and size, which remains distinct (and superior) as physical-chemical properties not only from a mere mechanical mixture, but also from silybin itself.
Even though the amorphous state is known to be less stable than the crystalline one, the amorphous Siliphos® solid dispersion is not affected by chemical nor physical instability.

Thanks to its specific formulation, Siliphos® optimizes bioabsorption of silybin, a compound otherwise characterized by poor oral absorption: silybin presents optimized bioabsorption when administered in form of Phytosome® as compared to unformulated extract[4] according to final formulation, as confirmed by biliary excretion also on humans[5] (fig. 1).

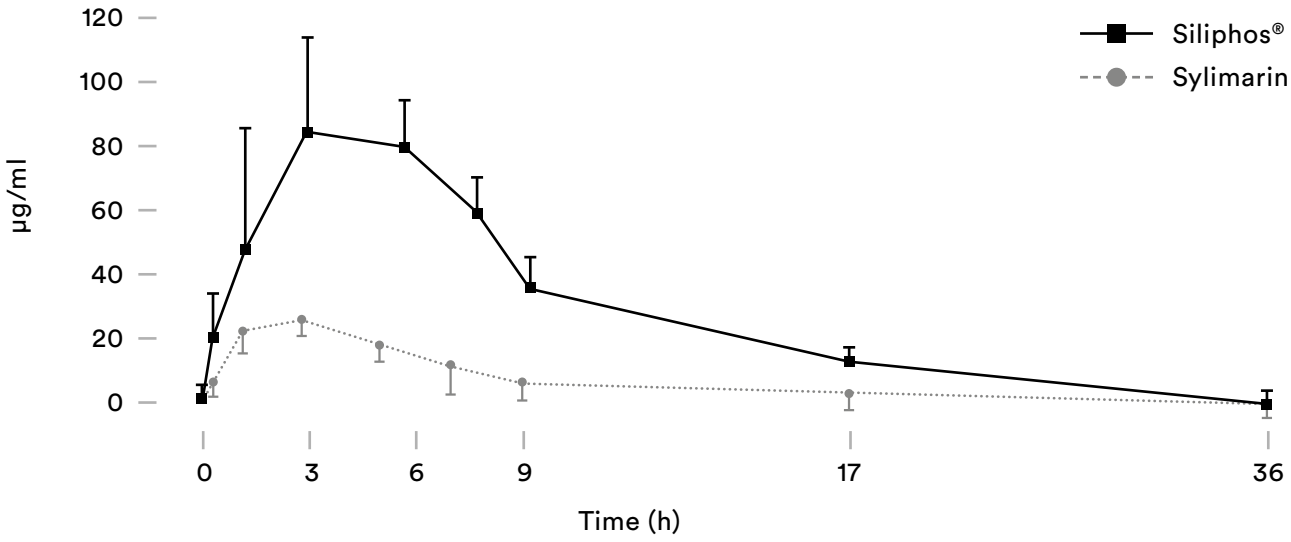


Fig. 1: Mean biliary concentrations (± S.E.M.) of silybin following administration of a single 120 mg oral dose (expressed as silybin equivalents) in Phytosome® form (■) and silymarin (●). Time points are medians of collection interval.

GREENSELECT® PHYTOSOME®

Greenselect® Phytosome® is a proprietary, caffeine free, catechin extract from green tea formulated with Phytosome® technology.
Optimization of oral absorption has been seen comparing the absorption of (-)-epigallocatechin 3-O-gallate (EGCG), the main constituent of Greenselect® Phytosome®.[6] Twelve healthy male volunteers were randomly divided in two groups: one receiving a single dose of Greenselect® (green tea extract containing 240 mg of tea catechins by HPLC) and the second group receiving 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® (fig. 2).

Further, the plasma levels of EGCG remain optimal with Greenselect® Phytosome® as with traditional green tea use.

