



Phytosomes: System for Delivering Bioactive Plant Extracts and Phytoconstituents

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ABSTRACT

Due to low lipid solubility and molecular size, herbal remedies with a high concentration of active components exhibit excellent bioactivity in vitro but modest bioactivity in vivo. As a consequence, the herbal extract's active ingredients are poorly absorbed and accessible. Phytosomes are phyto-phospholipid complex vesicles that may improve the bioavailability of herbal extracts and phytoconstituents in pharmaceuticals. Phytosomes are sophisticated herbal formulations that comprise the bioactive phytoconstituents of herbal extracts and may alter the cell membrane from a hydrophilic to a lipophilic state, resulting in a more effective pharmacokinetic and pharmacodynamic profile than typical herbal extracts. Suspensions, tablets, lotions, and gels are just a few of the options. The goal of this article is to provide complete research on phytosomes as a prospective drug delivery mechanism by discussing current breakthroughs in phytosomes as well as their utilization in various standardized herbal extracts.

Key Words: Phytosomes, Phyto-phospholipid complex, Phospholipids, Herbal Extract, Phytoconstituents, Drug Delivery

INTRODUCTION

Plant active compounds derived from herbal extracts, which have been employed in home treatments for centuries, are progressively finding their way into contemporary medicine. [1] On the other hand, certain phytoconstituents contain long side chains and high polarity, which prevents passive diffusion over lipidic skin. [2] The majority of phytoconstituents have been demonstrated to be extremely polar or water-soluble compounds, such as flavanoids, terpenoids, and polyphenolics. [3] These water-soluble components are unable to enter particularly lipid-rich cellular membranes due to their limited lipid solubility, resulting in poor bioavailability. [4] The use of solubility and bioavailability enhancers, structural alteration, and trapping in a lipophilic carrier are just a few of the strategies that have been developed to improve bioavailability. [5] The chemical complexity of the crude or partly distilled extract seems to have a role in the active components' bioavailability. [6] When taken orally, any elements in water-soluble extracts may be destroyed in the stomach environment. [7] The 'phytosome,' an unique phyto-phospholipid complexation technique that improves absorption and bioavailability, has emerged as one of the most successful strategies for boosting bioavailability of phyto-pharmaceuticals with poor solubility and difficulties penetrating biological membranes.

Despite having powerful in vitro pharmacological activity, some plant actives have failed to produce equivalent in vivo effects. [9] By combining these plant actives with dietary phospholipids, novel amphipathic cellular structures have been created, making them more systemically effective. [10] Indena, a prominent distributor of nutraceuticals components, developed the Phytosome patent to add phospholipids to a standardised extract to improve absorption, bioavailability, and consumption. [11]

PHYTO-PHOSPHOLIPID COMPLEX VESICLES

Phytosomes are cellular-like structures (Figure 1). Phytosome is a novel medication delivery technology that addresses the flaws of standard drug delivery technologies. [12] "Phyto" refers to a plant, and "some" refers to anything that looks like a cell. Phytosomes contain the bioactive phytoconstituents of plant extracts, which are encased in lipids. [13] Plant extracts or water-soluble bioactive plant ingredients are mixed with phospholipids to generate phytosomes, which are lipid-compatible molecular complexes that improve absorption and bioavailability. [14] The phytosome method produces a

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cell, which is a vital component of herbal extract that is not destroyed by digestive secretions or gut flora. [15] Phytosomes have a better ability to shift from a hydrophilic condition to the lipid-friendly environment of the enterocyte cell membrane, and then through the cell to the bloodstream. [16] Hydrophilic phytoconstituents may be complexed with therapeutically relevant phospholipids to create lipid-soluble complexes. Phytosomes, which are liposome-like vesicles, may be made using these complexes. [17]

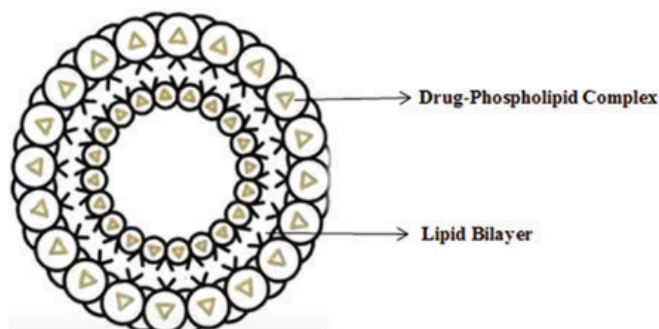


Figure 1: Structure of Phytosomes.

