Journal of Molecular Science

Journal of Molecular Science
Volume 36 Issue 2, Year of Publication 2026, Page 622-640
DoI-10.004687/1000-9035.2026.073

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Phytosomes-Based Herbal Nanocarriers for Diabetes Mellitus (DM): Advances in Formulations Strategies, Phytochemical Standardization, Preclinical and Clinical Translation: A Review

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Article Information
Received: 04-06-2026
Revised: 18-06-2026
Accepted: 13-07-2026
Published: 29-07-2026

Keywords
Phytosomes; diabetes mellitus; formulations; clinical; preclinical and nanocarriers.

ABSTRACT

Background: Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or both. Despite the availability of several synthetic antidiabetic agents, long-term therapy is often associated with adverse effects, poor patient compliance, and limited efficacy in preventing disease progression. Herbal phytochemicals possess significant antidiabetic potential through multiple mechanisms; however, their clinical application is hindered by poor aqueous solubility, low bioavailability, rapid metabolism, and limited intestinal absorption. Phytosome-based nanocarriers have emerged as a promising strategy to overcome these limitations by enhancing the physicochemical and pharmacokinetic properties of herbal bioactives. **Objective:** This review comprehensively summarizes recent advances in phytosome-based herbal nanocarriers for diabetes mellitus, emphasizing formulation strategies, phytochemical standardization, characterization techniques, molecular mechanisms of antidiabetic action, and progress from preclinical investigations to clinical translation. **Methods:** A comprehensive literature survey was conducted using major electronic databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Peer-reviewed studies published primarily during the last decade were critically evaluated, focusing on phytosome formulation approaches, quality control and standardization, physicochemical characterization, in vitro and in vivo antidiabetic efficacy, pharmacokinetic enhancement, safety assessment, and available clinical evidence. **Results:** Current evidence demonstrates that phytosomal delivery systems significantly improve the solubility, stability, permeability, and oral bioavailability of diverse antidiabetic phytoconstituents, leading to enhanced glycemic control, antioxidant activity, anti-inflammatory effects, β-cell protection, and improved insulin sensitivity in experimental diabetic models. Standardization of phytochemical content and optimization of formulation parameters further contribute to improved therapeutic reproducibility and product quality. Although preclinical findings are highly encouraging, clinical evidence remains limited due to insufficient large-scale randomized controlled trials and regulatory challenges. **Conclusion:** Phytosome-based herbal nanocarriers represent a promising next-generation platform for improving the therapeutic efficacy of herbal antidiabetic agents. Future research should prioritize robust phytochemical standardization, scalable manufacturing processes, comprehensive safety evaluation, regulatory harmonization, and well-designed multicenter clinical trials to facilitate successful clinical translation and commercialization.

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1. INTRODUCTION:

1.1 Global Burden and Pathophysiology of Diabetes Mellitus:

Diabetes mellitus (DM) is one of the most prevalent chronic metabolic disorders worldwide and represents a major public health challenge due to its increasing incidence, high mortality, and substantial socioeconomic burden. It is characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin action, or a combination of both, leading to disturbances in carbohydrate, lipid, and protein metabolism [1]. The International Diabetes Federation estimates that hundreds of millions of individuals are currently living with diabetes, with the prevalence expected to rise considerably over the coming decades owing to population aging, urbanization, sedentary lifestyles, obesity, and unhealthy dietary habits. Type 2 diabetes mellitus (T2DM) accounts for approximately 90-95% of all diabetes cases, whereas Type 1 diabetes mellitus (T1DM) results from autoimmune destruction of pancreatic β-cells, causing absolute insulin deficiency. Gestational diabetes mellitus (GDM) and other specific forms of diabetes further contribute to the global disease burden [2-3].

The pathophysiology of diabetes is multifactorial and involves complex interactions among genetic predisposition, environmental factors, oxidative stress, chronic inflammation, mitochondrial dysfunction, and metabolic abnormalities. In T2DM, insulin resistance in peripheral tissues such as skeletal muscle, liver, and adipose tissue initially develops, followed by progressive pancreatic β-cell dysfunction and impaired insulin secretion [4]. Chronic hyperglycemia promotes excessive production of reactive oxygen species (ROS), activation of inflammatory signaling pathways, formation of advanced glycation end products (AGEs), and endothelial dysfunction, ultimately leading to microvascular and macrovascular complications. These include diabetic nephropathy, retinopathy, neuropathy, cardiovascular disease, and impaired wound healing, significantly reducing quality of life and increasing healthcare costs. Therefore, developing effective therapeutic approaches that target multiple pathogenic pathways has become a major priority in diabetes management [5].

1.2 Limitations of Conventional Antidiabetic Therapy

Over the past several decades, numerous pharmacological agents have been introduced for diabetes management, including metformin, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin preparations. These medications effectively improve glycemic control and reduce the risk of diabetes-associated complications. Nevertheless, conventional therapies possess several limitations that restrict their long-term clinical success [6].

Many antidiabetic drugs are associated with adverse effects such as hypoglycemia, gastrointestinal disturbances, weight gain, fluid retention, hepatotoxicity, nephrotoxicity, and cardiovascular concerns. Furthermore, monotherapy frequently becomes insufficient because of progressive β-cell deterioration, necessitating combination therapy or insulin administration. Long-term treatment also presents challenges related to poor patient adherence, high treatment costs, and variable therapeutic responses among individuals. Importantly, many currently available drugs primarily focus on controlling blood glucose rather than addressing the underlying molecular mechanisms of oxidative stress, inflammation, and β-cell degeneration. Consequently, increasing attention has been directed toward alternative therapeutic approaches capable of simultaneously modulating multiple pathological pathways while minimizing adverse effects [7-8].

1.3 Herbal Medicines in Diabetes Management

Medicinal plants have been used for centuries in traditional healthcare systems such as Ayurveda, Traditional Chinese Medicine, Unani, and other indigenous medical practices for the prevention and treatment of diabetes. Numerous medicinal plants contain bioactive phytochemicals, including flavonoids, polyphenols, alkaloids, terpenoids, saponins, tannins, glycosides, and phenolic acids, which exhibit potent antihyperglycemic, antioxidant, anti-inflammatory, lipid-lowering, and insulin-sensitizing activities [9]. These phytoconstituents regulate glucose homeostasis through diverse mechanisms, including stimulation of insulin secretion, enhancement of insulin receptor signaling, inhibition of α-amylase and α-glucosidase enzymes, suppression of hepatic gluconeogenesis, improvement of peripheral glucose uptake, reduction of oxidative stress, and protection of pancreatic β-cells [10].

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Despite their promising pharmacological properties, the clinical application of herbal medicines remains limited by several biopharmaceutical challenges. Most phytochemicals exhibit poor aqueous solubility, low membrane permeability, chemical instability, rapid metabolism, limited gastrointestinal absorption, and extensive first-pass metabolism, resulting in poor oral bioavailability and inconsistent therapeutic outcomes [11]. In addition, variability in phytochemical composition due to differences in plant species, geographical origin, harvesting conditions, extraction procedures, and formulation methods complicates quality assurance and clinical reproducibility. Therefore, innovative delivery systems capable of improving the stability, absorption, and therapeutic performance of herbal bioactives are essential for translating their potential into effective clinical therapies [12].

1.4 Phytosomes as an Emerging Herbal Nanocarrier Platform

Nanotechnology-based drug delivery systems have transformed pharmaceutical research by enhancing the delivery efficiency of poorly bioavailable therapeutic compounds. Among various lipid-based nanocarriers, phytosomes have emerged as a highly promising platform for improving the clinical performance of herbal medicines. A phytosome is a molecular complex formed through the interaction of standardized plant phytoconstituents with phospholipids, particularly phosphatidylcholine, resulting in enhanced compatibility with biological membranes and improved oral absorption [13]. Unlike conventional herbal extracts or liposomes, phytosomes involve the formation of stable molecular complexes in which the phytochemical is chemically associated with phospholipid molecules, leading to greater physicochemical stability and superior bioavailability. This unique structural arrangement enhances aqueous dispersibility, membrane permeability, gastrointestinal absorption, and systemic circulation while protecting phytochemicals from enzymatic degradation and premature metabolism. Consequently, phytosomal formulations have demonstrated improved pharmacokinetic profiles, sustained drug release, enhanced tissue distribution, and greater therapeutic efficacy [14].

