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Review Article

EXPLORING POTENTIAL OF PLANTEROSOME AS A NOVEL DRUG DELIVERY SYSTEM; REVIEWING DECADES OF RESEARCH

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ABSTRACT
The delivery of effective level of therapeutically active compound influences the effectiveness any herbal medication. When administered orally or topically, severe limitations occur in the bioavailability of the same. Compared to the conventional phyto molecules or botanical extracts, planterosomes, which are newly, introduced herbal formulations, show much better bioavailability and actions produced as a result of better absorption profile. Nowadays, natural medicines are used to treat the malnutrition and other nutritional disorders as well as diseases which are prevailing in the recent times. Poor absorption and bioavailability can be observed in several plant extracts as well as phytoconstituents, due to their poor lipid solubility or improper size or sometimes both in combination, resulting in less or no *in-vivo* actions though they might demonstrate excellent bioavailability *in-vitro*. This in turn creates a need to work on the development of a new concept in herbal delivery system i.e., "planterosomes" which, due to the presence of phosphatidylcholine, can be absorbed and utilized better and hence produce results which are better in every aspect as compared to those of other conventional herbal extracts. The planterosomal preparations are especially advantageous in the treatment of acute as well as chronic diseases of the liver which may be of toxic or of infective origin or degenerative nature due to their substantially improved pharmacological and pharmacokinetic parameters. They can also be effectively used in the formulation of cosmetic and pharmaceutical compositions as well as in preparations which produce anti-inflammatory activity.
Keywords: Drug delivery system, Phosphatidyl choline, Phytoconstituent, Herbosomes, Phospholipid, Glycosidic aglycones.

INTRODUCTION

The term “plantero” means plant and “some” which means similar to cell. Planterosomes are novel formulations which, through the skin or gastrointestinal tract, offer enhanced bioavailability of hydrophilic flavonoids and other compounds which are similar to them. The phosphatidylcholine molecule in the planterosomal complex acts by pushing the phytoconstituent through the outer membrane of the intestinal epithelial cell, which in turn gains access to the bloodstream. Planterosomes (Figure 1) are also often known as phytosomes or herbosomes when compared to conventional herbal extracts, planterosomes exhibit better pharmacokinetic and pharmacodynamics profile. Novel drug delivery system aims at delivering drug as per the needs of the body in the course of treatment at a rate according to the requirement and direct the active drug molecules to the point of action to attain drug delivery which is controlled and targeted numerous novel drug delivery systems have been developed exploring various routes through which the drug can be administered. If selective absorption can be attained, the existence of drug in the systemic circulation can be sustained and the toxicity be minimized when such novel drug delivery system are used. One such system of drug delivery is the drug being encapsulated in vesicular structure as in liposomes, neosomes, transferosomes and pharmacosomes. Advances in this type of drug delivery system has led to the discovery of systems targeting drug action at specific sites and controlled or sustained release preparation which acts as a drug depot. Since ancient times phytomedicines which are complex chemical preparations made from plants have been used in the medicines when taken orally are absorbed poorly and therefore have limited effectiveness. Poor absorption of flavonoids, tannins, glycosisdicagycones which are water soluble phytoconstituent either due to their large molecular size or due to their poor lipid solubility cannot be absorbed by passive diffusion which severely limits their ability to pass across the lipid rich biological membrane resulting in poor bioavailability. Compositions, biological activities and health giving benefits of numerous plant extracts were established by the chemical and pharmacologic science over the past few centuries. But we could find that there was loss of activity or loss of the natural ingredient synergism often when individual components were separated from the whole of it. In order to resolve this problem, standardization was introduced. The clinical utility was often limited by the poor bioavailability when standardized extracts were introduced. Then, it was found that complexation with some other clinically use full nutrients substantially enhanced the bioavailability of those extracts. The nutrients were very useful for improving the absorption of certain other nutrients like phospholipids which are complex molecules that are used to make up the cell membrane of all known living organisms.