When phospholipids and water-soluble active plant components are complexed in phytosomes, chemical linkages are established, making them more stable. [18] Phytosomes significantly increase the bioavailability of these polar active compounds. For phytosome manufacture, soya phospholipids, egg lecithin, phosphatidylcholine, and other phospholipids have been found (Figure 2). [19] Phytosomes may swiftly cross lipid biomembranes and have been proven to increase the bioavailability of lipid-insoluble extracts by enhancing absorption in the gastrointestinal system. [20].

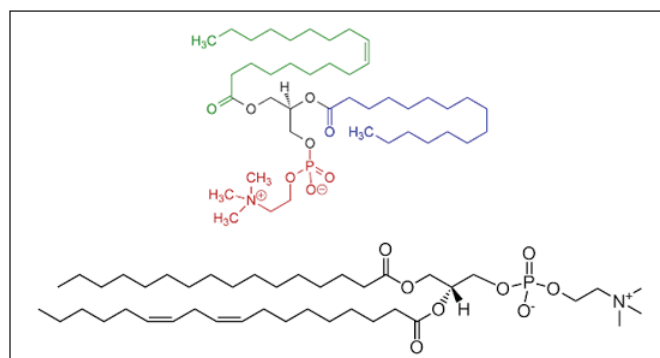


Figure 2: Structure of some common Phospholipid: Lecithin (Above) and Soya Phosphatidylcholine (Below).

ADVANTAGES OF PHYTOSOME VESICLES [21]

1. They enter the cell fast after passing through the cell membrane.
2. The drug's bioavailability has increased noticeably.
3. Phytosomes guarantee that herbal treatments may be used for a long period.
4. Phytosomes increase the absorption of hydrophilic polar phytoconstituents via nasal, topical, and other routes, improving their bioavailability.
5. Phytosomes are a kind of small cell that protects the beneficial components of herbal extracts from digestive secretions and microorganisms in the intestine.
6. Phytosomes encourage medicine to be delivered to the correct tissues.
7. The nutritional integrity of the herbal extracts does not have to be jeopardized by assigning the herbal medication as phytosomes.
8. The dosage needed has been lowered due to the maximal absorption of the primary ingredients.
9. They improve the absorption of physiologically active constituents while lowering dose requirements.
10. The phosphatidylcholine molecule forms chemical connections with phytoconstituents, indicating that phytosomes have a high stability profile.
11. Because of their improved skin penetration and high lipid profile, phytosomes are often utilised in cosmetics to improve phytoconstituent transdermal absorption.
12. Phytoconstituents in phytosomes are best absorbed when they travel swiftly through tissue walls in the colon.
13. Because the phytosome complex is biodegradable, there is no risk of drug entrapment.
14. Phytosomes enhance the effect of herbal substances by increasing absorption, increasing biological activity, and delivering to the target location; as a result, they are appropriate for pharmaceutical delivery.
15. Entrapment effectiveness is great because the chemical is coupled with lipids during vesicle formation.
16. When making phytosomes, drug entrapment isn't a concern.
17. Phosphatidylcholine, which is utilized to form phytosomes, is a component of the cell membrane that not only works as a messenger but also nourishes the skin.
18. Phytosomes surpass liposomes in skincare products.
19. Phytosomes have been shown to have a significant therapeutic benefit.
20. When mixed with hepatoprotective chemicals, phosphatidylcholine, which is employed in the creation of phytosomes and functions as a transporter as well as a hepatoprotective, has a synergistic effect.
21. Because of their limited water solubility, they may be made into a strong semisolid dose form.

22. Increases the solubility of bile salts, making liver targeting easier.
6. Phytosomes increase the solubility of bile in herbal ingredients, which aids liver targeting.

