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A Review Article on Phytosomes: Innovative Delivery System for Phytochemical

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Abstract: *Medicinal herbs and their phytochemicals are currently proving to be excellent remedies for several conditions, but this may be hindered by poor bioavailability and selectivity. Consequently, bioavailability becomes a significant hindrance to improving the bioefficacy of these phytochemicals derived from foods they consume. Various approaches have been proposed to create effective vehicular systems for enhancing the bioavailability of phytochemicals. Nano-vesicles have thus attracted attention as viable options for transporting insoluble phytochemicals. Owing to the uncomplicated assembly of bilayered vesicles and their flexibility, these have gained wide application and acceptance in the scientific literature. " Let me make a human. For the first part of the review, we shall focus on the introduction of phytosome technology and its applications, emphasizing formulations and characterization principles, while in the second section, it will provide an extensive discussion about biological activities such as commercial and noncommercial phytosomes, divided into systems and related pathologies. These figures confirm that the greater biological effectiveness of phytosomes is due either to their biological activity or a reduction in dosage levels, and they continue to be the most researched compounds, like curcumin, with silymarin formulations getting even more preference from the herbal product industry. Lastly, we highlight the promising clinical as well as experimental results of phytosome operations. The conclusion of this study encourages the researchers to transfer their knowledge from laboratories to the market for the further development of these products.*

Keywords: *phytochemical, nanomedicine, phytosome, delivery, vesicle, disease*

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1. Introduction

Medicinal herbs and their active constituents have been used in treating various diseases for some years now [1–5]. Herbal drugs are increasingly being used because: a) modern medicine does not always cure all human pathologies effectively; b) there is growing concern about the assurance and safety of synthetic drugs; and c) some natural products are showing more effectiveness than synthetic drugs without side effects [6]. However, the clinical application of many plants's active compounds is debated due to poor oral bioavailability [7, 8]. This absorption may be low-lipid soluble, resulting from their low absorption rates and the presence of polyphenols with multiple rings in them. Several solutions have emerged to address this issue, with human beings having invented such techniques as emulsion, liposome, and nanoformulation; altering the molecular structure of drugs; or converting them into prodrugs. However, among these methods, phyto-phospholipid complexes, or phytosomes, constitute by far the most effective approach towards increasing bioavailability levels. For instance, the term 'Phyto' puzzles a lot about'some' meaning as a plant cell. Phytosomes (also known as herbosomes) can be vesicular drug delivery systems that enhance the absorption and bioavailability of poorly soluble compounds [9, 10]. Aprotic solvent is used to bond phosphate dylcholine (or any hydrophilic polar head groups) and plant extracts together, resulting in the generation of phytosomes that are the amalgamations of phospholipids and natural active phytochemicals. These formulations prove more effective in drug action and kinetic phenomena compared with the ones that have been in existence for a long time. The hydrophilic phytoconstituent-choline complexes are covered by the lipid-soluble phosphatidyl groups in phytosomes. Phytosomes demonstrate high drug encapsulation, providing improved stability (the phytoconstituent [11] is able to form chemical bonds with the polar head of the amphiphile molecule in the formulation) and increased bioavailability. Furthermore, they increase the absorption rate, which means less active constituents are needed for the desired pharmacological effect even with polar phytoconstituents. The diverse uses of phytosomes discussed here refer to. It is worth noting that phytosomes provide high drug encapsulation with better stability due to conjugation between the amphiphilic head of the molecule and phytoconstituent [12]. Additionally, they facilitate faster absorption, leading to lower amounts of bioactive compounds required to produce therapeutic effects, especially for polar plant products. Various applications of phytosomes are thus reviewed in this article.

2. History of Phytosome

In 1991, Bombardelli invented a phytosome in Milan. In various books, it was calledphyto-vesicle', 'phytosphilipid complex', and 'Herbosome'.To improve absorption into the body, phospholipids like phosphotidylcholine and phosphotidylserine, among others, are often used [13]. Over the past century, there has been an evolution of the chemistry and pharmacology of plant extracts, defining their compositions, biological activities, and health properties. Nonetheless, the individual composition of the whole extract meant that their activity was lost. Extensive application of the phytosome process includes popular herbal extracts such as milk thistle, also known as silymarin [14]. Hence, an answer to this dilemma was found through standardization. It was found out that, through complexation with other clinically useful nutrients, significant improvement in the bioavailability of these extracts can be achieved. Such nutrients that were so helpful for enhancing the absorption of other nutrients were found to be phospholipids [15]. Phospholipids are known to be complex molecules found in all living organisms that make up cell membranes. The demonstration of increased bioavailability of phytosomes over simple noncomplex extracts developed from plants as well as kinetic studies by means of animals` and human experimentations. Phytosomes play an important role in the biological activity of phospholipids. Phytosomes have better pharmacokinetics and pharmacodynamics than crude herbal drugs [16, 17]. A phytosome is a patented technology that has been newly discovered, involving a complexation between a phytomolecule and a phospholipid via the formation of hydrogen bonds in between them. What's the concern here is that this technology enables formulations that are able to pass through the lipid layers of the enterocyte migrating from the external water phase in order to access the cells, therefore having an impact while entering the blood [18]. The complex is made by mixing an equal number of phospholipids and a particular polyphenolic phytoconstituent in a nonpolar solvent [19]. It has previously been shown that the main phospholipid-substrate interactions result from the formation of hydrogen bonds between the polar head groups of phospholipids (phosphate and ammonium groups) and those of the substrate. For instance, the formation of H-bonds involving the phosphate ion in the catechinphosphatidylcholine part of the complex, which is further backed up by 1 H-NMR and 13 C-NMR spectra for the complex along with those for the pure phytomolecule or the phenolic hydroxyl moiety at the end of the flavone [20]. Phytosomes are chemical molecules that contain at least one PC molecule. The main component used is phosphatidylcholine (PC), the primary molecular constituent of cell membranes. Peanut sauce is