Several phytosome-based formulations containing curcumin, quercetin, berberine, silymarin, resveratrol, naringenin, epigallocatechin gallate, and other bioactive phytochemicals have shown significant antidiabetic activity in experimental studies. These formulations effectively reduce oxidative stress and inflammation, improve insulin sensitivity, preserve pancreatic β-cell function, and ameliorate diabetes-associated complications. Furthermore, advances in formulation technologies, quality-by-design approaches, phytochemical standardization, and large-scale manufacturing are facilitating the translation of phytosome-based herbal medicines from laboratory research toward clinical application [15-16].

1.5 Scope and Objectives of the Review

Considering the growing global burden of diabetes and the increasing interest in plant-derived therapeutics, phytosome technology represents a promising strategy for overcoming the major limitations associated with conventional herbal formulations. This review comprehensively summarizes recent advances in phytosome-based herbal nanocarriers for diabetes mellitus, with particular emphasis on formulation strategies, phospholipid complexation techniques, physicochemical characterization, phytochemical standardization, and quality control[16-17]. Furthermore, the review discusses the molecular mechanisms underlying the antidiabetic effects of phytosomal formulations, including their antioxidant, anti-inflammatory, insulin-sensitizing, and β-cell protective activities. Current evidence from in vitro studies, animal models, and available clinical investigations is critically evaluated to assess their therapeutic potential and translational value. Finally, regulatory considerations, manufacturing challenges, safety aspects, and future research directions are highlighted to provide a comprehensive perspective on the development of phytosome-based herbal nanocarriers as next-generation therapeutic systems for diabetes mellitus [18].

2. PHYTOSOMES: Fundamentals And Pharmaceutical Characteristics

2.1 Definition and Historical Development

Phytosomes are advanced lipid-based nanocarrier systems designed to enhance the delivery and therapeutic efficacy of plant-derived bioactive compounds. The term "phytosome" is derived from the Greek word *phyto* (plant) and *some* (cell-like structure), referring to a molecular complex formed between a standardized phytochemical or herbal extract and a phospholipid, typically phosphatidylcholine. Unlike conventional herbal extracts, where phytoconstituents remain physically dispersed, phytosomes involve the formation of stable molecular complexes through specific intermolecular interactions, resulting in improved physicochemical stability, membrane permeability, and oral bioavailability [19].

The concept of phytosome technology was pioneered during the late twentieth century by the Italian pharmaceutical company Indena S.p.A.,

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which patented several phospholipid-based herbal formulations to improve the therapeutic performance of poorly bioavailable phytochemicals. Since its introduction, phytosome technology has gained considerable attention in pharmaceutical research because it effectively addresses the major limitations associated with herbal medicines, including poor aqueous solubility, rapid metabolism, low gastrointestinal absorption, and extensive first-pass metabolism [20]. Initially developed for hepatoprotective phytochemicals such as silymarin, the technology has subsequently been extended to numerous herbal bioactives, including curcumin, quercetin, berberine, resveratrol, epigallocatechin gallate, naringenin, and other polyphenolic compounds. Today, phytosomes are widely recognized as one of the most promising lipid-based nanocarrier platforms for improving the clinical translation of herbal therapeutics, particularly in chronic diseases such as diabetes mellitus [21].

2.2 Composition and Structural Organization

Phytosomes are primarily composed of two essential components: a standardized herbal extract or purified phytochemical and a phospholipid carrier. Phosphatidylcholine is the most commonly employed phospholipid because of its excellent biocompatibility, amphiphilic nature, and ability to interact with both hydrophilic and lipophilic molecules. Other phospholipids, including phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol, may also be utilized depending on the physicochemical properties of the active compound [22]. The structural organization of phytosomes differs fundamentally from that of conventional liposomes. In liposomes, bioactive compounds are merely encapsulated within an aqueous core or phospholipid bilayer through physical entrapment. In contrast, phytosomes consist of a molecular complex in which the polar functional groups of phytochemicals, such as hydroxyl, carboxyl, or carbonyl groups, form hydrogen bonds with the polar head group of phospholipids. The hydrophobic fatty acid chains of phospholipids orient outward, creating a lipid-compatible outer surface that facilitates interaction with biological membranes [23].

This unique molecular architecture substantially enhances membrane affinity and cellular uptake while protecting phytoconstituents against hydrolysis, oxidation, enzymatic degradation, and environmental stress. Furthermore, the amphiphilic characteristics of phytosomes improve both aqueous dispersibility and lipid solubility, enabling efficient absorption across gastrointestinal membranes. The stability and performance of phytosomes are influenced by factors such as phospholipid type, phytochemical-to-phospholipid ratio, preparation method, solvent system, particle size, surface charge, and storage conditions [24].

2.3 Mechanism of Phytosome Formation

The formation of phytosomes is based on the molecular interaction between phytoconstituents and phospholipids rather than simple physical encapsulation. During preparation, phytochemicals are dissolved together with phospholipids in an appropriate organic solvent under controlled temperature and stirring conditions. As solvent removal proceeds, strong intermolecular interactions occur between the active phytochemical and phospholipid molecules, resulting in the formation of a stable phytosome complex [25]. Hydrogen bonding represents the principal mechanism responsible for phytosome formation. Polar functional groups present in flavonoids, polyphenols, tannins, and phenolic acids interact with the phosphate and ammonium groups of phosphatidylcholine. In addition to hydrogen bonding, electrostatic interactions, van der Waals forces, and hydrophobic interactions further stabilize the complex. The resulting molecular assembly exhibits improved compatibility with lipid membranes, facilitating enhanced transcellular transport across intestinal epithelial cells [26].

Several preparation techniques have been employed to produce phytosomes, including solvent evaporation, anti-solvent precipitation, thin-film hydration, reflux methods, freeze-drying, spray drying, and supercritical fluid technology. Process variables such as solvent selection, reaction temperature, phospholipid concentration, mixing duration, and drying conditions significantly influence complexation efficiency, particle size distribution, zeta potential, encapsulation efficiency, and long-term stability. Appropriate optimization of these formulation parameters is essential to obtain reproducible phytosomal formulations with superior pharmaceutical performance [27].

2.4 Advantages over Conventional Herbal Formulations

Conventional herbal formulations often exhibit poor therapeutic performance because many phytochemicals possess unfavorable physicochemical characteristics, including low aqueous solubility, poor membrane permeability, instability in gastrointestinal fluids, rapid enzymatic degradation, and extensive hepatic metabolism. Consequently, only a small proportion of the administered dose reaches systemic circulation, resulting in inconsistent pharmacological responses [28]. Phytosome technology effectively addresses these limitations by significantly improving the absorption and systemic availability of herbal bioactives. The phospholipid complex enhances

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lipid membrane affinity, allowing efficient transport across intestinal epithelial cells and increasing oral bioavailability. Furthermore, phytosomes protect phytochemicals against oxidation, hydrolysis, and enzymatic degradation during gastrointestinal transit, thereby preserving their biological activity [29].

Another major advantage is the ability of phytosomes to achieve higher therapeutic efficacy at lower doses compared with conventional herbal extracts. Enhanced bioavailability reduces dose requirements, minimizes dosing frequency, and improves patient compliance. Phytosomes also exhibit greater physicochemical stability, prolonged circulation time, improved tissue distribution, and controlled release characteristics [30]. These features contribute to enhanced antioxidant, anti-inflammatory, antihyperglycemic, and cytoprotective activities observed in numerous experimental studies. Compared with other nanocarrier systems such as liposomes, nanoemulsions, polymeric nanoparticles, and solid lipid nanoparticles, phytosomes possess relatively simple manufacturing procedures, high loading efficiency for polyphenolic compounds, lower production costs, excellent biocompatibility, and greater suitability for oral delivery. These advantages make phytosomes an attractive pharmaceutical platform for herbal drug development and commercialization [31].