PROPERTIES OF PHYTOSOMES

Physicochemical properties

Phytosomes are synthetic compounds containing phospholipids. To make this combination, stoichiometric amounts of phospholipids and the substrate are mixed in a suitable solvent. The creation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functions of the substrate, according to spectroscopic evidence, is the major phospholipid-substrate interaction. When exposed to water, phytosomes take on a micellar shape, forming a liposomal structure. This may be determined by comparing the NMR of the complex to that of the pure predecessors. The indications of the fatty chain remain almost unchanged. The two long aliphatic chains wrap around the active material, generating a lipophilic envelope that protects the phospholipid's polar head and active ingredients, according to these studies. [22]

Biological properties

Phytosomes are sophisticated herbal components that are easier to swallow, use, and hence provide better results than traditional herbal extracts. The phytosome has a higher bioavailability than non-complexed botanical derivatives, according to pharmacokinetic and pharmacodynamic studies in laboratory animals and human subjects. [23]

PROSPECTS OF PHYTOSOME TECHNOLOGY [24]

When compared with conventional herbal formulation, phytosomes have the following prospects:

1. They improve lipid insoluble polar plant extracts' oral and topical absorption, resulting in increased bioavailability and hence therapeutic efficacy.
2. When the absorption of the active constituent(s) increases, a low dose will provide the desired results.
3. Phytosomes have a greater stability profile due to the formation of chemical linkages between the phosphatidylcholine molecule and the botanical extract.
4. Phytosomes are better at transitioning from a hydrophilic condition to the lipid-friendly environment of the enterocyte cell membrane and ultimately inside the cell, enabling systemic targeting.
5. Because phytosomes penetrate the skin efficiently and have a high lipid profile, they are commonly employed in cosmetics.

METHODS OF PREPARATION

Anti-solvent precipitation technique

The exact volume of plant extract and phospholipid were combined with 20 mL dichloromethane in a 100 mL circular bottom flask and refluxed for 2 hours at a temperature of not more than 60°C. The mixture is condensed to 5-10 mL. After carefully applying hexane (20 mL) with continuous stirring, the precipitate was filtered, collected, and kept in desiccators overnight. In a mortar, the crushed dry precipitate is sieved into #100 meshes. In an amber-colored glass container, the powdered compound was stored at room temperature. [25]

Rotary evaporation technique

In a revolving circular bottom flask, the specific volume of plant material and phospholipid were dissolved in 30 mL of tetrahydrofuran, then stirred for 3 hours at a temperature not exceeding 40°C. A thin layer of the sample was collected, then n-hexane was added and the mixture was continually stirred using a magnetic stirrer. The precipitate was removed and put in an amber-colored glass container at room temperature. [26]

Solvent evaporation technique

In a 100 mL round bottom flask, the correct amount of plant material and phospholipids is mixed with 20 mL acetone and refluxed for 2 hrs at 50-60°C. The precipitate was filtered and removed when the mixture was condensed to 5-10 mL. The dried precipitate phytosome complex was kept at room temperature in an amber-colored glass container. [27]

Ether-injection technique

In this procedure, the drug lipid complex is dissolved in an organic solvent. After that, the mixture is slowly injected into a heated aqueous agent, causing vesicles to form. The condition of amphiphiles is defined by their focus. When the concentration is low, amphiphiles adopt a monomer form; however, when the concentration grows, a variety of configurations, such as circular, cylindrical, disc, cubic, or hexagonal structures, may emerge. [28]

CHARACTERIZATION TECHNIQUES [29]

Visualization

Phytosomes may be seen using transmission electron microscopy (TEM). Internal structure, as well as many other properties of phytosomes, such as anatomy, crystallization, heat, and magnetic domains, may be revealed via TEM. The

surface of phytosomes is examined using scanning electron microscopy (SEM), which offers morphological information.

Particle size and zeta potential

Particle size and zeta potential may be determined using dynamic light scattering (DLS) using an automated inspection approach and photon similarity spectroscopy.

Entrapment efficiency

The ultracentrifugation method might be used to assess a drug's entrapment efficiency or potential to be entrapped in phytosomes. It calculates the proportion of medicine that is securely entrapped in phytosomes.

Transition temperature

In vesicular lipid systems, differential scanning calorimetry (DSC) may be used to determine the transfer temperature.

Surface tension activity measurement

The surface tension response of a medication in an aqueous solution may be calculated using the ring approach in a Du Nouy ring tensiometer.

Vesicle stability

Vesicles' size and form may be measured over time to determine their stability. The average scale is determined by DLS, while structural changes are monitored by TEM.

