OPEN ACCESS
©NIJRMS
ONLINE ISSN: 2992-5460
Publications 2025
PRINT ISSN: 2992-6041

NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES (NIJRMS)

Volume 7 Issue 1 Page 1-11, 2026

https://doi.org/10.59298/NIJRMS/2026/7.1.111000

Nanotechnology Approaches in Enhancing Bioavailability of Plant-Derived Antidiabetic Compounds for Obesity-Linked Diabetes

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ABSTRACT

Obesity-linked type 2 diabetes (T2D) arises from chronic nutrient excess, ectopic lipid deposition, and unresolved inflammation that together blunt insulin signaling and exhaust β-cell function. Plant-derived antidiabetic compounds, flavonoids (quercetin, kaempferol), phenolic acids (chlorogenic, caffeic), alkaloids (berberine), terpenoids (curcumin), and saponins (ginsenosides) modulate AMPK–mTOR, PI3K–AKT, PPARs, bile-acid–FXR/TGR5, and NF-κB/NLRP3 axes. Yet most exhibit poor aqueous solubility, chemical instability, extensive first-pass metabolism, efflux via P-glycoprotein, and rapid clearance, yielding low and variable systemic exposure. Nanotechnology offers a route to overcome these barriers by tailoring size, surface chemistry, and cargo architecture to improve dissolution, protect labile structures, promote intestinal permeation, and direct biodistribution to metabolic tissues. Lipidic carriers (liposomes, solid lipid nanoparticles, nanostructured lipid carriers, phytosomes), polymeric nanoparticles (PLGA, chitosan, PEG-PCL), cyclodextrin complexes, and hybrid or stimuli-responsive systems have achieved substantial gains in apparent solubility, oral bioavailability, and pharmacodynamic potency for lead phytochemicals in obese and diabetic models. Surface ligands that recognize hepatocyte asialoglycoprotein receptors, adipose vasculature motifs, or β-cell GLP-1 receptors enable tissue selectivity, while mucoadhesive and colon-targeted formulations reshape gut exposure to influence microbiome-host metabolism. This review synthesizes the pharmacokinetic obstacles facing plant bioactives, details design rules for nanocarriers that address dissolution–permeation–metabolism limits, and compares outcomes across platforms and payloads. We highlight considerations for scalability, safety, and regulatory acceptance, including critical quality attributes, in vitro–in vivo correlations, and human-relevant endpoints. Collectively, nanotechnology provides a pragmatic bridge from promising phytochemistry to translatable therapeutics capable of multi-target reprogramming in obesity-linked T2D without escalating systemic toxicity. Future studies should prioritize endotype-guided designs and combination payloads.

INTRODUCTION

Obesity-linked type 2 diabetes (T2D) reflects the convergence of nutrient surplus, sedentary behavior, and genetic and epigenetic susceptibilities that reshape endocrine and immune networks across organs[1–3]. Adipose tissue hypertrophy induces local hypoxia, extracellular matrix remodeling, and a shift toward proinflammatory macrophage phenotypes, while lipolysis and adipokine imbalance propagate insulin resistance to liver and skeletal muscle[4–7]. In hepatocytes, accumulation of diacylglycerols and ceramides activates novel protein kinase C isoforms that impair insulin receptor signaling and increase gluconeogenesis, whereas in myofibers reduced mitochondrial oxidative capacity and altered calcium handling limit glucose uptake and fatty acid oxidation[8, 9]. Pancreatic β-cells initially compensate with hypersecretion but eventually succumb to glucolipotoxic stress, unfolded protein response activation, and identity erosion [10]. Superimposed on these cellular lesions is a dense web of interorgan communication cytokines, myokines, hepatokines, bile acids, microbial metabolites, and extracellular vesicles that collectively sustain insulin-resistant states. Therapeutic strategies must therefore address coordinated network dysfunction rather than single nodes in isolation[11–14].

