Journal of Recent Advances in Nanomedicine & Nanotechnology

Juniper Publishers key to the Researchers

Review Article
Volume 2 Issue 1 - December 2025

J Recent Adv Nanomed & Nanotech

Nanophytosomes: Advanced Nanocarriers for Enhanced Phytochemical Delivery – A Comprehensive Review

M Niranjan Babu[1], Chandrasekar R[1], Supriya A[1], Aparna A[1], Harshitha B[1], Rohini K[1] Chaitanya Sree PR[2], and Sivagami B[3]*

[1]*Professor, Faculty of Pharmacy, Department of Pharmacognosy, Seven Hills College of Pharmacy, Tirupati, Chittoor, Andhra Pradesh India*

[2]*UG Students, Department of Pharmacognosy, Seven Hills College of Pharmacy, Tirupati, Chittoor, Andhra Pradesh India*

[3]*Associate Professor, Faculty of Pharmacy, Department of Pharmaceutical Analysis, Seven Hills College of Pharmacy, Tirupati, Chittoor, Andhra Pradesh India*

Submission: December 08, 2025; **Published:** December 15, 2025

***Corresponding author:** Sivagami B, Professor, Faculty of Pharmacy, Department of Pharmaceutical Analysis, Seven Hills College of Pharmacy, Tirupati, Chittoor, Andhra Pradesh, India

Abstract

It is widely accepted worldwide that using herbal medicine to treat different kinds of diseases can reduce costs and limit side effects. Synthetic drugs are obtained from the bioactive components that were extracted from the herbal source. The efficacy of any herbal medicine depends on how well the therapeutically active ingredient is delivered at the required dosage. Herbal products have more potential when they are combined with a cutting-edge drug delivery method within a conventional therapeutic paradigm. Because of their poor lipid solubility, inappropriate molecular size, or both, a number of plant extracts and phytoconstituents have little to no in vivo activity, even though they have great bioactivity in vitro. This leads to poor absorption and bioavailability. A comprehensive analysis of the techniques and characterization of nanophytosomes of herbal preparations is presented in this review. Nano technological systems have been developed for use as various types of carrier systems to improve the delivery of bioactive compounds and thus obtain better bioavailability. One such novel approach that enabled in making phytoconstituents more bioavailable is phytosome technology.

Keywords: Nanophytosomes; Phytoconstituents; Characterization; Chromatography; Spectroscopy

Introduction

Plant-derived compounds are becoming more and more well-known as dietary supplements and for their potential medical benefits in treating various diseases. Any drug, whether it be synthetic, derived from an animal, plant, or marine source, must be able to reach its target location quickly enough to cause a pharmacological reaction in order for it to be therapeutically effective. This dose form characteristic is known as bioavailability, biological availability, or physiologic availability [1].

Because phytochemicals have a global impact on a wide range of public health issues, researchers, industries, the general public, and policymakers view them as a new tool for managing public health. Since ancient times, phytomedicines have been an essential source of pharmaceuticals. Phytomedicine has increased in acceptance due to its superior therapeutic efficacy and low risk of adverse drug reactions as compared to allopathic drugs. Phytomedicines exhibit significant in vitro activity but less in vivo efficacy due to their low water solubility, lipophilicity, and incorrect molecular size, resulting in poor absorption and bioavailability. Understanding the biopharmaceutics and pharmacokinetics of phytomedicine might also aid in creating appropriate dosing regimens.

Nanotechnology has advanced to the point that novel substances and processes are being developed to revolutionize the medical and pharmaceutical industries. Several aspects of treatment for illness are already benefiting from the advantages of nanotechnology [2]. Over the last several years, significant progress has been achieved in the development of innovative drug delivery systems (NDDS) for plant actives and extracts.

Bioactive components and plant extracts have been used to develop a number of novel formulations, including polymeric nanoparticles, nano capsules, liposomes, herbosomes, nano

emulsions, microspheres, transferosomes, and ethosomes [3]. Phytosome approach has proved to overcome such issues and become more accessible than conventional herbal extracts due to their enhanced capacity to cross the lipoidal bio membrane and achieve bioavailability [4].