both in oil and in water, and it is administered orally and absorbed well. The ingredient phosphatidylcholine also has some protective properties for the drug when it is broken down by enzymes in your stomach [21]. The high solubilization capacity causes phytosomes to be more bioavailable. Therefore, it is able to cross the lipid bilayer membrane and achieve the desired therapeutic effect in the systemic circulation. Phytosome flavonoids' bioactive carrier is not phosphatidylcholine alone; this phospholipid functions as an active nutrient with documented hepatoprotective effects.

3. Overview on Phytochemicals

Phytochemicals, commonly known as plant chemicals, are a large group of natural bioactive compounds found in plants. A bioactive compound refers to the ability of such compounds to interact with different components of living organisms. Alkaloids, phenolics, lipids, carbohydrates, or terpenoids are major structural classes of phytochemicals, with the least similar structures among them being nitrogen-containing compounds, among others. Furthermore, there exist several subcategories of phytochemicals based on differences in biogenesis or biosynthetic pathways. As for them, only those with active hydrogen atoms (--COOH, --OH, --NH2, --NH, etc.) can get inside a phytosome structure; as an example, they are polyphenols [22]. A hydrogen bond can form between the hydrophilic esters of amphiphilic molecules and vegetal bioactives due to a hydrogen atom that is active. Natural sources are rich in polyphenols, among them plant-based foods. Polyphenols are plant-derived secondary metabolites that are found in various foods. They have also been reported to have anti-inflammatory properties. Polyphenols have also been found to have potential health effects in cancer, inflammation, as well as neurodegenerative and cardiovascular diseases like those associated with aging such as Alzheimer's disease, stroke, heart attack, etc.; type 2 diabetes mellitus and obesity are other diseases where these compounds have been employed. [23]. The most common forms are conjugated with sugar residues (one or more) at hydroxyl groups, with the sugar residues being attached directly to an aromatic carbon [24, 25]. Polyphenols are classified into two major groups: flavonoids and non-flavonoids. This paper describes the current findings on applying polyphenols in phytosomes with a detailed look into their structure, preparation techniques, and any health benefits linked to using phytochemical-loaded phytosomes.

4. Phytosome Structure and Preparation Methods

For the first time, Bombardelli et al. stated that there was a chemical bond between phospholipids and flavonoid vegetal derivative molecules.

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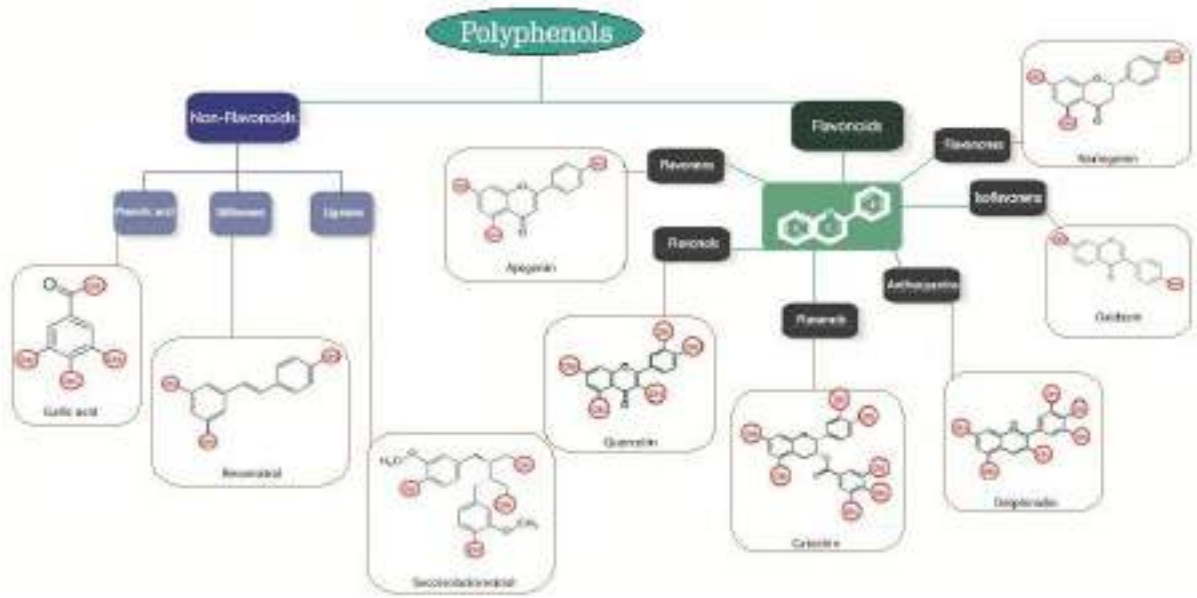