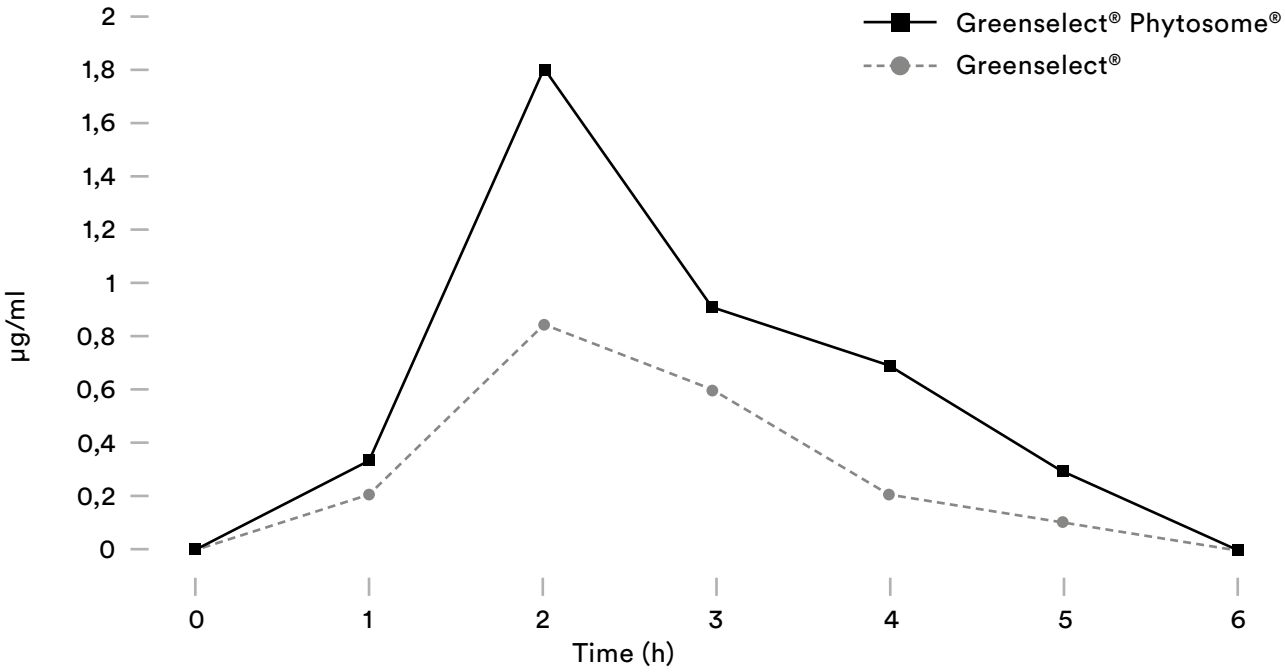


Fig. 2: Time course of plasma EGCG after ingestion of Greenselect® or Greenselect® Phytosome®.

MERIVA®

MERIVA® is a patent pending delivery form of curcumin. As curcumin typically exhibits poor oral absorption in the body, this natural ingredient has been formulated with proprietary Phytosome® technology to optimize its bioabsorption.

Pharmacokinetic comparison studies shown MERIVA® to have optimal bioavailability of curcuminoids.

Many studies conducted with MERIVA® demonstrated significant results related to stiffness, muscle soreness, physical function, liver and ocular health and overall quality of life while retaining the excellent safety profile.

MERIVA® is the food grade delivery form of curcumin formulated with proprietary Phytosome® technology.

In a comparative study on humans[7], the overall curcuminoids absorption was optimized compared to the unformulated curcuminoids mixture (fig. 3).

The optimized absorption and the unique plasma curcuminoids profile underline the relevant efficacy of Meriva® in more than 30 human studies and 10 different health conditions.