Development of Phytosomes

Active compounds derived from plant sources have been demonstrated to have strong in vitro pharmacological effects but poor in vivo bioavailability. Many active compounds derived from plants have low absorption when supplied orally, which limits their widespread use. The low absorption of these compounds results from the massive multi-ring structures of polyphenols to be absorbed by passive diffusion or non-active absorption, and the poor aqueous or lipid solubility of these compounds prevents them from passing through the outer membrane of gastrointestinal cells. The phospholipid complex approach can be used as a potent drugs delivery technology to increase the therapeutic index by encapsulating plant bioactive components. The complex phytoconstituents have become safer than their original form and can also serve as a better targeting agent to distribute these encapsulating agents at specified areas, therefore presenting viable candidates in several medical fields for improving health aspects. Phytosomes are a compound of natural water-soluble phytoconstituents and natural phospholipids that develop by reacting stoichiometric ratios in a solvent to achieve lipid-compatible molecular complexes and improve their absorption and bioavailability. Phytosomes have a higher bioavailability than typical herbal extracts because they are better absorbed than liposomes. As a result, pyrosomes have been found to provide superior benefits than liposomes in the delivery of herbal products and nutraceuticals [5]. The phytosome technology is a revolutionary paradigm for marked enhancement of bioavailability, significantly greater clinical benefit, guaranteed delivery to the tissues, and without affecting nutritional safety. They have been improved for pharmacokinetic and pharmacological parameters that are advantageous in the treatment of acute diseases as well as in pharmaceutical and cosmetic compositions [6]. Figure 2 Indicates Polyphenols, Flavonoids and Phenolic Compounds.

Preparation of Nanostructured Lipid carrier in Phytosome

In general, fats, phospholipids, and steroids are various forms of lipids found in the body that execute different physiological functions. Among these, phospholipids are key components of the cell membrane, which also functions as a vehicle, thereby enabling the design of drug delivery systems more flexible and appropriate for the body's requirements. Phospholipids are biocompatible and provide a number of benefits, including formulation flexibility and the ability to select different NDDS based on the intended use. Phospholipids are lipids that include phosphorus and have both polar and non-polar components in their structures. These are tiny lipid molecules in which the glycerol is attached to two fatty acids, rather than three as in triglycerides, and the remaining site is occupied by a phosphate group. A cell membrane is made up of various types of phospholipids, including phosphatidyl ethanolamine PE, phosphatidylinositol PI, phosphatidyl-choline PC, phosphatidic acid PA, and phosphatidyl-serine PS. PC has two neutral tail groups and a positive head group with an oxygen atom in the phosphate group, which has a high tendency to gain electrons while nitrogen loses electrons, a unique chemical property that allows PC to be miscible in both water and lipid environments. From an economic perspective, lecithin encompasses PC, PE, PS, PI, and other phospholipids. However, from a historical perspective, lecithin comprises phosphorus-containing lipids derived from brain and egg. However, scientifically, lecithin refers to PC. In herbal formulation investigation, incorporating nano-based formulations has a number of advantages for phytomedicine, including improved solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, stability improvement, increase in tissue macrophage distribution, sustained delivery, protection from physical and chemical degradation, and so on. Thus, nano-phytomedicines have a promising future for increasing activity and resolving issues associated with herbal remedies [6,7]. Figure 1 Depicts the preparation of Phytosomes.

Nano-phytosomes Preparation

In herbal formulation investigation, incorporating nano-based formulations has a number of advantages for phytomedicine, including improved solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity, stability improvement, increase in tissue macrophage distribution, sustained delivery, protection from physical and chemical degradation, and so on. Thus, nano-phytomedicines have a promising future for increasing activity and resolving issues associated with herbal remedies. Figure 2 Represents the preparation of Nanophytosomes by various methods.

Coacervation Technique

This approach incorporates pharmaceuticals without the use of sophisticated equipment or toxic solvents, making it cost-effective for laboratory and industrial applications. It is based on the interaction of a micellar solution of a fatty acid alkaline salt (soap) and an acid solution (coacervating solution) in the presence of several amphiphilic polymeric stabilizing agents: As the coacervating solution and soap solution exchange protons, fatty acid nanoparticles precipitate. A soap micellar solution is the starting point for the preparation of nanoparticles; it is obtained at a temperature higher than the soap's Krafft point, or the point at which the soap dissolves in water. The drug can be dissolved in the micellar solution directly, or it can be pre-dissolved in a small amount of ethanol to improve micellization. Regarding microemulsion templates, micellar solutions' strong solubilizing qualities enable numerous drugs, particularly those that are weakly water-soluble, to be advantageously loaded into nanoparticles [8].