Figure 1: Polyphenols classification, classes of polyphenols and their relationship to each other [24,25]

In two thousand sixteen, studied the molecular docking model of twenty (S)-protopanaxadiol (PPD) phospholipid complexes. The research findings demonstrated that two arms of the phospholipid molecule enclosed the hydrophobic part of the PPD skeleton, while one of the hydrophilic OH groups generated a hydrogen bond with the phospholipid bone of the P=O section. Many authors have reported that hydrogen bonds are the primary bonds in phytosome vesicles [26]. Phospholipids bind to polyphenols spontaneously to create supramolecular adducts with well-defined stoichiometry that can be determined from calorimetric studies. Semalty et al. investigated this aspect and noted that either hydrogen bond formation or hydrophobic interaction must have occurred between the two molecules. The phospholipid-active component forms hydrogen bond linkages between the polar head and polar functional groups of the active ingredient. Briefly, Figure 3 indicates that hydroxyl groups within polyphenol can interact satisfactorily with phospholipid nitrate and phosphate groups [27]. The hydroxyl groups of polyphenols seem to interact effectively with nitrate as well as the phosphate groups of phospholipids. Various methods have been proposed to prepare phytosomes, such as the rotary evaporator method, the anti-solvent precipitation technique, freeze drying cosolvency, and the salting out technique. The basic experiments for the formation of the phytosome are shown in Figure 3 [28,39].

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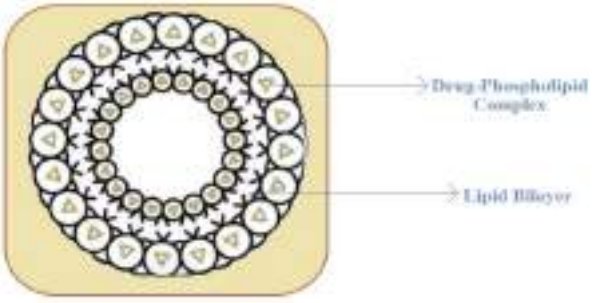

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Figure 2: Structure of Phytosomes [26].

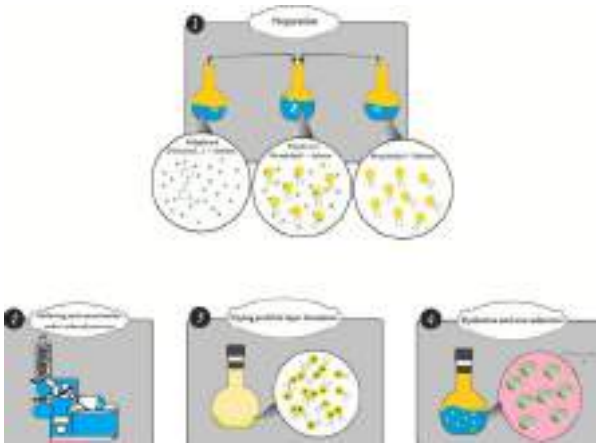

Figure3: Thin -film hydration as the most common method for phytosome preparation. Steps 1-4 are the procedure of phytosome preparation [28, 39].

5. Vesicular Systems in Phytosome Development

There are two main issues pharmacists should take into account when dealing with carriers of phytochemical drugs: targeted delivery and constant speed of therapy. [40] Several kinds of nano-systems would be used in various disease imaging or therapies, or as theranostics.[41] Vesicular drug delivery systems are the most common nanocarriers for phytochemicals. [42] a spherical structure that encapsulates active compounds.[43] Several kinds of vesicle-laden drug release systems, like the liposome, niosome, transfersome, and ethosome, have emerged. (Table 1) It also illustrates the schematic diagram of various vesicle architectures in the delivery of phytochemicals. [44].

