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## PHYTOSOMES: AN ADVANCED HERBAL DRUG DELIVERY SYSTEM

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**Abstract:** Phytoconstituents have been known since ancient times and are highly estimated all over the world as a rich source of therapeutic agents for the prevention of diseases and ailments. The effectiveness of any herbal medication is dependent on the delivery of effective level of the therapeutically active compound. But a severe limitation exists in their bioavailability when administered orally or by topical applications due to their hydrophilic nature and unique chemical structure. Phytosomes are novel herbal formulations that are better absorbed and as a result produce better bioavailability and actions than the conventional herbal extracts. Phytosomes are produced by a process whereby the standardized plant extract or its constituents are bound to phospholipids, mainly phosphatidylcholine producing a lipid compatible molecular complex. Phytosome exhibit better pharmacokinetic and pharmacodynamic profile than conventional herbal extracts.

**Keywords:** Phytosome, Phytoconstituent, Phospholipid, Liposomes, Formulation, Evaluation.



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## INTRODUCTION

Herbal drugs stand out as recent promising candidates for the treatment of various diseases. Fewer side effects and lower phytochemical costs from natural resources open new avenues for health maintenance by various means and highlight the era of 'back to nature' <sup>[1]</sup>. Most of the bioactive constituents of phytomedicines are secondary metabolites like flavonoids, glycosides etc. These are water-soluble molecules but limited in their effectiveness because they are poorly absorbed when taken orally or when applied topically, either due to their large molecular size which cannot absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich outer membranes of the enterocytes, the cells that line the small intestine, resulting poor bioavailability paving the way for a high influence of exogenous factors, such as diet and dosage regimen. Therefore, a large standard dose is usually required for oral dosage regimens. These aspects constitute a handicap against the widespread use of phytomedicines in the pharmaceutical field. The effectiveness of any herbal product is dependent upon delivering an effective level of the active compounds. The Phytosome technology <sup>[2]</sup> developed by Indena meets this challenge by markedly enhancing the bioavailability of selected phytomedicines <sup>[3,4]</sup>.

### THE PHYTOSOME TECHNOLOGY:

The term "Phyto" means plant while "some" means cell-like <sup>[5]</sup>. Phytosomes are little cell like structures. Phytosome is a novel form of herbal formulations which contains the bioactive phytoconstituents of herb extract complexed with phospholipids to produce lipid compatible molecular complexes. Phytosome is a newly introduced patented technology developed to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes (also often referred as herbosome in certain literature). 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 blood <sup>[6]</sup>. The lipid-phase substances that Indena successfully employed to make flavonoids lipid-compatible are phospholipids from soy, mainly phosphatidylcholine (PC). Phosphatidylcholine is the principal molecular building block of cell membranes miscible both in water and in oil environments, and is well absorbed when taken by mouth. Chemical analysis indicates that the phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. A bond is formed between these two molecules, creating a hybrid molecule <sup>[6]</sup>. This highly lipid-miscible hybrid bond is better suited to merge into the lipid phase of the enterocyte's outer cell membranes so they are more bioavailable as compared with conventional herbal extracts owing to their enhanced capacity to cross the lipid-rich biomembranes and, finally, reach the blood. They have improved

pharmacokinetic and pharmacological parameters which are advantageous in the treatment of acute diseases as well as in pharmaceutical and cosmetic compositions <sup>[7]</sup>.

Phosphatidylcholine is not merely a passive "carrier" for the bioactive flavonoids of the phytosomes, it itself is a bioactive nutrient with documented clinical efficacy for liver disease, including alcoholic hepatic steatosis, drug-induced liver damage and hepatitis. The phytosome process has been applied to many popular herbal extracts including ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, curcumin, quercetin, hesperetin, silymarin and ginseng. The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. Specifically, the choline head of the phosphatidylcholine molecule binds to these compounds while the fat-soluble phosphatidyl portion comprising the body and tail then envelopes the choline-bound material. As a result a little microsphere or cell like structure <sup>[8]</sup> will appear. 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 (Fig 1) and the molecular properties that suit PC for this role also render it close to ideal for its phytosome role.