Drug content

To determine the volume of medication current, an updated high-performance liquid chromatographic procedure or a suitable spectroscopic approach may be utilized.

Proton-Nuclear Magnetic Resonance (1H-NMR)

Spectroscopic investigations are often utilised to both verify and study the creation of complexes between phytoconstituents and the phospholipids moiety. The intricate formation of active phytoconstituents and the phosphatidylcholine molecule may be approximated using this method.

Carbon-Nuclear Magnetic Resonance (13C-NMR)

When the 13C-NMR of the phytoconstituents and the stoichiometric compound with phosphatidylcholine were recorded, the carbons of the phytoconstituents were not visible. The signals corresponding to the glycerol and choline parts have been widened, and others have been relocated, but the resonance of the bulk of the fatty acid chains has preserved its original crisp line shape.

Fourier-Transformed Infra-Red (FT-IR) Spectroscopy

By comparing the spectrum of the complex to the spectrum of the individual components and their mechanical mixes, FT-IR spectroscopy may be utilized to authenticate the complex's creation. FT-IR spectroscopy is a useful tool for regulating the stability of phytosomes whether they are micro-dispersed in water or put into very simple cosmetic gels. In practice, the stability of a complex may be determined by comparing the spectrum of the complex in solid form (phytosomes) to the spectrum of its micro-dispersion in water after different times of lyophilization.

In-vitro and in-vivo evaluations

The physiologically active phytoconstituents contained in plants are expected to have a medicinal effect. In-vitro and in-vivo assessment models are chosen using phytosomes.

PHYTOSOME FORMULATIONS DEVELOPMENT

Phytosome complexes may be transformed and manufactured into a range of dose formulations for oral and topically applied use. To gain the greatest effects from this technological innovation, a variety of products might be developed, both in terms of formulation manageability and enhanced bioavailability.

Soft gelatin capsules

For preparing phytosome complexes, soft gelatin capsules are an excellent option. The phytosome complex might be suspended in oily vehicles before being packed into soft gelatin capsules. Vegetable or semi-synthetic oils may be used for this. Indena recommends a granulometry of 100 percent for producing the best capsules. According to Indena's expertise, not all phytosome complexes behave the same when dispersed in oily vehicles and packed in soft gelatin capsules; as a consequence, early feasibility experiments should be done to find the optimum vehicle. [30]

Hard gelatin capsules

The phytosome complex may also be used to make hard gelatin capsules. Even though the phytosome complex's apparent low density limits the quantity of powder that can be packed into a capsule, a direct volumetric filling approach (without pre-compression) may be utilised (usually not more than 300 mg for a size 0 capsule). A piston tamp capsule filling process may enhance the quantity of powder that can be loaded in a capsule, however pre-compression can affect the disintegration duration. Indena recommends keeping a careful check on the key metrics as the product/process grows. A preliminary dry granulation procedure describes the optimal production approach. [31]

Tablets

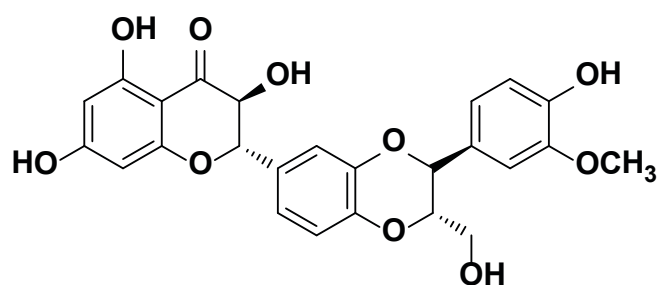
The safest method for producing tablets with greater unitary dosages and adequate technical and biological qualities is dry granulation. Due to the phytosome complex's limited flow capacity, possible stickiness, and low apparent density, direct compression should only be used for low unitary doses; note that if a direct compression process is used, the phytosome complex should be diluted with 60-70 percent excipients to maximise its technical properties and obtain tablets with sufficient morphology. Due to the adverse effects of water and heat (granulation/drying) on the phospholipid complex's stability, wet granulation should be avoided. [32]

