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Nanotechnology-Based Delivery Systems for Anti-Obesity and Antidiabetic Phytochemicals

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ABSTRACT

Phytochemicals have long served as bioactive agents against metabolic disorders such as obesity and type 2 diabetes mellitus (T2DM). However, their poor solubility, instability, rapid metabolism, and low bioavailability hinder clinical efficacy. Nanotechnology offers an advanced solution, improving the pharmacokinetics, targeted delivery, and therapeutic impact of these compounds. This review synthesizes current progress in nanocarrier systems such as liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, and metallic nanocomposites applied to anti-obesity and antidiabetic phytochemicals. Mechanistic insights are provided into how these systems enhance intestinal absorption, protect bioactive compounds from degradation, and improve metabolic targeting. Finally, the review addresses translational challenges, regulatory aspects, and future perspectives for clinical development of phytochemical-loaded nanocarriers in metabolic disease therapy.

Keywords: nanotechnology, phytochemicals, obesity, diabetes, bioavailability

INTRODUCTION

Obesity and type 2 diabetes mellitus (T2DM) represent intertwined global health epidemics with escalating socioeconomic burdens[1, 2]. Their shared etiopathogenesis rooted in energy imbalance, insulin resistance, and chronic low-grade inflammation underscores the necessity for integrated therapeutic strategies[3]. Phytochemicals, encompassing flavonoids, polyphenols, alkaloids, terpenoids, and saponins, have shown multifaceted metabolic benefits: improving insulin sensitivity, attenuating adipogenesis, enhancing lipid oxidation, and modulating gut microbiota[4–8]. Yet, despite robust preclinical efficacy, most plant-derived compounds fail to reach clinical translation due to pharmacokinetic and formulation limitations.

Many bioactive phytochemicals such as curcumin, resveratrol, quercetin, berberine, catechins, and chlorogenic acid suffer from poor aqueous solubility, instability in gastrointestinal (GI) fluids, and rapid first-pass metabolism[9–11]. As a result, their oral bioavailability is often below 5%, precluding sustained systemic exposure and therapeutic plasma levels[12, 13]. Moreover, phytochemicals generally undergo non-specific distribution, leading to suboptimal tissue targeting. This pharmacological inefficiency limits dose-response relationships and increases variability across individuals[14].

Nanotechnology provides a transformative approach to overcome these challenges by designing nanoscale carriers (10–500 nm) capable of encapsulating phytochemicals within biocompatible matrices[3, 15–18]. These systems can modulate drug release kinetics, enhance intestinal permeability, and shield active compounds from enzymatic degradation. Nanocarriers also offer the ability to preferentially deliver bioactives to metabolic tissues such as adipose, liver, and skeletal muscle thus enhancing site-specific pharmacodynamics. Importantly, by improving solubility and stability, nanocarriers lower the required therapeutic dose and mitigate adverse effects[19, 20].

In obesity, excessive lipid accumulation and adipocyte hypertrophy trigger endoplasmic reticulum stress and inflammatory cascades mediated by TNF- α , IL-6, and NF- κ B[21]. Many phytochemicals, such as curcumin and EGCG, attenuate these responses by modulating AMPK, PPAR γ , and SIRT1 signaling[22–25]. However, their therapeutic potential is hindered by degradation and low systemic retention. Encapsulation within nanocarriers can sustain release, maintain bioactivity, and facilitate passage through biological barriers such as the intestinal mucosa or blood–liver interface[26–28]. Similarly, in diabetes, nanoparticles enhance the transport of insulin—This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

sensitizing phytochemicals across intestinal epithelium and target pancreatic β -cells, improving glycemic control.

Several nanocarrier types have emerged. Liposomes, comprising phospholipid bilayers, effectively encapsulate both hydrophilic and hydrophobic molecules[26, 29, 30]. Polymeric nanoparticles, using biodegradable materials such as PLGA or chitosan, provide controlled release and mucoadhesion. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) improve lipid solubility and prolong circulation[31–34]. Nanoemulsions enhance the dispersion and absorption of lipophilic phytochemicals. More recently, metallic nanoparticles (e.g., gold, silver, zinc oxide) have demonstrated synergistic biological activity when conjugated with phytochemicals, further augmenting anti-inflammatory and antioxidant effects[35–37].

The impact of nanotechnology extends beyond pharmacokinetics to cellular signaling. For instance, curcumin-loaded nanoparticles activate AMPK and suppress mTOR more effectively than free curcumin, promoting autophagy and thermogenic pathways[38]. Quercetin nanoformulations modulate GLUT4 translocation, enhancing glucose uptake. Berberine nanoparticles increase mitochondrial function and inhibit adipogenesis through PPAR γ downregulation. These improvements stem from enhanced intracellular uptake and sustained availability at target sites[38].