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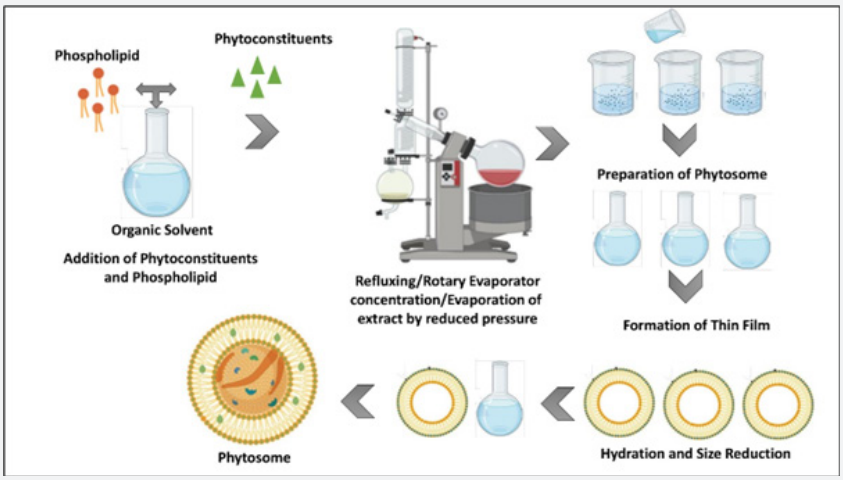

Figure 1: Depicts the preparation of Phytosomes.

Figure 2: Represents the preparation of Nanophytosomes by various methods.

High Pressure Homogenization Method

In this method, the drug is dissolved in a lipid that has been melted at temperatures 5-10 °C higher than its melting point. To prepare pre-emulsion, the drug-containing melt is stirred in a hot aqueous surfactant solution of the same temperature. Then it is driven under high pressure (100-2000 bar) through extremely high shear stress, causing particle disruption down to the nanoscale range. The high-pressure homogenization approach is a highly dependable and effective technology for large-scale synthesis of nanostructured lipid carriers, lipid drug conjugates, Solid Lipid Nanoparticles (SLNS), and parenteral emulsions. However, despite its many benefits and versatility, high-pressure homogenization involves critical process parameters such as high temperatures and high pressures, which can cause significant thermodynamic and mechanical stress in the resulting product: in particular, this method is not suitable for thermo-liable drugs. Suitable alternative strategies for lipid nanoparticle preparation have been extensively explored [9].

Lyophilization Method

Both synthetic and natural phospholipids, as well as phytoconstituents, are dissolved in separate solvents. Next, phospholipid solutions are combined with additional phytoconstituent solution and stirred until complex formation occurs. By lyophilization, the complex that has formed is isolated [10].

Solvent Emulsification Diffusion Technique

Utilizing an oil phase containing polymer and oil in an organic solvent, the method develops an o/w emulsion that is then emulsified with an aqueous phase containing stabilizer in a

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high shear mixer. Water is then added to encourage the organic solvent's diffusion, leading to the formation of the o/w emulsion [11].

Salting-out Technique

This technique is based on the observation that adding an electrolyte causes a non-electrolyte to become less soluble in water. After dissolving the phytoconstituent or standardized extract and phosphotidylcholine in an aprotic solvent (such as acetone or dioxane) and stirring the mixture for the overnight, the complex is separated by precipitating it out of a non-solvent (such as n-hexane) [12].

Solvent Evaporation Method

Phosphatidylcholine, either synthetic or natural, and a phytoconstituent are suspended in the suitable solvent and refluxed for a few hours. Under vacuum, the resulting clear mixture is being evaporated. You can put a certain amount of drug, polymer, and phospholipids into a flask with a spherical bottom and reflux it for two hours at 50–60°C with a particular solvent. To obtain the precipitate, which can be filtered and collected, the mixture can be concentrated to 5–10 ml [13]. Figure 3 Represents the preparation of phytosomes from phospholipids.

