

PHYTONIOSOMES: A PHYTOPLANKTON-DERIVED SYSTEM FOR TARGETED DRUG DELIVERY

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ABSTRACT

Niosomes increase drug bioavailability and address issues with drug insolubility, instability, rapid degradation, and lower treatment costs. By incorporating herbal medications into the delivery method, niosomes are created to enhance their toxicity protection, sustained delivery, pharmacological action, tissue macrophage distributions, and resilience to chemical and physical deterioration. By limiting a drug's activity to its intended target cells, niosomes make it less toxic and raise its therapeutic index. Niosomes, a novel medication delivery method, help increase therapeutic effects while decreasing adverse effects in herbal compositions. This study's goal is to draw attention to the use of phytoniosomes. Niosomes, a new type of drug delivery vehicle, are useful in herbal formulations because they lessen toxic effects while enhancing therapeutic effects. This article reveals details regarding niosomes and the use of herbs in niosomes. To acquire the data for the aforementioned study, research and review publications from different publishers, including Hindawi, Elsevier, Springer Nature, and Bentham Science, were examined using Google Scholar as a search engine. Herbal medicines containing water-soluble phytoconstituents are less absorbed due to their large molecular mass and less lipid solubility. To overcome these drawbacks, numerous experiments are being done that try to incorporate herbal components into cutting-edge pharmaceutical delivery systems like niosomes. Improvements in stability and pharmacological activity, are also brought about by the formulation of phytoniosomes. Numerous studies employing different phytoniosome have been conducted. However, more studies are required to gauge the potency of the phytoniosome using a variety of herbs.

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Introduction

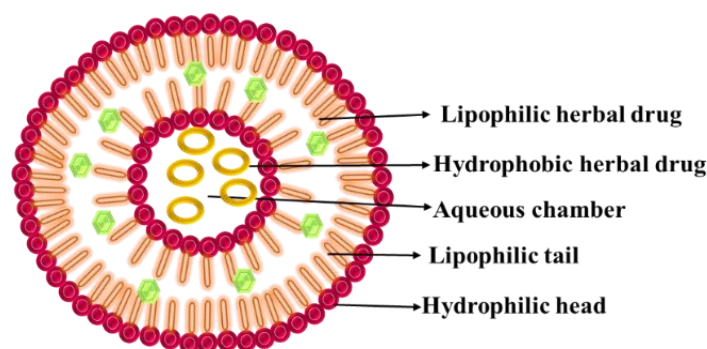
In current history, the delivery of drugs with targeted, controlled delivery has drawn a lot of attention. The use of nanotechnology in medicine has led to the creation of nanosystems that serve as drug carriers and can contain a variety of medications. Featuring promising qualities including drug protection from cleavage and degradation, controlled drug release and in the case of targeted drug delivery systems, the transport of bioactive compounds to the intended areas, nanocarriers present an excellent method for drug delivery [1]. A specific place inside the body or a cell could be reached by using nanoparticles as medication or gene delivery devices. The formulated stability and shelf-life, target and biodistribution, pharmaceutical, or many chemicals that can make up nanoparticles [2]. A particular nanoparticles toxicity encompasses both the interactions of that species and its nanostructured components with biological systems (organs, tissue incorporation and release, size, and shape of nanoparticles, physicochemical characteristics of an active pharmaceutical ingredient (API), safety

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and toxicity while keeping favorable effects are all factors that must be taken into consideration [2, 3]. In 1909, Paul Ehrlich started the research of targeted delivery when he had the idea for a medication delivery method that would selectively target injured cells. Agent aiming is the ability to deliver a therapeutic drug precisely to the desired site of activity with little to no touch on non-target tissue. Niosomes are biodegradable, nonimmunogenic, and compatible with the body. They permit controlled and continuous medication administration just at a target site and are highly stable and long-lasting [4]. The sizes of niosomes are microscopic and lie on a nanometric scale i.e., 10nm-100nm. Among the most promising drug delivery systems are niosomes, which are produced when non-ionic surfactant and cholesterol self-associate in a somewhat watery phase. It has been demonstrated that several non-ionic surfactant types can form niosomes, which enable the trapping of many medications with a range of solubilities. the function of several active ingredients, since all of the ingredients, work together synergistically. For the last many years, herbal remedies and natural products are being used to cure diseases. Contrary to the prevalent allopathic method, herbal treatments include thousands of active ingredients that all combat disease concurrently. Herbal formulations are affordable and consist of simple, quickly-digested natural components. Compared to conventional medications, herbal remedies are known to have fewer adverse effects and the potential to be curative. Herbal formulations are affordable and consist of simple, quickly-digested natural components. Compared to conventional medications, herbal remedies are known to have fewer adverse effects and the potential to be curative. The effectiveness of herbal remedies depends on how well they work overall. Each active participant has a vital function to perform, and all of them are connected [5]. Typically, oral administration is used to provide herbal medications. Due to their large molecular mass and poor lipid solubility, herbal medications with water-soluble phytoconstituents, such as flavonoids, tannins, and terpenoids, are poorly absorbed. Numerous phytoconstituents are well known for their quick metabolism and gastrointestinal breakdown. Numerous studies are being conducted that aim to include herbal constituents in cutting-edge medication delivery systems like niosomes to avoid such downsides. Generally speaking, these compositions are known as Phytoniosomes. Herbal components known as Phytoniosomes are described as being contained in a non-ionic vesicular structure. The addition of herbal medications to the delivery method also contributes to improvements in solubility, toxicity protection, stability, prolonged delivery, pharmacological activity, tissue macrophage distribution, and resistance to the chemical and physical deterioration [6].