#### **PHYTOSOMES DIFFER FROM LIPOSOMES:**

Although similar, fundamental differences exist between a phytosome and a liposome. Phytosomes are not liposomes and, structurally, the two are very different as shown in Fig 2. Unlike phytosomes, liposomes are formed by mixing a water-soluble substance with phosphatidylcholine. No chemical bond is formed and the phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound. In contrast, with the phytosome process, the phosphatidylcholine and the individual plant components actually form a complex 1:1 or a 2:1 complex depending on the substance <sup>[9, 10]</sup>.

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. The phytosome is a unit of a few molecules and this makes a difference so that the phytosomes are much better absorbed than liposomes. Phytosomes are also superior to liposomes in skin care products while the liposome is an aggregate of many phospholipid 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 phytosome products numerous studies prove they are markedly better absorbed and have substantially greater clinical efficacy.

## PROPERTIES OF PHYTOSOMES:

### 1) PHYSICO CHEMICAL PROPERTIES:

A phytosome is a complex between an herbal drug and a natural phospholipid, like soy phospholipid. Such a complex results from the reaction of stoichiometric amounts of phospholipid with the selected polyphenol (like simple flavonoids) in a nonpolar solvent<sup>[11]</sup>. On the basis of their physicochemical and spectroscopic data, it has been shown that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functional groups of the substrate. When treated with water, phytosomes assumes a micellar shape forming liposomal-like structures. In liposomes the active principle is dissolved in the internal pocket or floats in the layer membrane, while in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane. For example in the case of the catechindistearoyl-phosphatidylcholine complex, there is the formation of H-bonds between the phenolic hydroxyl end of the flavone moiety and the phosphate ion on the phosphatidylcholine moiety. Phosphatidylcholine can be deduced from the comparison of <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra of the complex with those of the pure precursors. The signals of fatty chain remain almost unchanged. Such evidence inferred that the too long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and flavonoid molecule and enables the complex to dissolve in low polarity solvents<sup>[12, 13]</sup>.

### 2) PHARMACOLOGICAL PROPERTIES:

Pharmacokinetic and pharmacodynamic studies in experimental animals and in human subjects have been used to demonstrate the biological behaviour of Phytosomes<sup>[14]</sup>. The increased bioavailability of the phytosomes over the non complexed botanical derivatives has been evaluated from these studies<sup>[15]</sup>.

## MERITS OF PHYTOSOMES OVER CONVENTIONAL DOSAGE FORMS:

- 1) Phytosomes have the following advantages<sup>[16]</sup>:
- 2) It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
- 3) They improve the absorption of active constituent(s) which further reduce its dose requirement.
- 4) They have appreciable drug entrapment.

- 5) Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.
- 6) Chemical bonds are formed between phosphatidylcholine molecules and phytoconstituent molecules, so the phytosomes show better stability profile.
- 7) Application of phytoconstituents in the form of phytosome improves their percutaneous absorption and act as functional cosmetics.
- 8) Assured delivery to the tissues.
- 9) The nutrient safety of the herbal extracts need not be compromised by converting the herbal drug as means of phytosomes.
- 10) Phytosomes produces a little cell where the valuable components of herbal extracts are protected from destruction by digestive secretions and gut bacteria.

#### PREPARATION METHODS:

Phytosomes are formulated by patented processes in which the standardized extract (having a standardized content of active principles) and/or active ingredients of herbs (like flavonoids and terpenoids) are bound to the phospholipids like phosphatidylcholine (PC) through a polar end. Phytosomes are prepared by reacting 3–2 moles (preferably with 1 mole) of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidyl- ethanolamine or phosphatidylserine, with one mole of phytoconstituent either alone or in the natural mixture in an aprotic solvent, such as dioxane or acetone, in a 1:2 or 1:1 ratio<sup>[17]</sup>. The optimum ratio of phospholipid to phytoconstituent is 1:1. The complex thus formed can be isolated by precipitation with an aliphatic hydrocarbon or by lyophilization or by spray drying<sup>[7]</sup>. Some liposomal drug complexes operate in the presence of water or buffer solution where the phytosomes interact with a solvent with a reduced dielectric constant. The common stages for the preparation<sup>[18]</sup> of phytosomes are charted in Fig 3. Maiti *et al.*,<sup>[19]</sup> Jiang *et al.*,<sup>[20]</sup> and Maiti *et al.*,<sup>[21]</sup> have described the methods used for phytosome preparation.

