

Phytosomes: Technical Revolution in Phytomedicine

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Abstract: Phytomedicines, complex chemical mixtures prepared from plants, have been used for health maintenance since ancient times. But many phytomedicines are limited in their effectiveness because they are poorly absorbed when taken by mouth. The PHYTOSOMETM technology, developed by Indena S.p.A. of Italy, markedly enhances the bioavailability of select phytomedicines. Most of the bioactive constituents of phytomedicines are flavonoids. However, a majority of the flavonoids are poorly bioavailable when taken by mouth—only a small fraction of a given dose reaches the blood.³ this report presents the evidence that by converting certain flavonoid nutrients to their phytosome equivalents, Indena's proprietary process increases their bioavailability by 2 xs to 6x, perhaps more.

Keywords: flavonoids, phytomedicines, Phytosome, bioavailability

Introduction

Over the past century, phytochemical and phytopharmacological sciences established the compositions, biological activities and health promoting benefits of numerous botanical products. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, glycosidic aglycones etc) are poorly absorbed either due to their large molecular size which can not absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich biological membranes, resulting poor bioavailability.¹ It has often been observed that the isolation and purification of the constituents of an extract may lead to a partial or total loss of specific biological activity for the purified constituent - the natural constituent synergy becomes lost probably due to the removal of chemically related substances contributing the synergistic effect of the active principle(s).² Very often the chemical complexity of the crude or partially purified extract seems to be essential for the bioavailability of the active constituents. Extracts when taken orally some constituents may get destroyed in the gastric environment. As standardized extracts are established, poor bioavailability often limits their clinical utility due to above said reasons.

Background to the Phytosome Technology: The poor absorption of flavonoid nutrients is likely due to two main factors. First, these are multiple ring molecules not quite small enough to be absorbed from the intestine into the blood by simple diffusion. Nor does the intestinal lining actively absorb them, as occurs with some vitamins and minerals. Second, flavonoid molecules typically have poor miscibility with oils and other lipids. This severely limits their ability to pass across the lipid-rich outer membranes of the enterocytes, the cells that line the small intestine. The PHYTOSOMETM technology meets this challenge. Certain of the water-phase flavonoid molecules can be converted into lipid-compatible molecular complexes, aptly called phytosomes. These are better able to transition from the water phase external to the enterocyte, into the lipid phase of its outer cell membrane and from there into the cell, finally reaching the blood¹. the lipid-phase substances that Indena successfully employed to make flavonoids lipid-compatible are phospholipids from soy, mainly phosphatidylcholine (PC). PC is miscible both in the water phase and in oil/lipid phases, and is excellently absorbed when taken by mouth. PC is the principal molecular building block for cell membranes and the molecular properties that suit PC for this role also render it close to ideal for its PHYTOSOME Precise chemical analysis indicates the unit phytosome is

usually a flavonoid molecule linked with at least one PC molecule. A bond is formed between the two molecules to create a hybrid molecule¹. This hybrid is highly lipid-miscible, better suited to merge into the lipid phase of the enterocyte's outer cell membrane (Fig. 1).

Once there it can cross the enterocyte and reach the circulating blood. Phosphatidylcholine is not merely a passive "carrier" for the bioactive flavonoids of the phytosomes, but a bioactive nutrient with documented clinical usefulness. The intakes of phytosome preparations sufficient to provide reliable clinical benefit often also provide substantial PC intakes. Phytosomes are not liposomes—structurally, the two are distinctly as shown in figure 2.

The phytosome is a unit of a few molecules bonded together, while the liposome is an aggregate of many phospholipids molecules that can enclose other phytoactive molecules but without specifically bonding to them. Liposomes are touted delivery vehicles, but for dietary supplements their promise has not been fulfilled. But for Indena's phytosome products numerous studies prove they are markedly better absorbed and have substantially greater clinical efficacy. Indena has successfully applied this technology to a number of standardized flavonoid preparations. The PHYTOSOMETM technology is a breakthrough model for:

- Marked enhancement of bioavailability
- significantly greater clinical benefit
- Assured delivery to the tissues
- No compromise of nutrient safety.