	MERIVA®		CURCUMIN (REFERENCE)		**RELATIVE ABSORPTION***
CURCUMINOIDS	AUC (ng/ml)	Cmax (ng/ml)	AUC (ng/ml)	Cmax (ng/ml)	
Curcumin	538.0 ± 130.7	50.3 ± 12.7	122.5 ± 29.3	9.0 ± 2.8	19.2
Demethoxycurcumin	655.0 ± 195.7	134.6 ± 40.6	55.8 ± 15.5	4.2 ± 1.1	68.3
Bisdemethoxycurcumin	142.2 ± 58.2	24.9 ± 8.1	24.6 ± 10.3	2.1 ± 0.8	56.8
TOTAL CURCUMINOIDS	1336.0 ± 357.1	206.9 ± 54.9	202.8 ± 53.8	14.4 ± 4.2	31.5

Fig. 3: Area Under Curve (AUC), Cmax, Tmax and relative absorption for each administration of curcuminoids. *Normalized AUCs, expressed in ng/ml (plasma) x h/mg ingested, were divided by the AUC value of the reference to calculate the relative absorption values.

CASPEROME®

CASPEROME® is a purified mixture of triterpenoid acids from the gum resin of *Boswellia serrata*.

The concentration of the six major BAs (boswellic acids: KBA, AKBA, βBA, AβBA, αBA and AαBA) was evaluated in human plasma when administered as single dose in form of Phytosome® (Casperome®) and as standard *Boswellia serrata* extract.[8]

The administration of Casperome® at equivalent weight dosage resulted in statistically optimized C_{max} and AUC for all main boswellic acids. These results clearly demonstrate an optimized absorption of BAs from the lecithinized Casperome® formulation compared to the non-formulated boswellia extract even though the administered amount of *Boswellia serrata* extract in the Phytosome® corresponded only to around one third of the amount contained in the standard extract formulation (fig. 4).

The unique BAs profile of Casperome® and their scientifically-proven bioavailability in the Phytosome® formulation correspond to a remarkable clinical efficacy demonstrated in several published human studies.

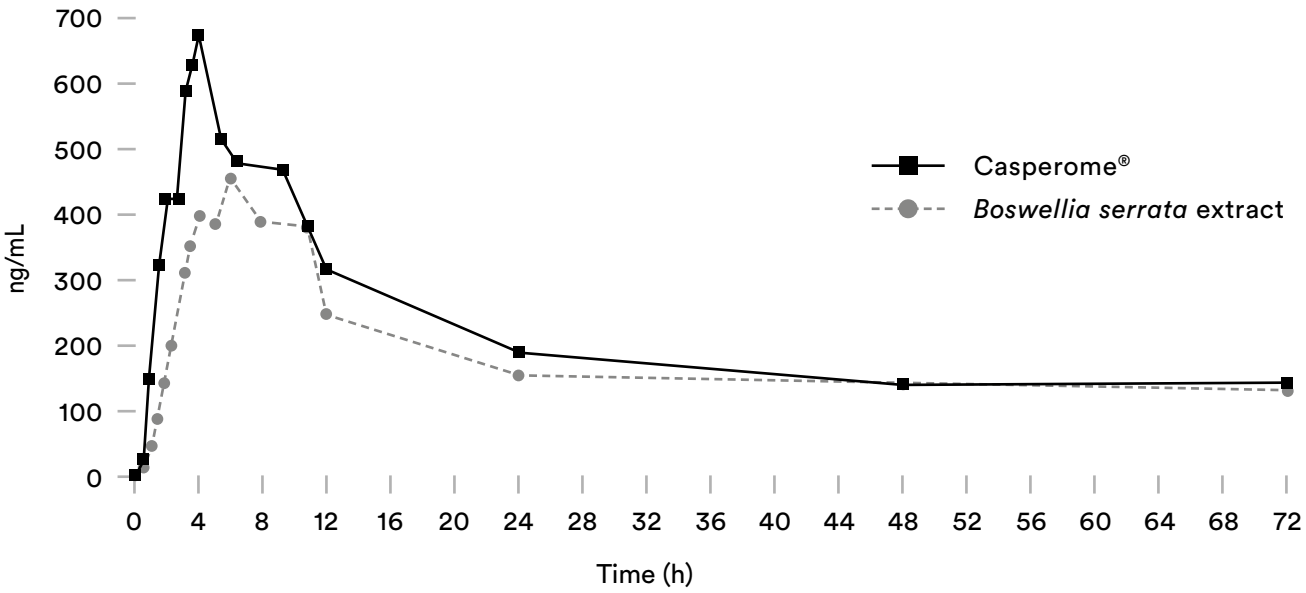


Fig. 4: Plasma concentrations of boswellic acids (BAs) after single oral administration of unformulated *Boswellia serrata* extract and Casperome®.