2.5 Pharmacokinetic and Biopharmaceutical Benefits

One of the principal advantages of phytosome technology lies in its ability to improve the pharmacokinetic behavior of poorly bioavailable phytochemicals. The phospholipid complex enhances dissolution, intestinal permeability, and membrane diffusion, leading to increased gastrointestinal absorption and greater systemic exposure. Improved pharmacokinetic parameters, including maximum plasma concentration (Cmax), area under the plasma concentration-time curve (AUC), and bioavailability, have been consistently reported for numerous phytosomal formulations [32]. The lipid-compatible surface of phytosomes promotes efficient transport across biological membranes while simultaneously reducing degradation by digestive enzymes and minimizing first-pass hepatic metabolism. Consequently, a larger proportion of the administered phytochemical reaches systemic circulation in its active form, thereby enhancing therapeutic efficacy. Improved pharmacokinetic performance also contributes to prolonged plasma residence time, sustained drug release, enhanced tissue distribution, and reduced interindividual variability in therapeutic response [33].

From a biopharmaceutical perspective, phytosomes improve aqueous dispersibility, dissolution rate, permeability, and overall absorption without altering the intrinsic pharmacological activity of the phytochemical. Enhanced delivery enables effective modulation of multiple molecular pathways involved in diabetes pathogenesis, including oxidative stress, chronic inflammation, insulin resistance, glucose transporter regulation, and pancreatic β-cell dysfunction. Experimental studies have demonstrated that phytosomal formulations of curcumin, quercetin, berberine, resveratrol, and other phytochemicals produce significantly greater antihyperglycemic, antioxidant, anti-inflammatory, and organ-protective effects than their corresponding conventional extracts [34-35].

Collectively, these pharmacokinetic and biopharmaceutical advantages position phytosomes as a highly promising nanocarrier platform for improving the therapeutic potential of herbal medicines and accelerating their successful translation from laboratory research to clinical practice in diabetes management[35].

3. Formulation Strategies For Herbal Phytosomes

The successful development of phytosome-based herbal nanocarriers depends on the rational design and optimization of formulation strategies that ensure maximum therapeutic efficacy, stability, and reproducibility. Unlike conventional herbal formulations, phytosomes require the formation of stable molecular complexes between phytochemicals and phospholipids to improve solubility, membrane permeability, and oral bioavailability. The selection of suitable medicinal plants, standardized phytochemical extracts, phospholipids, and auxiliary excipients plays a crucial role in determining the physicochemical and biopharmaceutical properties of the final formulation [36]. Furthermore, preparation techniques and process parameters significantly influence particle size, encapsulation efficiency, zeta potential, drug loading, and long-term stability. Recent advances in pharmaceutical development, including Design of Experiments (DoE), Quality by Design (QbD), and artificial intelligence (AI)-assisted optimization, have enabled the systematic development of robust and scalable phytosomal formulations. In addition, careful consideration of manufacturing processes, quality control, and storage conditions is essential to ensure batch-to-batch consistency and facilitate successful clinical translation and commercialization. This section discusses the key formulation strategies involved in the development of herbal phytosomes, highlighting critical factors that influence their quality, performance, and therapeutic potential in the

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management of diabetes mellitus [37].

3.1 Selection of Medicinal Plants and Bioactive Phytochemicals

The selection of medicinal plants and phytochemicals is the first and most critical step in phytosome formulation. Plants should possess well-established antidiabetic activity supported by ethnopharmacological evidence and preclinical or clinical studies. Bioactive constituents such as flavonoids, polyphenols, alkaloids, terpenoids, saponins, and phenolic acids are preferred because of their antioxidant, anti-inflammatory, insulin-sensitizing, and β-cell protective properties. Commonly investigated phytochemicals include curcumin, quercetin, berberine, resveratrol, epigallocatechin gallate (EGCG), naringenin, silymarin, and rutin. Selection criteria also include aqueous solubility, chemical stability, molecular weight, therapeutic dose, toxicity profile, and compatibility with phospholipids. Standardization of plant extracts based on marker compounds is essential to ensure batch-to-batch consistency, reproducibility, and therapeutic efficacy [38-39].

3.2 Selection of Phospholipids and Auxiliary Excipients

Phospholipids are the key structural components of phytosomes because they form stable molecular complexes with phytochemicals. Phosphatidylcholine is the most commonly used phospholipid owing to its excellent biocompatibility, amphiphilic nature, and ability to enhance membrane permeability. Other phospholipids, including phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol, may also be employed depending on formulation requirements. Auxiliary excipients such as cholesterol, stabilizers, surfactants, cryoprotectants, and antioxidants are incorporated to improve stability, particle size distribution, encapsulation efficiency, and shelf life. The selection of pharmaceutical-grade excipients is essential for ensuring safety, quality, and regulatory compliance [40].

3.3 Preparation Techniques

Several preparation methods have been developed for phytosome production, each influencing the physicochemical characteristics of the final formulation. The solvent evaporation method remains the most widely used due to its simplicity and high complexation efficiency. Other techniques include thin-film hydration, reflux method, anti-solvent precipitation, freeze-drying, spray drying, and supercritical fluid technology. Process variables such as solvent type, phospholipid-to-phytochemical ratio, reaction temperature, mixing speed, and drying conditions significantly affect particle size, zeta potential, entrapment efficiency, and long-term stability (**Fig. 1**). Appropriate selection and optimization of the preparation method are therefore essential for producing reproducible and high-quality phytosomal formulations [41].

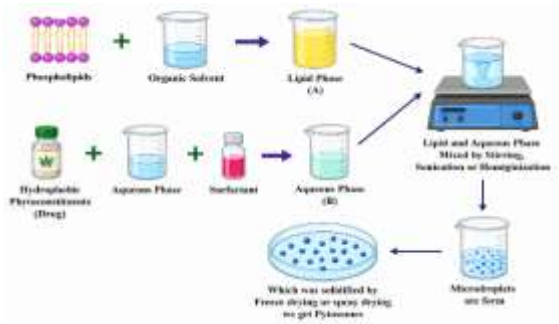

Figure 1: Schematic representation of the preparation of phytosomes using lipid and aqueous phases, followed by stirring, sonication or homogenization to form microdroplets and subsequent solidification by freeze-drying or spray-drying.

3.4 Optimization Approaches (DoE, QbD, AI-Based Optimization)

Modern pharmaceutical development emphasizes systematic optimization to achieve robust and reproducible formulations. Design of Experiments (DoE) enables simultaneous evaluation of multiple formulation and process variables while identifying their interactions and optimal operating conditions. Quality by Design (QbD) provides a risk-based framework that begins with defining the Quality Target Product Profile (QTPP), identifying Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs), followed by establishment of a design space for consistent product quality. More recently, artificial intelligence (AI) and machine learning algorithms have been employed to predict formulation performance, optimize processing conditions, reduce experimental workload, and accelerate formulation development. These advanced strategies improve manufacturing efficiency, reduce costs, and facilitate regulatory acceptance [42-43].

3.5 Scale-Up and Manufacturing Considerations

Successful clinical translation of phytosomal formulations requires scalable, reproducible, and economically feasible manufacturing processes. During scale-up, laboratory parameters must be carefully adapted to industrial production without altering product quality or therapeutic performance. Factors such as solvent recovery, process reproducibility, mixing efficiency, drying technology, equipment selection, batch uniformity, and compliance with Good Manufacturing Practice (GMP) standards must be considered. Standardized production protocols and validated analytical

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methods are essential for maintaining consistent product quality at commercial scale [44].

3.6 Stability and Storage Challenges

The stability of phytosomal formulations is a major determinant of their pharmaceutical quality and clinical performance. Phospholipids are susceptible to oxidation and hydrolysis, while phytochemicals may undergo degradation upon exposure to moisture, oxygen, heat, and light. Such degradation can alter particle size, zeta potential, encapsulation efficiency, and therapeutic efficacy. Therefore, stability studies should be performed under International Council for Harmonisation (ICH) guidelines to evaluate physical, chemical, and microbiological stability throughout the product's shelf life. Appropriate packaging materials, moisture-resistant containers, inert atmospheric conditions, antioxidants, and controlled storage temperatures can significantly improve formulation stability. Comprehensive stability evaluation is essential to ensure product safety, efficacy, and successful commercialization of phytosome-based herbal nanocarriers [45].