Phytoniosome

Herbal components known as Phytoniosomes are described as being contained in a non-ionic vesicular structure. Several studies are being conducted that aim to include herbal constituents in cutting-edge medication delivery systems like niosomes to avoid such downsides, these compositions are known as Phytoniosomes. Non-ionic surfactant-based liposomes are known as niosome. Cholesterol is mostly included as an excipient in the formation of niosomes. Excipients may also be utilized in other ways. Niosomes are more capable of penetrating than earlier emulsion formulations. Although they share a bilayer structurally with liposomes, niosomes are far more advantageous than liposomes in that they are prepared using ingredients that make them more stable. Niosome sizes are minuscule and are found on the nanometric scale. The range of particle sizes is 10 nm to 100 nm. A typical niosome vesicles would be made up of a non-ionic surfactant like Span-60, a vesicle-forming amphiphile typically stabilized by the presence of cholesterol, and a little amount of an anionic surfactant like diacetyl phosphate, that also aids in stabilizing the vesicle. Moreover, phytoniosomes are the bi-layered form of non-ionic surface-active substances (**Figure 1**). Only when surfactants and cholesterol are combined in the right proportions and the temperature exceeds the gel liquid transition point can such thermodynamically stable bi-layered complexes emerge [7]. In the middle of this two-layered construction lies a hollow area. Due to the unique geometry of their structure, phytoniosomes can encapsulate both hydrophilic and hydrophobic medicines. While hydrophobic medications partition through the bilayer structure to enter the phytoniosome, hydrophilic drugs can bind to the surface of the bilayer or the core aqueous domain to become entrapped in the phytoniosome [7]. Among the long list of its pros and cons, a few points regarding phytoniosome have been mentioned in **Figure 2**.



PHYTONIOSOME

Figure 1. Structure of Phytoniosome

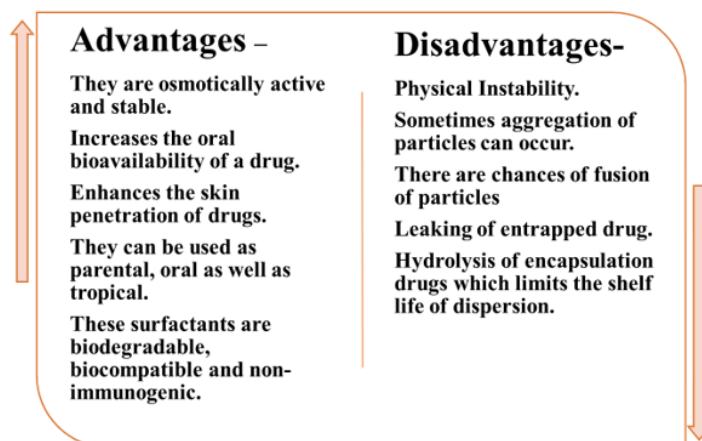


Figure 2. Enlist the various favorable and unfavorable characteristics of the phytoniosome.

Factors Influencing the Preparation of Phytoniosomes

There are several factors influencing the preparation of Phytoniosomes which are elaborated below-

Type and Structure of Surfactants

The type of vesicle that will be generated in a process is influenced by a surfactant's hydrophilic-lipophilic balance (HLB), gel transition temperature, and Critical Packing Parameter (CPP). In the part before, all of these factors were already covered in great detail. The geometry of the vesicles that will be generated using critical packing parameter can be estimated in the manner that follows. critical packing parameter less than 1/2 will result in the formation of spherical micelles. If critical packing parameter is greater than 1/2 but below 1, bilayer micelles will develop. If critical packing parameter is greater than 1, inverted micelles will occur [8].

Cholesterol

Similar to how it influences the properties of a biological membrane, cholesterol also has an impact on the phytoniosomes membrane properties. It lessens the membrane's flexibility and the drug's ability to pass through it. The hydrophilic-lipophilic balance value of the surfactant determines how much cholesterol should be utilized.

Quantity of Lipid and Surfactant

Any variation in the surfactant and cholesterol ratio affects both the viscosity of the system and the amount of medication entrapped. The characteristics of phytoniosomes may alter if the above ratio changes during the hydration step [9].

Nature of the Medication

Drug entrapment is influenced by drug attributes including molecular weight, structural characteristics, hydrophilic or lipophilic character, and the balance between the two. Drug and surfactant interactions may increase vesicle size [10]. It was previously stated in certain articles that a hydrophilic drug's maximum entrapment efficiency in niosomes could range from 10 to 20% [11].

The pH of the Hydration Medium

The pH of a hydrating fluid is another factor that could have an impact on how well the medication is trapped. For instance, flurbiprofen exhibits higher entrapment at acidic pHs (max 94.6% at pH 5.5). The entrapment efficiency of flurbiprofen improves when the pH falls from 8 M to 5.5, and it significantly decreases at pH 6.8 [12].

Method of Preparation

Phytoniosome size and entrapment effectiveness may vary depending on how they are made. Niosomes of naltrexone were created by Abdelkader *et al.* [13] using freeze-thaw, dehydration-rehydration, and reverse-phase evaporation methods as well as thin-film hydration techniques. According to the findings, the pre-treatment technique had a substantial impact on the effectiveness of the trapping. Abdelkader *et al.* developed prednisolone ethoniosomes (ethanol-based niosomes) using the thin film hydration technique and the ethanol injection method. He discovered that while the ethanol injection approach creates smaller niosomes than the thin-film hydration method, both methods yield niosomes with a higher degree of entrapment efficiency. Reverse-phase evaporation and the microfluidization process can also be used to create small-sized niosomes. Better entrapment efficiency is demonstrated by niosomes made using the transmembrane pH technique [14].

