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Phytochemical Nanoformulations for Insulin Resistance and β-Cell Protection in Diabetes

Nabuuma Ruth Nambi

Department of Pharmacy Kampala International University Uganda
Email: nambi.nabuuma@studwc.kiu.ac.ug

ABSTRACT

Insulin resistance and progressive pancreatic β-cell failure are the twin biological engines of type 2 diabetes and major determinants of long-term complications. Phytochemicals such as curcumin, resveratrol, quercetin, epigallocatechin gallate, berberine, ginsenosides, and thymoquinone can enhance insulin signaling, reduce hepatic gluconeogenesis, improve adipokine balance, attenuate oxidative stress, and limit β-cell apoptosis. Yet translation is constrained by poor solubility, low oral bioavailability, chemical instability, rapid metabolism, and non-specific biodistribution. Nanoformulations such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, and polysaccharide nanogels address these barriers by protecting labile compounds, improving dissolution and permeability, and enabling controlled or stimuli-responsive release. Surface engineering with peptides, sugars, or antibodies can bias delivery toward insulin-responsive tissues or inflamed islets, while glucose- and ROS-responsive matrices provide on-demand release in hyperglycemic, oxidative microenvironments. Preclinical studies frequently show superior reductions in fasting and postprandial glucose, improved HOMA-IR, restoration of GLUT4 translocation, and preservation of β-cell mass compared with free phytochemicals, with early human data emerging for select formulations. This review summarizes mechanistic targets, nanocarrier designs, evidence trends, safety considerations, and translational priorities for phytochemical nanomedicine. We emphasize rational carrier selection, standardized extract characterization, and head-to-head comparisons that disentangle carrier effects from payload activity, guiding scalable, clinically relevant future development.

Keywords: phytochemicals; nanoformulations; insulin resistance; β-cell protection; targeted delivery

INTRODUCTION

Type 2 diabetes mellitus (T2DM) emerges when insulin-responsive tissues become resistant to insulin and pancreatic β-cells progressively fail to sustain compensatory insulin secretion[1–3]. In early disease, skeletal muscle insulin resistance reduces postprandial glucose disposal, while hepatic insulin resistance drives inappropriate fasting glucose production through persistent gluconeogenesis and glycogenolysis. In parallel, adipose insulin resistance increases lipolysis, raising the flux of free fatty acids to liver and muscle and promoting ectopic lipid deposition[4]. Lipid intermediates, oxidative stress, and pro-inflammatory cytokines interfere with insulin receptor signaling and create a self-reinforcing cycle of metabolic dysregulation[5].

The clinical consequence is not only elevated mean glucose but also high glycemic variability, which contributes to endothelial dysfunction and accelerates microvascular and macrovascular injury[6]. Because T2DM is multifactorial, effective therapy must address both impaired insulin signaling in peripheral tissues and declining β-cell reserve that limits endogenous insulin supply. β-cell compensation initially increases insulin output, but chronic nutrient overload, islet inflammation, and endoplasmic reticulum stress trigger loss of secretory capacity and apoptosis[7]. Preserving β-cell function therefore matters as much as improving insulin sensitivity.

Modern antidiabetic drugs provide powerful tools, including metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and diverse insulin formulations[8]. Nevertheless, each class carries limitations: gastrointestinal intolerance with metformin, weight gain and hypoglycemia with secretagogues and insulin, fluid retention with thiazolidinediones, and class-specific adverse effects that may restrict use in some patients. Even when tolerated, pharmacologic durability is limited because the underlying biology continues to evolve, prompting dose escalation and combination therapy[8-13]. These realities motivate

interest in adjunct strategies that act on inflammation, oxidative stress, mitochondrial function, and lipid handling in addition to glycemia.

Phytochemicals bioactive constituents from medicinal plants and foods—have attracted renewed attention as complementary agents and as leads for new therapeutics[9, 10,14-20]. Polyphenols such as quercetin, resveratrol, curcumin, and catechins can activate AMP-activated protein kinase (AMPK), enhance insulin receptor substrate signaling through PI3K/Akt, suppress NF-κB–mediated inflammation, and improve mitochondrial biogenesis. Alkaloids such as berberine influence hepatic glucose output and lipid handling, partly through AMPK activation and modulation of gut microbial metabolites. Terpenoids, saponins, and phenolic acids can attenuate lipotoxicity, improve adipokine balance, and reduce β-cell oxidative injury[11, 12,21-25]. Importantly, these molecules often exert pleiotropic effects that fit the network nature of T2DM pathogenesis.