Characteristic features of Planterosome

-In human beings, and other higher animals, where phospholipids are also employed as natural digestive aids and as carriers for both fat and water miscible nutrients.
-The simpler noncomplex plant extracts have comparatively lesser bioavailability than that of planterosomes, which can be demonstrated by the pharmacokinetic or the tissue distribution and the activity studies which were performed in a group of animals as well as human beings.
-Health giving activity of the phospholipids themselves has been proven, and is an added dimension of planterosome.[1]

Properties of Planterosome

The factors such as physical size membrane permeability, chemical composition and percent entrapped solutes, as well

as the purity and quality of the starting materials governs the behaviour of planterosomes in both physical and biological systems. Therefore, planterosomes are characterized for physical attributes like shape, size, distribution, percentage drug capture, entrapped volume, percentage drug released and chemical composition.[2]

Chemical properties

-A complex between a soy phospholipid (natural phospholipid) and a natural product is called a planterosome.
-In an appropriate solvent, by reacting stoichiometric amounts of phospholipids and the substrate, this complex is obtained.
-The main phospholipid substrate interaction as obtained from spectroscopic data is due to the formation of hydrogen bond between the polar functionalities of the substrate and polar head of the phospholipids, i.e. phosphate and ammonia groups.
-Planterosomes assume a shape as that of a micelle forming a liposomal like structure, when treated with water.
-In liposomes the active principle is dissolved in the internal pocket or it is floating in the layer membrane, while in planterosomes, becoming an integral part of the membrane, the active principle is anchored to the polar head of phospholipids.
-For example, in the case of catechindistearoylphosphatidylcholine complex, there is hydrogen bond formation between the phosphate ion on the phosphatidylcholine side and phenolic hydroxyls of the flavone moiety. By comparing the NMR of the complex with those of pure precursors, this can be deduced.
-The fatty chain signals undergo changes.
-These evidences are an inference that the two long aliphatic chains wrap the active principle. In this manner, a lipophilic envelope is produced, wherein the polar head of the phospholipid and the catechin are shielded.

Biological properties

-In comparison with the conventional herbal extracts, planterosomes which are advances form of herbal products, are better absorbed, utilized thereby producing better results.
-By pharmacokinetic studies or by pharmacodynamics tests in experimental animals and in human subjects, it has been demonstrated that planterosomes have an increased bioavailability over the non-complexes botanical derivatives.[3]

Advantages of Planterosome

-Significantly enhanced therapeutic benefit and better bioavailability is achieved via oral as well as topical route through absorption of lipid insoluble polar phytoconstituents by planterosomes.
-Appreciable drug entrapment.
-Percutaneous absorption of planterosome is enhanced and it acts as a functional cosmetic when phyto constituents are applied in the form of planterosomes.
-Dose requirement is reduced when the absorption of active constituent is improved.
-Besides acting as a carrier, phytoconstituents are used in the preparation of planterosomes, also acts as a hepatoprotective, hence giving synergistic effect when hepatoprotective agents are used.
-The valuable components of the herbal extracts are protected from destruction or inactivation by digestive secretions and gut bacteria by creating a little cell of planterosome whereby the process assures delivery to the tissues with no compromise in nutrient safety.
-Due to absorption of chief constituent, dose requirement is reduced.
-There is no problem of drug entrapment since the drug itself is forming vesicles in conjugation with lipids and hence entrapment efficiency is fairly high and moreover predetermined.
-Planterosomes show better stability profile because chemical bonds are formed between phosphatidylcholine molecules and phytoconstituents.
-Phosphatidylcholine (Figure 2) used in the planterosomes process besides acting as a carrier, also nourishes the skin, because it is essential part of the cell membrane.
-Planterosomes are also superior to liposomes in skin care products. The particular structure of planterosome elicits peculiar properties and advantages in cosmetic application.

