A NOVEL DRUG APPROACH ON PHYTOSOME FLAVANOIDS

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ABSTRACT:

An attempt has been made to review some flavonoid-rich medicinal plants of Maharashtra with the intention of their use in herbal drug delivery systems. In this direction, a list of indigenous medicinal plants has been prepared, detailing their taxonomic names, vernacular names, families, and the parts used, based on existing literature. This review covers 181 medicinal plants of Maharashtra belonging to 67 different families. Among these, 48.07% are herbs, 27.07% are trees, 17.13% are shrubs, alongside several climbers, creepers, and weeds, all noted for their flavonoid content. Analysis of plant parts reveals that leaves generally contain higher levels of flavonoids compared to roots, stems, seeds, flowers, fruits, and bark. Furthermore, the highest content of flavonoids (as flavonols) is found in the Asteraceae family, serving as a chemotaxonomic marker. Compounds such as terpenes, edusmocoides, ginsenoside, flavonoids, epigallocatechin-3-O-gallate, procyanidins, and flavone polyphenols are identified as crucial candidates for phytosome development. Consequently, relative lipophilicity, capacity constant (K), and the hydroxylation pattern of the C2-C3 position are taken into consideration for the final selection of the most appropriate biomolecules for phytosomes."

KEYWORDS: Phytosome, Flavanoids, Bioavailability, Asteraceae

INTRODUCTION :

Plants have been associated with human health from time immemorial and have been an important source of medicine since the dawn of human civilization. They have played a significant role in maintaining human health and improving the quality of life, serving as valuable components in medicine, beverages, cosmetics, and dyes. The growing popularity of herbal medicine in recent times is based on the premise that plants contain natural substances that promote health and help alleviate illness. Consequently, the focus on plant research has increased globally, as herbal drugs, medicinal plants, their extracts, and isolated compounds have demonstrated a wide spectrum of biological activities."

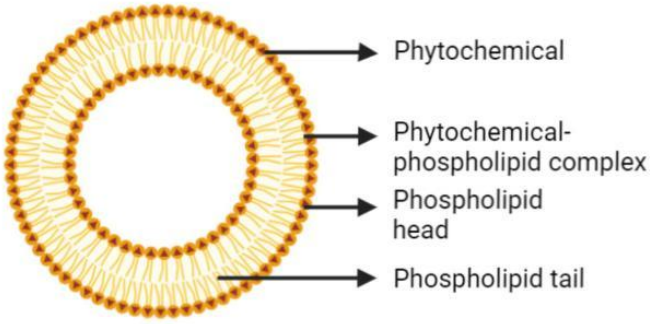

Fig 1 : Structure of phytosome

The aim of this review is to compile data on indigenous medicinal plants of Maharashtra that contain flavonoids. It also provides an overview of flavonoid chemistry, their absorption, and current knowledge regarding phytosomes as an herbal drug delivery system, including the methodology for preparing flavonoid-based phytosomes. Generally, phytosomes consist of three main components: phospholipids, active phytoconstituents, and solvents. Phospholipids, which are found in the membranes of humans, animals, and plants, consist of a polar head and nonpolar acyl chains. Due to variations in their hydrophilic groups, aliphatic chains, and alcohols, many types of phospholipids exist—such as phosphatidylcholine, cardiolipin, phosphatidylethanolamine, phosphatidylserine, sphingolipids, and phosphatidylinositol. These are widely used in formulations, particularly natural, synthesized, or hydrogenated forms like soy lecithin.

CHARACTERISTICS OF PHYTOSOMES AND FLAVANOIDS:

Phytocomplexes are typically prepared through a reaction between a substrate and a polymer (phospholipid), usually in ratios of 1:1 or 1:2, depending on the required quantity. Evidence suggests that hydrogen bonding occurs between the polar regions of both the phospholipids and the substrate molecules, a process that can be investigated using spectroscopic apparatus. From a biological perspective, phytosomes represent a sophisticated technology for herbal drugs, designed to enhance absorption and improve bioavailability compared to conventional botanical herbs.

CHEMISTRY OF FLAVANOIDS :

Flavonoids are one of the largest classes of naturally occurring polyphenolic compounds and are largely responsible for the pigments in various fruits and flowers. To date, over 4,000 flavonoid compounds have been characterized and classified based on their chemical structure. The term “flavonoid” is derived from the Latin flavus (yellow), although these compounds can also appear in red, blue, purple, or white. Chemically, they are C_6-C_3-C_6 compounds, where the two C_6 groups are substituted benzene rings, and the C_3 unit contains a pyran ring. Flavonoids occur either as O- or C-glycosides or in a free state as aglycones, often featuring hydroxyl or methoxyl groups.