Jiang *et al.*, (2001) have optimized the preparation conditions using a uniform design and step regression and have prepared Herba Epimedii total flavonoid phytosomes (EFP) by means of solvent evaporation and investigated the cumulative dissolution of different ratios of EFP-PVP precipitates by means of dissolution release. The optimized preparation conditions are as follows: solvent-tetrahydrofuran, lecithin to PVP ratio 2:5, temperature 40°C and reaction time 3 hrs. The oil/water apparent partition coefficient of icariin was enhanced more than 4-fold by phospholipid. The cumulative dissolution of Herba Epimedii flavonoids of the EFP-PVP

precipitate was significantly higher than that of its physical mixture and a Herba epimedii extract tablet<sup>[20]</sup>.

Yanyu *et al.*, (2006) prepared a silybin-phospholipid complex using ethanol as a reaction medium. Silybin and phospholipids were resolved into the medium, after the organic solvent was removed under vacuum condition, and a silybin-phospholipid complex was formed<sup>[22]</sup>.

#### **FORMULATION OF PHYTOSOMES:**

Phytosome complexes can be formulated both orally and topically. In order to obtain the best performances of this technological innovation both in terms of formulating manageability and enhanced bioavailability (as appropriate disintegration and dissolution time of oral forms, for instance).

##### **Soft gelatin capsules:**

Soft gelatin capsules represent an ideal solution to formulate phytosome complexes. The phytosome complex can be dispersed in oily vehicles to obtain suspensions to be filled in soft gelatin capsules. Vegetable or semi-synthetic oils can be used to this purpose. Indena recommend a granulometry of 100% <200 µm to best perform capsule production. According to Indena experience, not all the phytosome complexes behave in the same way when dispersed in oily vehicles and when the oily suspension is filled in the soft gelatin capsules; for this reasons preliminary feasibility trials should be performed to select the most suitable vehicle.

##### **Hard gelatin capsules:**

The Phytosome complex can be formulated in hard gelatin capsules as well. A direct volumetric filling process (without precompression) can be applied, even if the apparently low density of the phytosome complex seems to limit the maximum amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule). With a piston tamp capsule filling process, however, it is possible to increase the amount of powder which can be filled in a capsule, but precompression might affect the disintegration time. Indena recommend to carefully monitor the related parameters during product/ process development. A preliminary dry granulation process is advisable define the best manufacturing process.

##### **Tablets:**

Dry granulation represents the ideal manufacturing process to obtain tablets with higher unitary doses and with suitable technological and biopharmaceutical properties. However, due to the limited flowability, potential stickiness and low apparent density of the phytosome

complex, a direct compression process can be applied only for low unitary doses; note that whenever a direct compression process is applied, the phytosome complex should be diluted with 60-70% of excipients to optimize its technological properties and to obtain tablets with appropriate technological and biopharmaceutical characteristics. On the other hand, wet granulation should be avoided due to the negative effect of water and heat (granulation/drying) on the stability of the phospholipid complex.

#### **Topical dosage forms:**

The phytosome complex can be formulated topically as well. The ideal process to incorporate the phytosome complex in emulsion is to disperse the phospholipidic complex in a small amount of the lipidic phase and add it to the already created emulsion at low temperatures (not higher than 40°C). The phytosome complexes are dispersible in the main lipidic solvents employed in topical formulations. In case of formulations containing a limited amount of lipids, the phytosome complex might also be dispersed into the watery phase, and again added to the final formulation at temperature lower than 40°C.

### **EVALUATION OF PHYTOSOMES**

#### **1) CHARACTERIZATION:**

The following are the characterization techniques used for Phytosomes in characterizing its physical attributes.

##### **a) Visualization:**

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) <sup>[24]</sup>.

##### **b) Particle size and Zeta potential:**

The particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS) <sup>[25]</sup>.