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Table 1; Most used nanovesicle encapsulated herbal formulations

Navovesicle	phytochemicals	Features	References
Liposomes	Aphanamixis polystachya leaf	Mice have shown significant improvement in memory function, locomotion, and markers of dementia.	45
	curcumin	The fast permeation rate across the blood brain barrier that is attributed to an endothelial monolayer having good durability against digestive enzymes	46
	Anthocyanins	Enhance the stability of physiological conditions under laboratory conditions for a period of two weeks and boost skin absorption and ROS-scavenging efficacy.	47
Niosome	Carum carvi	Enhance the stability of physiological conditions under laboratory conditions for a period of two weeks and boost skin absorption and ROS-scavenging efficacy.	47,48
	lawsone	70% entrapment efficiency, with sustained release profile, and anti-tumor activity significantly increased.	48
	Fumaria officinalis	Rapidly degrades stability in stimulated gastrointestinal condition and indicates anti-diabettic and anti-inflammatory potential.	48
	Annona squamosa	"Aid the purification of the body from harmful impurities and antioxidants using topical drug enhancers that can be applied directly to the skin.".	49
Transfersome	Mulberry leaves	Aid the purification of the body from harmful impurities and antioxidants using topical drug enhancers that can be applied directly to the skin.	49
	Apigenin	Long-term apigenin release is greatly improved by high stability measurements of 84.24% drug entrapment.	45
	Emodin	The regulation of ATGL up reduces body weight and adipocyte size by downregulating G0s2 expression in adipose tissue which improves insulin sensitivity hence leading to high efficiency and stability.	45

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Ethosome	Thymoquine	The upshot is an improvement in the efficiency of trapping drugs on cytotoxins that will yield 99% results for 0.95/ml MCF-7 cell lines.	50
	Capsaicin	Ethosomal hydrogels enhance the efficacy of a capsaicin treatment and increase patient compliance.	50
	Terminalia chebula	The anti-arthritic activity of the effective release composition presented in the gel containing the extract was compared (in vitro) to that of plain diclofenac, showing significant anti-arthritic effect.	51
	Paeonol	‘138.58ug/cm and 52.60ug/cm were observed as the amounts of transdermal absorption and skin retention for ethosomes loaded with it.	51

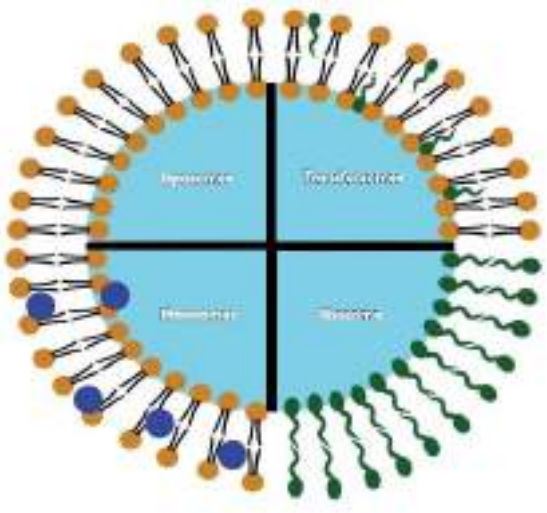

Figure 4; Schematic diagram of various vesicle in delivery of phytochemicals [52]

6. Phytosome Characterization

The area of measuring nanomaterials is growing fast, and it employs effective means when it comes to physical and chemical characterization [77]. Phytosomes are getting more favored as a kind of fast-developing nanovesicles for phytochemical delivery. A number of methods were used to determine the size, chemical composition, morphology, and many other features of phytosomes. Physical properties can be studied using different methods. Alternate options are determined by various pros and cons that exist in choosing the most suitable method, and it may be a combined methodology [53]. Also, some statistical studies are needed for good application in the real world [54]. Phytosomes possess certain essential features, such as their size and shape, surface charge, chemical composition, lamellarity and stability, encapsulation efficiency, and release behavior. This chapter intends to present an exhaustive survey of the various analysis tools that have been used for characterizing phytosomes, culminating in recent reports.

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Table 2: Overview of the Analytical methods used for the Characterization of Phytosomes featured in this review.

Parameter	Techniques
Size and shape	Dynamic light scattering, scanning electron microscopy, transmission electron microscopy, fluorescence microscopy techniques, atomic force microscopy, field flow fractionation, nanoparticle tracking, scanning ion occlusion sensing, flow cytometry, size-exclusion chromatography, centrifugal sedimentation, and differential scanning calorimetry are examples of techniques
Surface charge	Direct laser writing of DNA, transgenic animals, and laser Doppler auscultation.
Chemical composition	There are a number of techniques used in forensic science. FTIR, HI, NMR, GC-MS, DSC, TGA, MS, and TLC are some of these.
Encapsulation Efficiency and release behavior	Centrifugation within mini columns is a method that employs high-performance liquid chromatography (HPLC) together with ultra-high-performance liquid chromatography (UPLC). Other assorted techniques used include ultraviolet-visible spectrometry (UV-vis) and dialysis. Additionally, there are other methods known as enzymatic assays, gel electrophoresis, field flow fractionation, spray drying, freeze drying, atomization and spray granulation, spray coating of powders and suspensions, rotary and vibratory fluidized-bed granulation, aseptic spray drying covering fill-finish sterile manufacturing operations of biologics, and non-viable spray drying for proteins, peptides, and other pharmaceuticals (KenChic, 2015).
Lamellarity and stability	Third-line perpendicular electronegativity: nuclear magnetism; nano-scale, quartz-colloidal radiation; TEMs as well as electrons. Differential vulnerability regarding samples through heat computation was performed using digital casting components, which are protection techniques for microphones designed to measure stress intervals in between parts of metal hystereses and hands-on surface development.
Optimization	Design an experiment employing the box Behnken design.