4. Phytochemical Standardization And Quality Control

The therapeutic efficacy and reproducibility of phytosome-based herbal formulations largely depend on the quality, consistency, and standardization of the herbal extracts used during formulation. Variations in plant source, cultivation conditions, harvesting time, extraction methods, and storage can significantly influence the phytochemical composition and biological activity of herbal products. Therefore, comprehensive phytochemical standardization and rigorous quality control are essential to ensure batch-to-batch consistency, safety, efficacy, and regulatory compliance. Modern analytical techniques and standardized quality assurance protocols play a vital role in identifying bioactive constituents, evaluating formulation quality, and supporting the successful clinical translation of phytosome-based herbal nanocarriers [46].

4.1 Selection and Standardization of Plant Extracts

The selection of medicinal plants represents the foundation of phytosome formulation. Plants should be selected based on ethnopharmacological evidence, scientific validation, phytochemical richness, and demonstrated antidiabetic efficacy in preclinical and clinical studies. Herbal extracts rich in flavonoids, polyphenols, alkaloids, terpenoids, lignans, tannins, saponins, and phenolic acids are particularly attractive because of their multitarget mechanisms, including antioxidant, anti-inflammatory, insulin-sensitizing, β-cell protective, and glucose-lowering activities. Several factors influence the quality of plant extracts, including botanical identity, geographical location, climate, soil composition, harvesting period, plant maturity, drying conditions, extraction solvent, and extraction technique. Improper identification or contamination may result in adulteration, reduced efficacy, or safety concerns. Consequently, authentication of plant materials through macroscopic, microscopic, pharmacognostic, and DNA barcoding techniques is recommended before formulation development [47].

Standardization involves controlling extraction procedures and quantifying one or more biologically active marker compounds. Modern extraction methods such as ultrasound-assisted extraction, microwave-assisted extraction, pressurized liquid extraction, and supercritical fluid extraction improve extraction efficiency while preserving thermolabile phytochemicals. Standardized extracts ensure uniform phytochemical composition, consistent biological activity, and improved reproducibility during pharmaceutical development. In addition, testing for heavy metals, pesticide residues, microbial contamination, aflatoxins, and residual solvents is essential to ensure the safety of herbal raw materials before phytosome preparation [48].

4.2 Phytochemical Profiling and Marker Compounds

Phytochemical profiling is a critical step in quality assessment because it identifies, characterizes, and quantifies the chemical constituents responsible for therapeutic activity. Since herbal extracts contain hundreds of phytochemicals, comprehensive profiling helps establish chemical fingerprints that serve as quality benchmarks for formulation development and manufacturing. Marker compounds are selected based on their pharmacological significance, abundance, chemical stability, and analytical detectability. Depending on the medicinal plant, marker compounds may include curcumin from *Curcuma longa*, berberine from *Berberis* species, quercetin from *Allium cepa* and various medicinal plants, silybin from *Silybum marianum*, resveratrol from grapes, catechins from green tea, and naringenin from citrus fruits. Quantification of these markers ensures batch-to-batch consistency and allows correlation between phytochemical content and therapeutic efficacy [49].

Both qualitative and quantitative phytochemical analyses are essential. Preliminary phytochemical screening confirms the presence of major classes of secondary metabolites such as flavonoids, alkaloids, glycosides, tannins, steroids, terpenoids, and phenolic compounds. Quantitative estimation of total phenolic content (TPC), total flavonoid content (TFC), and antioxidant capacity further supports

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extract standardization. Chemical fingerprinting using chromatographic and spectroscopic techniques provides a reliable method for detecting adulteration, verifying authenticity, and monitoring formulation consistency throughout product development [50].

4.3 Analytical Characterization Techniques

Accurate analytical characterization is essential for evaluating herbal extracts, confirming phytosome formation, and ensuring pharmaceutical quality. Modern analytical technologies provide detailed information regarding chemical composition, molecular interactions, structural integrity, and formulation stability. High-performance liquid chromatography (HPLC) remains the gold standard for quantitative estimation of marker compounds because of its excellent sensitivity, precision, and reproducibility. Ultra-performance liquid chromatography (UPLC) offers improved resolution, shorter analysis time, and greater analytical efficiency. Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) enables highly sensitive identification of phytochemicals and their metabolites, whereas gas chromatography-mass spectrometry (GC-MS) is particularly useful for analyzing volatile compounds and essential oils [51].

High-performance thin-layer chromatography (HPTLC) provides rapid qualitative fingerprinting of herbal extracts and is frequently employed for routine quality control. Ultraviolet-visible (UV-Vis) spectroscopy is commonly used for estimation of total phenolic and flavonoid contents, while Fourier-transform infrared spectroscopy (FTIR) confirms hydrogen bonding and molecular interactions between phytochemicals and phospholipids during phytosome formation. Thermal analysis using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) provides valuable information regarding thermal stability, phase transitions, and compatibility between phytochemicals and phospholipids. Together, these analytical techniques establish the identity, purity, stability, and structural characteristics of phytosome formulations while ensuring compliance with pharmaceutical quality standards [52-53].

4.4 Physicochemical Characterization of Phytosomes

Comprehensive physicochemical characterization is essential for evaluating formulation quality, predicting in vivo performance, and ensuring reproducibility of phytosome-based nanocarriers. The physicochemical properties directly influence drug loading, stability, dissolution, absorption, pharmacokinetics, and therapeutic efficacy. Particle size is one of the most important quality attributes because it determines intestinal absorption, cellular uptake, and biodistribution [54]. Nanometer-sized phytosomes generally exhibit superior membrane permeability and enhanced oral bioavailability. Particle size and polydispersity index (PDI) are commonly determined using dynamic light scattering (DLS), while zeta potential provides information regarding colloidal stability. Higher absolute zeta potential values indicate improved electrostatic stabilization and reduced particle aggregation. Encapsulation efficiency and drug loading are critical parameters that determine the amount of phytochemical successfully incorporated into the phytosomal complex. High encapsulation efficiency minimizes drug loss and improves therapeutic effectiveness. Morphological characteristics, including particle shape and surface architecture, are evaluated using scanning electron microscopy (SEM), transmission electron microscopy (TEM), or atomic force microscopy (AFM) [54-55].

FTIR spectroscopy confirms successful phytochemical–phospholipid complexation through characteristic shifts in functional group vibrations, whereas XRD demonstrates changes in crystallinity following complex formation. Differential scanning calorimetry provides evidence of molecular interactions by identifying alterations in melting behavior and thermal transitions. Additional quality parameters include aqueous solubility, dissolution rate, in vitro drug release, hygroscopicity, moisture content, pH, and storage stability [56].

4.5 Regulatory Requirements for Quality Assurance

Regulatory quality assurance plays a fundamental role in the successful commercialization and clinical translation of phytosome-based herbal nanocarriers. Regulatory agencies require manufacturers to demonstrate consistent quality, safety, efficacy, and manufacturing reproducibility before product approval. Since herbal formulations contain complex natural mixtures, regulatory evaluation is considerably more challenging than for conventional synthetic drugs. Manufacturing should comply with internationally accepted Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), and International Council for Harmonisation (ICH) quality guidelines [57]. Comprehensive quality assurance includes authentication of botanical raw materials, validated extraction procedures, standardized phytochemical content, impurity profiling, microbial testing, heavy metal analysis, pesticide residue evaluation, residual solvent determination, and stability testing under accelerated and long-term storage conditions. ICH stability guidelines recommend evaluation of physical appearance, phytochemical content,

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particle size, zeta potential, encapsulation efficiency, moisture uptake, and dissolution characteristics throughout the product shelf life. Documentation of Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs) under a Quality by Design (QbD) framework further strengthens manufacturing consistency and regulatory acceptance [58].

Despite significant progress in herbal nanomedicine, global regulatory harmonization remains limited because different countries apply varying requirements for herbal products and nanotechnology-based formulations. Future regulatory frameworks should establish standardized guidelines specifically addressing phytosome characterization, nanocarrier safety assessment, bioequivalence, pharmacokinetic evaluation, and clinical validation. Such harmonization will accelerate the clinical translation and worldwide commercialization of phytosome-based herbal therapeutics for diabetes mellitus and other chronic diseases[59].