Nonetheless, translation to clinical applications remains challenging. The biocompatibility of carrier materials, long-term safety, and potential nanoparticle accumulation must be rigorously assessed[39]. Regulatory frameworks for nanoformulations of natural products remain underdeveloped, complicating approval pathways. Furthermore, cost-effective scale-up, reproducibility, and stability under physiological conditions require optimization. Despite these challenges, nanotechnology represents a frontier for unlocking the therapeutic promise of phytochemicals against obesity and diabetes[39].

This review explores six major themes: nanocarrier classes, pharmacokinetic enhancements, mechanistic interactions, preclinical efficacy, clinical prospects, and translational challenges. Collectively, they illustrate how nanosystems are redefining the pharmacology of phytochemicals toward next-generation metabolic therapeutics.

2. Nanocarrier Systems for Phytochemical Delivery

Nanocarriers vary widely in composition, structure, and functionality. Liposomes, composed of phospholipid bilayers enclosing aqueous cores, remain the gold standard for encapsulating amphiphilic phytochemicals[40]. Their biomimetic nature allows fusion with cell membranes, enhancing intracellular delivery. Curcumin-loaded liposomes, for example, display increased stability and greater adipose tissue accumulation in obese animal models compared to free curcumin[41]. Polymeric nanoparticles, often built from biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA) or chitosan, offer precise control over release kinetics. Chitosan's mucoadhesive property prolongs intestinal residence, improving absorption of hydrophobic compounds such as resveratrol[31–34].

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) utilize lipid matrices that encapsulate lipophilic phytochemicals, protecting them from hydrolysis and oxidation. SLNs provide high stability, while NLCs integrate liquid lipids to improve payload capacity[42, 43]. EGCG-loaded NLCs, for instance, demonstrate enhanced thermogenic activation in brown adipose tissue. Nanoemulsions, a kinetically stable mixture of oil, water, and surfactant, improve the solubilization and intestinal diffusion of poorly soluble molecules. Their small droplet size (20–200 nm) facilitates lymphatic uptake, bypassing hepatic first-pass metabolism[42].

Emerging nanocarriers include dendrimers, micelles, and metallic nanoparticles. Dendrimers feature branched architectures capable of high drug loading and surface functionalization for targeted delivery[44, 45]. Micelles self-assemble from amphiphilic polymers, entrapping hydrophobic cores ideal for polyphenols. Metallic nanoparticles such as gold or zinc oxide, when conjugated with phytochemicals, provide both delivery and intrinsic bioactivity through redox modulation. Each platform offers distinct advantages depending on molecular polarity, desired release profile, and target tissue.

3. Enhancement of Pharmacokinetics and Bioavailability

Phytochemicals often exhibit limited oral absorption due to poor solubility and extensive presystemic metabolism. Nanocarriers mitigate these barriers by increasing apparent solubility, protecting labile molecules, and promoting alternative absorption pathways[26, 46]. Nanoemulsions and lipid carriers facilitate lymphatic transport via chylomicron formation, avoiding hepatic degradation[47]. Polymeric nanoparticles improve intestinal retention through mucoadhesion, while PEGylation of nanocarriers prolongs circulation time and reduces macrophage clearance[47].

For example, quercetin-loaded PLGA nanoparticles increased oral bioavailability up to tenfold in diabetic rats compared to the free compound[48]. Curcumin nanoformulations displayed extended half-life, higher C_{max}, and improved tissue distribution, correlating with enhanced AMPK activation and lipid-lowering effects. Nanocarriers can also promote cellular uptake via endocytosis, resulting in sustained intracellular retention. Controlled release properties maintain steady-state concentrations, minimizing fluctuation-induced toxicity or inefficacy[48].

Importantly, nanocarriers can bypass P-glycoprotein (P-gp) efflux transporters, a major obstacle in phytochemical absorption. Coating with surfactants like Tween 80 or lecithin inhibits efflux pumps and tight junction closure, improving paracellular permeability[49, 50]. The result is a marked increase in systemic exposure, which translates to better glycemic control and adipose regulation in animal models.

4. Mechanistic Insights into Nanophytochemical Activity

Nanocarrier systems not only enhance pharmacokinetics but also modulate cellular signaling dynamics. Curcumin nanoparticles upregulate AMPK and SIRT1 more potently than free curcumin, leading to increased fatty acid oxidation and mitochondrial biogenesis. Similarly, berberine-loaded liposomes exhibit higher affinity for hepatic tissues, resulting in improved glucose tolerance through inhibition of hepatic gluconeogenesis and enhancement of insulin signaling[41].