7. Phytosomes and Cardio Vascular Protection

The isoproterenol (ISO)-induced cardiotoxicity model has been used to evaluate the protective effects of Ginkgo biloba phytosomes in rats. The results showed that Ginkgo biloba phytosome (200 mg/kg) alleviated ISO-induced myocardial necrosis considerably, as confirmed by histopathological studies. Moreover, the myocardial necrosis diminished and the endogenous antioxidants increased, thus overall making evident the

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cardioprotective effect [81]

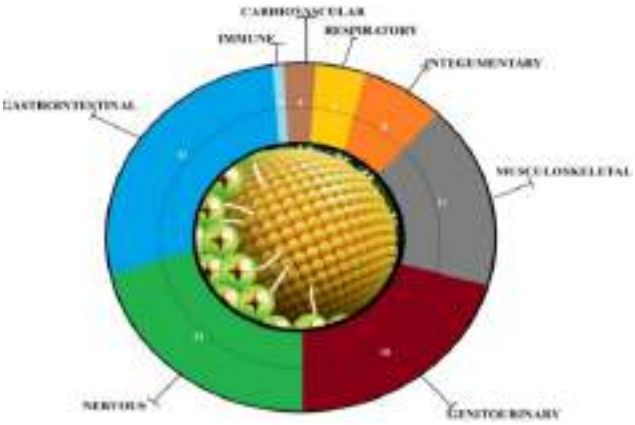

Figure 5: This figure shows the number of papers related to phytosomes and their biological activities, divided according to the system under study. The gastrointestinal, nervous, genitourinary, and musculoskeletal systems together account for almost 75% of the published works.

The same researchers explored the possible protection from cardiovascular injuries by a combined treatment of Ginkgo biloba phytosome (100 mg/kg) and Ocimum sanctum extract (OS) (50 and 75 mg/kg) in isoproterenol (ISO) (85 mg/kg)-induced myocardial necrosis in rats. The treatment inhibited the increase of serum marker enzymes and the lipid peroxidation marker malondialdehyde (MDA), both induced by ISO. However, none of the combined treatments possessed better cardioprotective or antioxidant activity than the single treatment with Ginkgo biloba phytosome or OS [82]. Tisato et al. investigated the anti-inflammatory effect of Ginkgo biloba phytosome and α-lipoic acid on cytokines and chemokines released by vein endothelial cells (VEC) isolated from patients at different stages of CVD. The anti-inflammatory effects of both Ginkgo biloba derivatives and α-lipoic acid were confirmed by the reduction of cell adhesion molecules ICAM-1 and VCAM-1. Ginkgo biloba phytosome diminished the basal release of PDGF and the TNF-α-induced PDGF, CXCL10, and RANTES levels. Based on the data collected, α-lipoic acid exhibited a wider and more potent inhibitory activity on the release of cytokines and chemokines concerning Ginkgo biloba phytosome. This study recognized that α-lipoic acid markedly counteracted TNF-α-induced NF-κB and p38/MAPK activation, whereas Ginkgo biloba mostly acted on Akt [55]. A commercial formulation was examined in a large sample of CVD patients enrolled in 54 Italian centers. The supplement contains phytosomes of polyphenolic extract from Vitis vinifera L. seeds, extract from Melilotus officinalis (L.) Pall, and bromelain 100 mg. A total of 648 patients were enrolled and received 1 tablet per day and/or standard compression stockings for 90 days. In all groups, it was reported a notable reduction in the malleolus circumference, both at the left and right limbs. A comparable pattern was observed for the severity of the disease and symptomatology [56]. Muir et al. have investigated the clinical efficacy of the Ginkgo biloba phytosome in the treatment of Raynaud's phenomenon (RP). A painful condition characterized by episodic digital ischemia. A

total of 22 patients with RP and without other associated conditions were enrolled. A number of 11 patients were randomized to receive Ginkgo biloba extract (120 mg three times a day for a final amount of 360 mg/day), while 11 patients received matching PlaCebo. The number of RP episodes per week before treatment with Ginkgo biloba phytosome (13.2 ± 16.5) was reduced by 56%, whereas the placebo reduced the number by only 27% ($p < 0.00001$). There were no significant dissimilarities in hemorrhology among the two groups [57].