5. Mechanisms Of Antidiabetic Action Of Phytosomal Herbal Nanocarriers

Phytosome-based herbal nanocarriers exert antidiabetic effects through multiple complementary mechanisms by improving the delivery, bioavailability, and therapeutic efficacy of plant-derived bioactive compounds. Conventional herbal extracts often exhibit limited clinical efficacy because of poor aqueous solubility, low gastrointestinal absorption, rapid metabolism, and extensive first-pass elimination. Complexation of phytochemicals with phospholipids significantly enhances their pharmacokinetic profile, allowing greater systemic exposure and improved interaction with molecular targets involved in glucose homeostasis. Consequently, phytosomal formulations regulate oxidative stress, chronic inflammation, insulin signaling, pancreatic β-cell survival, and glucose and lipid metabolism more effectively than conventional herbal preparations (**Fig. 2**). The major mechanisms underlying their antidiabetic activity are discussed below [60-61].

5.1 Enhancement of Oral Bioavailability

One of the principal advantages of phytosomal nanocarriers is their ability to improve the oral bioavailability of poorly soluble phytochemicals. The phospholipid complex increases lipid solubility and membrane affinity, facilitating efficient transport across the intestinal epithelium. In addition, phytosomes protect phytoconstituents from degradation in the gastrointestinal tract and reduce first-pass hepatic metabolism, thereby increasing systemic drug exposure. Enhanced dissolution, intestinal permeability, and prolonged circulation lead to greater therapeutic concentrations of phytochemicals such as curcumin, berberine, quercetin, and resveratrol. Improved bioavailability ultimately results in superior glycemic control and enhanced pharmacological efficacy compared with conventional herbal extracts [62].

5.2 Antioxidant and Anti-inflammatory Activities

Oxidative stress and chronic inflammation are central contributors to the development and progression of diabetes mellitus and its associated complications. Persistent hyperglycemia stimulates excessive production of reactive oxygen species (ROS), leading to lipid peroxidation, mitochondrial dysfunction, protein oxidation, DNA damage, and endothelial injury. Simultaneously, inflammatory mediators including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and C-reactive protein (CRP) aggravate insulin resistance and β-cell dysfunction [62].

Phytosomal formulations markedly enhance the antioxidant capacity of herbal phytochemicals by increasing their cellular uptake and biological availability. These formulations effectively scavenge free radicals, restore endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while suppressing lipid peroxidation and inflammatory cytokine production. Consequently, phytosomal herbal nanocarriers reduce oxidative damage, improve endothelial function, and protect tissues from diabetes-induced complications[63].

5.3 Improvement of Insulin Sensitivity

Insulin resistance is a hallmark of type 2 diabetes mellitus and is characterized by impaired responsiveness of peripheral tissues to insulin. Phytosomal herbal nanocarriers improve insulin sensitivity by enhancing insulin receptor signaling and promoting glucose utilization in skeletal muscle, adipose tissue, and liver. Improved bioavailability enables phytochemicals to exert stronger insulin-sensitizing effects through activation of intracellular signaling pathways that regulate glucose transport and metabolism. Several phytochemicals incorporated into phytosomes stimulate glucose uptake by increasing GLUT4 translocation to the plasma membrane, suppress hepatic gluconeogenesis, improve glycogen synthesis, and reduce circulating free fatty acids. Collectively, these actions restore insulin responsiveness, decrease hyperglycemia, and improve overall metabolic homeostasis [64].

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Volume 36 Issue 2, Year of Publication 2026, Page 622-640
DoI-10.004687/1000-9035.2026.073

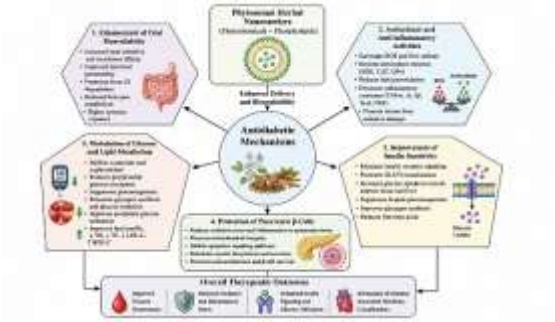

Figure 2: Mechanisms of antidiabetic action of phytosomal herbal nanocarriers. Phytosomal delivery enhances the bioavailability and cellular uptake of bioactive phytochemicals, resulting in antioxidant and anti-inflammatory effects, improved insulin sensitivity, protection of pancreatic β-cells, and modulation of glucose and lipid metabolism. These complementary mechanisms contribute to improved glucose homeostasis, reduced oxidative and inflammatory stress, enhanced insulin signaling and glucose utilization, and overall attenuation of diabetes-associated metabolic complications.

5.4 Protection of Pancreatic β-Cells

Progressive dysfunction and apoptosis of pancreatic β-cells are major pathological events in diabetes progression. Chronic oxidative stress, inflammation, glucotoxicity, and lipotoxicity impair insulin secretion and accelerate β-cell destruction. Phytosome-based formulations provide significant cytoprotective effects by enhancing the intracellular delivery of antioxidant phytochemicals to pancreatic tissues. Enhanced antioxidant activity reduces ROS-mediated cellular damage, preserves mitochondrial integrity, inhibits apoptotic signaling pathways, and promotes β-cell survival. Furthermore, several phytochemicals stimulate insulin biosynthesis and secretion while preserving islet architecture. These protective effects contribute to improved endogenous insulin production and delay disease progression in experimental diabetic models [65].

5.5 Modulation of Glucose and Lipid Metabolism

Diabetes is frequently associated with disturbances in both glucose and lipid metabolism, resulting in hyperglycemia, dyslipidemia, obesity, and increased cardiovascular risk. Phytosomal herbal nanocarriers regulate multiple metabolic pathways involved in carbohydrate and lipid homeostasis. Enhanced delivery of bioactive phytochemicals inhibits intestinal carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, thereby reducing postprandial glucose absorption. In addition, phytosomal formulations suppress hepatic gluconeogenesis, enhance glycogen synthesis, stimulate glucose oxidation, and improve peripheral glucose utilization. They also regulate lipid metabolism by decreasing triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol while increasing high-density lipoprotein (HDL) cholesterol. These combined effects improve metabolic control and reduce the risk of diabetes-associated cardiovascular complications [66].

Table 1. Mechanisms of Antidiabetic Action of Phytosomal Herbal Nanocarriers [67-70]

Mechanism	Biological Target/Process	Therapeutic Effect	Representative Phytochemicals
Enhancement of oral bioavailability	Improved intestinal permeability, phospholipid-mediated absorption, reduced first-pass metabolism	Increased systemic exposure and therapeutic efficacy	Curcumin, Berberine, Quercetin, Resveratrol
Antioxidant activity	ROS scavenging, increased SOD, CAT, GPx, reduced lipid peroxidation	Protection against oxidative stress and diabetic complications	Curcumin, EGCG, Quercetin, Naringenin
Anti-inflammatory activity	Inhibition of TNF-α, IL-1β, IL-6, COX-2, iNOS, NF-κB	Reduced chronic inflammation and insulin resistance	Berberine, Curcumin, Resveratrol
Improvement of insulin sensitivity	Activation of insulin receptor signaling, enhanced GLUT4 translocation	Increased glucose uptake and improved insulin responsiveness	Berberine, Quercetin, Resveratrol
Protection of pancreatic β-cells	Reduced apoptosis, decreased oxidative stress, improved insulin secretion	Preservation of β-cell mass and function	Curcumin, Silymarin, Quercetin
Modulation of glucose metabolism	Inhibition of α-amylase and α-glucosidase, reduced hepatic gluconeogenesis	Lower fasting and postprandial blood glucose	Berberine, EGCG, Naringenin
Regulation of lipid metabolism	Decreased triglycerides, LDL, total cholesterol; increased HDL	Improved lipid profile and reduced cardiovascular risk	Resveratrol, Curcumin, Berberine
Activation of AMPK pathway	Increased glucose utilization and fatty acid oxidation	Enhanced insulin sensitivity and metabolic homeostasis	Berberine, Resveratrol
Activation of PI3K/Akt pathway	Improved insulin signaling and glycogen synthesis	Enhanced glucose uptake and glycemic control	Quercetin, Curcumin
Activation of Nrf2 pathway	Upregulation of HO-1, SOD, CAT, GPx	Enhanced antioxidant defense and cytoprotection	Curcumin, EGCG
Inhibition of NF-κB pathway	Suppression of inflammatory cytokines	Reduced inflammation and β-cell protection	Curcumin, Resveratrol, Berberine