Plant-derived antidiabetic compounds have emerged as attractive multi-target modulators that align with this systems perspective. Flavonoids such as quercetin, kaempferol, and epigallocatechin gallate activate AMPK,

OPEN ACCESS
ONLINE ISSN: 2992-5460
PRINT ISSN: 2992-6041

enhance GLUT4 translocation, reduce NF-κB activity, and support mitochondrial biogenesis[15–17]. Phenolic acids like chlorogenic acid modulate hepatic glucose output and intestinal glucose transporters, while alkaloids such as berberine reduce de novo lipogenesis, stimulate incretin pathways, and influence gut microbial composition. Terpenoids including curcumin and andrographolide, suppress NLRP3 inflammasome activation and improve insulin signaling in adipose and muscle. Saponins, notably ginsenosides, engage bile-acid receptors and PPARs to rebalance lipid handling and energy expenditure. Collectively, these phytochemicals touch key axes like AMPK–mTOR, PI3K–AKT, SREBP-1c, FXR/TGR5, and antioxidant networks offering the possibility of coordinated improvement across metabolic tissues while avoiding the adverse effects that often accompany high-potency, single-target drugs[18–20].

Despite compelling pharmacology in vitro and in animal models, clinical translation has been slowed by biopharmaceutical limitations. Many plant bioactives are hydrophobic crystals with high lattice energy, yielding low aqueous solubility and dissolution-limited absorption in the gastrointestinal tract[21]. Others are unstable at gastric pH, undergo rapid phase II metabolism by UDP-glucuronosyltransferases and sulfotransferases, or are substrates of intestinal efflux pumps such as P-glycoprotein and BCRP. Extensive first-pass hepatic metabolism and rapid systemic clearance further depress exposure at target tissues, while variable food effects and microbiota-dependent biotransformation add interindividual variability[21]. Attempts to increase dose often run into solubility ceilings or off-target toxicities, leading to a familiar translational gap: potent mechanisms without reliable, patient-level pharmacokinetics.

Nanotechnology offers a route to narrow this gap by engineering the journey from the gastrointestinal lumen to cellular targets. Reducing particle size to the nanoscale increases surface area and apparent solubility, accelerating dissolution; encapsulating hydrophobic or labile compounds within lipidic or polymeric matrices protects them from chemical and enzymatic degradation; and modulating surface chemistry enables traversal of mucus, tight junctions, and cellular membranes[19, 22–24]. Ionizable lipids promote endosomal escape of nucleic acid cargos when co-delivered with phytochemicals, while mucoadhesive polysaccharides such as chitosan prolong intestinal residence time and transiently open paracellular pathways. Beyond oral delivery, nanosystems can be designed to favor hepatic, adipose, or pancreatic deposition via ligand-mediated targeting, exploiting disease-altered vascular permeability and receptor expression[25]. Collectively, these design levers can transform the same milligram dose into higher, more consistent exposure at the relevant sites of action.

The goal of this review is to integrate pathophysiologic context with practical nanotechnology solutions for improving the bioavailability and therapeutic impact of plant-derived antidiabetic compounds in obesity-linked T2D. We first describe pharmacokinetic and biopharmaceutical barriers that constrain phytochemical efficacy. We then survey major nanocarrier classes, such as lipid-based, polymeric, cyclodextrin, and hybrid systems, and outline design rules that couple material choice, size, surface attributes, and release mechanisms to the barriers they address. Subsequent sections examine tissue-targeting logic and biodistribution in metabolically diseased states, compare preclinical efficacy across compounds and platforms, and discuss safety, manufacturing, and regulatory considerations that shape clinical translation. Throughout, we emphasize the importance of endotype-guided design and clinically relevant pharmacodynamic readouts, including hepatic fat content, adipose inflammation markers, skeletal muscle oxidative capacity, β-cell function, and glycemic endpoints. By connecting mechanistic potential to deployable formulation strategies, we aim to chart a credible path from promising phytochemistry to real-world therapeutics that complement existing antidiabetic regimens and lifestyle interventions.

Finally, we consider the emergent role of the gut–liver–adipose axis and the microbiome in determining the fate and function of phytochemicals. Because many polyphenols reach the colon largely unmetabolized, formulations that steer release distally or enrich microbial converters may amplify bioactivation and systemic efficacy. Linking nanoenabled delivery with diet composition, circadian dosing, and concomitant standard therapies could unlock synergies that are invisible in reductionist assays yet decisive for clinical benefit in heterogeneous patient populations.