8. Phytosomes in Neurodegenerative Diseases

Neurodegenerative brain dysfunction is responsible for the development of dementia in older people. Bahadur S. investigated the nanoparticle system to improve drug delivery or active compounds with poor availability to the brain [58]. Langasco et al. studied the brain delivery of the isoflavone genistein, testing various nanotechnological approaches; oxidative stress in PC12 cells (a neuron cell line) was diminished by treatment with phytosomes, and the effect was better than that of the unformulated genistein. [86] Among phytochemicals, curcumin phytosome was found to increase curcumin bioavailability in the hippocampus and frontal lobe following repeated oral administration of the formulation for five days (134 mg/kg/die as curcuminoid equivalent) in rats. In the frontal lobe, curcumin appeared 30 minutes after treatment, peaked at 1 hour, and tended towards normalization after 3 hours, demonstrating that curcumin phytosomes can reach the brain in rats [60]. Since curcumin possesses anti-amyloid and anti-inflammatory activities, which are mostly used against neurodegenerative diseases, including Alzheimer's disease, this finding may be useful for future studies aimed at better drug delivery [59].

9. Phytosomes In Migraine

In two studies of the same research group, the efficacy of Ginkgo biloba terpenes phytosome (60 mg), vitamin B2 (8.7 mg), and coenzyme (11 mg) as ingredients, administered twice daily, was investigated in fifty subjects suffering from migraine with aura. Positive effects in reducing migraine with aura, both frequency and duration, were already clear within a four-month treatment. These effects were probably due to the presence of ginkgolide B, the most abundant terpene identified in the Ginkgo biloba leaf extract [60]. Ginkgolide B was found to modulate or reduce glutamate neurotransmission in the CNS, which plays a pivotal role in the onset of migraine [61]. The efficacy of the same formulation in the acute stage of migraine with aura was tested in an open study; during the first symptoms of aura, patients orally consumed two capsules of Ginkgo biloba terpenes phytosome, with no restriction on analgesic intake during the

pain phase. About 60% of patients enrolled in the study experienced a reduction of neurological symptoms after treatment; moreover, the pain phase was completely abolished in almost 20% of patients [62]. Balzano et al. investigated the beneficial effects of a mixture of magnesium, vitamins (riboflavin, niacin, and vitamin D), L-tryptophan, and the Boswellia serrata extract-loaded phytosome in patients with transient tension migraine and migraine without aura. The authors considered pain modulation (NRS scale), monthly attack number, and analgesic intake. Amitriptyline was used as a reference compound. The authors found an improvement in all the outcomes, with greater compliance and no side effects for patients who consumed the phytosome formulation [63].

10. Phytosomes in Gastrointestinal System

Phytosomes and Gut Microbiota

A recent study compared the influence of two different curcumin-based products, unformulated curcuminoids and lecithin-curcuminoid formulations, on human colonic metabolism. Both extracts were subjected to fermentation using an in vitro fecal model. Mass spectrometry was used for curcuminoid quantification, assessment of possible curcuminoid degradation, and detection of the main metabolites in the human fecal fermentation. The results showed that the fermentation of lecithin-formulated curcu minoids caused a more pronounced occurrence of curcu minoid catabolites [64].

11. Phytosomes Effect in Integumentary System

Formulations assessed on the skin level

11.1 The Phytosomes in Skin Inflammatory Conditions

Two clinical studies showed the effect of phytosomes in the field of skin inflammation. A first blind trial with 30 volunteers investigated the topical effect of a quercetin phytosome in comparison to a formulation containing 1% dexchlorphenir amine on different types of skin insults.Quercetin phospholi pids 1% and dexchlorpheniramine 1% obtained similar results by significantly reducing UV-induced erythema (−10.05% vs −14.05%, respectively) and histamine prick test (−13.25% vs −12.23%, respectively). When erythema was induced by sodium lauryl sulfate (SLS) or glycolic acid (GA), only quercetin phospholipids 1% induced a significant increase in hydration, but both formulations reduced erythema. In a Phase III randomized,single-dose, and double-blind placebo clinical trial, 49 patients with chronic psoriasis were treated orally for 12 weeks with phytosome (2 g per day) or placebo while topically applying a once-daily methylprednisolone aceponate 0.1% ointment on psoriasis plaques. Curcumin phytosomes

obtained a better effect on PASI compared to placebo. No significant reduction of IL-17 serum levels was observed between the groups, but IL-22 serum levels were lower in the curcumin-treated group (−11.8 pg/mL). [65] Another study evaluated the effects of curcumin phytosomes in carrageenan-treated mice. Indomethacin, curcumin, or a nano-phytosome of curcumin at 15 mg/kg were administered orally to animals for one week. The nano-phytosome treatment was more antioxidant than curcumin ($P < 0.05$) in the case of SOD, CAT, GPx, and GR and had a higher latency time compared to curcumin in hot plate and tail-pinch tests [66]. Three studies evaluated the topical effects of three different phytosomes on carrageenan-induced edema in Wistar rats. The Lawsone-containing phytosome complex (Lawsonia inermis L.) had a higher anti-inflammatory effect than plant extract gel at 4 h ($P < 0.001$). 30 β-sitosterol (ES) phytosome 5% hydrogel showed significantly improved efficacy in antihyperalgesic activity compared to escin and ibuprofen 5% gel. A resveratrol phospholipid complex, topically applied with patches, reduced the swelling to 6.1% after 24 h, a value significantly lower than control (38.4%) and diclofenac sodium gel groups (23.2%) ($P < 0.05$). Resveratrol phospholipid complex-containing patches resulted in non-irritant effects in albino rabbits, with a skin irritation score (erythema and edema) of less than 1. Silymarin in the nanostructured lipid carriers (NLC) complex was topically applied in rats subjected to UVB irradiation (0.115–0.23 J/cm2). Silymarin-NLC gel application decreased the epidermal thickness and wrinkle score in UV-exposed animals [67].