TABLE 1 : LIST OF FLAVANOID MEDICINAL PLANTS

Serial no	BOTANICAL FAMILY	FAMILY	COMMON NAME	PLANT TYPE	PLANT PART USED	
01	Adathoda vasica *nees*	Acanthaceae	Adulsa	S	L	
02	Ruella *ruberosa linn*	Acanthaceae	Ruwel	H	Wp	
03	Barlesia prionitis linn	Acanthaceae	Kate - korani	H	Fl	
04	Andrographis paniculate linn	Acanthaceae	Kalmegh	H	L	
05	Agave sisalana *linn*	Agavaceae	Kheti	S	Fr	
06	Aervalanata lenin	Amaranthaceae	Maduri	H	A	

PREPARATION OF PHYTOSOMES :

Phytosomes are generally prepared by interacting 3–2 moles of natural or synthetic phospholipid (primarily phosphatidylcholine) with one mole of a phytoconstituent, with the most preferred molar ratio ranging between 0.5 to 2.0 moles. The common preparation process involves dissolving the phospholipid and the drug/extract in an organic solvent (1:1), followed by drying to form a thin film, hydration, formation of the phytosomal complex, and finally isolation through precipitation, lyophilization, or spray drying. Specific techniques used include.

. Solvent evaporation method : A natural or synthetic phospholipid and phytoconstituent are suspended in an appropriate solvent and refluxed for several hours, followed by evaporation under vacuum.

. Salting outing method : The phytoconstituent or standardized extract and phospholipid are dissolved in an aprotic solvent, such as dioxane or acetone, stirred overnight, and the complex is then isolated via precipitation using a non-solvent like n-hexane.

. Lypholization technique : Both the phytoconstituent and phospholipid are dissolved in a solvent and stirred to form a complex, which is isolated by lyophilization

PROPERTIES OF PHYTOSOMES :

Complex formation : A phytosome is a complex formed through the reaction between a phytoconstituent and a phospholipid in a suitable solvent.

Structural interaction : Spectroscopic analysis confirms that a hydrogen bond forms due to the interaction between the polar heads of phospholipids (specifically the phosphate and ammonium groups) and the polar functionalities of the substrate.

Micellar structure: When treated with water, phytosomes assume a micellar shape that forms liposomal-like structures.

Spectroscopic Evidence: As an example, in the case of a catechin distearoyl-phosphatidylcholine complex, the formation of hydrogen bonds between the phenolic hydroxyl ends of the phytoconstituent and the polar

head of the phospholipid can be deduced by comparing the 1H-NMR and 13C-NMR spectra of the complex against those of pure precursors.

COMMON STAGES OF PREPARATION OF PHYTOSOMES:

1.**DISSOLUTION** *:*

1.Phosolipid is dissolved in an organic solvent containg the drug extract (in a 1:1 ratio).

⬇

2. **DRYING :**

1.The solution is dried to remove the solvent .

⬇

3.FORMATION OF THIN FILM :

1.A thin film of the mixture is formed on the vessel surface.

⬇

4.HYDRATION :

1.The thin film undergoes hydration.

⬇

5.FORMATION OF PHYTOSOMAL COMPLEX :

1.The phytosomal complex is successfully formed.

⬇

6. ISOLATION :

1.isolation is done by precipitation.

2.Final product is obtained via Lyophilization or drying.

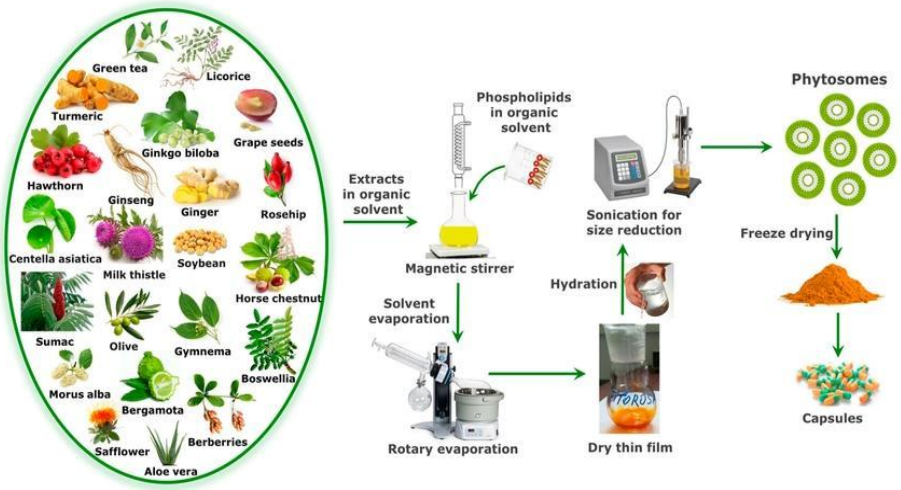

Fig 2 : Common stages of preparation of phytosomes.