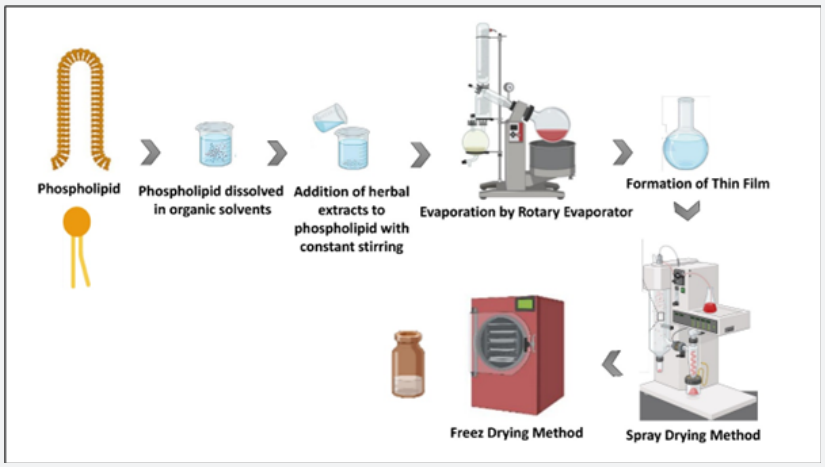

Figure 3: Represents the preparation of phytosomes from phospholipids.

Characterization of Nano-phytosomes

Crystallinity and polymorphism

The phenomenon known as "crystal polymorphism" describes how different forms can be taken by crystals made of the same types of molecules depending on how they are arranged amongst one another. Because of these variances in chemical qualities, including solubility, there may be significant variations in the efficacy of drugs. When preparing tablets, pharmaceutical crystals are occasionally combined with excipients, which no pharmaceutical effect like lactose or cellulose, to hold them together [14].

X-Ray powder diffraction (XRD)

A useful technique for analyzing the microstructure of various amorphous materials as well as crystal materials is X-ray diffraction. The sample is scanned with an X-ray powder diffractometer across an angle range of 6° to 40°. A Ni monochromator will be used to pick the Cu Kα1 radiation, and a step scan model with a current of 30 mA, voltage of 30 kV, and step size of 0.02° will be used to capture the diffraction patterns. The lack of a crystalline peak in phytophospholipid complexes indicates that the components of the complex with phospholipids are either molecular or amorphous. This could explain the finding that phytophospholipid complexes exhibit superior hydrophilicity and lipophilicity in comparison to active ingredients [15].

Differential scanning calorimetry (DSC)

The distinctive peaks of a physical mixture typically differ significantly from those of phytophospholipid complexes. By comparing the transition temperature, the appearance of new peaks, the disappearance of old peaks, melting points, and variations in the area of the relative peak, one can discover interactions in DSC. Under nitrogen flow (60 ml/min), the sample is put in an aluminum crimp cell and heated from 30 to 300 °C at a rate of 10 °C/min [16].

Spectroscopic and Chromatographic Techniques

Fourier transform infrared spectroscopy (FTIR)

Samples were blended into pellets after being mixed 1:100

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with dry crystalline KBR. For every sample, a spectrum is captured in the wavenumber range of 500–4000 cm−1. FTIR is an effective structural analysis technique that produces several functional groups with unique band number, position, shape, and intensity properties. By contrasting the phospholipid complexes' spectra with that of physical mixtures, it is possible to confirm the production of phytophospholipid complexes.

Nuclear Magnetic Resonance (NMR)

H-NMR

An NMR spectrometer was used to examine the phytophospholipid complex sample after it has been dissolved in an appropriate solvent. The acquired spectrum is compared with the drug and combination. 13C-NMR: The 13C-NMR spectrum is obtained in order to verify the complex formation and the drug-phospholipid interaction. After dissolving the phyto-phospholipid complex sample in an appropriate solvent, the NMR spectrometer is used to evaluate it. It is possible to compare the acquired spectra for the drug and complex.

High-performance thin layer chromatography (HPTLC)

Using a Hamilton syringe, a standard solution of phytophospholipid complex is applied in triplicate to an HPTLC plate. The plates were developed in an appropriate solvent system at a temperature of 25 ± 2 °C and a relative humidity of 40% until the desired distance was reached. The plates are dried and scanned after development. Using winCATS software, the peak areas are identified, Rf values are noted, and the plain and complex drug comparisons are made [17].