Resistance to Osmotic Stress

The sizes of the niosome diminish when a hypertonic solution is added to a niosomal suspension. When phytoniosomes are maintained in a hypotonic salt solution, the drug is first released slowly, causing swelling. This slow release may be caused by the inhibition of fluid eluting from vesicles. Later, a faster release phase was observed. This faster release phase may be caused by the disruption of the phytoniosome's mechanical structure as a result of mechanical stress [15].

Cosurfactant

Comparatively to non-ionic water-soluble surfactants, various researchers observed that mixing non-ionic water-insoluble surfactants resulted in large vesicle size and less effective methylene blue entrapment. This might be due to the bilayer's poor membrane structure, which allows for drug leakage, caused by competition between the lipophilic cosurfactant and cholesterol [16].

Characterization of Phytoniosomes

Phytoiosomes are characterized by the following parameters:

Entrapment Efficiency

It can be computed by deducting the overall amount of medicine added from the quantity number of drugs unloaded. Techniques like thorough dialysis, filtering, gel chromatography, or centrifugation can be used to identify the unloaded drug [17]. Niosome can be dissolved in 50% n-propranolol or 0.1% Triton X-100 to determine the concentration of loaded medicines, and the resulting solution can then be tested using any particular technique [18]. The % encapsulation efficiency can be calculated using the following equation:

$$\% \text{Entrapment Efficiency} = 100 \times \frac{\text{Quantity of Drug Loaded in the Phytoniosome}}{\text{Total Amount of Drug in the Suspended}} \quad (1)$$

Size Distribution, Morphology, and Size of Phytoniosomes

The size of phytoniosomes and their morphology can be determined using a variety of methods, including microscopic examination, photon correlation spectroscopy, coulter counter, electron microscopic analysis, SEM (scanning electron microscope), transmission electron microscope (TEM), freeze-fracture replicator, zeta sizer, spectrophotometry, and metal sizer. Because the two methods apply different measurement philosophies, the TEM approach yields smaller particle sizes than the (light scattering dynamic) DLS method [19]. Atomic force microscopy was employed by Rinaldi *et al.* to examine the size, morphological characteristics, and orders of magnitude of the niosome sample.

Number of Lamellae

The numbers of lamellae can be determined using a variety of techniques, including (AFM), (NMR), (small-angle X-ray spectroscopy), and (electron microscopy). Small-angle X-ray scattering and in-situ energy-dispersive x-ray diffraction can be utilized to characterize the thickness of bilayers [20].

Membrane Rigidity

The mobility of the fluorescent probe can be employed as a result of temperature to assess membrane stiffness. Fluorescence polarisation can be used to determine the micro-viscosity of the membranes to comprehend the packing structure of the niosomal membrane. Pentamidine niosomes' membrane characterization was been out by Rinaldi *et al.* They employed DPH and pyrene because Pyrene exhibits lateral diffusion inside the bilayer and DPH provides information on the lipid order [21].

Charges on Phytoniosome and Zeta Potential

The charge on phytoniosomes causes them to repel one another. And by preventing their aggregation and fusion, electrostatic repulsion maintains their stability. Zeta potential is used to estimate the charge on niosomes. The zeta potential is measured using an ionic conductivity analyzer, mastersizer, microelectrophoresis, ionic strength fluorophores, elevated capillary electrophoresis, and DLS equipment [22].

When (dicetyl phosphate) DCP was employed to generate the surface charges on niosomes, Bayindir and Yuksel found that electrostatic repulsion between the particles kept the system stable at a minus zeta potential value within the range of 41.7 to 58.4 mV. Galliderminniosomes were created by Manosroi *et al.* [23] utilizing two distinct charges (anionic and cationic). They noticed a difference in the size of the niosome as in the case of anionic vesicles, the charge was neutralized with the positive ions of gallidermin, resulting in the formation of small-sized niosomes, whereas in the case of cationic vesicles, the niosomes created were large due to repugnance between the cationic charges.

Stability Studies

As a result of aggregate and fusion during storage, the medication can leak from phytoniosomes. Niosome stability experiments were carried out by Kopermsub *et al.* by subjecting the preparation to various temperature conditions (40, room temperature, and 450) for two months. Nanoparticles are also subjected to different levels of humidity and ultraviolet (UV) light. Size, shape, and entrapment effectiveness are some of the variables that are periodically assessed during stability investigations. The

stability of niosomes and phytoniosomes prepared from green tea extract [24], lornoxicam, cefdinir, and ginkgo respectively has been tested similarly.

In-vitro Release

The procedure including the dialysis membrane is used to study in vitro release. This procedure involves placing niosomes in a dialysis bag, which is then deposited in a container with a dissolution medium, often a buffer. This entire assembly is kept at the same temperature of 37 °C on a magnetic stirrer. A sample from the receptor region is collected at predetermined intervals, and the drug concentration is assessed using any method that has been described elsewhere. The dialysis approach was used for the in-vitro discharge of temozolomide niosomes, benazepril hydrochloride niosomes, paclitaxel and curcumin cationic PEGylated niosomes [25], and diltiazemniosomes. Aboul Einien studied the effects of soaking a cellophane membrane in glycerin: water (1:3) for 15 minutes. the ascorbic acid derivative's release from the aspasomes. They used a USP dissolving apparatus I was filled with 0.5g of aspasomes that were placed inside this membrane and securely fastened. The experiment was carried out in (250 ml of buffered phosphate (pH 7.4) at 32 °C 0.5 °C and 50 rpm. At predefined intervals, the materials were spectrophotometrically examined.