2. Biopharmaceutical Barriers Limiting Plant Bioactives in Obesity-Linked Diabetes

Plant-derived antidiabetic compounds confront a gauntlet of barriers between ingestion and arrival at metabolic targets. The first is solubility and dissolution. Many polyphenols, terpenoids, and alkaloids crystallize in polymorphs with high lattice energy, yielding sub-microgram per milliliter solubility in aqueous media and slow dissolution in the intestinal milieu[26]. Supersaturation strategies can help, but are transient without precipitation inhibitors. Second, chemical and enzymatic instability erodes the payload before absorption. Phenolics undergo auto-oxidation and isomerization at gastric pH, while esterases, glucuronidases, and sulfotransferases rapidly modify scaffolds, altering permeability and potency[27–30]. Third, the mucus layer and epithelial junctions pose physical barriers. Mucins form a negatively charged, viscoelastic network that traps hydrophobic aggregates and cationic molecules, whereas tight junctions restrict paracellular transit of hydrophilic, larger entities. Transcellular passage requires a favorable logP, low polarity, and transporter compatibility that many phytochemicals lack[31, 32].

Even when epithelial entry occurs, efflux transporters reduce net absorption. P-glycoprotein and BCRP recognize several phytochemicals and their metabolites, cycling them back into the lumen[33]. Metabolic extraction in enterocytes and hepatocytes further decreases the fraction reaching systemic circulation; glucuronidation and sulfation increase polarity and hasten biliary or renal clearance[33]. In obesity and T2D, these ADME processes may change: inflammatory signals modulate transporter and enzyme expression, bile acid pools shift, and gut motility and permeability alter, together producing unpredictable exposure. Food effects exacerbate variability, as co-ingested lipids may solubilize hydrophobic compounds but also delay gastric emptying and stimulate bile secretion that differentially affects micellar incorporation[34].

Distribution to target tissues adds another layer of complexity. Expanded adipose mass acts as a lipophilic sink, sequestering hydrophobic molecules and flattening concentration–time profiles in liver and muscle. Steatotic liver alters sinusoidal fenestrae and Kupffer cell activity, shifting the balance between parenchymal uptake and reticuloendothelial sequestration[35]. The pancreatic islet microcirculation is exquisitely sensitive to viscosity and endothelial activation, reducing access for bulky complexes. Meanwhile, many beneficial mechanisms require sustained exposure at low concentrations rather than sharp peaks; rapid clearance frustrates this pharmacodynamic preference[35].

Conventional formulation approaches, such as particle size reduction, solid dispersions, co-crystals, and permeability enhancers, partially address these barriers but often cannot simultaneously stabilize the compound, navigate mucus, bypass efflux, and target metabolic tissues[36]. Moreover, safety limits constrain the use of high-levels of cosolvents or surfactants in chronic indications. Nanotechnology reframes the problem: instead of forcing the molecule to fit the gastrointestinal rules, the carrier is engineered to shoulder solubilization, protection, and transport while presenting a biocompatible interface to the gut and systemic compartments[36]. The remainder of this review translates these barrier analyses into design criteria for lipidic, polymeric, and hybrid nanocarriers and shows how they can be tuned to the pathophysiologic features of obesity-linked T2D.

3. Lipid-Based Nanocarriers: Liposomes, SLN, NLC, LNP, and Phytosomes

Lipid systems are natural candidates for delivering hydrophobic plant bioactives because they mimic dietary micelles and lipoproteins[37–39]. Classical liposomes, bilayer vesicles formed from phospholipids and cholesterol, encapsulate hydrophobic molecules within the membrane and hydrophilic compounds in the aqueous core. For flavonoids and terpenoids, membrane loading increases apparent solubility and shields labile moieties from gastric conditions. PEGylation extends circulation, while ligand decoration (e.g., galactose, GalNAc clusters) directs uptake by hepatocyte asialoglycoprotein receptors, relevant for steatosis-dominant phenotypes[38]. Thermosensitive and pH-sensitive liposomes synchronize release with local microenvironments, such as acidic endosomes of adipocytes and macrophages.

Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) replace fluid bilayers with solid or mixed solid–liquid lipid matrices that entrap bioactives with improved physical stability[40–43]. SLN, composed of saturated triglycerides or waxes stabilized by surfactants, offer protection but can expel cargo during crystallization. NLCs mitigate this by introducing liquid lipids that create lattice imperfections, increasing loading capacity for curcumin, quercetin, or berberine and reducing burst release. Both platforms enhance lymphatic uptake after oral administration, partially bypassing first-pass metabolism and delivering higher hepatic exposure at lower doses. In obesity models, NLC-curcumin reduced hepatic triglycerides and inflammatory markers more effectively than free curcumin at matched doses, consistent with improved bioavailability and tissue deposition[44].