Added nutritional benefits of phospholipids

-Planterosomes permeate the non-lipophilic botanical extracts to be better absorbed in the intestinal lumen.
-Planterosomes have been used to give liver protectant flavonoids because they are easily bioavailable.
-By improving the solubility of bile to herbal constituents liver targeting can be facilitated.
-Unlike liposome, chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the planterosomes show better stability profile. Added nutritional benefit of phospholipids and marked enhancement of bioavailability.[4-6]

Disadvantages of Planterosome

-In planterosomes, phytoconstituents are rapidly eliminated.
-It has a short half life.
-Hydrolysis, fusion, leakage and oxidation is undergone by the phospholipid.
-It has a high cost of production and sometimes occurrence of allergic reactions to the planterosomal constituents may be observed.
-Because of their larger size problems can occur while trying to target to the various tissues.
-They are taken up quickly by the R.E.S cells.[4-7]

Significance of Planterosome

- The process of planterosome which consists of valuable components of herbal extracts is well protected from destruction by the secretion of the gastro intestinal tract as well as the bacterium in the gut. The process is a small cell in itself.
- Planterosomes are aptly called so because the phytoconstituents (Table 1) which are water soluble can be transformed into molecular complexes which are lipid compatible.
- Phosphatidylcholine, a phospholipid from soy which is a lipid phase substance is used to make phytoconstituents compatible with liquid.
- The principle molecular building block of cell membranes, phosphatidylcholine is absorbed efficiently when administered through the oral route since it is miscible with both water and oil phase.
- In accordance with the chemical analysis, planterosomes are indicated to be usually a phytoconstituent linked at least with one molecule of phosphatidylcholine.

- Being documented clinically efficacious for liver diseases such as alcoholic hepatic steatosis, drug induced liver damage and hepatitis, phosphatidylcholine is merely not just a passive carrier for the bioactive phytoconstituent of the planterosome but also is a bioactive nutrient by itself.
- Planterosome preparation intake often makes phosphatidylcholine available and therefore provides reliable clinical benefits.
- The planterosome process finds it application in many popular herbal extracts which include milk thistle, Ginseng, Gingko biloba, Grape seed, hawthorn and green tea.
- The direct binding to phosphatidylcholine are quite well lend themselves by the phytoconstituents which means that the phytoconstituents are bound by the choline head while the phosphatidyl portion comprising the body and the tail which is fat soluble then envelops the choline-bound material. This produces a little microsphere or eventually results in a cell being formed.[8,9]

Method of Preparation

- 2-3 moles (preferably 1 mole) of natural or synthetic phospholipid (say, phosphatidylcholine/ phosphatidylethanolamine/ phosphatidyserine) + 1 mole of component (like flavolignanans). These are either alone or in the natural mixture in an appropriate solvent such as dioxane or acetone. Complex can be isolated by precipitation with non-solvent such as aliphatic hydrocarbons or either using lipophilization or spray drying from this mixture. The ratio of phospholipids to flavonoids in the complex formation of planterosomes is in the range of 0.5:0.2 moles, the most preferred being 1:1.[10]
- Equal moles of narigenin and phosphatidylcholine are taken to prepare narigenin-phosphatidylcholine complex. To a 100 ml round bottom flask add the complex and reflux in dichloromethane for 3 hours. 30 ml n-Hexane is to be added to the mixture in order to concentrate the solution to 5-10 ml and as to precipitate the complex. Further, after filtration the precipitate is to be collected and kept in vacuum desiccators.[11]
- Into 100 ml round bottom flask, the required quantity of drug and phospholipids are taken and dissolved in anhydrous ethanol. Under vacuum at 40oc, evaporate the ethanol off and the residue which were dried were gathered and is to be transferred into a glass bottle. The bottle must be flushed with nitrogen and stored at room temperature.[12,13]

Evaluation of Planterosome
Characterization Method

- Visualization: Using TEM and SEM planterosomes can be visualized.
- Particle size: Using PCS vesicle size and zeta potential can be determined by DLS.
- Vesicle stability: By assessing the structure, size of the vesicle can be evaluated over time. Structural differences are observed by TEM and the average size is determined by DLS.
- Efficacy of entrapment: By using ultracentrifugation method, the entrapment efficacy of planterosome can be evaluated.
- Temperature of transition: By differential scanning calorimetry, the transition temperature of vesicular lipid system can be measured.
- Measurement of surface tension activity: The surface tension of the drug in aqueous solution can be determined by Du-Nouy ring method.