5.6 Molecular Signaling Pathways (AMPK, PI3K/Akt, GLUT4, NF-κB, Nrf2)

Table 2: The antidiabetic activity of phytosomal herbal nanocarriers is mediated through modulation of several interconnected

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molecular signaling pathways [70-73]:

Signaling Pathway	Primary Function	Effect of Phytosomal Phytochemicals	Antidiabetic Outcome
AMPK	Cellular energy regulation	Activates glucose uptake and fatty acid oxidation	Improved insulin sensitivity
PI3K/Akt	Insulin signaling	Enhances glycogen synthesis and GLUT4 activation	Reduced hyperglycemia
GLUT4	Glucose transport	Promotes GLUT4 translocation to cell membrane	Increased peripheral glucose uptake
NF-κB	Inflammatory signaling	Inhibits pro-inflammatory cytokine production	Reduced insulin resistance and inflammation
Nrf2/HO-1	Antioxidant defense	Upregulates antioxidant enzymes	Protection against oxidative stress
MAPK	Cell survival and inflammation	Modulates cellular stress responses	Reduced diabetic tissue injury
PPAR-γ	Lipid and glucose metabolism	Improves insulin sensitivity and adipocyte function	Better glycemic and lipid control

Overall, the simultaneous modulation of AMPK, PI3K/Akt, GLUT4, NF-κB, and Nrf2 pathways enables phytosome-based herbal nanocarriers to exert multitarget therapeutic effects, making them a promising nanomedicine platform for the prevention and management of diabetes mellitus and its associated complications.

6. Preclinical Evidence Of Phytosomal Herbal Nanocarriers

Preclinical investigations provide the scientific foundation for evaluating the therapeutic potential, pharmacokinetic behavior, and safety of phytosome-based herbal nanocarriers before clinical application. Numerous in vitro and in vivo studies have demonstrated that phytosomal formulations significantly improve the biological performance of herbal phytochemicals by enhancing their solubility, stability, membrane permeability, and systemic bioavailability. These improvements result in superior antihyperglycemic, antioxidant, anti-inflammatory, and organ-protective activities compared with conventional herbal extracts. Furthermore, pharmacokinetic and toxicological studies have confirmed the favorable safety profile and enhanced therapeutic efficacy of phytosomal formulations, supporting their potential as promising nanomedicines for diabetes mellitus [74].

6.1 *In Vitro* Studies

In vitro studies are essential for the preliminary evaluation of phytosomal formulations and provide valuable information regarding their physicochemical characteristics, drug release behavior, cellular uptake, antioxidant activity, and antidiabetic potential. Cell-based models such as Caco-2 intestinal epithelial cells, HepG2 hepatocytes, L6 skeletal muscle cells, 3T3-L1 adipocytes, INS-1 pancreatic β-cells, and MIN6 cells are commonly employed to investigate intestinal permeability, glucose uptake, insulin secretion, and cytoprotective effects. Numerous studies have demonstrated that phytosomal formulations significantly enhance cellular uptake and intracellular accumulation of poorly soluble phytochemicals compared with free compounds. Improved delivery leads to increased antioxidant activity, suppression of inflammatory mediators, enhanced glucose uptake, inhibition of α-glucosidase and α-amylase enzymes, and protection of pancreatic β-cells against oxidative damage. In vitro release studies further indicate that phytosomes provide controlled and sustained release, thereby improving therapeutic efficiency [75].

6.2 Animal Models of Diabetes Mellitus

Animal models remain indispensable for evaluating the in vivo efficacy of phytosomal herbal nanocarriers. Experimental diabetes is commonly induced using streptozotocin (STZ), alloxan, high-fat diet (HFD), or combined HFD-STZ protocols to mimic different aspects of type 1 and type 2 diabetes mellitus. Studies in diabetic rodents have consistently shown that phytosomal formulations produce greater reductions in fasting blood glucose, glycated hemoglobin (HbA1c), and insulin resistance than corresponding conventional herbal extracts. In addition, phytosomal phytochemicals improve glucose tolerance, preserve pancreatic β-cell morphology, reduce oxidative stress, suppress inflammatory cytokines, and restore antioxidant enzyme activities. Histopathological examinations have demonstrated improved pancreatic, hepatic, renal, and cardiac architecture following phytosomal treatment, indicating protection against diabetes-induced organ damage. These findings collectively support the superior therapeutic efficacy of phytosome-based herbal nanocarriers in preclinical diabetic models [76].

6.3 Pharmacokinetics and Biodistribution

One of the major advantages of phytosome technology is its ability to improve the pharmacokinetic profile of poorly bioavailable phytochemicals. Pharmacokinetic studies have demonstrated increased maximum plasma concentration (Cmax), larger area under the plasma concentration-time curve (AUC), prolonged half-life (t½), improved oral absorption, and enhanced systemic bioavailability compared with

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conventional herbal formulations. The phospholipid complex facilitates efficient transport across biological membranes and protects phytochemicals from gastrointestinal degradation and extensive first-pass metabolism. Biodistribution studies further indicate greater accumulation of phytosomal phytochemicals in metabolically active tissues such as the liver, pancreas, skeletal muscle, kidneys, and adipose tissue. Improved tissue targeting contributes to enhanced glucose regulation, reduced oxidative stress, and improved therapeutic outcomes in experimental diabetes [77].

6.4 Toxicological and Safety Evaluation

Safety evaluation is a critical component of preclinical development. Acute, subacute, and chronic toxicity studies have generally demonstrated that phytosome-based herbal formulations are well tolerated at therapeutic doses. Hematological, biochemical, and histopathological analyses have shown no significant evidence of systemic toxicity or organ damage following repeated administration in experimental animals. The phospholipids used in phytosome preparation are biodegradable, biocompatible, and generally recognized as safe, contributing to the favorable safety profile of these nanocarriers. Nevertheless, comprehensive toxicity assessment, including immunotoxicity, reproductive toxicity, genotoxicity, long-term toxicity, and nanotoxicological evaluation, remains necessary before clinical translation. Standardized safety testing according to OECD and regulatory guidelines is essential to ensure successful pharmaceutical development [78].

6.5 Comparative Performance with Conventional Herbal Extracts

Comparative studies consistently demonstrate that phytosomal formulations outperform conventional herbal extracts owing to their superior physicochemical and pharmacokinetic properties. The phospholipid complex markedly enhances aqueous solubility, intestinal permeability, membrane transport, and systemic bioavailability, leading to greater therapeutic efficacy at lower doses.

Table 3. Summary of Preclinical Evidence Supporting Phytosomal Herbal Nanocarriers for Diabetes Mellitus [79-82]

Study Category	Experimental Model	Key Findings	Advantages of Phytosomal Formulation
In vitro studies	Caco-2, HepG2, L6 myotubes, 3T3-L1 adipocytes, INS-1/MIN6 β-cells	Increased cellular uptake, enhanced glucose uptake, antioxidant activity, improved insulin secretion	Better membrane permeability, sustained release, enhanced intracellular delivery
Antidiabetic efficacy	STZ-induced diabetic rats/mice	Reduced fasting blood glucose, HbA1c, oxidative stress, inflammatory cytokines	Greater antihyperglycemic activity than free extracts
Type 2 diabetes model	High-fat diet (HFD) and HFD-STZ models	Improved insulin sensitivity, glucose tolerance, lipid profile, pancreatic function	Enhanced oral bioavailability and metabolic control
Histopathological evaluation	Pancreas, liver, kidney, heart	Restoration of tissue architecture and reduced diabetes-induced injury	Superior organ protection and β-cell preservation
Pharmacokinetic studies	Rodent pharmacokinetic models	Increased Cmax, AUC, half-life, and oral bioavailability	Reduced first-pass metabolism and improved tissue distribution
Biodistribution studies	Liver, pancreas, skeletal muscle, kidney	Greater accumulation in target organs	Improved therapeutic targeting
Safety assessment	Acute and repeated-dose toxicity studies	No significant hematological, biochemical, or histopathological toxicity	Good biocompatibility and favorable safety profile
Comparative studies	Phytosomes vs. conventional herbal extracts	Higher efficacy at lower doses with prolonged therapeutic response	Improved stability, absorption, and clinical translation potential

Compared with free herbal extracts, phytosomes exhibit improved antioxidant and anti-inflammatory activities, stronger glucose-lowering effects, enhanced insulin sensitivity, better preservation of pancreatic β-cell function, and greater protection against diabetic complications. Moreover, phytosomal formulations frequently require reduced dosing frequency and produce more sustained pharmacological responses because of prolonged circulation and controlled drug release. These advantages strongly support the continued development of phytosome technology for diabetes management and justify its progression toward clinical evaluation.