MECHANISM OF PHYTOSOME COMPLEX :

The mechanism of phytosome complex formation is an effective process designed to enhance the solubility and bioavailability of phytochemicals that are poorly soluble in water. Phospholipids are characterized by their amphiphilic nature, consisting of a hydrophilic "head" and two hydrophobic "tails," which allow them to form bilayers. During the complexation process, lipophilic or hydrophobic phytoconstituents interact with the hydrophobic region of the phospholipid, resulting in the formation of a phytophospholipid complex. This complex exhibits enhanced solubility in water because the outer hydrophilic region of the phospholipid facilitates interaction with aqueous environments. Furthermore, the complex may improve the permeability of biological membranes, allowing the compound to cross biological barriers more effectively. It is important to note that the specific efficiency and exact mechanism of this process can vary depending on the particular phospholipid and phytochemical used

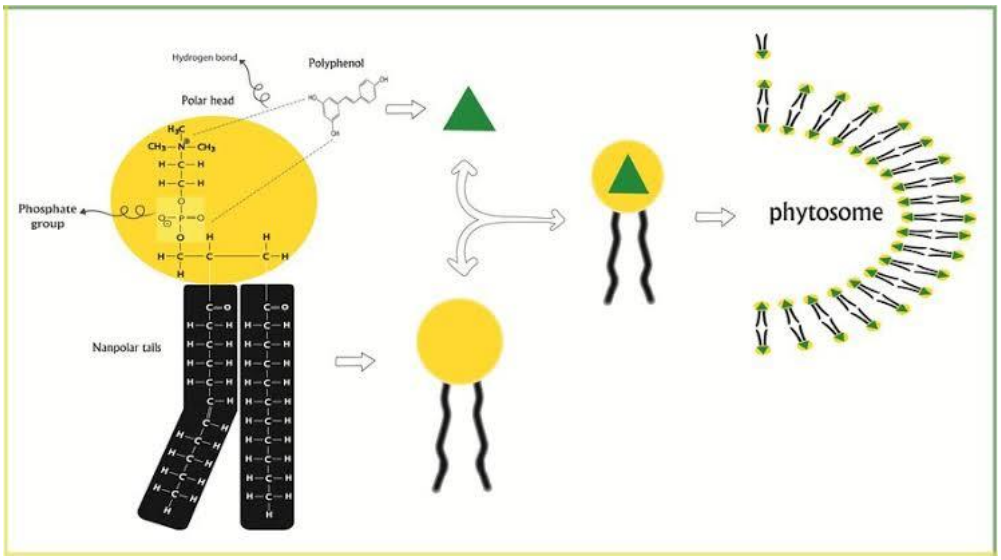

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Fig 3 : Mechanism of phytosome complex in Flavanoids

The formation of a phytosome complex is primarily driven by the interaction between the active phytoconstituents and phospholipids, typically forming a stable molecular complex. This process involves a chemical reaction where the phospholipid—often phosphatidylcholine—acts as a carrier to enhance the solubility and bioavailability of the botanical substance. During the synthesis (generally in a 1:1 or 1:2 ratio), hydrogen bonding is established between the polar head groups of the phospholipids and the polar functional groups (such as hydroxyl or carbonyl groups) of the substrate molecules. This interaction creates a lipophilic-hydrophilic balance that allows the phytosome to cross biological membranes more effectively than the non-complexed botanical ingredient. Spectroscopic analysis often confirms this structural association, showing that the botanical substrate is integrated into the phospholipid's polar surface, thereby shielding the active molecule and facilitating superior absorption and systemic circulation within the body.