12. Phytosomes Role in Respiratory System

Diseases the phytosomes in asthma and bronchitis

In a multicentre study, 32 asthmatic subjects were enrolled and received a combination of corticosteroids and beta-agonists, the standard management for patients with mild or severe persistent asthma. The subjects were randomized to receive Boswellia serrata phytosomes at 500 mg/day or no additional treatment for 4 weeks. Patients in the phytosome group needed a lower number of inhalations compared to patients who received only the standard therapy. The treatment with phytosome was well accepted; only mild-to-moderate adverse events such as insomnia and nausea were registered [99]. Yu et al. designed and developed a novel phytosome to promote the pulmonary bioavailability of naringenin. One of the main lipids occurring in pulmonary surfactant, dipalmitoyl phosphatidylcholine (DPPC), was efficiently used to deliver naringenin. The pharmacodynamics of naringenin-loaded DPPC phytosomes for dry powder inhalation (NPDPIs, 10 mg/rat, containing about 3 mg naringenin) were studied in rats with acute lung injury, and the relevant mechanisms of action were

explored. These phytosomes have demonstrated protection against lung injury in rats when directly administered into the lungs. The data showed that NPDPIs alleviated pulmonary edemas with less fluid exudation and significantly down-regulated the expression of cytokines, including COX-2 and ICAM-1. Moreover, naringenin and DPPC suppressed oxidative stress by upregulating SOD activity in rats, and the application of NPDPIs improved this effect. [100] Singh et al. have evaluated in vitro and in vivo a gingerol phytosome complexed with chitosan for the treatment of respiratory disease. The sustained release of gingerol from the phytosome was demonstrated in vitro, as were its antioxidant and anti-inflammatory activities. Antimicrobial activity against the respiratory infective bacterial organ isms was concentration-dependent. The phytosome complex showed an important sustained-release profile and supported better oral absorption of gingerol in a pharmacokinetic study in vivo. The pharmacodynamic parameters showed effective, prolonged antibacterial and considerable anti-inflammatory activity against bacteria responsible for respiratory infections, in both Gram-positive and Gram-negative [68].

13. Phytosomes Role in Lung Cancer

Curcumin formulated with phosphatidylcholine was evaluated as an antitumor agent in the mammary gland tumor cell line (ENU1564), which was injected into the mammary fat of athymic nude mice. The effect of the phytosome was comparable to that of free curcumin. Both substances did not affect tumor volume, but curcumin phytosome significantly decreased lung metastasis and the expression of MMP-9, a protein associated with progression and tumor invasion, including breast cancer. Mao et al. evaluated the biological activities of oral administration of grape seed phytosomes in subjects participating in a lung cancer chemoprevention trial. The effects of phytosomes on prostacyclin and 15-HETE eicosanoid pathways in human lung premalignant and malignant cells were determined. The results of this study support phytosome groups as chemo-preventive and anti-neoplastic agents against lung cancer [69]. In another study, oral administration of grape seed phytosome to athymic nude mice (200, 300, and 400 mg/kg/day for the group, containing GSE 56, 84, and 112 mg/kg/day, respectively) down-regulated the oncomiRs miR-19a/b and miR-17-92 cluster host gene (MIR17HG) expressions. This was correlated with the in vitro grape seed phytosome activity in lung neoplastic cells observed in the same study [104]. The maximum grape seed phytosome dose was well tolerated; at the end of treatment in bronchial biopsies, a significant decrease of Ki-67 labeling index (−55%) was observed, as well as a substantial reduction of bronchial histopathology grading and a significant

downregulation of the expressions of miR-19a, miR-19b, and miR-106b in serum [70].

14. Recent Patented Technologies on Phytosomes

In 2011, a leading dealer of nutraceutical ingredients elaborated a patented process for Phytosomes. There were several scientists from academic and industries who found out innovative processes and developed phytosome formulationss. The dif ferent summarized patents on phytosomes and their related innovative technologies are presented in Table 3.