7. Clinical Translation Of Phytosomal Herbal Formulations

The successful clinical translation of phytosome-based herbal formulations represents a critical step in transforming promising preclinical findings into effective therapeutic interventions for diabetes mellitus (DM). Although numerous phytosomal formulations have demonstrated enhanced bioavailability, pharmacokinetic profiles, and superior antidiabetic efficacy in experimental studies, only a limited number have progressed to clinical evaluation. Clinical translation requires rigorous assessment of efficacy, safety, quality,

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manufacturing consistency, regulatory compliance, and long-term therapeutic outcomes. In addition, standardized herbal extracts, reproducible manufacturing processes, and well-designed randomized controlled clinical trials are essential to establish the clinical utility of phytosomal formulations. Despite these challenges, increasing advances in nanotechnology, pharmaceutical manufacturing, and regulatory science are accelerating the development of phytosome-based herbal medicines and improving their potential for clinical application [83].

7.1 Completed and Ongoing Clinical Studies

Clinical investigations of phytosomal herbal formulations have increased considerably during the past decade, particularly for phytochemicals such as curcumin, quercetin, berberine, silymarin, green tea polyphenols, and resveratrol. While many clinical studies have focused on metabolic syndrome, obesity, non-alcoholic fatty liver disease, and chronic inflammatory disorders, several investigations have also reported beneficial effects on glycemic control and insulin sensitivity in patients with type 2 diabetes mellitus. Available clinical evidence suggests that phytosomal formulations produce significantly higher plasma concentrations than conventional herbal extracts due to improved oral absorption and reduced first-pass metabolism. Improved pharmacokinetic performance has translated into better therapeutic responses, including reductions in fasting blood glucose, glycated hemoglobin (HbA1c), oxidative stress biomarkers, inflammatory cytokines, and lipid abnormalities. Nevertheless, most available clinical studies involve relatively small sample sizes, short treatment durations, and heterogeneous study designs. Therefore, large multicenter randomized controlled trials with standardized phytosomal formulations are required to establish definitive clinical efficacy in diabetes management [84].

7.2 Clinical Efficacy and Safety Outcomes

Clinical studies have demonstrated that phytosomal formulations are generally well tolerated and exhibit a favorable safety profile. Enhanced oral bioavailability allows therapeutic effects to be achieved at lower doses than conventional herbal preparations, thereby reducing the risk of dose-related adverse effects. Improvements in glycemic control have been accompanied by reductions in oxidative stress, systemic inflammation, insulin resistance, and dyslipidemia, all of which contribute to better metabolic control. Safety evaluations have shown that most phytosomal herbal formulations do not produce significant alterations in hepatic, renal, hematological, or cardiovascular parameters when administered at recommended therapeutic doses. Mild gastrointestinal discomfort has occasionally been reported but is generally transient and self-limiting. Importantly, phosphatidylcholine, the principal phospholipid used in phytosome preparation, possesses excellent biocompatibility and biodegradability, contributing to the overall safety of these formulations. However, long-term safety data remain limited, and further clinical studies are needed to evaluate chronic administration, herb-drug interactions, and use in elderly patients and individuals with multiple comorbidities [85].

7.3 Patient Compliance and Therapeutic Benefits

Patient adherence is a major determinant of successful diabetes management. Phytosome technology offers several advantages that may improve patient compliance compared with conventional herbal formulations. Enhanced bioavailability enables therapeutic efficacy at lower doses, reducing pill burden and dosing frequency. Improved absorption also minimizes variability in drug response, leading to more predictable clinical outcomes. In addition to glycemic control, phytosomal herbal formulations provide multitarget therapeutic benefits by reducing oxidative stress, suppressing inflammation, improving insulin sensitivity, preserving pancreatic β-cell function, and correcting lipid abnormalities. These pleiotropic effects may reduce the progression of diabetes-associated complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease. The use of naturally derived phytochemicals with improved pharmaceutical performance also aligns with the growing patient preference for evidence-based herbal medicines, potentially enhancing acceptance and long-term treatment adherence [86].

7.4 Regulatory Approval and Commercial Products

The commercialization of phytosomal formulations requires compliance with stringent pharmaceutical quality and regulatory standards. Regulatory agencies require comprehensive evidence regarding product quality, manufacturing consistency, safety, pharmacokinetics, and clinical efficacy before market approval. Standardization of herbal extracts, validated analytical methods, Good Manufacturing Practice (GMP), and adherence to International Council for Harmonisation (ICH) guidelines are essential components of regulatory approval. Several phytosomal products containing curcumin, silymarin, green tea extract, grape seed extract, ginkgo, and other herbal bioactives are already commercially available as nutraceuticals or dietary supplements in many countries. Their successful commercialization demonstrates the feasibility of phytosome technology for improving herbal drug delivery [87].

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7.5 Challenges in Clinical Translation

Despite considerable scientific progress, several challenges continue to limit the widespread clinical application of phytosomal herbal formulations. One of the major obstacles is the lack of standardized herbal extracts, which results in variability in phytochemical composition and therapeutic efficacy. Differences in formulation methods, phospholipid composition, manufacturing processes, and quality control further complicate reproducibility across studies.

Additional barriers include limited large-scale clinical trials, insufficient long-term safety data, high manufacturing costs, scale-up difficulties, and the absence of harmonized international regulatory guidelines for herbal nanomedicines. Furthermore, variability in patient populations, dosage regimens, and clinical endpoints often makes comparison among studies difficult. Addressing these limitations will require multidisciplinary collaboration among pharmaceutical scientists, clinicians, regulatory agencies, and industry partners. Future research should focus on standardized formulation protocols, Quality by Design (QbD)-based manufacturing, pharmacokinetic optimization, multicenter randomized clinical trials, and internationally harmonized regulatory frameworks to accelerate the successful clinical translation of phytosome-based herbal therapies for diabetes mellitus [88].

8. Current Challenges And Future Perspectives

The successful clinical translation of phytosome-based herbal formulations represents a critical step in transforming promising preclinical findings into effective therapeutic interventions for diabetes mellitus (DM). Although numerous phytosomal formulations have demonstrated enhanced bioavailability, pharmacokinetic profiles, and superior antidiabetic efficacy in experimental studies, only a limited number have progressed to clinical evaluation. Clinical translation requires rigorous assessment of efficacy, safety, quality, manufacturing consistency, regulatory compliance, and long-term therapeutic outcomes. In addition, standardized herbal extracts, reproducible manufacturing processes, and well-designed randomized controlled clinical trials are essential to establish the clinical utility of phytosomal formulations. Despite these challenges, increasing advances in nanotechnology, pharmaceutical manufacturing, and regulatory science are accelerating the development of phytosome-based herbal medicines and improving their potential for clinical application [89].

8.1 Standardization and Batch-to-Batch Reproducibility

Clinical investigations of phytosomal herbal formulations have increased considerably during the past decade, particularly for phytochemicals such as curcumin, quercetin, berberine, silymarin, green tea polyphenols, and resveratrol. While many clinical studies have focused on metabolic syndrome, obesity, non-alcoholic fatty liver disease, and chronic inflammatory disorders, several investigations have also reported beneficial effects on glycemic control and insulin sensitivity in patients with type 2 diabetes mellitus.

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8.2 Large-Scale Manufacturing and Commercialization

Clinical studies have demonstrated that phytosomal formulations are generally well tolerated and exhibit a favorable safety profile. Enhanced oral bioavailability allows therapeutic effects to be achieved at lower doses than conventional herbal preparations, thereby reducing the risk of dose-related adverse effects. Improvements in glycemic control have been accompanied by reductions in oxidative stress, systemic inflammation, insulin resistance, and dyslipidemia, all of which contribute to better metabolic control. Safety evaluations have shown that most phytosomal herbal formulations do not produce significant alterations in hepatic, renal, hematological, or cardiovascular parameters when administered at recommended therapeutic doses. Mild gastrointestinal discomfort has occasionally been reported but is generally transient and self-limiting. Importantly, phosphatidylcholine, the principal phospholipid used in phytosome preparation, possesses excellent biocompatibility and biodegradability, contributing to the overall safety of these formulations. However, long-term safety data remain limited, and further clinical studies are needed to evaluate chronic administration, herb-drug interactions, and use in elderly patients and individuals with multiple comorbidities [91].