CHARACTERIZATION OF PHYTOSOMES:

1. **Entrapment efficiency :**The entrapment efficiency of a phytosomal formulation is typically measured using the centrifugation technique. In this process, the prepared drug-phytosomal complex is subjected to centrifugation to separate the entrapped phytosomes from the non-entrapped (free) drug. Following separation, the concentration of the drug is quantified using ultraviolet (UV) spectroscopy. The entrapment efficiency is then calculated according to the following to

Entrapment Efficiency (%) = [(Weight of total drug – Weight of free drug) / Weight of total drug] × 100

2. **Zeta potential :**Zeta potential and particle size analysis are critical parameters for characterizing the stability and physical properties of phytosomal formulations. Zeta potential is typically determined using laser Doppler velocimetry, which provides insights into the surface charge and stability of the particles in a suspension. While various analytical techniques are available, the most commonly used methods for particle size distribution and analysis are photon correlation spectroscopy (PCS) and dynamic light scattering (DLS). These techniques are highly effective in providing accurate data on the size, distribution, and overall quality of the phytosomes, ensuring they meet the required specifications for drug delivery applications.
3. **Spectroscopic assessment :**The confirmation of the lipid-compatible complex in phytosomes is primarily achieved through advanced spectroscopic techniques, including ^1H-NMR, ^{13}C-NMR, and Fourier-Transform Infrared (FT-IR) spectroscopy. ^1H-NMR spectroscopy serves as a definitive tool to confirm the development of the complex between active phytoconstituents and phospholipids; the chemical bonding is indicated by significant shifts in signals for the atoms involved in complex formation. Specifically, the broad signals originating from the phytoconstituents and phospholipids, alongside a chemical shift matching the choline N-methyl group, provide conclusive evidence of phytosome formation. Similarly, ^{13}C-NMR analysis is employed to observe shifts in fatty acid chains, which clarifies the stoichiometric interaction between phosphatidylcholine and the herbal extract. Furthermore, FT-IR spectral analysis is utilized to evaluate the solid-state characteristics of the phytosomal complex following lyophilization, allowing for a comparative study against micro-dispersions in water across various time intervals.

- **Transition Temperature**: The Differential Scanning Calorimetry (DSC) technique is a vital analytical tool used to measure the thermal properties of a sample by monitoring changes in physical characteristics as a function of temperature and time. In the context of phytosome characterization, this method is primarily employed to determine the transition temperature, which provides essential data regarding the thermodynamic stability and the physical state of the phytosomal complex. By analyzing these thermal transitions, researchers can effectively verify the structural integrity and the successful interaction between the botanical substrate and the phospholipid components within the formulation.

ADVANTAGES OF PHYTOSOMES :

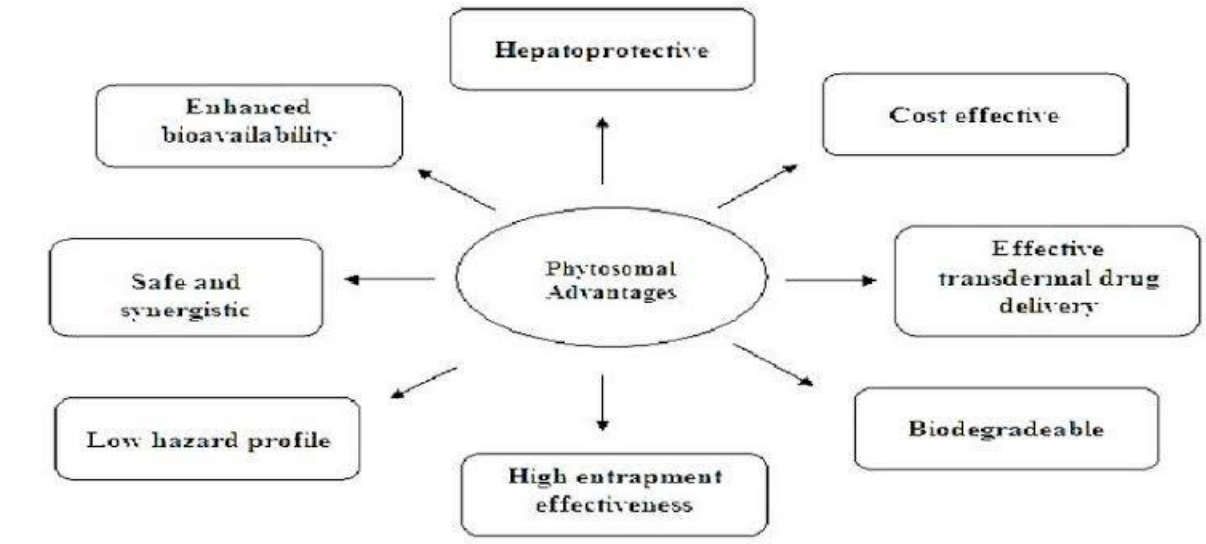

Fig 4 : Advantage of phytosomes

DISADVANTAGES OF PHYTOSOMES:

INFLUENCING FACTOR FOR PHYTOSOME PREPARATION : Phytosome preparation involves the development of a delivery system that enhances the bioavailability and efficacy of phytochemicals, particularly plant extracts. Several factors influencing the preparation of phytosomes

PROPERTIES OF PHYTOSCHEMICAL : The physicochemical properties of the phytochemicals, such as solubility, lipophilicity and molecular weight play a crucial role in phytosome preparation. These properties determine the compatibility of the phytochemicals with the phospholipids used to form phytosomes

SELECTION OF PHOSPHOLIPID: Phytosomes are typically formed by complexing phytochemicals with phospholipids. The choice of phospholipid is crucial as it affects the stability, solubility and compatibility of the resulting phytosomes. Different phospholipids, such as phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine can be used based on the specific requirements of the phytochemical.

SOLVENT SELECTION : Solvents are used to dissolve both the phytochemicals and phospholipids before the complexation process. The choice of solvent depends on the solubility of the phytochemical and the phospholipid. Common solvents include ethanol, chloroform, methanol and their combinations.

APPLICATIONS :

A.Enhance Bioavailability:

1.Efficiently delivers lipophilic plant extracts through the skin.

2.Overcomes the protective barrier of the stratum corneum.

3.Enhances the solubility of poorly water-soluble active ingredients.

4.Maximizes therapeutic efficacy at targeted local treatment sites.

B. Improve Stability:

1.Phospholipids and plant extracts form robust chemical bonds that grant phytosomes exceptional structural stability.

2.Phosphatidylcholine molecules achieve a significantly enhanced stability profile through these newly established connections with phytoconstituents.

3.The technique relies on noninvasive and inactive components, making commercialization straightforward and highly scalable.

4.These bonds protect sensitive active ingredients from premature degradation during storage and application.

C. Application in skin disorder:

1.Successfully treats chronic inflammatory skin disorders such as psoriasis and eczema.

2.Accelerates natural wound healing processes through enhanced targeted delivery.

3.Improves skin elasticity and firmness when incorporated into advanced anti-aging formulations.

4.Delivers powerful botanical compounds like silymarin and rutin directly to affected skin layers.

5.Exhibits potent antioxidant and anti-inflammatory properties to neutralize free radicals

PHYTOSOME VS LIPOSOME

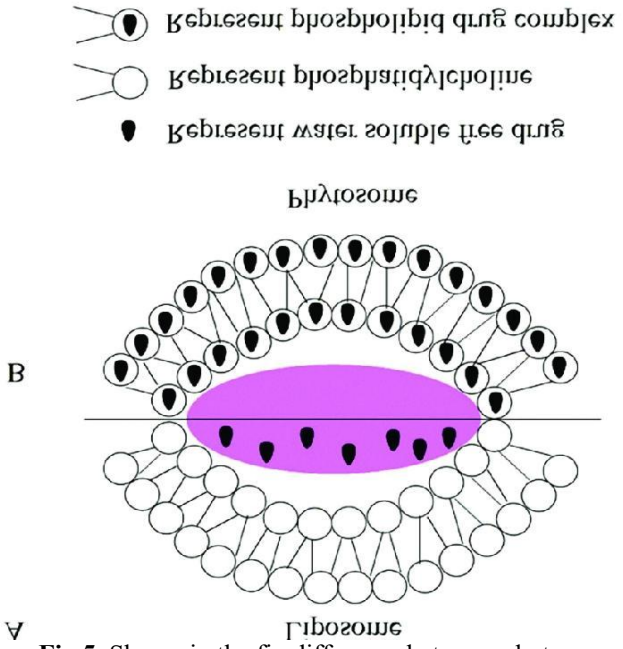

Fig 5. Shown in the fig difference between phytosome and liposome

The key difference between phytosomes and liposomes is that phytosomes are complexes of natural active ingredients and phospholipids, while liposomes are spherical vesicles of a bilayer of phospholipids that enclose an aqueous solvent containing targeted drugs and nutrients.

Phytosomes and liposomes are two different types of delivery vesicles or formulations. They are also known as the king of nanoparticles, as they serve as imperative tools for the delivery of various active compounds and drugs into the human body. However, most phytosomes contain only plant-based molecules like flavanones and terpenes, which have poor solubility. On the other hand, liposomes can encapsulate both hydrophobic as well as hydrophilic molecules.

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