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Natural Product–Based Nanocarriers for Precision Glycemic Control: Innovations in Diabetes Nanomedicine

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ABSTRACT

Diabetes mellitus (DM) is a complex metabolic disorder characterized by chronic hyperglycemia and progressive vascular complications. Despite advances in pharmacotherapy, achieving sustained glycemic control without adverse effects remains challenging. Natural products including polyphenols, alkaloids, terpenoids, polysaccharides, and bioactive lipids exhibit potent antidiabetic properties, yet their clinical translation is limited by poor solubility, low bioavailability, rapid metabolism, and non-specific tissue distribution. Recent advances in nanomedicine have enabled the development of natural product–based nanocarriers that not only deliver phytochemicals efficiently but also serve as functional biomaterials themselves. These nanocarriers, including chitosan nanoparticles, alginate nanogels, lipid-based systems, protein nanoparticles, and plant-derived extracellular vesicle–like nanostructures, offer biocompatibility, biodegradability, and intrinsic bioactivity. Precision glycemic control is achievable through targeted delivery to pancreatic β-cells, hepatocytes, adipose tissue, and skeletal muscle, as well as glucose-responsive and stimuli-sensitive release systems. This review examines the integration of natural biomaterials and nanotechnology for diabetes management, highlighting mechanistic pathways, innovative design strategies, preclinical evidence, safety considerations, and translational challenges. Natural product–based nanocarriers represent a promising frontier in precision diabetes nanomedicine.

Keywords: diabetes nanomedicine, natural products, nanocarriers, precision glycemic control, phytochemicals

INTRODUCTION

Diabetes mellitus (DM) remains a leading cause of morbidity and mortality worldwide, driven by persistent hyperglycemia resulting from insulin deficiency, insulin resistance, or a combination of both. Type 1 diabetes (T1DM) is characterized by autoimmune-mediated destruction of pancreatic β-cells, whereas type 2 diabetes (T2DM), which accounts for the majority of cases, arises from progressive insulin resistance and β-cell dysfunction[1–3]. Chronic hyperglycemia contributes to microvascular complications such as nephropathy, neuropathy, and retinopathy, as well as macrovascular complications including cardiovascular disease and stroke[4].

Conventional antidiabetic therapies, including insulin, metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists, have significantly improved disease management. However, limitations persist. These include hypoglycemia risk, gastrointestinal disturbances, weight gain, cardiovascular concerns, therapeutic resistance, and limited tissue specificity[5–8]. Furthermore, many patients fail to achieve durable glycemic control due to disease heterogeneity and progressive β-cell decline [9]. These challenges have prompted exploration of complementary and innovative therapeutic strategies.

Natural products have historically played a central role in metabolic disease management. Bioactive compounds derived from medicinal plants, marine organisms, fungi, and dietary sources exhibit diverse antihyperglycemic mechanisms. Polyphenols such as quercetin and resveratrol activate AMP-activated protein kinase (AMPK), enhance insulin sensitivity, and reduce oxidative stress[10]. Alkaloids such as berberine modulate glucose metabolism via AMPK activation and gut microbiota regulation. Terpenoids, saponins, and polysaccharides improve insulin secretion and inhibit carbohydrate-digesting enzymes. Many natural products also exert anti-inflammatory and antioxidant effects, mitigating the chronic low-grade inflammation characteristic of T2DM[1, 11, 12].

Despite their therapeutic promise, most natural compounds face pharmacokinetic challenges. Poor aqueous solubility, instability in gastrointestinal environments, rapid hepatic metabolism, and low systemic bioavailability limit their clinical effectiveness[13]. Additionally, non-specific distribution reduces drug concentration at target tissues, diminishing therapeutic precision. For example, curcumin demonstrates potent antidiabetic and anti-inflammatory activity in vitro but exhibits extremely low oral bioavailability in humans[13].

Nanomedicine offers transformative solutions to these limitations. Nanocarriers, typically ranging from 1 to 200 nanometers, enable improved drug solubility, enhanced permeability across biological membranes, protection from enzymatic degradation, and controlled or sustained release[14–16]. Importantly, nanocarriers can be engineered for targeted delivery, thereby increasing therapeutic concentration at specific organs such as pancreatic islets, liver, adipose tissue, or skeletal muscle.

Natural product–based nanocarriers represent an emerging paradigm in diabetes nanomedicine. Unlike synthetic polymeric systems alone, these platforms utilize naturally derived biomaterials such as chitosan, alginate, dextran, gelatin, lipid vesicles, and plant-derived nanovesicles to construct delivery systems[17–19]. These materials offer inherent biocompatibility, biodegradability, low immunogenicity, and sometimes intrinsic biological activity. For instance, chitosan possesses mucoadhesive properties that enhance intestinal absorption, while alginate provides pH-responsive drug release.