PHYTOSOMES, Highly Bio available Plant Extracts: Phytomedicines, complex chemical mixtures prepared from plants, have been used in medicine since ancient times and continue to have widespread popular use. PHYTOSOME dietary supplements are the modern culmination of this great tradition. PHYTOSOME is a patented process developed by Indena, a leading supplier of nutraceutical ingredients, to incorporate phospholipids into standardized extracts and so vastly improve their absorption and utilization. As standardized extracts became established, poor bioavailability often limited their clinical utility. Then it was discovered that complexation with certain other clinically useful nutrients substantially improved the bioavailability of such extracts. The nutrients so helpful for enhancing the absorption of other nutrients are the phospholipids. Phospholipids are complex molecules that are used in all known life forms to make cell membranes. They are cell membrane building blocks, making up the matrix into which fit a large variety of proteins that are enzymes, transport proteins, receptors, and other biological energy converters. In humans and other higher animals the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients. Increased bioavailability of the PHYTOSOMES over the simpler, noncomplex. Plant extracts has been demonstrated by pharmacokinetic (tissue distribution) and activity studies, conducted in animals as well as in humans. PHYTOSOME has an added dimension: the proven health giving activity of the phospholipids themselves.

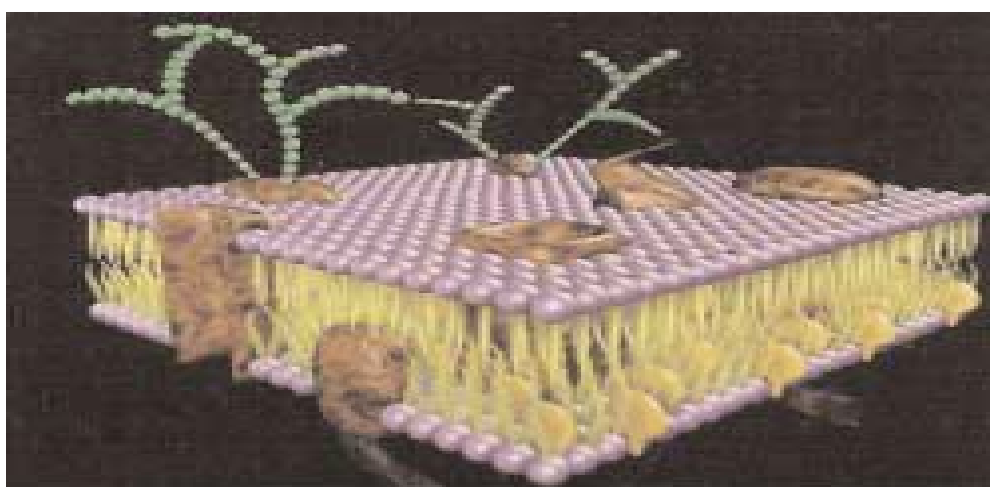


Fig.1: Cell membranes are largely lipid-phase. A double molecular layer consisting of PC and other phospholipids provides a continuous matrix into which the proteins insert. From Singer and Nicolson.4

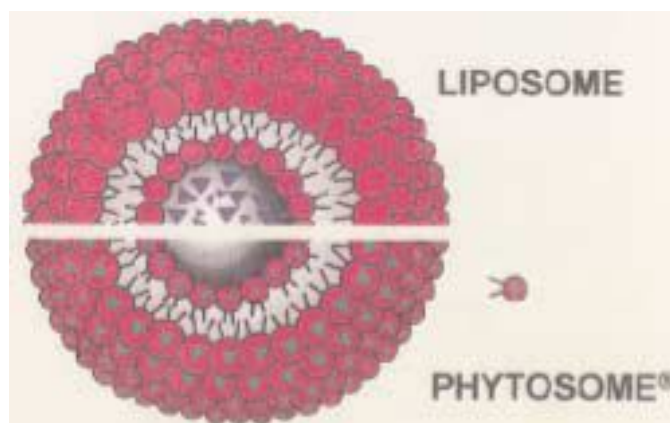


Fig.2: The molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment). The unit phytosome is PC linked to the flavonoid molecule (lower right). From Bombardelli et al.2