Table 3: Phytosomes Related Patents on the Developed Technologies

S. No	Title	Novelty/Innovation	Patent no. (year of grant)	Reference
1	Phospholipid complex of curcumin improved bioavailability	Phospholipid complexes of curcumin provide a higher systemic level of parent agent than uncomplexed curcumin.	WO2009/10155 (2009)	71
2	Phospholipid complexes of olive fruits or leaves extract having improved bioavailability	Olive fruits/leaves extracts bioavailability enhance using phospholipids complexes.	EPI844785 (2007)	71
3	Compositions comprising ginkgo biloba derivatives for the treatment of asthmatic and allergic conditions.	Compositions of the fraction gained from ginkgo biloba for the treatment of asthma and allergic conditions.	EPI1813280 (2007)	71
4	Treatment of skin and wound repair with thymosin beta-4	The formulation developed containing Thymosin beta-4 wound healing	US/2007 0015698 (2007)	72
5	Oral compositions for the treatment of cellulite	Oral and cosmetic pharmaceutical formulations containing Centella asiatica triterpenes ,extract of vitis vinifer and ginkgo biloba flavonoids in the free or complexed form with phospholipids .	US7691422 (2007)	72
6	Fatty acid monoesters of sorbitol firfural and compositions for cosmetic and dematological use.	The selected fatty acid monoesters of Sorbityl furfural are lipophillic agents for specific anti hydroxyl radical activity	EPI 690862 (2006)	72
7	Cosmetic and dematological compositions for the treatment of aging or photodamaged skin	The topical or dermatological preparation containing atleast one collagen synthesis - stimulating agent for anti wrinkles treatment	EPI1640041 (2006)	73
8	Soluble isoflavone composition	Isoflavone compositions enhanced the solubility texture characteristics ,taste and color of the formulation.	WO/2004/04554 (2005)	73
9	An anti oxidant prepation based on plant extract for the treatment of circulation and adiposity problems.	The formulation developed having the plant extract possessing the antioxidant activity for the treatment of hemorrhoid, bp.	EPI1214084 (2004)	74
10	Phospholipid complexes prepared from the extract of vitis vinifera as anti-otherosclerotic agents.	Vitis vinifera extract phospholipid complexes for the prevention and the treatment of atherosclerosis	US6297218 (2001)	75

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15. Phytosomal Products Commercialization

Efficient nanocarrier delivery systems are considered as Phytosomes. Even though there are many advantages, very few last-stage phytosomal products get commercialized due to the long journey from product development to success. After creating a proper formula, the most important obstacle that must be cleared before phytosomes can enter the market is proving their safety. The reason why individuals have chosen these kinds of treatments lately is due to the fact that they are bio-friendly, safe, and inexpensive [76]. Moreover, due to their simplicity, phytosome commercialization processes have been accelerated and phytomosol technology can be easily promoted on a commercial basis [77, 78].

Table 4: Commercially available phytosomal product [79].

S.No	Trade Name	Chief constituents	Source	Dose	Use
1	Gentella phytosomes	Triterpine	Centella asiatica	-	Cicatrizing, Trophodermic
2	Ginselect phytosomes	Ginsenosides	Gingko biloba	120mg	Adaptogenic
3	Greenselect phytosomes	Polyphenols	Camellia sinesis	-	Free radical scavenging activity
4	Leucoselect	polyphenols	Vitis vinifera	300mg	Anti -oxidant
5	Meriva	Curcuminoids	Curcuma longa	200-300mg	Anti - inflammatory
6	Silymarin	Silymarin	Silybum marianum	-	Antihepatotoxic
7	Bilberry	Triterpine	Vaccinium myritillus	-	Potent Anti-oxidant
8	Visnadine	visnadine	Ammi visnaga	-	Circulation improver
9	Rexatrol	Resveratrol	Polygonum cuspidatum	-	Anti-aging , Anti -oxidant
10	pA2 phytosomes	Proanthocynidin	Horse chestnut bark	-	Anti -wrinkles Uv protectant

16. Conclusion

Research will now be updated on its medicinal benefits in a biological environment due to the recent increase in the number of newly discovered phytochemicals. This could help in enhancing these characteristics at this point, during which knowledge gaps about specific drug delivery systems still exist. These vesicles have been known for their amazing entrapment abilities; hence, they show potential as ideal carriers of some useful phytochemicals at the

cellular level owing to their remarkable safety and biocompatibility. The joint study results reveal in a general sense that use of such formulations generally improves the bioavailability of bioactive phytochemicals, which may lead to either a decreased dosage from non-formulated compounds or increased activity in biomass, so to speak. Nevertheless, relatively few studies have conducted clinical trials aimed at defining the edge of the drug and its individual ingredients. There is no understanding of (Quercetin 288) and (Bergamot 292) bioavailability-related research as well as likening the anti-adhesive effectiveness of cranberry extract-fueled subjects' urine; 241 in the end, almost everywhere formulas demonstrated increased characteristics. Among the phytochemicals' sources, Curcuma longa and Silybum marianum have the most clinically respectable examination, verified by good results. Clinical studies are currently inadequate to ascertain the biological activities of the individual preparations. However, the overall evidence for these formulations is promising. Hence, there is a need for continued research in this area. Indeed, future clinical trials should focus on standardized products that demonstrate enhanced effectiveness over the unformulated molecules or extracts so as to attract more interest in these technologies.

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