##### **c) Entrapment efficiency:**

The entrapment efficiency of a drug in phytosomes can be measured by the ultracentrifugation technique <sup>[25]</sup>.

##### **d) Transition temperature:**

The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry <sup>[26]</sup>.

**e) Surface tension activity measurement:**

The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer <sup>[27]</sup>.

**f) Vesicle stability:**

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. The mean size is measured by DLS and structural changes are monitored by TEM <sup>[28]</sup>.

**g) Drug content:**

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method <sup>[29]</sup>.

**2) SPECTROSCOPIC EVALUATION:**

The spectroscopic evaluations are widely employed in order to confirm the formation of complex between phytoconstituents and the phospholipid moiety as well as to study the corresponding interaction between the two.

**a) <sup>1</sup>H-NMR:**

The complex formation between the active phytoconstituents and the phosphatidylcholine molecule can be estimated by this method. Bombardelli *et al.*, studied the NMR spectra of phytosome complex in nonpolar solvents. There is a marked change in <sup>1</sup>H-NMR signal originating from atoms involved in the formation of complex, without any summation of the signal peculiar to individual molecules. The signals from protons belonging to the phytoconstituents are broadened. In phospholipids there is broadening of signals while the singlet corresponding to the N-(CH<sub>3</sub>)<sub>3</sub> of choline undergoes an up field shift <sup>[30]</sup>.

**b) <sup>13</sup>C-NMR:**

In the <sup>13</sup>C NMR of the phytoconstituents and the stoichiometric complex with the phosphatidylcholine when recorded in C<sub>6</sub>D<sub>6</sub> at room temperature all the phytoconstituents carbons were invisible. The signals corresponding to the glycerol and choline portion are broadened and some are shifted, while most of the resonance of the fatty acid chains retains their original sharp line shape <sup>[31, 32, 33]</sup>.

**c) FTIR:**

The formation of the complex can be also be confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the individual components and their mechanical

mixtures. FTIR spectroscopy is also a useful tool for the control of the stability of phytosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water after lyophilization, at different times. In the case of simple formulations, it is necessary to subtract the spectrum of the excipients (blank) from the spectrum of the cosmetic form at different times, comparing the remaining spectrum of the complex itself [31, 32, 33].

### 3) *IN-VITRO* AND *IN-VIVO* EVALUATIONS:

Models of *in-vitro* and *in-vivo* evaluations are selected on the basis of the expected therapeutic activity of the biologically active phytoconstituents present in the Phytosomes [34]. For example, *in-vitro* anti hepatotoxic activity can be assessed by the antioxidant and free radical scavenging activity of the phytosomes. For assessing anti hepatotoxic activity *in-vivo*, the effect of prepared phytosomes on animals against thioacetamide, paracetamol alcohol induced hepatotoxicity can be examined [35, 36]. Skin sensitization and tolerability studies of glycyrrhetic acid Phytosome® ointment, a commercial product, describe the *in-vivo* safety evaluation methodology [37]. Filburn *et al.*, studied the bioavailability of a silybin-phosphatidylcholine complex in dog models to examine the pharmacokinetic parameters of this new complexed form [38].

### SOME PATENTED TECHNOLOGIES RELATED TO PHYTOSOMES:

There are a number of innovative processes and formulation research studies in the field of phytosomes carried out by a number of academic scientists as well as by industrial laboratories. Some patents for phytosomes and other related technologies along with their applications and innovations are listed in table 1.

### APPLICATIONS OF PHYTOSOMES:

To examine the various advantages of phytosomes, especially their ability to enhance the bioavailability of polar phytoconstituents, various therapeutic applications of phytosomes have been explored. The details of the type of phytosomes, active constituents, the daily dose and specific indications are given in table 2.