Zeta-potential and vesicle size

The Zeta potential (ZP) and mean Particle Size (PS) of the phytosomal formulation can be determined using the Dynamic Light Scattering (DLS) method. At a detection angle of 173°, this device uses a non-destructive backscattering approach to quantify the particle size. Particle size and zeta potential are important properties of complexes related to stability and reproducibility. In general, the average phospholipid complex particle size ranged from 50 nm to 100 µm [18].

Complexation efficiency

Drugs containing phospholipids have their complexing efficiency assessed indirectly. The phyto phospholipid complex sample was vigorously vortexed and dispersed in deionized water. The free, uncomplicated drugs will eventually become insoluble in water due to the solubility difference. The remaining unreacted drug is separated using slow centrifugation, diluted in ethanol, and then measured using spectrophotometry in comparison to phospholipid as the blank solution. (m2/m1) × 100 = [(m1–m3) / m1] × 100 is the complexation rate (%). where m1 represents the total amount of drug added, m2 the amount of drug contained in a complex, and m3 the amount of drug that is free [19].

Determination of partition coefficient (log p) value

Each phytosome sample is combined with octanol and shaken in a water bath at 25 °C and 100 rpm for a 24 h in sealed glass containers. After adding the potassium dihydrogen phosphate (pH 6.8) aqueous phase to the n octanol solutions, the mixture was agitated for a further twenty-four hours at 25 °C and 100 rpm. Following their separation, the water phase and n-octanol phase are centrifuged for 15 minutes at 10,000 rpm. A membrane filter (0.45 µm) filters out the water and n-octanol phases. The filtrates were suitably diluted with ethanol, and spectrophotometry was used to measure the number of phytosomes. Using the following formula, log P values of the free drug and phyto-phospholipid complex are determined: Co/Cw is the partition coefficient. Where Co-Concentration in the oil phase, Cw- Concentration in the water phase [20].

Solubility complexes studies

Compared to phytoconstituents, the phyto-phospholipid has superior lipophilicity and hydrophilicity, and it usually shows better lipophilicity. Glass vials with the required quantity of phyto-phospholipid are filled with distilled water and various vehicles, sealed, and subjected to a 24-hour shaking water bath at 25 °C and 100 rpm. Following a 24-hour equilibrium period at 25°C, the samples underwent a 10-minute centrifugation at 10,000 rpm, and the resulting supernatant was filtered through millipore filters (0.45 µm). UV spectrophotometry is used to examine the filtrates, with the appropriate suitable medium serving as a blank [21].

In-vitro release study

Phytosomal formulation's in-vitro release profiles can be studied with a dialysis bag method. Aliquots of phytosomes with a molecular weight cutoff of 12-14 KDA are placed into a sealed dialysis bag. The dialysis bags are placed in a shaking water bath at 37 °C and 75 rpm, and they are submerged in the release medium, which is buffer saline with a pH of 6.8 and 0.25% (w/v) 80 to provide sink conditions. At various intervals, release medium samples are removed, and the same volume of fresh release medium is used as compensation. After passing through a 0.45 millipore filter, the samples were subjected to spectrophotometric measurements using the fresh release media as a blank [22].

Release kinetics

To gain a better understanding of the process of drug release from phytosomes, the concentration data from the in-vitro release study can be fitted using the DD-solver excel sheet program to typical kinetics release models (Zero-order, First order, Higuchi, and Korsmeyer Peppas models) [23].

Drug content

To obtain 2 µg/ml, the phytosome is dissolved in methanol and then measured using spectrophotometry. To make 2 µg/

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ml solutions, prepare the blank by mixing phospholipid and methanol and then diluting it. This solution serves as a blank. For the optimized batch, the drug content is computed as follows: Drug-loading content (%) is equal to the sum of the NPS's drug content /100 [24].

Stability study

The phyto phospholipid complex's short-term chemical stability can be tested for three months at 30 ± 2 °C and 65 ± 5% relative humidity. For three months, the complex samples should be examined every thirty days, and the in-vitro permeation should be compared. ANOVA is used to statistically examine and validate these data [25].