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8.3 Regulatory and Intellectual Property Considerations

Patient adherence is a major determinant of successful diabetes management. Phytosome technology offers several advantages that may improve patient compliance compared with conventional herbal formulations. Enhanced bioavailability enables therapeutic efficacy at lower doses, reducing pill burden and dosing frequency. Improved absorption also minimizes variability in drug response, leading to more predictable clinical outcomes.

In addition to glycemic control, phytosomal herbal formulations provide multitarget therapeutic benefits by reducing oxidative stress, suppressing inflammation, improving insulin sensitivity, preserving pancreatic β-cell function, and correcting lipid abnormalities. These pleiotropic effects may reduce the progression of diabetes-associated complications such as nephropathy, neuropathy, retinopathy, and cardiovascular disease. The use of naturally derived phytochemicals with improved pharmaceutical performance also aligns with the growing patient preference for evidence-based herbal medicines, potentially enhancing acceptance and long-term treatment adherence [92].

8.4 Personalized Phytosomal Therapy

The commercialization of phytosomal formulations requires compliance with stringent pharmaceutical quality and regulatory standards. Regulatory agencies require comprehensive evidence regarding product quality, manufacturing consistency, safety, pharmacokinetics, and clinical efficacy before market approval. Standardization of herbal extracts, validated analytical methods, Good Manufacturing Practice (GMP), and adherence to International Council for Harmonisation (ICH) guidelines are essential components of regulatory approval. Several phytosomal products containing curcumin, silymarin, green tea extract, grape seed extract, ginkgo, and other herbal bioactives are already commercially available as nutraceuticals or dietary supplements in many countries. Their successful commercialization demonstrates the feasibility of phytosome technology for improving herbal drug delivery. However, phytosomal formulations specifically approved as pharmaceutical products for diabetes mellitus remain limited, highlighting the need for stronger clinical evidence and regulatory harmonization to support future approvals [93].

8.5 Artificial Intelligence and Advanced Drug Delivery Approaches

Despite considerable scientific progress, several challenges continue to limit the widespread clinical application of phytosomal herbal formulations. One of the major obstacles is the lack of standardized herbal extracts, which results in variability in phytochemical composition and therapeutic efficacy. Differences in formulation methods, phospholipid composition, manufacturing processes, and quality control further complicate reproducibility across studies.

Additional barriers include limited large-scale clinical trials, insufficient long-term safety data, high manufacturing costs, scale-up difficulties, and the absence of harmonized international regulatory guidelines for herbal nanomedicines. Furthermore, variability in patient populations, dosage regimens, and clinical endpoints often makes comparison among studies difficult. Addressing these limitations will require multidisciplinary collaboration among pharmaceutical scientists, clinicians, regulatory agencies, and industry partners. Future research should focus on standardized formulation protocols, Quality by Design (QbD)-based manufacturing, pharmacokinetic optimization, multicenter randomized clinical trials, and internationally harmonized regulatory frameworks to accelerate the successful clinical translation of phytosome-based herbal therapies for diabetes mellitus [94].

8.6 Future Research Directions

Future research should focus on developing standardized phytosomal formulations with improved stability, scalability, and reproducibility. Large, well-designed clinical trials are needed to establish their long-term safety, efficacy, and optimal dosing in patients with diabetes mellitus. Additionally, integrating advanced nanotechnology, targeted drug delivery approaches, and personalized medicine strategies may further enhance therapeutic outcomes. Addressing regulatory requirements and manufacturing challenges will be essential for the successful clinical translation and commercialization of phytosome-based herbal nanocarriers [95-97].

CONCLUSION:

Phytosome-based herbal nanocarriers have emerged as a promising strategy to enhance the therapeutic potential of herbal phytochemicals for the management of diabetes mellitus (DM). By improving the solubility, stability, permeability, and oral bioavailability of plant-derived bioactive compounds, phytosomes effectively overcome many limitations associated with conventional herbal formulations. Preclinical studies have consistently demonstrated enhanced antidiabetic efficacy through improved glycemic control, insulin sensitivity, antioxidant activity, anti-inflammatory effects, and protection against diabetic complications. Despite these encouraging findings,

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clinical translation remains limited due to the scarcity of large-scale clinical trials, lack of standardized phytochemical formulations, regulatory challenges, and manufacturing constraints. Therefore, rigorous phytochemical standardization, quality control, optimized formulation strategies, and well-designed clinical studies are essential to validate their long-term safety and therapeutic efficacy. Overall, phytosome-based herbal nanocarriers represent a promising next-generation drug delivery platform that bridges traditional herbal medicine with modern nanotechnology. Continued advances in formulation development, clinical evaluation, and regulatory harmonization are expected to facilitate their successful translation into safe, effective, and commercially viable therapies for diabetes mellitus.

LIST OF ABBREVIATIONS:

DM – Diabetes Mellitus
T1DM – Type 1 Diabetes Mellitus
T2DM – Type 2 Diabetes Mellitus
GDM – Gestational Diabetes Mellitus
ROS – Reactive Oxygen Species
AGEs – Advanced Glycation End Products
GLP-1 – Glucagon-Like Peptide-1
DPP-4 – Dipeptidyl Peptidase-4
SGLT2 – Sodium-Glucose Cotransporter-2
AMPK – Adenosine Monophosphate-Activated Protein Kinase
PI3K/Akt – Phosphoinositide 3-Kinase/Protein Kinase B
GLUT4 – Glucose Transporter Type 4
NF-κB – Nuclear Factor Kappa B
Nrf2 – Nuclear Factor Erythroid 2-Related Factor 2
HO-1 – Heme Oxygenase-1
MAPK – Mitogen-Activated Protein Kinase
PPAR-γ – Peroxisome Proliferator-Activated Receptor Gamma
TNF-α – Tumor Necrosis Factor-Alpha
IL-1β – Interleukin-1 Beta
IL-6 – Interleukin-6
CRP – C-Reactive Protein
SOD – Superoxide Dismutase
CAT – Catalase
GPx – Glutathione Peroxidase
HbA1c – Glycated Hemoglobin
Cmax – Maximum Plasma Concentration
AUC – Area Under the Curve
t½ – Half-Life
HPLC – High-Performance Liquid Chromatography
UPLC – Ultra-Performance Liquid Chromatography
LC-MS/MS – Liquid Chromatography–Tandem Mass Spectrometry
GC-MS – Gas Chromatography–Mass Spectrometry
HPTLC – High-Performance Thin-Layer Chromatography
FTIR – Fourier-Transform Infrared Spectroscopy
NMR – Nuclear Magnetic Resonance
XRD – X-Ray Diffraction
DSC – Differential Scanning Calorimetry
TGA – Thermogravimetric Analysis
DLS – Dynamic Light Scattering
PDI – Polydispersity Index
SEM – Scanning Electron Microscopy
TEM – Transmission Electron Microscopy
AFM – Atomic Force Microscopy
GMP – Good Manufacturing Practice
GLP – Good Laboratory Practice
ICH – International Council for Harmonisation
QbD – Quality by Design
DoE – Design of Experiments
QTPP – Quality Target Product Profile
CQA – Critical Quality Attribute
HDL – High-Density Lipoprotein
EGCG – Epigallocatechin Gallate

ACKNOWLEDGEMENT:

The authors would like to thank their respective institutions and colleagues for their support and encouragement during the preparation of this review article.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest, financial or otherwise, related to the preparation and publication of this manuscript.

AUTHOR CONTRIBUTION:

All authors contributed to the conception and design of the review, literature search and analysis, interpretation of the available evidence, preparation and critical revision of the manuscript, and approved the final version for publication.

FUNDING:

The authors received no specific grant, financial support, or funding from any public, commercial, or not-for-profit organization for the preparation of this review article.

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