Spectroscopic evaluation

Content of drug: By suitable spectroscopic method, the amount of drug can be quantified.

***In-vivo* and *in-vitro* evaluation**

- Several *in-vitro* and *in-vivo* and spectroscopic evaluations are carried out on planterosomes.
- These complexes can be characterized by transmission electron microscopy (TEM), proton nuclear magnetic resonance spectroscopy (1HNMR), carbon-13NMR or sometimes referred to as carbon NMR (13C-NMR), phosphorous-31 NMR spectroscopy (31P-NMR) and Fourier transform infrared spectroscopy (FI-IR).
- On the basis of expected therapeutic activity of biologically active phytoconstituents present in planterosomes, models of *in-vitro* and *in-vivo* evaluations are selected.
- The activity of the active principle is increased by complexation.
- Using IR and UV spectroscopic studies, a chemical spectral characteristic is identified in phospholipid complexes.
- Liquid chromatography/atmospheric pressure chemical ionization mass spectrometry (LC/APCI-ITMS), a newly developed LC-APCI mass spectrometric method is described for human plasma determination of atovaquone using lapachol internal standard, proved to be a very powerful tool for pharmacokinetic study of phytochemicals.
- After administration of gingko biloba extracts in free (gingko select) or phospholipid complex (gingko select phytosome) forms, the levels of gingkolides A and B and bilobalide were evaluated in plasma of volunteers by using this technique.
- In human subjects, the study of vasomotor activity and skin microcirculation of the cheeks, hands, limbs, and female breast by using techniques such as infra-red-Photo pulse-Plethysmography, laser Doppler thermography, and computerized video thermography were carried out to identify the effects of gingko bilobadimeric flavonoids in planterosome form.
- To compare pharmacokinetic parameters between pure extracts and its phospholipid complexes, studies were performed on beagle dogs, rodents, wistar rats *in-vivo*.[14]

CONCLUSION

Planterosome is complex between dietary phospholipids and polar polyphenolics. It shows specific spectroscopic and physiochemical features. New avenues open up when recent technology of drug delivery are applied to botanicals, exploring maximum therapeutic potential of plant substances that are polar in nature. Planterosomal complexes were investigated for cosmetic applications in the beginning, but over the past few years, evidences have shown that it has paramount potential for drug delivery and can be applied with beneficial activity as a hepatoprotective, anti-inflammatory, cardiovascular and anti-cancer drug.

Table 1: Types of Phytoconstituents used in Planterosome Preparation

Phytoconstituents	Definition	Classification	Use	Example
Flavonoids/Bioflavonoids	Class of plant secondary metabolite	a) Anthocyanidins b) Flavanols c) Flavanones d) Flavonols e) Flavones f) Isoflavones g) Catechins h) Chalcones	Antioxidants, Anticancer	Black tea, Blue berries
Tannins	Bitter plant polyphenolic compound	a) Hydrolysable tannins b) Condensed tannins c) Phloro tannins	Astingent, Anti-inflammatory, Antiulcer	Pomegranate Nuts, Berries, Clove
Alkaloids	Basic nitrogenous compounds.	a) True alkaloids b) Proto alkaloids c) Pseudo alkaloids	Antiarrhythmic, Analgesic, Antihypertensive, Antitumor	Ephedra, Coffee, Tea Cinchona, Ergot
Glycoside	Organic compound with glyconeand aglycone part	a) Alcoholic b) Anthraquinone c) Coumarin d) Cyanogenetic e) Cardiac f) Saponin	Analgesic, Antipyretic, Anti-inflammatory	Senna, Aloe, Bearberry