Tissue Distribution/In-Vivo Study

The method of distribution, drug concentration, action, and duration of medicament presence in organs such as the liver, spleen, lung, and bone marrow all affect in-vivo investigations for phytoniosomes. Animal models can be used to study how a medication is distributed throughout the tissue. Various tissues obtained from sacrificed animals such as the kidney, liver, heart, lungs, and spleen should be taken, washed with buffer, homogenized, and centrifuged to investigate the distribution pattern. The number of drugs in the supernatant is examined. I.T.O. *et al.* [26] conducted in-vivo bioavailability tests of benzylpenicillin niosomes on albino rats. They utilized the intubation tube to administer each mixture (0.1 ml) orally. Retro-orbital puncture was utilized to collect blood samples over 24 hours at predefined intervals, and the precipitate was used to calculate.

Materials and Methods

There are several different methods by which niosome can be prepared shown in (Table 1).

Table 1. Enlist the various methods for preparing for niosome along with the method and their characterization.

S.no.	Method	Preparation	Characterization	Reference
1.	Reverse Phase Evaporation Method (REV).	<ul style="list-style-type: none"> The medication is dissolved in a solution (ether + chloroform), and then added niosomal components. After sonicating, to create an emulsion, the organic layer is evaporated. 	<ul style="list-style-type: none"> The evaporation of the organic solvent results in the formation of large unilamellar vesicles. 	[27]
2.	Micro fluidization Method.	<ul style="list-style-type: none"> Is based on the submerged jet theory. The drug and surfactant's fluidized streams interact in precisely planned microchannels inside the interaction chamber at extremely high speeds. Niosomes are formed as a result of the energy and high-speed impact. 	<ul style="list-style-type: none"> This approach gives more uniformity, <ul style="list-style-type: none"> Smaller size Unilamellar vesicles High repeatability in the niosome formulation. 	[28]
3.	(Thin-Film Hydration Method) TFH.	<ul style="list-style-type: none"> It is an easy and well-liked preparation technique. In this procedure, Surfactants are dissolved with, the use of an organic solvent., cholesterol, and various additives like-charged molecules in a round-bottomed flask. The organic phase is then eliminated using a rotary evaporator to produce a thin coating on the flask's interior wall. The dry surface is hydrated above the drug's transition temperature (Tc) by the addition of an aqueous solution surfactant for a specified time with constant shaking. 	<ul style="list-style-type: none"> This process produces multilamellar niosomes. 	[29]
4.	(Ether Injection Method) EIM.	<ul style="list-style-type: none"> The ether injection method involves gently injecting the surfactants and additives through a needle into a watery drug solution that is maintained at a temperature that is higher than the standard point of the extraction liquid. The organic solvent is evaporated using a rotary evaporator. Single-layered vesicles are formed during the vaporization process. 	<ul style="list-style-type: none"> To achieve maximum drug entrapment, the formulation technique was optimized for hydrate time and hydrated medium volume. 	[30]

5.	Proniosome	<ul style="list-style-type: none"> The sorbitol and mannitol water-soluble carriers are coated with surfactant when using the pronosome approach. A dry formulation is created as a result of the coating process. This substance is known as "Proniosomes," and it must be hydrated before usage. The aqueous phase is added, and this results in the formation of niosomes. 	<ul style="list-style-type: none"> Reduces physical stability issues including aggregation, leakage, and fusion issues, and makes dosing, distributing, transporting, and storing easier while producing better outcomes than conventional niosomes 	[31]
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Applications

For their effectiveness against a variety of disorders, some of which have been documented in **Table 2**, niosomal drug delivery is potentially applicable to numerous pharmacological substances.

Table 2. Niosomes applications [32]

S. No	Applications of Niosomes	Description
1.	Niosomes as Drug Carriers	<ul style="list-style-type: none"> X-ray imaging solubilization matrix local depot for the steady release of medicine.
2.	Drug Targeting	<ul style="list-style-type: none"> metastasizes to the liver and other organs to treat liver parasite infections. direct medications away from the RES and toward other organs.
3.	Anti-neoplastic Treatment	<ul style="list-style-type: none"> modify metabolism, increase circulation, reduce extending the drug's shelf life lessen its adverse effects. slow down the rate at which tumors proliferate
4.	Delivery of Peptide Drugs	<ul style="list-style-type: none"> polypeptideniosomes successfully shields peptides from gastrointestinal peptide degradation. enhanced peptide stability.
5.	Use in Immune Response Research	<ul style="list-style-type: none"> immunological selectivity, minimal toxicity, better stability
6.	Niosomes as Carriers for Haemoglobin	<ul style="list-style-type: none"> niosomal vesicle allows oxygen to pass through serve as a hemoglobin carrier in anaemic patients.
7.	Sustained Release	<ul style="list-style-type: none"> Since medications with low therapeutic indices and poor water solubilities might be kept in circulation through niosomal sustained release action of niosomes can be applied to those substances.
8.	Localized Drug Action	<ul style="list-style-type: none"> achieve localized drug activity Enhance the drug's ability to penetrate connective tissue and epithelium.