### CONCLUSION:

Despite the wide therapeutic potential of phytoconstituents, especially those containing flavonoids and other phenolic compounds, their phenolic nature renders them polar but has poor solubility in water and most of the organic solvents as well. Poor drug dissolution is responsible for scarce absorption and poor bioavailability. These aspects constitute a handicap against the widespread use of flavonoids in the pharmaceutical field. These hindrances can be

tackled by formulating an appropriate drug delivery system. Phospholipid based drug delivery system has been found promising for better and effective delivery of natural drug and can enhance the rate and extent of drug absorption across the lipoidal biomembrane. Phytosomes are novel phospholipid based drug delivery system, which offer improved bioavailability of hydrophilic flavonoids and other similar compounds through the skin or gastrointestinal tract. They have many distinctive advantages over other conventional formulations. The formulation methodology for phytosome is simple and can be easily upgraded to a commercial scale. The characterization methodologies and analytical techniques are well established for this type of novel formulation. Many patents are already approved for innovative formulations, processes and applications of phytosomes. As far as the potential of phytosome technology is concerned, it has a great future for use in formulation technology and applications of hydrophilic plant compounds.

## FIGURES

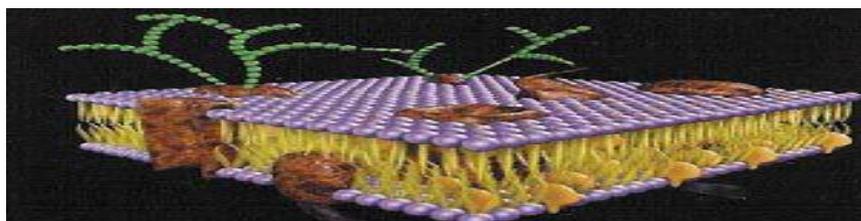


Figure No. 1: Cell membranes are largely lipid phase. A double molecular layer consisting of PC and other phospholipids provides a continuous matrix into which the proteins insert

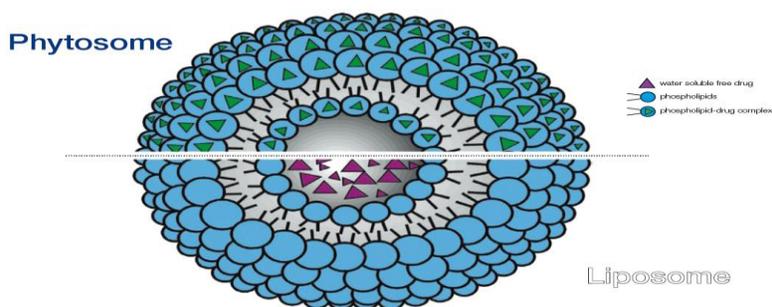


Figure No. 2: Major difference between liposome and phytosome. The molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment)

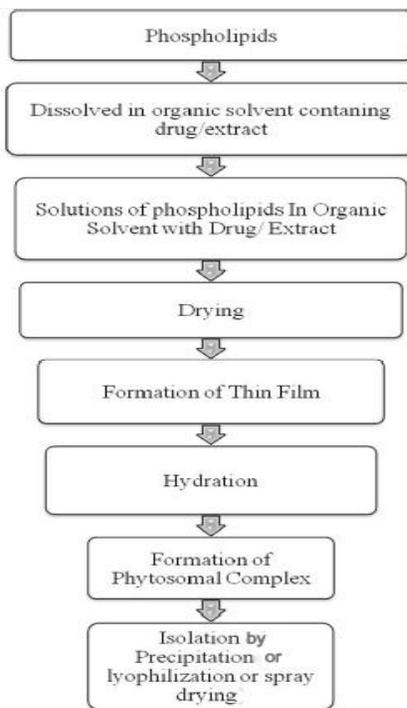


Figure No. 3: Flow chart for method of preparation of phytosome

Table No. 1: Some patented technologies related to phytosome

TITLE OF PATENT	INNOVATION	PATENT No.	REFERENCE
Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	Phospholipids complexes of olive fruits or leaves extracts or compositions containing it having improved bioavailability.	EP/1844785	39
Compositions comprising <i>Ginkgo biloba</i> derivatives for the treatment of asthmatic and allergic conditions	Compositions containing fractions deriving from <i>Ginkgo biloba</i> , useful for the treatment of asthmatic and allergic conditions.	EP1813280	40
Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use	Fatty acid monoesters of sorbityl furfural selected from two diff series of compounds in which side chain is a linear or branched C <sub>3</sub> -C <sub>19</sub> alkyl radical optionally containing at least one ethylenic unsaturation.	EP1690862	41