PHYTOSOMES, Highly Bio available Plant

Extracts: Phytomedicines, complex chemical mixtures prepared from plants, have been used in medicine since ancient times and continue to have widespread popular use. PHYTOSOME dietary supplements are the modern culmination of this great tradition. PHYTOSOME is a patented process developed by Indena, a leading supplier of nutraceutical ingredients, to incorporate phospholipids into standardized extracts and so vastly improve their absorption and utilization. As standardized extracts became established, poor bioavailability often limited their clinical utility. Then it was discovered that complexation with certain other clinically useful nutrients substantially improved the bioavailability of such extracts. The nutrients so helpful for enhancing the absorption of other nutrients are the phospholipids. Phospholipids are complex molecules that are used in all known life forms to make cell membranes. They are cell membrane building blocks, making up the matrix into which fit a large variety of proteins that are enzymes, transport proteins, receptors, and other biological energy converters. In humans and other higher animals the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients. Increased bioavailability of the PHYTOSOMES over the simpler, noncomplex. Plant extracts has been demonstrated by pharmacokinetic (tissue distribution) and activity studies, conducted in animals as well as in humans. PHYTOSOME has an added dimension: the proven health giving activity of the phospholipids themselves.

SILIPHOS™ Milk Thistle PHYTOSOME: The liver is especially responsible for processing potentially toxic substances such as alcohol, pharmaceuticals and drugs of abuse, pollutants, excess hormones, and others. The detoxication process can deplete essential bio molecules and damage the liver. A standardized extract from *Silybum marianum* (milk thistle) is an excellent liver protectant but very poorly

absorbed. Pharmacokinetic and clinical studies prove that the PHYTOSOME complex of milk thistle (called SILIPHOS) is far better absorbed, as well as safe and effective in subjects with impairment of liver function that ranges from mild to severe. Other Indena PHYTOSOME extracts include: **Ginkgoselect®** PHYTOSOME is a more fully absorbable form of the standardized extract of *Ginkgo biloba* leaves. Its major indications are cerebral insufficiency and peripheral vascular disorders, and it also can ameliorate reduced cerebral circulation. Its improved oral bioavailability and good tolerability makes it the ideal Ginkgo product even for long term treatment. **Leucoselect®** PHYTOSOME is composed of oligomeric polyphenols (grape procyanidins) of varying molecular size, complexed with phospholipids. The markedly improved oral bioavailability of these procyanidin flavonoids offers marked protection for the cardiovascular system and other organs through a network of mechanisms that extend beyond their great antioxidant potency. **Greenselect®** PHYTOSOME contains a totally standardized polyphenolic fraction (not less than 66.5 percent) obtained from green tea leaves and mainly characterized by the presence of epigallocatechin and its derivatives. These compounds are potent modulators of several biochemical processes linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis. The complexation of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability. **Mirtoselect®** PHYTOSOME contains an extract of bilberry which provides anthocyanosides. These improve capillary tone, reduce abnormal blood vessel permeability, and are potent antioxidants. They hold great potential for the management of retinal blood vessel problems and venous insufficiency. **Sabalselect®** PHYTOSOME includes an extract prepared from saw palmetto berries through supercritical CO₂ (carbon dioxide) extraction. It delivers fatty acids, alcohols and sterols that benefit prostate health. In particular this extract may benefit

non-cancerous prostate enlargement. **Lymphaselect**™ PHYTOSOME includes a standardized extract from *Melilotus officinalis*. This preparation is particularly indicated for venous disorders, including chronic venous insufficiency of the lower limbs. **Oleaselect**™ PHYTOSOME is a newer preparation from olive oil polyphenols. These are potent free radical scavengers (antioxidants), inhibit harmful oxidation of LDL cholesterol, and also have anti-inflammatory activity. **Polinacea**™ is an immunomodulating preparation made from *Echinacea angustifolia*. It includes echinacosides and a unique high-molecular weight polysaccharide. This preparation especially enhances immune function in response to a toxic challenge. For all these breakthrough phytomedicines, the PHYTOSOME technology enables cost effective delivery AND synergistic benefits from the phospholipids nutraceuticals intrinsic to life.