Precision glycemic control requires therapeutic strategies that respond dynamically to metabolic cues. Glucose-responsive nanocarriers represent a significant innovation, enabling insulin or bioactive compound release in response to elevated glucose levels. Similarly, inflammation-responsive and oxidative stress–sensitive systems enable localized release within metabolically dysregulated tissues[20]. These intelligent nanoplatforms reduce hypoglycemia risk and improve therapeutic specificity.

Additionally, natural product–based nanocarriers support combination therapy. Co-delivery of multiple phytochemicals or integration of phytochemicals with conventional drugs can address multifactorial disease pathways simultaneously targeting oxidative stress, inflammation, mitochondrial dysfunction, and insulin resistance in parallel[20]. However, challenges remain. Large-scale manufacturing, reproducibility, long-term safety, nanoparticle accumulation, regulatory classification, and quality control standards require systematic evaluation. As regulatory agencies refine nanomedicine guidelines, ensuring safety and efficacy will be paramount[21–23].

This review explores the development of natural product–based nanocarriers for precision glycemic control. It examines classes of natural biomaterial nanocarriers, mechanisms of action, targeted and stimuli-responsive systems, preclinical evidence, safety considerations, and translational perspectives. The integration of phytochemistry and nanotechnology may redefine therapeutic approaches in diabetes management.

2. Classes of Natural Product–Based Nanocarriers

Natural biomaterials provide versatile platforms for nanocarrier development in diabetes therapy.

Chitosan Nanoparticles: Derived from chitin, chitosan is a cationic polysaccharide with mucoadhesive and permeation-enhancing properties[24]. Chitosan nanoparticles improve intestinal absorption of hydrophobic phytochemicals and protect bioactives from gastric degradation. Their positive charge facilitates interaction with negatively charged mucosal membranes, enhancing uptake.

Alginate and Pectin Nanogels: Alginate, extracted from brown algae, forms hydrogels in the presence of divalent cations. These nanogels enable pH-responsive drug release, protecting compounds in the acidic stomach while releasing them in the intestine. Pectin-based systems offer similar colon-targeting advantages[25].

Protein-Based Nanoparticles: Gelatin, zein, and albumin nanoparticles provide biodegradable and non-toxic carriers. Zein nanoparticles effectively encapsulate polyphenols such as curcumin and resveratrol, enhancing stability and bioavailability[26].

Lipid-Based Nanocarriers: Natural lipid vesicles, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) improve solubility of lipophilic compounds. Phospholipid-based liposomes mimic biological membranes, facilitating cellular uptake[27].

Plant-Derived Extracellular Vesicle–Like Nanostructures: Recent research identifies plant-derived nanovesicles capable of delivering bioactive molecules with low immunogenicity. These vesicles may inherently modulate metabolic pathways[28]. Each platform provides distinct physicochemical advantages, enabling tailored design for specific therapeutic needs.

3. Mechanisms Supporting Precision Glycemic Control

Precision glycemic control represents a paradigm shift in diabetes therapy, moving from generalized systemic drug administration toward targeted modulation of key metabolic tissues that directly regulate glucose homeostasis[29]. Natural product–based nanocarriers play a central role in this transition by enabling spatially precise delivery of bioactive compounds to organs and cellular networks that govern insulin sensitivity, glucose production, and metabolic signaling.

In skeletal muscle and hepatic tissues, nanocarriers engineered to deliver AMPK-activating phytochemicals enhance insulin sensitivity and metabolic efficiency by directly modulating intracellular energy-sensing pathways[30]. Targeted hepatic delivery is particularly significant, as it suppresses excessive gluconeogenesis, improves hepatic insulin signaling, and restores lipid metabolic balance, thereby reducing both hyperglycemia