<b>Cosmetic and dermatological composition for the treatment of aging or photodamaged skin</b>	Composition for topical treatment of the skin comprises a substance that stimulates collagen synthesis and a substance that enhances the interaction between extracellular matrix and fibroblasts. Cosmetic or dermatological composition for topical treatment.	EP1640041	42
<b>Treatment of skin, and wound repair, with thymosin beta 4</b>	Compositions and methods for treatment of skin utilizing thymosin $\beta$ 4.	US/2007/0015698	43
<b>Soluble isoflavone compositions</b>	Isoflavone compositions exhibiting improved solubility (e.g., light transmittance), taste, color, and texture characteristics, and methods for making.	WO/2004/045541	44
<b>An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems</b>	Preparation based on plant extracts which has an anti-oxidant effect and is particularly useful in treatment of circulation problems such as phlebitis, varicose veins, arteriosclerosis, haemorrhoids and high blood pressure.	EP1214084	45
<b>Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions containing them</b>	Complexes of saponins with natural or synthetic phospholipids have high lipophilia and improved bioavailability and are suitable for use as active principle in pharmaceutical, dermatologic and cosmetic compositions.	EP0283713	46

**Table No. 2: Therapeutic applications of different phytosomes with their dose** <sup>[47-50]</sup>

PHYTOSOMES	PHYTOCONSTITUENT COMPLEXED WITH PC	DAILY DOSAGE	INDICATION
<b>Leucoselect<sup>®</sup> phytosome</b>	Procyanidolic oligomers (PCOs) from grape seeds	50–100mg	Systemic antioxidant, specific. Best choice for most people under age of fifty. Also specific for the eyes, lungs, diabetes, varicose veins, and protection against heart disease.
<b>Greenselect<sup>®</sup> phytosome</b>	Epigallocatechin 3-O-gallate from camelia sinensis (Green tea)	50–100mg	Systemic antioxidant. Best choice for protection against cancer and damage to cholesterol.
<b>Ginkgoselect<sup>®</sup> phytosome</b>	24 % ginkgo flavono glycosides From Ginkgo biloba	120mg	Best choice for most people over the age of 50. Protects brain and vascular lining <sup>51</sup> .
<b>Silybin phytosome</b>	Silybin from silymarin (milk thistle)	120mg	Best choice if the liver or skin needs additional antioxidant protection.
<b>Siliphos<sup>™</sup> milk thistle phytosome</b>	Silybin from silymarin	150mg	Good choice for liver or skin support <sup>52</sup> .
<b>Hawthorn phytosome</b>	Flavonoids	100mg	Best choice in heart disease.
<b>Panax ginseng phytosome</b>	37.5% ginsenosides from roots of Panax ginseng	150mg	As a Food Product.
<b>Glycyrrhiza phytosome</b>	18-beta glycyrrhetic acid	-	Anti-inflammatory Activity <sup>53</sup> .
<b>Mirtoselect<sup>®</sup> Phytosome</b>	Anthocyanosides from an extract of Bilberry	-	These improve capillary tone, reduce abnormal blood vessel permeability & are potent antioxidants. They hold great potential for the management of retinal blood vessel problems and venous insufficiency.

<b>Sabalselect<sup>®</sup> phytosome</b>	An extract of saw palmetto Berries through supercritical CO <sub>2</sub> (carbon dioxide) extraction	-	It delivers fatty acids, alcohols and sterols that benefit prostate health. Also beneficial for non-cancerous prostate enlargement
<b>Polinacea<sup>™</sup> phytosome</b>	Echinacosides and a unique high-molecular weight Polysaccharide from Echinacea angustifolia	-	It enhances immune function in response to a toxic challenge.
<b>Oleaselect<sup>™</sup> phytosome</b>	Polyphenols from olive oil	-	As potent antioxidants, inhibit harmful oxidation of LDL cholesterol, and also have anti-inflammatory activity.
<b>Lymphaselect<sup>™</sup> phytosome</b>	A standardized extract of melilotus officinalis	-	Indicated for venous disorders, including chronic venous insufficiency of the lower limbs.

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