Herbs Incorporated as Phytiosome

- Gymnema Sylvestre (Gurmar)* - *Gymnema Sylvestre* extract-loaded phytiosomes were developed and characterized by Bhagyashree Kamble *et al.* utilizing nonionic surfactant, and their hypoglycemic activity in contrast to the original extract was assessed. Thin-film hydration was used to create *G. Sylvestre* extract-loaded niosomes made of nonionic surfactants. The effectiveness of the components being captured by the improved formulation was tested, along with other factors like release kinetics, vesicle size, zeta potential, and stability tests. In an animal study of diabetes induction by alloxan, the hypoglycemic potential of the original extract and the improved niosomal preparation was examined. This study highlights the benefits of niosomes that have been loaded with *G. Sylvestre* extract and supports their potential to increase the effectiveness of *G. Sylvestre* extract as an anti-diabetic.
- Calendula Officinalis (pot marigold)* - The production, evaluation, and cell culture usage of phyto-niosomes of marigold extract were covered by Rabia Nur Una *et al.* The best *C. officinalis* extract was selected to develop novel formulations in an attempt to boost their bioactivity, purity, and efficacy after thorough cell-based and cell-free *in vitro* experiments. The development of a novel composition based on the addition of *C. officinalis* extract into surfactant-based vesicular carriers was the survey's second objective. After niosomes and extract-loaded phyto-niosomes were characterized, their biological functions, such as cytotoxicity, wound repair, and protection from oxidative distress were examined. Comparisons between the activities acquired through the usage of free extract and the outcomes of phyto-niosomes on Vero cells were used to evaluate the results [30].

3. *Curcumin (turmeric)* - A proniosomal carrier system for curcumin was created by Kapil Kumar *et al.* for transdermal administration. Curcumin proniosomes were created by injecting the medication into a solution of Span 80, cholesterol, and diethyl ether. These proniosomes were then tested as a TDDS. The formed complexes under different storage settings were evaluated for dimensions, entrapment efficiency, angle of repose, rehydration rate, and vesicular integrity. Studies on in vitro drug release study were carried out on albino rat skin. The proniosome preparation technique produced an encapsulating yield of 82.3–86.8%. Examination using SEM revealed that the particles' surfaces were smooth. Proniosomes are a very robust and potential long-term delivery method for curcumin, they concluded [33].
4. *Terminalia Chebula Galls (Black Myrobalan)* - To improve transdermal administration, AranyaManosroi *et al.* studied a gel that contained elastic niosomes laden with gallic acid that were extracted from Terminalia chebula galls. The semipurified fraction or different gel preparations including elastic niosomes laden with gallic acid were used to perform vertically Franz diffusion cell of gallic acid penetration through rat skin. Negative zeta potential values and mixtures of unilamellar and multilamellar complexes were seen in elastic and nonelastic niosomes laden with gallic acid or the semipurified fraction, which ranged in size from 200 to 400 nm. For three months, laden elastic and nonelastic niosomes both showed excellent physicochemical characteristics. Comparatively to nonelastic niosomes, elastic niosomes showed larger proportions of gallic acid via rat skin.
5. *Camellia Sinensis (Black Tea)*- Niosomes were examined by Meng-I Yeh *et al.* to see if it was possible to administer black tea extract (BTE) topically in an in vitro setting as a sunscreen. A described earlier technique of lipid hydration films was used to produce multi-lamellar niosomes. Niosomes' viability as a topical application was assessed using in vitro penetration tests on the naked epidermis. In a stable state, penetration levels of niosomes loaded with caffeine and gallic acid were greater than those of aqueous medium distribution. Increased transdermal absorption rates were observed for skin penetration with mixtures of caffeine and gallic acid. They concluded that BTE will soon be dermally supplied by niosomes as a sunscreen agent.
6. *Papain (Papaya Proteinase)*-Papain permeability from gel formulations comprising niosomes and nanospheres packed with papain were compared by Charinya Chankhampan *et al.* All of the niosomes and nanospheres in the gel preparation had vesicular diameters between 220.7 and 520.2 nm. On rabbit skin, none of the gel solutions containing papain encapsulated in niosomes and nanospheres caused discomfort. Gel carrying free papain was not as chemically stable as a gel having papain packed in elastic niosomes. This work has shown the possibility of niosomes, particularly elastic niosomes, for improving papain transdermal absorption in rat skin and improving scar eradication in rabbit ear models, both of which will be helpful for the creation of topical scar therapy solutions (**Table 3**).

Table 3. List the herbs used to synthesize niosomes along with their medicinal advantages.

S.no	Herbs used as noisome	Extract/powder/oil etc.	Therapeutic Uses of Phytoniosome	Reference
1.	Ginkgolide B and Puerarin	• Extract	• Parkinson's disease	
2.	Marigold (Calendula officinalis)	• extract	• free radical scavenging	[34]
3.	Proniosomal carrier system of curcumin	• powder	• Used as Transdermal Delivery System.	[35]
4.	Terminalia chebula galls	• gallic acid	• strong in vitro DPPH radical scavenging and MMP-2 inhibitory.	[36]
5.	Black tea	• extract	• sunscreen agent	[37]
6.	Niosomes of Ascorbic Acid and α -Tocopherol	• extract	• During cerebral ischemia-reperfusion, systemic protection against an increase in oxygen-free radical concentration is provided for the brain's tissue.	[38]
7.	Myrtuscommunis (myrtle) Essential Oil	• essential Oil	• cure mouth ulcers • burns • wounds • used externally to treat hyperglycemia • Diarrhea • Stomachaches • Coughs • pulmonary problems.	[39]
8.	Green Tea	• Extract	• Used as antioxidants.	[40]
9.	Hypericum Perforatum	• extract	• treatment of wounds and scars.	[41]