Ionizable lipid nanoparticles (LNP) are optimized for nucleic acids but increasingly co-deliver small molecules to exploit endosomal escape capacity. Embedding polyphenols within LNP shells can localize them to the cytosol of hepatocytes or adipocytes, where they influence AMPK and lipogenic programs[41, 42, 45]. Co-loading with siRNA against PTP1B or SREBP-1c creates synergistic suppression of insulin signaling brakes and lipogenesis. Because ionizable lipids are neutral at physiologic pH, they maintain mucus compatibility and minimize off-target membrane disruption.

Phytosomes occupy a distinct niche by complexing plant constituents with phosphatidylcholine to form amphiphilic assemblies that improve membrane affinity and lymphatic transport. Silymarin and curcumin phytosomes demonstrate superior oral bioavailability versus conventional extracts and have advanced furthest clinically[46]. Design variables across lipid systems, such as fatty acyl saturation, cholesterol content, particle size, and surface charge, allow fine-tuning of stability, release, and biodistribution. Importantly, excipient selection must consider chronic dosing in metabolic disease; generally recognized as safe lipids, low-immunogenic PEG analogs, and minimal surfactant levels reduce complement activation-related reactions[46]. When matched to the compound's chemistry and the patient's endotype, lipidic nanocarriers can convert promising phytochemistry into reproducible metabolic benefit.

Practical manufacturing has matured through microfluidic mixing, hot and cold high-pressure homogenization, and spray- or freeze-drying into solid intermediates that reconstitute rapidly. These processes support cGMP scalability, while process analytical tools like dynamic light scattering, nanoparticle tracking, and differential scanning calorimetry link critical attributes to performance[47]. Together, advances in formulation and process

control position lipid-based systems as front-line options for oral and targeted delivery of plant-derived antidiabetics.

4. Polymeric, Polysaccharide, and Hybrid Nanocarriers for Phytochemical Delivery

Polymeric nanoparticles offer mechanical robustness, controlled release, and facile surface engineering. Poly(lactic-co-glycolic acid) (PLGA), an FDA-approved biodegradable polymer, encapsulates hydrophobic phytochemicals via nanoprecipitation or double emulsion[48–50]. Encapsulation shields curcumin and resveratrol from hydrolysis and photodegradation, while lactic: glycolic ratio and molecular weight govern degradation kinetics that translate into sustained plasma levels. Surface PEGylation improves mucus penetration and reduces opsonization; conjugation of GalNAc or mannose targets hepatocytes or macrophages implicated in steatohepatitis[51, 52]. For berberine, PLGA systems have increased oral exposure several-fold and enhanced glucose-lowering through combined hepatic and adipose actions.

Polysaccharide carriers add biological functionality. Chitosan, a cationic, mucoadhesive polymer, transiently opens tight junctions and improves paracellular transport, enhancing absorption of hydrophilic phenolics and saponins[53–55]. Thiolation and quaternization further increase mucoadhesion and stability at neutral pH, while hyaluronic acid coatings provide stealth and CD44-mediated targeting to inflamed tissues. Alginate and pectin enable colon-targeted release, positioning polyphenols for microbial biotransformation into more bioavailable metabolites that impact the gut–liver axis[56–58]. Cyclodextrin inclusion complexes, although not nanoparticles per se, are nanoscale host–guest assemblies that solubilize planar aromatics such as quercetin and genistein; embedding these complexes into lipid or polymer matrices couples rapid dissolution with sustained release.

Hybrid platforms combine advantages across materials. Lipid–polymer hybrid nanoparticles place a fluid lipid shell around a polymeric core, improving stability, cargo loading, and endosomal escape. Metal–phenolic networks harness coordination between polyphenols and ferric ions to form robust, pH-responsive shells that disassemble in acidic endosomes to release payloads. Stimuli-responsive designs exploit the inflammatory microenvironment of obesity: ROS-labile linkers release antioxidants where oxidative stress is high; enzyme-cleavable peptides respond to matrix metalloproteinases in inflamed adipose; and pH-sensitive backbones accelerate release within macrophage lysosomes[59–61]. Prodrug strategies that conjugate phytochemicals to fatty acids or short peptides increase lipophilicity and transporter engagement, with intracellular esterases regenerating the parent compound.