QUERCEFIT™

QUERCEFIT™ is the food grade delivery system of quercetin from *Sophora japonica L*.

Recent data showed that Phytosome® formulation optimized quercetin solubility of 11-fold in simulated intestinal fluids[9].

The bioavailability of quercetin flavanol was then evaluated in a randomized cross-over pharmacokinetic study in twelve healthy volunteers.

This study showed that Quercefit™, administered at 250 mg and 500 mg as single dose, is able to optimize plasma concentrations compared to unformulated quercetin (fig. 5).[9]

Quercefit™ demonstrates once more the effectiveness of Phytosome® formulation in optimizing solubility and bioabsorption of natural compounds.

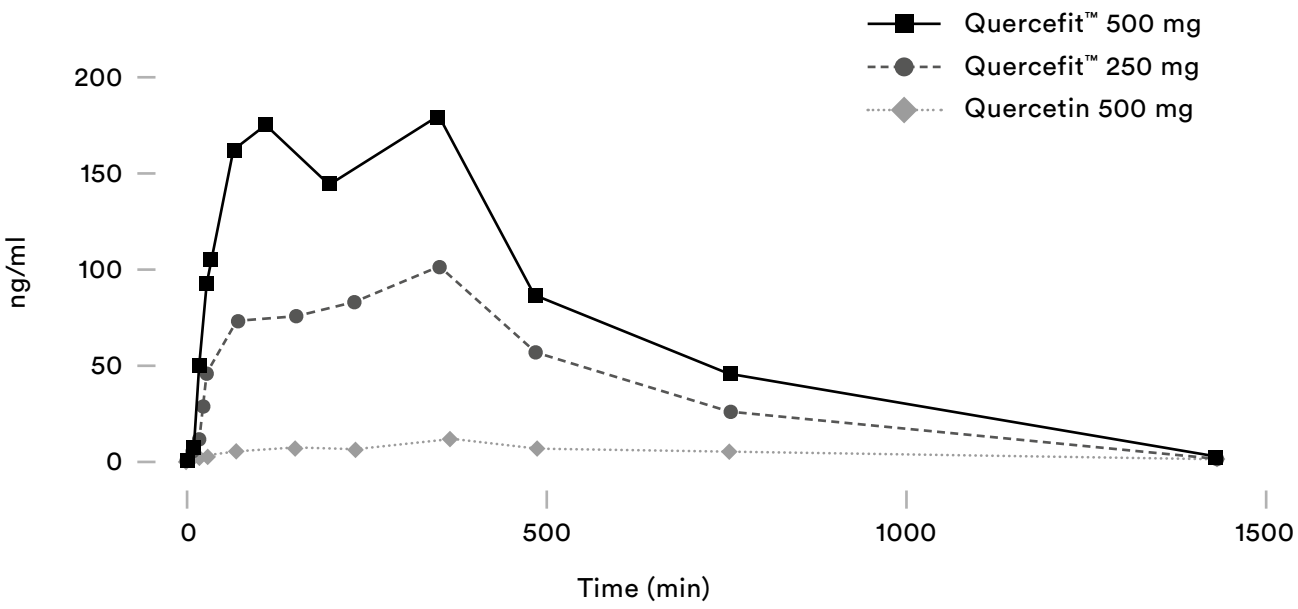


Fig. 5: Plasma concentrations of quercetin obtained after single oral administration of unformulated quercetin (500 mg) and Quercefit™ (250 mg and 500 mg).

VAZGUARD™

Vazguard™ is the bergamot extract, with a unique phytochemical profile, formulated with Phytosome® delivery system.