Drug entrapment efficiency

Using a cooling centrifuge machine, phytosomes are diluted one-fold with 10 ml of solvent and centrifuged at 18,000 rpm for 30 min at -4 °C. UV spectroscopy can be used to measure the amount of free active ingredient in the separated supernatant liquid. Fuel can be mixed with 0.1 ml of the phytosome-loaded suspension to make 10 ml, which can be used to measure the total amount of active ingredient. The following formula can be used to calculate the entrapment efficiency. Entrapment efficiency (%) is calculated as follows: total drug amount - amount of free drug × 100 / total drug amount [26].

Visualization Techniques

Scanning electron microscopy (SEM)

The phytophospholipid's surface appearance and particle size distribution can be verified with scanning electron microscopy. Place the dried sample in an ion sputter on a brass stub for an electron microscope that has been coated with gold. The phytosome loaded can be digitally photographed by scanning the stub at random magnifications of 1000, 5000, 10,000, and 30,000 X.

Transmission electron microscopy (TEM)

Using TEM, a chosen phytosome is examined morphologically. After dilution with 1:20 distilled water, sonicate the sample for 5 minutes. A droplet containing the drug-loaded phytosome dispersion is applied on a copper grid coated with carbon and allowed to develop a thin layer. After applying 2% (w/w) ammonium molybdate as a negative stain and removing any remaining stain with filter paper, the film will be allowed to air dry. After that, the dyed films were examined under a TEM.

In-vivo evaluation

With the use of appropriate animal models, in-vivo assessments can be carried out in accordance with the therapeutic activity measurement parameters of the physiologically active phytoconstituents included in the loaded phytosomes (Table 1).

Table 1: Specifies the plant species, methodology, activity and characterization of some phytoconstituents.

Plant name	Phytoconstituents	Methodology	Activity	Characterization
Andrographis paniculata	Andrographolide AG-loaded phytosomes	l-α-phosphatidylcholine (PC):AG1:2.7 for AG: PC	Antiproliferative activity of AG-PTMs was investigated against the liver cancer cell line HepG2	[27]
Andrographis paniculata	Nanophytosomes		Hepatoprotective, alcohol-induced hepatotoxicity	[28]
Andrographis paniculata	Nanophytosomes			1H NMR, DSC, and FTIR PXRD and SEM [29]
Mucuna prureins	Nanophytosomes		In vivo antidepressant activity	PXRD SEM1H NMR, DSC, and FTIR [30].
Vitamin D3	Vitamin D3/ lecithin		Antioxidant activity, Fickian diffusion mechanism	Scanning calorimetry, morphology, stability, (FTIR), antioxidant activity, moisture content, solubility, and in vitro release kinetics [31].
Juniperus polycarpos fruit extract	Nanophytosome-loaded high phenolic fraction		Antiproliferation effects against breast cancer in mice model	Anticancer, pro-apoptotic, and antioxidative activities [32].
Flavonoid compound	Nano-phytosome myricetin formulation	thin-sonication hydration method solvents using ethanol and acetone	Myricetin: phosphatidylcholine: cholesterol ratio (1: 1: 0.4)	Particle size, polydisperse index, zeta potential, absorption efficiency and antioxidant activity, and TEM test [33].
Aloe vera whole extract	l-carnosine, an endogenous dipeptide		l-carnosine/A. vera (25:1) combination ratio	Reactive dicarbonyl's impaired angiogenic effects free radical scavenging potency nitric oxide synthesizing capacity [34].