Figure 1: Structure of Planterosome

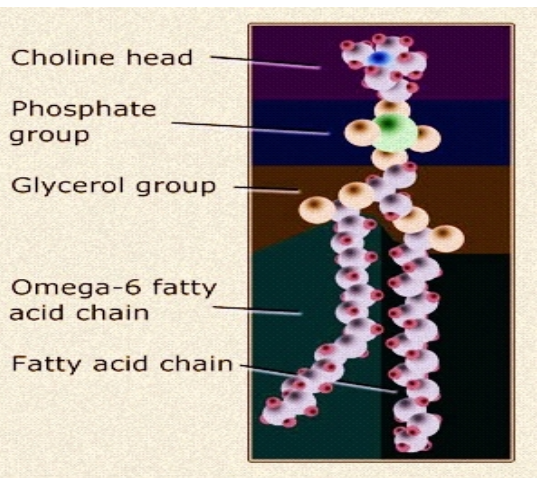

Figure 2: Phosphatidylcholine Structure

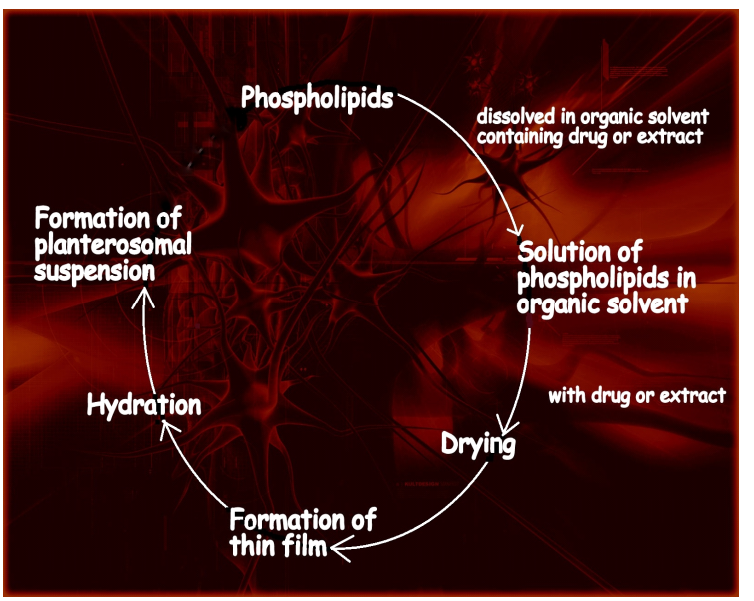

Figure 3: Common Stages in the Preparation of Planterosome

A new drug delivery technology called planterosome obtained by forming a complex of standardized plant extracts or tannins, xanthones, terpenoids, flavonoids, which are mainly polar phytoconstituents and phosphatidylcholine which is a phospholipid, has substantially enhanced bioavailability exhibiting better absorption profile and subsequently improved lipid solubility which enables them to cross the biological membrane following oral administration. At similar or less dose as compared to the conventional extracts, more of active constituent of planterosome is present at the site of action (liver, brain, heart, kidney etc.) for a prolonged period of time, the use of it being advantageous in the treatment of various acute diseases owing to its improved pharmacokinetic and pharmacological activity.

Recent Aspects

According to recent research, planterosomes show better bioavailability and absorption when compared to conventional drug delivery systems. Milk thistle (Silybummarianum) is used for the study of planterosomes as it contains premier liver protectant flavonoids. According to recent research, various kinds of liver diseases like hepatitis, cirrhosis, fatty infiltration of the liver and inflammation of the bile duct has been treated by silymarin Oligomeric poly phenols of varying molecular size complexed with phospholipids produce grape seed planterosome. Antioxidant capacity and marked protection for the cardiovascular system is offered by procyanidin flavonoid of grape seed.

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