Plasmatic concentration of main flavanon naringin has been investigated in a 30 days human study[10] to compare the effect of the daily administration of unformulated bergamot extract at the dose of 1300 mg and Vazguard™ at the dose of 1000 mg.

Despite Vazguard™ contained only 40% of bergamot extract and, furthermore, was used at lower daily dosages, plasmatic concentration of naringin resulted to be the same when administered in form of Phytosome® and unformulated extract.

Normalizing the results in terms of administered bergamot extract amount, naringin resulted in statistically significant plasmatic levels when administered in form of Vazguard™ (fig. 6).

These results demonstrate the optimized bioabsorption of narinign flavanon when administered in form of Phytosome® as Vazguard™ compared to the unformulated extract.

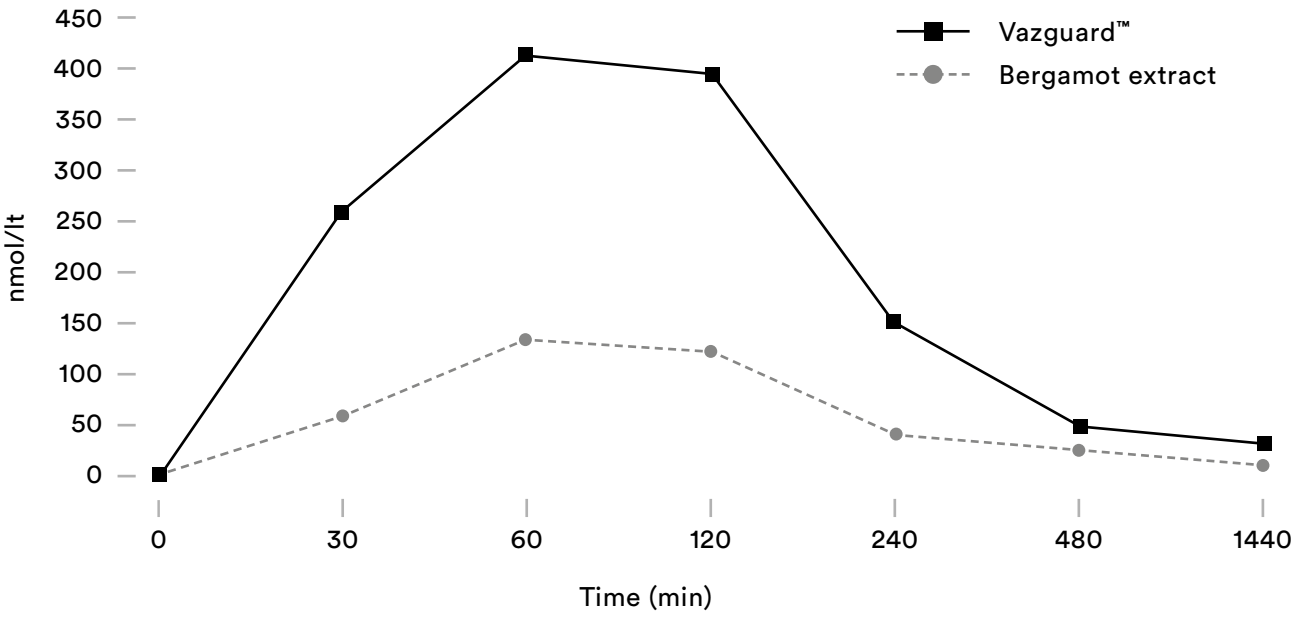


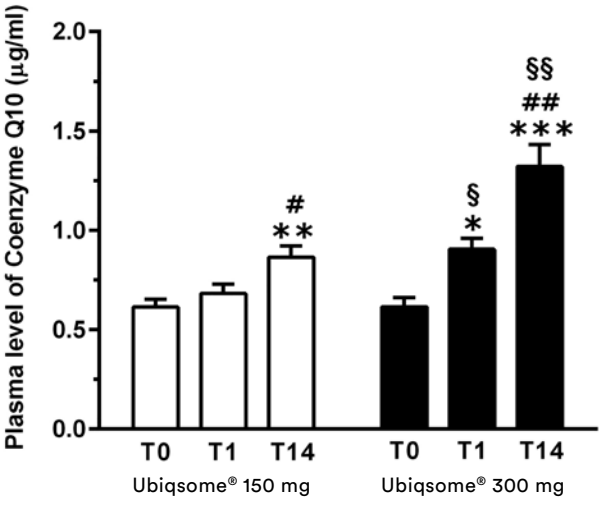
Fig. 6: Time vs plasma concentration curves for naringin after administration of the same amount of bergamot extract as unformulated extract or Vazguard™.

UBIQSOME®

Phytosome® delivery system has been successfully adopted also for non-botanical compounds, like coenzyme Q10. Ubiqsome® is the bioavailable form of coenzyme Q10 (CoQ10) which, according to the results obtained in single and repeated pharmacokinetic studies[11] in healthy volunteers, guarantees optimized physiological CoQ10 plasma levels after one single use and after 2 weeks of supplementation with 2 different dosages (150 and 300 mg daily). Furthermore, a dose-dependent profile has been also evidenced comparing results between the 2 different dosages of Ubiqsome®.