Topical dosage forms

The phytosome complex may also be used topically. The only way to include the phytosome complex into an emulsion is to disperse the phospholipidic complex throughout a small volume of the lipidic phase and then add it to an emulsion that has already been made at low temperatures (below 40°C). In the most common lipidic solvents used in topical preparations, the phytosome complexes dissolve. The phytosome complex should be disseminated in the watery process and then added to the final formulation at a temperature below 40°C in the case of formulations with low lipid content. [33]

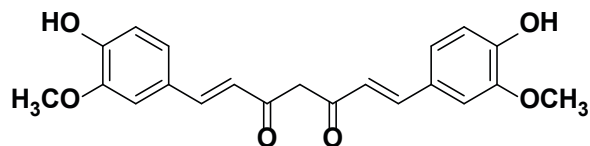
REPORTED PHYTOSOMES PRODUCTS

Silymarin Phytosomes



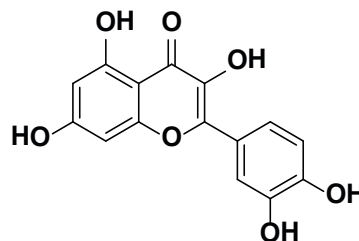
The majority of phytosomal research has focused on *Silybum marianum* (milk thistles), which generates liver-protective flavonoids in large quantities. In rats, the pharmacokinetics of silymarin phytosome was studied. Because of an outstanding increase in the lipophilic characteristics of the complex and an improvement in the biological activity of silybin, the bioavailability of silybin in rats was considerably enhanced following oral administration of silybin-phospholipid combination. It was discovered that silymarin phytosomes had higher anti-hepatotoxic action than silymarin alone, and that they may protect broiler chicks against aflatoxin B1 toxicity. [34]

Curcumin Phytosomes



Curcumin (flavonoid from *Curcuma longa*, turmeric) and naringenin (flavonoid from grapefruit, *Vitis vinifera*) phytosomes were created by the researchers. The complex's antioxidant activity was much greater than pure curcumin in all dose levels tested. Another study found that the generated phytosome of naringenin had better antioxidant activity and a longer length of action than the free compound, perhaps due to the molecule's slower departure from the body. [35]

Quercetin Phytosomes



The quercetin-phospholipid Phytosomal complex was created using a simple and reproducible method, and researchers found that the mixture had more therapeutic effectiveness than the molecule in rat liver damage caused by carbon tetrachloride. [36]

Grape seed extract Phytosomes

It is made up of various molecular sizes of oligomeric polyphenols (grape proanthocyanidins or Procyanidin from *Vitis vinifera* grape seed extract) that are complexed with phospholipids. Grape seed Procyanidin flavonoids have several properties, including an increase in total antioxidant capacity and stimulation of physiological defenses in plasma, protection against ischemia/reperfusion-induced heart damage, and protective effects against atherosclerosis, all of which provide significant protection for the cardiovascular system and other organs through a network of mechanisms. [37]

Ginkgo biloba leaves Phytosomes

Ginkgo phytosomes (produced from a standardized extract of *Ginkgo biloba* leaves) have been proven to outperform other plant extracts in studies (24 percent ginkgo flavones glycoside and 6 percent terpenes lactones). In a bioavailability testing with healthy human volunteers, the quantity of *G. biloba* components (flavonoids and terpenes) from the phytosomal form peaked after 3 hours and remained for at least

5 hours after oral administration. According to the results, phytosomal G. biloba generated a 2-4 times greater plasma concentration of terpenes than non-phytosomal G. biloba. It is used to treat cerebral insufficiency, peripheral vascular disease, and cerebral circulation problems. It is the best ginkgo product for long-term usage because to its improved oral bioavailability and tolerability. Ginkgo phytosomes have also been proven to be more effective than standardized extract in protecting isolated rat hearts from ischemia in studies. [38]

Green tea Phytosomes

The presence of epigallocatechin 3-O-gallate, a polyphenolic molecule, distinguishes green tea leaves (*Thea sinensis*). These chemicals are effective modulators of a wide range of metabolic processes involved in the breakdown of homeostasis in illnesses including cancer and atherosclerosis. Green tea possesses antioxidant, anticarcinogenic, antimutagenic, hypocholesterolemic, and cardioprotective effects, among other things. [39]

Olea Europaea oil Phytosomes

On the market is Oleaselect phytosome, a commercially generated phytosome focusing on olive oil polyphenols. Antioxidant, anti-inflammatory, and anti-hyperlipidemic effects are all present in it. It protects the heart by preventing LDL cholesterol from being oxidised. [40]