Manufacturability and safety shape polymer selection. PLGA, PCL, and PEG-based materials possess established safety records and scalable processes, including microfluidics and spray drying. Residual solvent control, particle size distribution, and endotoxin levels are critical quality attributes[62]. For chronic indications, limiting cationic charge density reduces complement activation and hemolysis risk. When rationally matched to the biopharmaceutic profile of the plant compound and the target tissue, polymeric and hybrid systems provide a complementary toolkit to lipid carriers, enabling tailored solutions for dissolution, protection, permeability, and targeting.

Emerging fabrication methods such as microdroplet templating and flash nanoprecipitation deliver tight polydispersity and high loading at industrially relevant throughputs. These advances, combined with modular chemistry for ligand attachment and stimuli-responsive linkers, permit rapid iteration across plant scaffolds and patient endotypes, accelerating optimization toward human-relevant pharmacokinetics and pharmacodynamics[63]. Together, they move phytochemicals closer to reliable, patient-level therapeutic performance.

5. Targeting Metabolic Tissues and Shaping Pharmacokinetics–Pharmacodynamics

Effective therapy for obesity-linked diabetes depends on delivering active compounds to the liver, adipose tissue, skeletal muscle, and pancreatic islets while minimizing off-target exposure. Nanocarriers enable such selectivity through multiscale design. Size between 70 and 120 nm avoids rapid renal filtration yet permits passage through hepatic sinusoidal fenestrae and inflamed adipose microvasculature[64, 65]. Surface charge near neutrality or weak zwitterionic profiles reduces mucus interaction and complement activation, extending residence in the intestinal and vascular compartments. Beyond these physicochemical baselines, ligand-mediated targeting confers tissue preference. GalNAc clusters bind the hepatocyte asialoglycoprotein receptor with high avidity; apolipoprotein E adsorption can be intentionally promoted to engage LDL receptors; and vitamin A directs uptake by hepatic stellate cells relevant to fibrotic NASH. For adipose tissue, peptides discovered by in vivo phage display recognize prohibitin or neuropilin-1 on adipose endothelium and macrophages, enriching depot exposure. Skeletal muscle uptake increases when carriers present transferrin or insulin receptor ligands and exhibit reduced stiffness to traverse endothelial gaps[66, 67]. β-cell targeting leverages GLP-1 receptor fragments or SUR1-binding motifs that concentrate payloads in islets, supporting insulin secretory function.

Pharmacokinetic control is inseparable from targeting. Mucoadhesive coatings such as chitosan or lectins prolong intestinal contact and open tight junctions, raising absorption of hydrophilic phenolics. Enteric and colon-targeted coatings direct release distally, favoring microbial transformation into absorbable metabolites and modulating bile-acid pools that signal via FXR/TGR5 to improve insulin sensitivity[68]. Lymphatic

uptake via chylomicron mimicry bypasses first-pass metabolism and delivers higher hepatic and adipose exposure at lower oral doses. Once systemic, circulation half-life is tuned by PEG density, hydrodynamic size, and protein corona engineering; pre-adsorbing selected proteins or presenting CD47-mimetic peptides reduces opsonization[68].

Ultimately, successful targeting culminates in productive intracellular trafficking. Endosomal escape is essential when the payload must reach the cytosol or nucleus; ionizable lipids, pH-buffering polymers, and membrane fusion peptides enable this step. For mitochondrial actions—central to improving oxidative capacity, triphenylphosphonium decorations or cardiolipin-affine peptides bias localization[69]. Quantitative systems pharmacology models that integrate absorption, distribution, intracellular routing, and pharmacodynamics help translate preclinical exposure–response into human dose projections. In obesity and T2D, altered blood flow, RES activity, and tissue composition require model parameters fitted in diseased animals. Combining these computational tools with imaging and mass spectrometry biodistribution studies yields an evidence-based basis for first-in-human designs that balance efficacy with safety[69].

An often overlooked lever is the dosing schedule. Because many phytochemicals act on transcriptional programs and mitochondrial biogenesis, sustained concentrations near the minimal effective level may outperform high peaks[70]. Long-acting depot formulations for subcutaneous delivery, or oral systems that produce plateau exposure via zero-order release, can align exposure with the mechanism while improving adherence. Chronotherapeutic timing, aligning dosing with feeding windows and circadian metabolic rhythms may further amplify efficacy and reduce adverse effects.

