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Review

Supramolecular phospholipids–polyphenolics interactions: The PHYTOSOME® strategy to improve the bioavailability of phytochemicals

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ABSTRACT

The poor and/or erratic oral bioavailability of polyphenolics can be improved using the PHYTOSOME® [1] delivery system, a strategy that enhances the rate and the extent of solubilization into aqueous intestinal fluids and the capacity to cross biomembranes. Phospholipids show affinity for polyphenolics, and form supramolecular adducts having a definite stoichiometry. This article reviews the preparation and characterization of PHYTOSOME® complexes and their activity in various medicinal (cardiovascular, anti-inflammatory, hepatoprotective, anticancer) and cosmetic (skin aging) realms of application.

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[1] PHYTOSOME® is a registered trademark of Indena S.p.A. Milan, Italy.

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1. Introduction

For good bioavailability, natural products must have a good balance between hydrophilicity (for dissolving into the gastrointestinal fluids) and lipophilicity (to cross lipidic biomembranes). Many phytoconstituents like 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.

Water-soluble phytoconstituents (mainly polyphenolics) can be converted into a lipid-compatible molecular complex known as PHYTOSOME®. 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 [2–5]. Phospholipids are small lipid molecules where glycerol is bonded to two fatty acids, with the third hydroxyl, normally one of the two primary methylenes, bearing a phosphate group [6]. Phospholipids from soy, mainly phosphatidylcholine, are lipophilic substances and readily complex polyphenolics. In this context, phosphatidylcholine, the major molecular building block of cell membranes and a compound miscible in both water and in oil/lipid environments, is well absorbed orally, and has the potential to act as a chaperon for polyphenolics, accompanying them through biological membranes [7].

PHYTOSOME® complexes were developed at Indena (Milan, Italy) in the late Eighties. Many popular standardized herbal extracts [e. g. *Ginkgo biloba* L., grape (*Vitis vinifera* L.) seeds, milk thistle (*Silybum marianum* (L.) Gaertn), green tea (*Camellia sinensis* (L.) O. Kuntze), ginseng (*Panax ginseng* C.A. Meyer), licorice (*Glycyrrhiza glabra* L.), horse chestnut (*Aesculus hippocastanum* L.), *Centella asiatica* (L.) Urban, olive (*Olea europea* L.), *Terminalia sericea* Burch. Ex. DC, *Amni visnaga* (L.) Lam, turmeric (*Curcuma longa* L.) and hawthorn (*Crataegus spp.*)] are currently commercially available in the PHYTOSOME® form (see Table 1). Flavonoids and terpenoids from herbal extracts undergo different absorption pathways when bound to phospholipids, and this article reviews various aspects and the latest trends of PHYTOSOME® research, highlighting recent advances in their therapeutic potential.

2. Physical and chemical properties

The first PHYTOSOME® generation was prepared by combining selected polyphenols or polyphenol extracts with phospholipids in non-polar solvents [2], but, more recently, a newer PHYTOSOME® generation was developed using hydro-ethanolic solvents. Products obtained in this way comply with current food specifications [8,9], and expand the PHYTOSOME®' potential from the pharma/cosmetic field to the health-food one.

A PHYTOSOME® is an amphiphilic substance with a definite melting point, generally soluble in nonpolar solvents (where its hydrophilic moiety is not), and moderately soluble in fats. The low solubility in aqueous media makes the formation of stable emulsions and creams possible (Fig. 1), improving the biopharmaceutical properties of both highly lipid insoluble and poorly water-soluble phytoconstituents.

The PHYTOSOME® formulation increases the absorption of active ingredients when topically applied on the skin [10–19], and improves systemic bioavailability when administered orally [20–24]. In water medium, a PHYTOSOME® will assume a micellar shape, forming a liposome-like structure. Fundamental differences exit, however, between a PHYTOSOME® and a liposome. In liposomes, the active principles are dissolved in the central part of the cavity, with no possibility of molecular interaction between the surrounding lipid and a hydrophilic substance. On the contrary, the PHYTOSOME® complex can somewhat be compared to an integral part of the lipid membrane (Fig. 2), where the polar functionalities of the lipophilic guest interact via hydrogen bonds with the polar head of a phospholipid (i.e. phosphate and ammonium groups), forming a unique arrangement that can be evidenced by spectroscopy [10,11,18,25–28].

Thus, IR and multi-nuclear spectroscopic studies show that a PHYTOSOME® is not a mechanical mixture of two constituents,

Table 1
Available PHYTOSOME® complexes on the market. PHYTOSOME® and all other trademarks are owned by Indena S.p.A. Milan, Italy.

Trade name	Phytoconstituent complexed with phospholipid	Indication
Escin ß-sitosterol Phytosome®	Escin ß-sitosterol from horse chestnut fruit	Anti-oedema
Siliphos®	Silybin from milk thistle seed	Hepatocyte protection
Silymarin Phytosome®	Silymarin from milk thistle seed	Antihepatotoxic
Meriva™	Curcuminoids from turmeric rhizome	
Virtiva®	Ginkgoflavonglucosides, ginkgolides, bilobalide from *Ginkgo biloba* leaf	Vasokinetic
Ginkgoselect® Phytosome®	Ginkgoflavonglucosides, ginkgolides, bilobalide from *Ginkgo biloba* leaf	Vasokinetic
Ginselect® Phytosome®	Ginsenosides from *Panax ginseng* rhizome	Skin elasticity improver, adaptogenic
Leucoselect® Phytosome®	Polyphenols from grape seed	Antioxidant, capillarotropic
Centella Phytosome®	Triterpenes from *Centella asiatica* leaf	Cicatrizing, trophodermic
18 ß-glycyrrhetinic acid Phytosome®	18 ß-glycyrrhetinic acid from licorice rhizome	Soothing
Crataegus Phytosome®	Vitexin-2″-O-rhamnoside from Hawthorn flower	Antioxidant
Ginkgo biloba Dimeric Flavonoids Phytosome®	Dimeric flavonoids from *Ginkgo biloba* leaf	Lipolytic, vasokinetic
Ginkgo biloba Terpenes Phytosome®	Ginkgolides and bilobalide from *Ginkgo biloba* leaf	Soothing
Sericoside Phytosome®	Sericoside from *Terminalia sericea* bark root	Anti-wrinkles
Greenselect® Phytosome®	Polyphenols from green tea leaf	Prevention of free radical-mediated tissue damages and weight management
Visnadex®	Visnadin from *Amni visnaga* umbel	Vasokinetic
PA_2 Phytosome®	Proanthocyanidin A_2 from horse chestnut bark	Anti-wrinkles, UV protectant