10.	Morusin	• extract	<ul style="list-style-type: none"> • The root bark of <i>Morus alba</i> contains a prenylated flavonoid called musin, which has anti-inflammatory <ul style="list-style-type: none"> • Antioxidant • Antibacterial properties. 	[42]
11.	<i>Fummaria officinalis</i>	• extract	<ul style="list-style-type: none"> • anti-inflammatory • anti- painful ailments 	[43]
12.	Ivy plant – <i>Hedera helix</i>	• extract	<ul style="list-style-type: none"> • breast cancer 	[44]
13.	<i>Glycyrrhiza</i>	• extract	<ul style="list-style-type: none"> • dermatitis • eczema • psoriasis 	[45]
14.	<i>Carumcarvil</i>	• seeds	<ul style="list-style-type: none"> • cancer therapy 	[46]
15.	<i>Wrightiatinctoria</i>	• extract	<ul style="list-style-type: none"> • Anti-Psoriatic activity 	[47]
16.	<i>Vinca rosea</i>	• extract	<ul style="list-style-type: none"> • Enhance oral activity 	[48]
17.	<i>Annona squamosa</i>	• extract	<ul style="list-style-type: none"> • Antibacterial • Antidiabetic • Antioxidant • Anticancerous • Improves transdermal bioavailability 	[49]
18.	<i>Xanthium strumarium</i>	• extract	<ul style="list-style-type: none"> • For the treatment of Tinea Corporis 	[50]

Future Perspectives

Phytoniosomes are cutting-edge nanoscale drug carriers that can be used to create efficient drug delivery systems. They provide act as a powerful for loading hydrophilic, lipophilic, or a combination of the two medicines. Numerous investigations using various niosome kinds have been carried out to give anti-diuretic characteristics, stomach effects, anti-diabetic effects, anti-hyperlipidemic effects, anticancer agents, anti-inflammatory agents, and employed in diarrhea and stomach problems. The pertinent research showed that phytoniosomes enable targeted administration to a particular tissue type, lower the dose, and improve the stability of the medication enclosed. The use of unique preparations, loading, and modification techniques for specific administration routes can improve the structural qualities and traits of the niosomes. Consequently, phytoniosomes offer themselves as prospective strategies in therapies that are now on the market.

Phytoniosomes are nontoxic and immune-neutral drug delivery systems that have received extensive research for cutaneous medication administration. They were created to treat cosmeceutical conditions such as melasma, vitiligo, and the administration of antioxidants for anti-aging, as well as topical diseases like skin cancer, acne, inflammation, fungal and bacterial infections, psoriasis, and hair loss. Numerous studies have demonstrated that drug localization in the target location (skin) due to drug integration into phytoniosomes results in a decrease in side effects and an increase in therapeutic efficacy. These benefits make phytoniosomes an appealing topical delivery system, although more research is required to demonstrate the clinical effectiveness of niosomes.

Results and Discussion

It has been demonstrated in the past that nanosystems formed from various structures can boost the cell's effectiveness or the tolerability of active compounds. Due to their superior adjustable biological and physiochemical performance over their competitors, nanoparticle or nanomaterials have made significant advances in nanotechnology. The best novel drug delivery agents with the greatest potential for tailored drug delivery are niosomes. There are several advantages and limitations of the niosome as discussed. The capacity of niosomes to form different forms, including proniosome and aspasome, makes them advantageous as drug delivery vehicles. Niosomes have been extensively researched for cutaneous drug administration since they are harmless and nonimmunogenic drug carriers. The pertinent research showed that niosomes provide targeted administration to a particular type of tissue, lower the dose, and enhance the durability of the drug enclosed. The use of unique formulations, loading, and modification techniques for specific administration routes can improve the structural qualities and traits of the niosomes. Several attempts have been made to construct a medication delivery system based on herbs and their phytoconstituents with niosomes to improve therapeutic effects and bioavailability. Phytoniosomes were created and improved using a variety of niosomal preparation techniques. Thus, it appears that phytoniosome research will continue to grow and may result in efficient marketing formulation in the pharmaceutical business. An in-depth study is being done on new medicine targeting and delivery methods for phyto actives and extracts. However, exploratory studies are currently being done in this field. Additionally, greater focus should be placed on the study of carrier substances to create better carriers that can lessen the toxicity of medications, increase their activity, and boost the general effectiveness of the agents. The huge therapeutic potential of herbal medications should be investigated using certain value-added drug delivery methods. When given through a new

drug delivery method, standardized plant extracts or mostly polar phytoconstituents such as flavonoids, tannins, terpenoids, and xanthenes have substantially superior absorption profiles that allow them to traverse the biological barrier, resulting in increased bioavailability. In contrast to the traditional herb extract or Phyto molecule, a greater amount of the active element is therefore located at the site of activity (brain, cardiac, liver, kidney, etc.) at a similar or lower dose. As a result, the therapeutic effect is improved, easier to notice, and lasts longer. There has been many research using various phytoniosome. However, additional studies are needed to determine the potency of the phytoniosome using a range of herbs.