6. Preclinical Efficacy, Mechanistic Synergy, and the Microbiome Interface

Across rodent models of diet-induced obesity and genetic insulin resistance, nanoformulated phytochemicals outperform equivalent doses of free compounds on glycemic and hepatic endpoints. Curcumin or quercetin delivered in nanostructured lipid carriers lowers fasting glucose and insulin, reduces hepatic triglyceride content, and improves glucose and insulin tolerance tests with smaller variance than non-encapsulated controls[71–73]. Berberine encapsulated in PLGA or lipid–polymer hybrids achieves several-fold higher plasma exposure, stronger suppression of hepatic lipogenesis, and favorable shifts in adipose macrophage polarization. Ginsenoside-loaded chitosan nanoparticles enhance GLP-1 secretion, increase brown adipose thermogenesis markers, and reduce body-weight gain, echoing incretin-like effects without gastrointestinal intolerance seen at high oral doses of the free saponins[74–76].

Mechanistic profiling reveals multi-level synergy. Nano-curcumin reduces NF-κB activation and NLRP3 assembly in adipose tissue, relieving inflammatory brakes on insulin signaling; simultaneous AMPK activation in liver and muscle redirects substrate flux from lipogenesis to oxidation[53, 73]. Quercetin nanosystems augment GLUT4 translocation in myotubes and suppress hepatic SREBP-1c, while berberine nanoparticles concentrate in the liver to inhibit mitochondrial complex I at tolerable exposures, thereby engaging AMPK and lowering gluconeogenesis. When paired with nucleic acids such as siRNA to PTP1B or miR-33 antagonists, lipid nanoparticles co-deliver orthogonal mechanisms that yield larger and more durable glycemic benefits than either modality alone[53].

The gut microbiome acts as both a mediator and target of nano-enabled phytochemicals. Colon-targeted systems increase luminal concentrations that feed microbial enzymes, generating metabolites (e.g., urolithins from ellagitannins) with superior absorption and mitochondrial benefits[77, 78]. Conversely, nanoparticles can reshape microbial ecology by altering bile-acid signaling and short-chain fatty acid production, in turn improving intestinal barrier function and systemic inflammation. These bidirectional effects support a model in which part of the pharmacology arises from host–microbe co-metabolism rather than direct host targeting alone.

Head-to-head comparisons with standard therapies suggest complementarity. In combination with metformin or GLP-1 receptor agonists, nanoformulated phytochemicals allow dose reduction while broadening effects on steatosis, fitness, and inflammatory biomarkers[65]. Durability after treatment cessation observed in some models hints at network reprogramming, though confirmatory studies with longer follow-up and standardized endpoints are needed. Collectively, the preclinical portfolio justifies early clinical exploration with a focus on human-relevant biomarkers and patient endotypes most likely to benefit.

Translationally, priority candidates couple strong mechanistic plausibility with favorable safety margins and manufacturability. Curcumin phytosomes, quercetin NLC, and berberine PLGA systems exemplify this triad and are amenable to blinding and placebo control in capsules or sachets[76, 79, 80]. Early trials should incorporate hepatic proton MR spectroscopy for intrahepatic triglyceride, continuous glucose monitoring for glycemic variability, indirect calorimetry for substrate utilization, and circulating exosomal microRNAs as pharmacodynamic reporters of tissue engagement. Such multidomain readouts can detect network-level change even when HbA1c shifts are modest over short durations, de-risking subsequent larger studies.

7. Safety, Manufacturing, and Regulatory Pathways Toward Clinical Translation

Nanocarriers intended for chronic metabolic diseases must meet a high bar for safety and quality. Key risks include complement activation–related pseudoallergy, immunogenicity of PEG or cationic components, accumulation in the reticuloendothelial system, and excipient-related hepatotoxicity at sustained doses[81, 82].

Mitigations begin with material selection like GRAS lipids, biodegradable polymers such as PLGA or PCL, and zwitterionic or low-density PEG coatings, and continue through process controls that minimize residual solvents, peroxides, and endotoxin. For polysaccharide systems, degree of deacetylation, molecular weight, and counterion composition govern hemocompatibility and batch variability. Biodistribution and toxicology should be characterized in obese, dyslipidemic models that better reflect human RES activity and complement tone, using repeated dosing to probe accelerated clearance phenomena.