Quercetin and resveratrol nanoparticles act synergistically to enhance GLUT4 translocation and reduce adipogenic gene expression[48, 51, 52]. EGCG nanoemulsions amplify thermogenic gene expression in brown adipose tissue via PGC-1 α activation. These mechanisms illustrate how nanocarrier-mediated improvements in stability and intracellular concentration potentiate metabolic pathway modulation.

Nanocarriers can also alter biodistribution to favor metabolic tissues. For instance, PEGylated nanoparticles demonstrate preferential accumulation in inflamed adipose and hepatic tissues due to enhanced permeability and retention (EPR) effects[53]. Metallic phytochemical conjugates introduce redox-active properties that mitigate oxidative stress and inflammation, which are the key drivers of insulin resistance. Thus, nanoformulations amplify both pharmacodynamic and pharmacokinetic dimensions of phytochemical action.

5. Preclinical Efficacy Studies

Animal models have validated the superior efficacy of nanophytochemical formulations compared to free compounds. Curcumin nanoparticles reduced weight gain, hepatic steatosis, and fasting glucose levels more effectively than native curcumin in high-fat diet-induced obese mice[54]. Resveratrol nanoemulsions enhanced insulin sensitivity and lipid metabolism in diabetic rats by upregulating AMPK and suppressing SREBP-1c expression. Berberine nanoparticles produced greater reductions in blood glucose and lipid levels while minimizing gastrointestinal discomfort associated with free berberine[43, 55, 56].

EGCG-loaded SLNs promoted browning of white adipose tissue and increased energy expenditure, correlating with reduced adiposity[57]. Quercetin nanoparticles improved endothelial function and attenuated oxidative stress in diabetic models. These studies collectively highlight how nanocarriers enhance target engagement, tissue bioavailability, and therapeutic outcomes at lower doses[57]. The convergence of improved pharmacokinetics and mechanistic potency establishes nanotechnology as an indispensable platform for advancing phytochemical therapy in metabolic diseases.

6. Clinical Translation and Regulatory Perspectives

Despite strong preclinical data, few nanophytochemical formulations have progressed to clinical trials. Regulatory uncertainty surrounding nanoparticle-based nutraceuticals remains a major barrier[58]. Most agencies, including the FDA and EMA, require a comprehensive characterization of nanoparticle size, charge, surface chemistry, and biodegradability. Long-term toxicity studies are necessary to assess potential accumulation or immunogenicity. Moreover, scaling laboratory nanoformulations to industrial production introduces issues of reproducibility, cost, and stability[58].

Nevertheless, early-phase clinical studies are promising. Curcumin nanomicelles and resveratrol nanoformulations have demonstrated enhanced bioavailability and tolerability in human volunteers[59]. Liposomal berberine supplements improved glycemic markers with minimal side effects. These outcomes indicate that nanotechnology can feasibly bridge the gap between dietary phytochemicals and pharmaceutical-grade metabolic interventions[59].

Future regulatory frameworks must balance innovation with safety, recognizing nanocarriers as functional excipients rather than active drugs when appropriate. Standardized characterization protocols and clear labeling of nanoscale ingredients will foster consumer and clinician confidence. Collaboration between academia, industry, and health authorities will be critical to advance these technologies toward clinical acceptance.

7. Future Directions

The convergence of nanotechnology and phytochemistry heralds a new era in metabolic disease management. Future research should prioritize smart nanocarriers with stimuli-responsive release triggered by pH, temperature, or enzymatic activity within metabolic tissues. Combining multiple phytochemicals in a single nanoformulation may yield synergistic modulation of insulin signaling, lipid metabolism, and inflammation. Integration with targeted ligands such as peptides or antibodies directed to GLUT4 or adipose vasculature could further refine tissue specificity.

Translational success will depend on comprehensive pharmacokinetic modeling, safety profiling, and scalable manufacturing. Advanced imaging and omics technologies can elucidate biodistribution and mechanistic pathways in vivo. Importantly, regulatory harmonization across nutraceutical and pharmaceutical domains will be essential to facilitate global adoption.

CONCLUSIONS

In conclusion, nanotechnology-based delivery systems offer a transformative platform to realize the therapeutic potential of anti-obesity and antidiabetic phytochemicals. By overcoming intrinsic pharmacokinetic barriers, enhancing cellular targeting, and amplifying mechanistic efficacy, nanosystems redefine the pharmacological landscape of natural bioactives. Continued interdisciplinary innovation promises to translate these formulations from experimental models to mainstream clinical therapeutics, offering safer, more efficient, and biologically integrated interventions for obesity and diabetes.

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