In a 30-days human study[12] in over-50s healthy athletes, Ubiqsome® was confirmed to significantly optimize plasmatic CoQ10 levels.
Moreover, a significantly optimization of CoQ10 levels was also observed in muscle after Ubiqsome® administration, further displaying a good tolerance profile.

These findings support the plasmatic and muscular bioavailability in humans of CoQ10 when administered as food-grade Phytosome® delivery formulation.



*: P<0.01, **: P<0.005 and ***: P<0.0001 vs T0 of the same treatment group (A or B) by two-way ANOVA;
#: P<0.05 and ##: P<0.0001 vs T1 of the same treatment (A or B), by Tukey's test;
§: P<0.01 vs T1 of A; §§: P<0.0001 vs T14 of A, by Bonferroni's test.

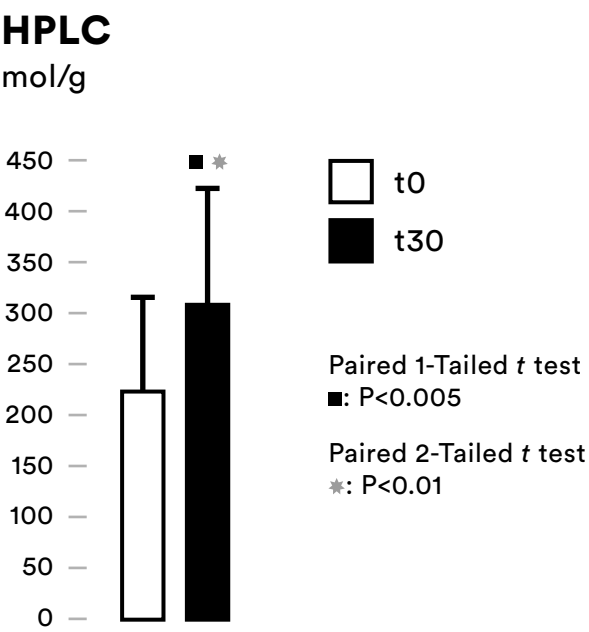


Fig. 7: Plasmatic levels of CoQ10 after 14-days repeated administration of 150 mg and 300 mg of Ubiqsome® respectively.
Fig. 8: Muscular levels of CoQ10 after 30-days repeated administration of 500 mg of Ubiqsome® in over-50s healthy athletes (HPLC determination).

PHYTOSOME®
highlights

- Food-grade dietary ingredients only
- Absence of synthetic ingredients or adjuvants
- Optimized bioabsorption
- Tailor-made for selected natural products
- Already applied at industrial scale
- Solid technology with long experience and know-how pioneered and developed by Indena
- Absence of nanoparticles
- Good physical and technological properties
- Suitable for formulation in most common dosage forms
- IP and proprietary know-how available
- Supported by strict scientific studies

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