and dyslipidemia. Hepatocyte-specific targeting strategies enable localized therapeutic action while minimizing systemic exposure[30].
Pancreatic targeting further strengthens glycemic regulation by supporting β-cell survival, functional preservation, and insulin secretion. Nanocarriers functionalized with tissue-specific ligands enhance selective uptake by pancreatic islets, allowing protective phytochemicals to counteract oxidative stress, inflammatory damage, and apoptotic signaling within β-cells. This targeted intervention not only preserves endogenous insulin production but also contributes to long-term metabolic stability[17, 19, 21].
In adipose tissue, directed nanodelivery reduces chronic low-grade inflammation and restores adipokine balance, two major drivers of insulin resistance[31]. By delivering anti-inflammatory phytochemicals directly to adipocytes and immune cells within adipose depots, nanocarriers mitigate cytokine signaling, improve insulin responsiveness, and reestablish metabolic homeostasis at the tissue level.
Advanced stimuli-responsive systems add dynamic control to precision therapy. Glucose-responsive nanocarriers, incorporating components such as phenylboronic acid or glucose oxidase, trigger drug release specifically under hyperglycemic conditions, enabling on-demand therapeutic action. Similarly, inflammation-responsive and ROS-sensitive nanoparticles release phytochemicals within oxidative and inflammatory microenvironments, counteracting chronic inflammation and oxidative stress that perpetuate metabolic dysfunction[32, 33]. Collectively, these strategies enhance therapeutic specificity, metabolic targeting, and adaptive drug release, enabling precise glycemic regulation while minimizing systemic adverse effects, toxicity, and off-target pharmacological burden.

4. Innovative Design Strategies in Diabetes Nanomedicine

Recent advances in nanotechnology have enabled the development of smart, multifunctional, and highly adaptable nanoplatforms for diabetes therapy, transforming conventional drug delivery into precision-based therapeutic engineering[34, 35]. Central to these innovations is surface functionalization, where nanoparticles are decorated with targeting ligands such as peptides, antibodies, aptamers, and sugars to enhance tissue and cell-type specificity. These functional moieties enable receptor-mediated uptake in pancreatic β-cells, hepatocytes, adipocytes, and skeletal muscle fibers, significantly improving localized drug accumulation while minimizing off-target exposure and systemic toxicity[36–38].
Equally transformative are stimuli-responsive nanocarriers, which enable controlled drug release in response to specific physiological cues such as glucose concentration, pH changes, temperature shifts, and oxidative stress levels. Glucose-responsive systems allow therapeutic release under hyperglycemic conditions, while pH-sensitive nanoparticles respond to acidic inflammatory microenvironments, enabling spatial and temporal precision in drug delivery[33, 39]. Such systems introduce dynamic adaptability into therapy, aligning drug release with disease states rather than fixed dosing schedules.
Co-delivery nanoplatforms represent another major design innovation, allowing the simultaneous encapsulation of multiple phytochemicals or the combination of phytochemicals with synthetic antidiabetic drugs[40]. These systems enable synergistic targeting of complementary pathways, including insulin resistance, oxidative stress, inflammation, and mitochondrial dysfunction, thereby addressing the multifactorial nature of diabetes pathogenesis more effectively than monotherapies.[40]
Beyond systemic metabolism, nanoformulations are increasingly being designed to enhance gut microbiota modulation, improving the intestinal bioavailability of prebiotic phytochemicals that regulate microbial composition, metabolite production, and metabolic signaling[40]. Looking forward, integration of nanomedicine with wearable glucose-monitoring and biosensor technologies may enable closed-loop therapeutic systems capable of real-time sensing, adaptive dosing, and autonomous metabolic regulation, marking a paradigm shift toward intelligent, self-regulating diabetes care platforms.

5. Preclinical and Translational Evidence

A growing body of preclinical evidence strongly supports the therapeutic superiority of natural product–based nanocarriers in diabetes management. Animal and cellular studies consistently demonstrate improved glycemic control, enhanced insulin sensitivity, and reduced oxidative and inflammatory damage when phytochemicals are delivered via nanotechnology platforms rather than conventional formulations. These benefits arise primarily from improved solubility, stability, bioavailability, and tissue-specific delivery.
Chitosan-encapsulated berberine represents a well-characterized example, exhibiting significantly enhanced oral bioavailability and improved insulin sensitivity in diabetic models. Nanoencapsulation protects berberine from rapid degradation and intestinal efflux mechanisms, allowing sustained systemic exposure and amplified metabolic effects[41, 42]. Similarly, curcumin-loaded lipid nanoparticles have demonstrated substantial reductions in fasting blood glucose levels, oxidative stress biomarkers, and inflammatory mediators, while improving insulin signaling pathways and mitochondrial function[43, 44].
Resveratrol nanoformulations further illustrate the translational promise of nanotechnology, showing superior β-cell protection, enhanced antioxidant capacity, and improved glucose homeostasis compared to free resveratrol administration[45–47]. These nano-enabled systems enable efficient intracellular delivery and prolonged therapeutic action, strengthening their disease-modifying potential.
At the clinical level, early-phase trials involving nano-curcumin formulations indicate improved pharmacokinetic profiles, including enhanced absorption, prolonged plasma half-life, and increased systemic

exposure. However, despite encouraging signals, large-scale randomized clinical trials remain limited, creating a translational gap between preclinical success and clinical implementation. Bridging this gap will require standardized production methods, reproducible nanoformulation protocols, robust safety validation frameworks, and coordinated translational research pipelines to support regulatory approval and clinical adoption.