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Codium tomentosum Sambucus nigra L.	Elderberry anthocyanin-enriched extract	SC-Nanophytosomes	Neurodegenerative diseases	Ex vivo assays [35]
Phycocyanin	Lipid-based nano-carriers	Phosphatidylcholine (PC)	Total phenolic content	Entrapment efficiency (EE), particle size, poly-dispersity index (PDI) [36]
Gymnema inodorum	Phenolic acids, flavonoids and triterpene	Macrophages and adipocytes	Anti-inflammatory and anti-insulin-resistant activities	T2DM [37]
Rutin, a phenolic antioxidant bioflavonoid	Rutin-loaded nanophytosomal formulation	Phosphatidylcholine (PC) and cholesterol by thin layer hydration method Rutin: PC molar ratio of 1:2	Superoxide radical antioxidant property	FTIR, DSC [38].
Cuscuta reflexa	Phosphatidyl choline HECR-soya lecithin complex	Soya lecithin (1:1-1:3 percent w/v)		PDI, zeta potential, entrapment efficiency, FTIR, DSC, TEM, and in vitro release [39].
Silver nanoparticles (AgNPs) using rutin	CT-DNA and HS-DNA was studied spectrophotometrically	DPPH assay, highest radical scavenging activity	Antibacterial activity was evaluated by the standard well-diffusion method against Ecoli and Saureus, and cytotoxicity was assessed against human WBCs by MTT assay	UV–visible spectroscopy FESEM and zeta sizer analysis XRD and AFM, FTIR. [40]
Zataria multiflora	Nanoemulsions, nanoparticles and nanophytosome		Antioxidant and antimicrobial activities	FTIR, field emission SEM, confocal laser scanning microscopy, optical microscope and antioxidant activity, MIC Listeria monocytogenes [41]
Zataria Multiflora Essential Oil (ZEO)	Loaded into chitosan (CS) nanoparticles	Prepared in aqueous solution by mild emulsification into nanometric particles	Proliferation inhibition rate of Breast cancer cells as confirmed by MTT	FTIR [42]
CEO-loaded nanophytosomes (NP)	CEO to phosphatidylcholine (PC)	Thin layer hydration technique		Polydispersity index (PDI), encapsulation efficiency (EE), CEO-PC ionic interactions, antioxidant activity, turbidity, stability and release behavior were investigated [43].
Encapsulation of garlic essential oil (GEO) in nanophytosomes			Antioxidant activity, physical stability and antibacterial effects against food-borne pathogens i.e. Escherichia coli and Staphylococcus aureus were investigated	Dynamic light scattering (DLS), Fourier transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM) [44]
Hesperidin and hesperetin		Phospholipon 90G with a 2:1 or 3:1 molar ratio		XRD, FTIR, NMR [45]
Bergamot essential oil	Loaded nano-phytosomes (NPs) with spironolactone (SP)	Thin-film hydration	Acne vulgaris	Entrapment efficiency percent (EE%), particle size (PS), polydispersity index (PDI), and zeta potential (ZP) [46].
Curcumin-decorated nanophytosomes			Antimicrobial activities A. actinomycetemcomitans	Photo-sonosensitizer, its particle size, polydispersity, ζ-potential surface morphology, physical stability, drug release, and entrapment efficiency [47].
Stachys pilifera Benth's	Encapsulated into liposomes using bile duct ligation-(BDL-) induced hepatic cholestasis in rats	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), malondialdehyde (MDA), total thiol (T-SH) content,	Protein carbonyl (PCO), total bilirubin (TBIL), albumin (ALB), and nitric oxide (NO) metabolite levels were measured in either liver tissue or plasma to assess liver damage.	Anticholestatic potential [48].
Casuarina equestifolia extract	Phytosome	Antisolvent precipitation method	Antidiabetic and antihyperlipidemic activity	Entrapment efficiency Zeta potential. [49].
Euglena gracilis (EG)	β-1,3-glucan (BG)	solvent evaporation method	lipid phosphatidylcholine	FTIR, XRD, SEM, TEM [50].

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Conclusion

Any disease can be treated with greater efficacy and safely by developing novel drugs or by making better use of currently available ones. One of the most significant methods for boosting the bioavailability of herbal products is the phyto-phospholipid complexation approach. It provides appropriate lipid membrane permeability at larger doses and addresses the challenges of sustained therapeutic levels in plasma with a slower rate of elimination. This multidisciplinary project is producing enhanced nanosized herbal remedies as prospective phytopharmaceuticals that will benefit public health by combining traditional medicinal products with state-of-the-art, novel drug delivery methods.

Competing Interests

Authors have declared that no competing interests exist.

Acknowledgements

Authors express their sincere gratitude to Seven Hills College of Pharmacy, Tirupati, for continuous motivation, support, and guidance.

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How to cite this article: M Niranjan Babu, Chandrasekar R, Supriya A, Aparna A, Harshitha B, et al. Nanophytosomes: Advanced Nanocarriers for Enhanced Phytochemical Delivery – A Comprehensive Review. J Recent Adv Nanomed & Nanotech. 2025; 2(1): 555576.

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