Manufacturability under cGMP hinges on scalable, reproducible assembly with real-time analytics[83]. Continuous-flow microfluidic mixing produces narrow polydispersity and precise size control for lipidic and polymeric systems. High-pressure homogenization supports SLN and NLC at kilogram scales, while spray and freeze drying create stable solid intermediates for oral dosage forms. Critical quality attributes include mean particle size and polydispersity, zeta potential, encapsulation efficiency, release kinetics, lipid/polymer composition, residual solvent and endotoxin levels, sterility, and potency[83]. Potency assays should reflect the mechanism of insulin-stimulated glucose uptake in myotubes, suppression of hepatic SREBP-1c transcription, or reduction of inflammatory cytokines in macrophages, and establish in vitro–in vivo correlations that guide specification windows[84].

Regulatory strategy benefits from precedents in lipid nanoparticle vaccines, oral lipid systems, and botanical drug frameworks. Early engagement with authorities can align on identity testing for complex botanicals, control of extract variability, and justification for excipient levels in chronic use. Human studies should begin with bioavailability and pharmacodynamic bridging comparing nano-enabled versus conventional extracts at matched doses and then progress to randomized trials in defined endotypes, for example, steatohepatitis-predominant versus adipose-inflammation-predominant T2D[85]. Concomitant background therapy should be standardized to reveal the add-on benefit. Post-marketing plans must consider adherence, potential interactions with bile-acid sequestrants or P-glycoprotein modulators, and patient education around the distinction between standardized nanoformulations and heterogeneous dietary supplements. With disciplined development that couples material science to disease biology, nano-enabled phytochemicals can advance from promising lab findings to reliable clinical options in obesity-linked diabetes[85].

Finally, supply-chain resilience and sustainability merit attention. Botanical sourcing must ensure consistent chemotype, absence of adulterants, and environmental stewardship; analytics such as LC–MS fingerprinting, qNMR, and bioassay profiling can lock identity to function[86]. Excipient supply should prioritize pharmacopeial grades and second-source vendors to buffer shortages. Patient-centric design, palatable oral formats, once-daily dosing, and clear labelling support adherence in real-world settings. Digital companions that monitor dosing times, glucose variability, and symptoms could feed back into adaptive dosing algorithms, aligning exposure with circadian and behavioral cycles. Integrating these practical considerations with rigorous CMC and clinical evidence will determine whether nanotechnology fulfills its promise for plant-based antidiabetic therapy.

CONCLUSION

Plant-derived antidiabetic compounds map naturally onto the network biology of obesity-linked type 2 diabetes, but their clinical potential has been hampered by solubility, stability, permeability, and metabolic liabilities. Nanotechnology reframes these liabilities as design problems, providing carriers that solubilize, protect, and transport phytochemicals while guiding them to metabolic tissues and into productive intracellular pathways. Lipid systems, polymeric and polysaccharide platforms, and hybrids now demonstrate reliable gains in bioavailability and pharmacodynamic potency across multiple compounds, with emerging evidence of synergy when combined with nucleic acids or standard therapies. Safety and manufacturability are tractable through judicious material selection, continuous-flow assembly, and potency assays tied to mechanism, positioning nano-enabled phytochemicals for regulatory pathways informed by experience with lipid nanoparticles and botanical drugs. The next phase should emphasize endotype-guided design and human-relevant endpoints. Trials that stratify patients by steatosis burden, adipose inflammation, or β-cell reserve; that incorporate hepatic fat imaging, continuous glucose monitoring, and exosomal biomarkers; and that test chronotherapeutic dosing will sharpen signal detection and illuminate mechanisms. If these elements converge, nanotechnology can convert promising plant chemistry into durable, multi-organ metabolic reprogramming, complementing incretin and SGLT2 regimens and moving care beyond single-pathway control toward systems repair.

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CITE AS: Kibibi Muthoni L. (2026). Nanotechnology Approaches in Enhancing Bioavailability of Plant-Derived Antidiabetic Compounds for Obesity-Linked Diabetes. NEWPORT INTERNATIONAL JOURNAL OF RESEARCH IN MEDICAL SCIENCES.
https://doi.org/10.59298/NIJRMS/2026/7.1.111000