GREENSELECT® PHYTOSOMETM The tea plant *Camellia sinensis* (Family Theaceae) is native to either China or India. Its leaves contain a variety of polyphenolic substances that provide many health benefits. The most active of these are flavonoids of the flavan-3-ol class—catechins and their various gallate derivatives^{7,8}. Tea drinking dates back to at least 2000 BC⁷. In China, its medicinal properties were apparent by the late 8th Century AD, when the “Chajing” (Tea Bible) by Lu Yu stated “...it makes abscesses maturate, it has diuretic and expectorant functions, it calms cough; it has a cooling effect and keeps awake⁷.” According to Chinese folk medicine, tea possesses stimulant, digestive, diuretic, analgesic, and antitoxic properties. The stimulant and other invigorating properties of tea were appreciated by the Buddhist monks, who helped spread its use throughout China and Japan, and from there to the rest of the world. There are 3 main classes of teas: green tea, black tea, and oolong tea. Green tea is made simply from dried leaves, while black tea comes from fermented leaves and oolong is partly fermented. Fermentation tends to oxidize the polyphenols, potentially lowering their antioxidant potential. Thus green tea is strongest in antioxidant power and black tea substantially less so, with oolong intermediate. The Indena GREENSELECT® green tea extract is a decaffeinated, standardized polyphenolic fraction (not less than 66.5 percent) obtained from green tea leaves (refer to the HPLC profile). For this extract also, Indena took advantage of its sophisticated phospholipid technology to complex the green tea polyphenols with phospholipids and markedly improve their limited oral bioavailability. This preparation is the GREENSELECT® PHYTOSOMETM. In 1998 Pietta and collaborators did a study on absorption of the Indena GREENSELECT® preparations in healthy volunteers 2 Each volunteer received a single dose of

400 mg tea flavanols, either as Indena’s standardized, noncomplexed REENSELECT® extract or as the GREENSELECT® PHYTOSOMETM. Absorption was measured as EGCG blood levels. As shown in Fig. T3, over the study period of 6 hours the blood concentration of EGCG was more than doubled when coming from the phytosomal versus the non-phytosomal extract. The antioxidant capacity of the volunteers⁸ blood also increased. 2 Antioxidant capacity was measured as TRAP (Total Radical-trapping Antioxidant Parameter). The peak antioxidant effect was a 20% enhancement, this coming earlier from the phytosomal GREENSELECT® and lasting longer than from the non-phytosomal form⁹.

LEUCOSELECT® PHYTOSOMETM preparation may help protect smokers against the massive free radical load they carry. At an intake of 300 mg (flavonoids) per day it partially protected the blood lipids against peroxidation and improved the oxidation resistance of the circulating LDL⁹.

Lowering of oxidative stress in diabetics. Twenty (20) diabetic patients not dependent on insulin participated in a randomized, double-blind crossover trial, 9 designed similarly to the smoker study just described. They were first “washed out” for 6 weeks to clear drugs and supplements, and then randomized to receive either LEUCOSELECT®PHYTOSOMETM (at 300 mg per day of flavonoids) or a placebo. After 4 weeks they were again washed out for 4 weeks, then their supplements switched for 4 additional weeks. The result was that urine levels of an oxidative stress marker, 8-epi PGF2alpha, were significantly reduced by the phytosomal LEUCOSELECT® but not reduced by the placebo treatment.

LEUCOSELECT® PHYTOSOMETM

Protection against ischemic-reperfusion damage

In rat heart.¹⁰ Young and old rats were fed for 30 days on a diet fortified with LEUCOSELECT® PHYTOSOMETM. Their hearts were isolated and set up with controlled flow of oxygenated nutrient solution via the coronaries. Following a 20-minute period of flow deprivation (ischemia) the flow was restored (reperfusion). Normally this can trigger considerable oxygen free radical release—reperfusion injury—that damages the heart muscle.

Therefore left ventricular developed pressure (LVDP) was monitored as a measure of the Heart muscle strength. Hearts from rats previously fed the phytosome preparation were able to recover and develop significantly greater muscle performance than control hearts.¹⁰ while the young hearts performed better than the old hearts, as would be expected, both young and old developed significantly greater LVDP following reperfusion, as compared against the control young and old hearts.

Stimulation of prostacyclin release from isolated rabbit hearts.¹⁰ Prostacyclin is a protective prostaglandin, usually released from the healthy endothelial cells that line the blood vessels. In a rabbit heart ischemia-reperfusion model, set up similarly to the rat model, young and old hearts from rabbits previously maintained on diet plus the LEUCOSELECT® PHYTOSOMETM produced markedly greater quantities of prostacyclin than did the controls.

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Conclusion

Various experiments shown that phytosome preparation was found to have at least 10 potential action mechanisms, all operative at concentrations that can be realistically attained in humans. It is anti-inflammatory as well as antioxidant. In experimental animal models it improved resistance to atherosclerotic lesion development, enhanced a protective prostaglandin, and protected ventricular heart pump muscle against damage from circulatory deprivation.

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