RECENT MARKETING PRODUCTS

Ginkgoselect®

It's a convenient absorbable version of a generic Ginkgo biloba leaf extract. Brain insufficiency and peripheral vascular disease are the most prevalent symptoms, and it's a valuable tool when cerebral function is reduced. It is a suitable alternative for long-term care because to its higher oral absorption and tolerability. It's a more readily absorbed generic extract of G. biloba leaves. The most prevalent indications include cerebral insufficiency and peripheral vascular disorders, and they may also aid with poor cerebral circulation. It is the ideal Ginkgo product for long-term use because to its improved oral bioavailability and tolerability. [41]

Greenselect®

It is made up of a perfectly homogenous polyphenolic fraction (no less than 66.5 percent) isolated from green tea leaves, with epigallocatechin and derivatives being the most prominent components. These chemicals have been found to be effective in vitro modulators of a variety of biochemical pathways linked to the etiology of chronic degenerative illnesses such as cancer and atherosclerosis. Because green tea polyphenols are complexed with phospholipids, their oral bioavailability is greatly improved. It's made up of a per-

fectly uniform polyphenolic fraction generated from green tea leaves (no less than 66.5 percent), with epigallocatechin and its variations being the most predominant. These chemicals are effective modulators of a wide range of metabolic processes involved in the breakdown of homeostasis in illnesses including cancer and atherosclerosis. When green tea polyphenols are complexed with phospholipids, their limited oral bioavailability is considerably increased. [42]

Siliphos®

It protects the liver against a range of ailments. It is presently the most absorbable source of silybin, allowing it to reach the target organ, the liver, at levels that have been shown to be antihepatotoxic. [43]

Mirtoselect®

It includes anthocyanoside-producing bilberry extract. These antioxidants promote capillary tone while also increasing capillary tone and decreasing aberrant blood vessel permeability. They hold a lot of potential for treating venous insufficiency and retinal blood flow abnormalities. [44]

Sabalselect®

It contains a supercritical CO₂ (carbon dioxide) extracted saw palmetto fruit extract. It contains fatty acids, alcohols, and sterols, all of which are beneficial to the prostate. This extract is very beneficial for non-cancerous prostate enlargement. [45]

Lymphaselect™

Melilotus officinalis extract is produced. This drug is used to treat venous disorders in the lower limbs, such as chronic venous insufficiency. [46]

Oleaselect™

It's a more recent formulation derived from the polyphenols found in olive oil. These are active free radical scavengers (antioxidants) that have anti-inflammatory characteristics and help to keep LDL cholesterol from oxidizing. [47]

Polinacea™

This immunomodulating preparation is made from *Echinacea angustifolia*. It's made up of echinacosides and a one-of-a-kind high-molecular-weight polysaccharide. In the face of a hazardous assault, this supplement boosts immune function. For any of these ground-breaking phytomedicines, the phytosome technology enables for cost-effective distribution and synergistic benefits from the phospholipid nutraceuticals present in nature. [48]

CONCLUSION

Phytosomes are novel structures built up of lipophilic plant components including *S. marianum*, *G. biloba*, and ginseng, as well as typical phospholipids. Phytosomes are often produced using unconventional ways. When phytosomes are used as a medicine, their absorption in the GI tract is somewhat greater than the real portion, resulting in a higher plasma level. Phytosomes will be studied in depth in the future, with the goal of using them in medicines. Phytosomes act as a link between conventional and non-traditional distribution networks. Phytosomes allow pharmaceutical businesses to develop new products based on water-soluble medicines and include new pharmacological technologies. The chemical may be delivered topically and orally using this method. Originally employed in cosmetics, phytosome complexes are now extensively utilised as a drug delivery method in antioxidants, gastrointestinal, anti-inflammatory, hepatoprotective, and anti-cancer therapies. The phyto-phospholipid complexing technology has revolutionised herbal therapy, allowing it to have a major effect in vivo despite promising in vitro outcomes. Phytosomes are a potential medication delivery system that may improve the efficacy, purity, and targetability of active plant ingredients and herbal extracts.

CONFLICTS OF INTEREST

No conflict of interest is declared.

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