6. Safety, Toxicity, and Regulatory Considerations

Safety and regulatory evaluation constitute essential foundations for the clinical translation of diabetes nanomedicine. Natural biomaterial-based nanocarriers, including chitosan, alginate, PLGA, and lipid nanoparticles, generally exhibit favorable safety profiles due to their biocompatibility and physiological degradabilit[48, 49]y. Biodegradability significantly reduces long-term accumulation risks and facilitates metabolic clearance, making these materials preferable for chronic metabolic disease applications.

Nevertheless, nanoparticle safety is highly dependent on particle size, surface charge, composition, and surface chemistry, all of which influence biodistribution, cellular uptake, immune recognition, and organ accumulation. Smaller nanoparticles exhibit deeper tissue penetration but may pose higher cytotoxic risks, while positively charged surfaces increase cellular uptake but can disrupt membrane integrity[50, 51]. These parameters necessitate rational design strategies guided by safety optimization.

Comprehensive evaluation must include immunogenicity profiling, long-term organ accumulation studies, metabolic clearance pathways, genotoxicity screening, and chronic exposure assessments[52]. Particular attention is required for liver, spleen, kidney, and lymphatic tissues, where nanoparticles may accumulate through reticuloendothelial system uptake[52].

From a regulatory perspective, nanomedicine classification remains complex, often requiring additional safety documentation, characterization protocols, and approval pathways beyond conventional phytotherapy frameworks. Regulatory agencies increasingly demand detailed physicochemical characterization, reproducibility data, and risk–benefit analyses specific to nanoscale systems[14, 53]. Consequently, standardization, quality control, batch reproducibility, and manufacturing consistency are essential prerequisites for clinical translation and regulatory approval, forming the backbone of responsible nanomedicine development[54].

7. Future Directions and Clinical Translation

Future research in diabetes nanomedicine should prioritize precision targeting, scalable manufacturing, and personalized therapeutic design to enable real-world clinical impact. Precision nanotherapy platforms must integrate tissue-specific targeting strategies with disease-responsive delivery systems to maximize efficacy while minimizing systemic toxicity. At the same time, scalable, cost-effective manufacturing processes are essential to ensure accessibility and global clinical relevance.

The integration of nanotechnology with omics-driven medicine, including genomics, metabolomics, proteomics, and nutrigenomics, offers a powerful pathway toward personalized nanotherapy. These approaches may enable individualized phytochemical–nanocarrier combinations tailored to patient-specific metabolic profiles, inflammatory states, and genetic predispositions, transforming diabetes treatment from standardized protocols to precision-based interventions.

Smart glucose-responsive nanoplatforms represent one of the most promising innovations, enabling drug release in hyperglycemic states while minimizing exposure during normoglycemia, thereby reducing hypoglycemia risk and improving safety. Such systems introduce adaptive therapeutic control into metabolic disease management. However, clinical translation remains limited by the scarcity of large-scale, long-term clinical trials evaluating efficacy, safety, and durability of nano-enabled therapies. Addressing this gap is critical for regulatory approval and clinical integration. Progress will depend on interdisciplinary collaboration among pharmacologists, nanotechnologists, clinicians, regulatory scientists, data scientists, and industry partners. Through coordinated translational ecosystems, diabetes nanomedicine can evolve from experimental innovation to clinically transformative therapy.

CONCLUSION

Natural product–based nanocarriers represent a transformative advancement in diabetes nanomedicine. By combining the therapeutic versatility of bioactive natural compounds with the precision of nanoscale delivery systems, these platforms address longstanding challenges of poor bioavailability, instability, and non-specific distribution. Targeted and stimuli-responsive nanocarriers enable refined glycemic control while minimizing systemic toxicity and hypoglycemia risk. Preclinical evidence strongly supports enhanced pharmacokinetic and pharmacodynamic outcomes compared to conventional formulations. Nevertheless, translation to clinical practice requires rigorous safety validation, standardized manufacturing, and regulatory clarity. As research advances, natural biomaterial nanocarriers may redefine precision glycemic management, offering safer, more effective, and personalized therapeutic strategies for individuals living with diabetes.

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