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References

1. Ag Seleci D, Seleci M, Walter JG, Stahl F, Scheper T. Niosomes as nanoparticulate drug carriers: fundamentals and recent applications. *J Nanomater.* 2016;2016.
2. De Jong WH, Geertsma RE, Borchard G. Regulatory safety evaluation of nanomedical products: key issues to refine. *Drug Deliv Transl Res.* 2022;12(9):2042-7.
3. Cauerhff A, Martinez YN, Islan GA, Castro GR. Nanostability. In *Nanotoxicology 2014* (pp. 57-95). Springer, New York, NY.
4. Mishra V, Nayak P, Singh M, Sriram P, Suttee A. Niosomes: Potential Nanocarriers for Drug Delivery. *J Pharm Clin Res.* 2020;11(03):389-94.
5. Kanaani L, Ebrahimifar M, Kheyavi AA, Mehrdiba T. Effects of cisplatin-loaded niosomal nanoparticles on BT-20 human breast carcinoma cells. *Asian Pac J Cancer Prev: APJCP.* 2017;18(2):365.
6. Farmoudeh A, Akbari J, Saeedi M, Ghasemi M, Asemi N, Nokhodchi A, et al. Methylene blue-loaded niosome: preparation, physicochemical characterization, and in vivo wound healing assessment. *Drug Deliv Transl Res.* 2020;10(5):1428-41.
7. Abdelkader H, Alani AW, Alany RG. Recent advances in non-ionic surfactant vesicles (niosomes): self-assembly, fabrication, characterization, drug delivery applications, and limitations. *Drug Deliv.* 2014;21(2):87-100.
8. Agrawal SS, Gurjar PN, Mutke A. DOE-based Formulation development and Evaluation of Niosomal dispersion of Pregabalin. *Optimi.* 2022;510:67-2.
9. Rajabalaya R, David SR, Chellian J, Xin Yun G, Chakravarthi S. Transdermal delivery of oxybutynin chloride proniosomal gels for the treatment of overactive bladder. *Drug Deliv.* 2016;23(5):1578-87.
10. Verma S, Utreja P. Vesicular nanocarrier based treatment of skin fungal infections: Potential and emerging trends in nanoscale pharmacotherapy. *Asian J Pharm Sci.* 2019;14(2):117-29.
11. Meng S, Sun L, Wang L, Lin Z, Liu Z, Xi L, et al. Loading of water-insoluble celestrol into niosome hydrogels for improved topical permeation and anti-psoriasis activity. *Colloids Surf B Biointerfaces.* 2019;182:110352.
12. Priprem A, Damrongrungruang T, Limsitthichaikoon S, Khampaenjiraroach B, Nukulkit C, Thappasaphong S, et al. Topical niosome gel containing an anthocyanin complex: a potential oral wound healing in rats. *Aaps Pharm sci-tech.* 2018;19(4):1681-92.
13. Moghtaderi M, Mirzaie A, Zabet N, Moammeri A, Mansoori-Kermani A, Akbarzadeh I, et al. Enhanced antibacterial activity of Echinacea angustifolia extract against multidrug-resistant Klebsiella pneumoniae through niosome encapsulation. *Nanomater.* 2021;11(6):1573.
14. Bartelds R, Nematollahi MH, Pols T, Stuart MC, Pardakhty A, Asadikaram G, et al. Niosomes, an alternative for liposomal delivery. *PLoS One.* 2018;13(4):e0194179.
15. Barani M, Mirzaei M, Torkzadeh-Mahani M, Nematollahi MH. Lawsone-loaded Niosome and its antitumor activity in MCF-7 breast Cancer cell line: a Nano-herbal treatment for Cancer. *Daru.* 2018;26(1):11-7.
16. Bhardwaj P, Tripathi P, Gupta R, Pandey S. Niosomes: A review on niosomal research in the last decade. *J Drug Deliv Sci Technol.* 2020;56:101581.
17. Gunes A, Guler E, Un RN, Demir B, Barlas FB, Yavuz M, et al. Niosomes of Nerium oleander extracts: In vitro assessment of bioactive nanovesicular structures. *J Drug Deliv Sci Technol.* 2017;37:158-65.
18. Joy C, Nair SK, Kumar KK, Dineshkumar B. Niosomes as nano-carrier based targeted drug delivery system. *J Drug Deliv Ther.* 2021;11(4-S):166-70.
19. Ma H, Guo D, Fan Y, Wang J, Cheng J, Zhang X. Paeonol-loaded ethosomes as transdermal delivery carriers: design, preparation, and evaluation. *Molecules.* 2018;23(7):1756.

20. Wahab S, Ahmad MP, Hussain A, Qadir SF. Nanomaterials for the delivery of Herbal Bioactive Compounds. *Curr Nanosci.* 2022;18(4):425-41.
21. Badri S, Sailaja P, Annagowni NR, Lunjala RS, Seshu D. A review on niosomes as novel drug delivery system. *Int J Indig Herbs Drugs.* 2022:87.
22. Ebrahimipour M, Akhlaghi M, Hemati M, Ghazanfary S, Shahriary S, Jafari Ghalekohneh S, et al. In vitro evaluation and comparison of anticancer, antimicrobial, and antifungal properties of thyme niosomes containing essential oil. *Nanomed J.* 2022;9(4):307-18.
23. Kheilnezhad B, Hadjizadeh A. Factors Affecting the Penetration of Niosome into the Skin, Their Laboratory Measurements and Dependency to the Niosome Composition: A Review. *Curr Drug Deliv.* 2021;18(5):555-69.
24. Li XX. Preparation of glycyrrhetic acid niosomes and optimization of its prescription process. *Zhong Cao Yao.* 2016:240-5.
25. Ammar HO, Haider M, Ibrahim M, El Hoffer NM. In vitro and in vivo investigation for optimization of niosomal ability for sustainment and bioavailability enhancement of diltiazem after nasal administration. *Drug Deliv.* 2017;24(1):414-21.
26. Baghel S, Gidwani B, Kaur CD. Novel drug delivery systems of herbal constituents used in acne. *Seed.* 2017;10:2.
27. Alam MS, Ahad A, Abidin L, Aqil M, Mir SR, Mujeeb M. Embelin-loaded oral niosomes ameliorate streptozotocin-induced diabetes in Wistar rats. *Biomed Pharmacother.* 2018;97:1514-20.
28. Aroraa S, Dhoke V, Moharir K, Yende S, Shah S. Novel Drug Delivery System of Phytopharmaceuticals: A Review. *Curr Tradit Med.* 2021;7(5):73-86.
29. Sanghadeep G, Jat RK. Stability and biodistribution study of taraxacum officinale niosomes. *Trop J Pharm Life Sci.* 2022;9(2):01-10.
30. Verma H, Prasad SB, Yashwant SH. Herbal drug delivery system: A modern era prospective. *Int J Curr Pharm Rev Res.* 2013;4:88-101.
31. Shree D, Patra CN, Sahoo BM. Novel Herbal Nanocarriers for Treatment of Dermatological Disorders. *Pharm Nanotechnol.* 2022;10(4):246-56.
32. Jamaludin R, Daud NM, Sulong RS, Yaakob H, Aziz AA, Khamis S, et al., Andrographis paniculata-loaded niosome for wound healing application: Characterisation and in vivo analyses. *J Drug Deliv Sci Technol.* 2021;63:102427.
33. Yeo PL, Lim CL, Chye SM, Ling AP, Koh RY. Niosomes: a review of their structure, properties, methods of preparation, and medical applications. *Asian Biomed.* 2017;11(4):301-14.
34. Kamble B, Talreja S, Gupta A, Patil D, Pathak D, Moothedath I, et al. Development and biological evaluation of *Gymnema Sylvestre* extract-loaded nonionic surfactant-based niosomes. *Nanomed.* 2013;8(8):1295-305.
35. Budhiraja A, Dhingra G. Development and characterization of a novel antiacne niosomal gel of rosmarinic acid. *Drug Deliv.* 2015;22(6):723-30.
36. Akhlaghi M, Ebrahimipour M, Ansari K, Parnian F, ZarezadehMehrizi M, Taebpour M, et al. Synthesis, study and characterization of nano niosomal system containing *Glycyrrhiza glabra* extract in order to improve its therapeutic effects. *N Cell Mol Biotechnol J.* 2021;11(42):65-82.
37. Poorani V, Selvakumar K, Kumar GV. Improving Bioavailability of Phytochemicals through Niosomes. *J Drug Deliv Ther.* 2020;10(6-s):119-21.
38. Oh J, Lee MS, Jeong JH, Lee M. Deoxycholic acid-conjugated polyethylenimine for delivery of heme oxygenase-1 gene in rat ischemic stroke model. *J Pharm Sci.* 2017;106(12):3524-32.
39. Aleksic V, Knezevic P. Antimicrobial and antioxidative activity of extracts and essential oils of *Myrtus communis* L. *Microbiol Res.* 2014;169(4):240-54.
40. Wilson DK, Shyamala G, Paulpandi M, Narayanasamy A, Siram K, Karuppaiah A, et al. Development and characterization of phytoniosome nano vesicle loaded with aqueous leaf extracts of *Justicia adhatoda* and *Psidium guajava* against dengue virus (DEN-2). *J Clust Sci.* 2021;32(2):297-304.
41. Knauth A, Mittag S, Bloch L, Albring KF, Schmidt M, Werz O, et al. Hyperforin and Myrtucommulone Derivatives Act as Natural Modulators of Wnt/ β -Catenin Signaling in HCT116 Colon Cancer Cells. *Int J Mol Sci.* 2022;23(6):2984.
42. Beylankouhi S, Ghanbarzadeh B, Pour Farzad A, Hamisheh Kar H, Rasouli MO. Development of a Novel Niosomal System (Phyto-niosome) for Encapsulation of Grape Stem Extract. *Iran J Biosyst Eng.* 2020;51(1):183-93.
43. Isnani AP, Jufri M. Formulation of niosomal gel containing green tea extract (*Camellia sinensis* L. Kuntze) using thin-layer hydration. *Int J Appl Pharm.* 2017;9:38-43.
44. Jamal M, Imam SS, Aqil M, Amir M, Mir SR, Mujeeb M. Transdermal potential and anti-arthritis efficacy of ursolic acid from niosomal gel systems. *Int Immunopharmacol.* 2015;29(2):361-9.
45. Sabry S, Okda T, Hasan A. Formulation, characterization, and evaluation of the anti-tumor activity of nanosized galangin loaded niosomes on chemically induced hepatocellular carcinoma in rats. *J Drug Deliv Sci Technol.* 2021;61:102163.
46. Singhal T, Mujeeb M, Ahad A, Aqil M, Rahman SO, Najmi AK, et al. Preparation, optimization, and biological evaluation of gymnemic acid loaded niosomes against streptozotocin-nicotinamide induced diabetic-nephropathy in Wistar rats. *J Drug Deliv Sci Technol.* 2019;54:101328.
47. Rahman HS, Othman HH, Hammadi NI, Yeap SK, Amin KM, Samad NA, et al. Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. *Int J Nanomed.* 2020;15:2439.

48. Rezaeirosan A, Saeedi M, Morteza-Semnani K, Akbari J, Gahsemi M, Nokhodchi A. Development of trans-ferulic acid niosome: An optimization and an in-vivo study. *J Drug Deliv Sci Technol.* 2020;59:101854.
49. Kumari S, Goyal A, Garg M. Phytoconstituents Based Novel Nano-Formulations: An Approach. *ECS Trans.* 2022;107(1):7365.
50. Sarangi MK, Padhi S. Novel herbal drug delivery system: An overview. *Arch Med Health Sci.* 2018;6(1):171.