However, translating phytochemical promise into consistent clinical outcomes has been difficult. Many compounds are poorly soluble in water, unstable under gastric conditions, or rapidly conjugated and eliminated after absorption. Oral bioavailability can therefore be low and highly variable, making dose–response relationships uncertain. Some phytochemicals require high doses to achieve measurable systemic exposure, increasing gastrointestinal side effects and the likelihood of interactions with conventional drugs[13–15,26-30]. For botanical extracts, additional variability arises from cultivar, climate, harvesting, and processing, complicating standardization and reproducibility.

Nanoformulations offer a strategy to overcome these constraints by engineering delivery rather than altering the active molecule[16,17,31-34]. Encapsulation in polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, or polysaccharide nanogels can improve apparent solubility, protect cargo from enzymatic degradation, and enable sustained or pulsatile release. Surface modification can tune mucus interaction for oral uptake, prolong circulation by reducing opsonization, and bias biodistribution toward liver, adipose tissue, muscle, or pancreatic islets[18, 19,35-40]. Stimuli-responsive matrices that react to glucose, pH, or reactive oxygen species can further align release with hyperglycemic and oxidative microenvironments.

A central premise is that insulin resistance and β-cell stress are coupled: when peripheral tissues resist insulin, β-cells must secrete more insulin to maintain euglycemia, increasing proinsulin synthesis, oxidative load, and vulnerability to apoptosis[20,41-46]. Interventions that improve insulin sensitivity can indirectly preserve β-cell function by reducing secretory demand, while direct cytoprotective agents stabilize insulin production and weaken glucotoxic feedback on insulin signaling. For nanoformulations, this coupling encourages integrated endpoints, including fasting glucose, oral glucose tolerance, HOMA-IR, insulin secretion indices, inflammatory biomarkers, and β-cell mass[20,47-52].

Design choices should reflect the intended site of action. Some phytochemicals act locally in the gut by inhibiting digestive enzymes or altering incretin biology and microbiota metabolites; for these, prolonged intestinal residence and minimal systemic exposure may be optimal[21]. Others require systemic distribution to liver, muscle, adipose tissue, or islets, favoring carriers that enhance absorption and control biodistribution[21,53-57]. Translational success also depends on reproducible manufacturing, robust quality control, and nanotoxicology evaluation, because nanoscale properties can alter immune recognition and organ accumulation.

Phytochemical nanomedicine therefore reframes "natural product therapy" as a controllable pharmaceutical approach. The goal is not to replace established drugs indiscriminately, but to create standardized, testable formulations that improve insulin sensitivity and protect β-cells through complementary mechanisms, potentially lowering required doses and limiting toxicity. This review examines (i) molecular targets linking insulin resistance to β-cell stress, (ii) key phytochemicals with evidence for insulin sensitization and islet protection, (iii) nanocarrier platforms and design variables, (iv) targeting and stimuli-responsive strategies, and (v) safety and translational considerations that must be addressed to move phytochemical nanoformulations toward clinical use.

2. Mechanistic Targets in Insulin Resistance and β-Cell Failure

Insulin resistance reflects a reduced biological response to insulin at a given concentration and can arise from defects at multiple levels of the insulin signaling network[2, 22, 23,58-64]. In muscle and adipose tissue, impaired activation of the insulin receptor and insulin receptor substrates (IRS proteins) blunts downstream PI3K/Akt signaling, reducing GLUT4 translocation and glucose uptake[23, 24,65-68]. In the liver, weakened Akt signaling fails to suppress gluconeogenic gene expression, allowing continued glucose output despite hyperinsulinemia. A recurring proximal driver is lipid overload: excess free fatty acids are converted to diacylglycerols and ceramides that activate stress kinases such as PKC, JNK, and IKK, which serine-phosphorylate IRS proteins and disrupt signaling[24, 25,69-75]. Mitochondrial overload and incomplete fatty acid oxidation further increase reactive oxygen species (ROS) and amplify insulin resistance.

Inflammation provides a second, interlinked axis. Hypertrophic adipocytes release chemokines that recruit macrophages, which secrete TNF-α, IL-6, and other mediators that inhibit insulin signaling and promote systemic insulin resistance. Adipokine imbalance—reduced adiponectin with increased leptin resistance—shifts metabolism toward lipolysis and ectopic lipid deposition[23, 26,76-80]. In parallel, gut barrier perturbation and altered microbiota can increase exposure to endotoxin-like ligands that activate toll-like receptors, sustaining

metabolic inflammation. These features create multiple intervention points for phytochemicals with anti-inflammatory, antioxidant, and lipid-modulating activity.

β-cell dysfunction develops as a consequence of both intrinsic vulnerability and the demands imposed by insulin resistance. To compensate, β-cells increase insulin synthesis and secretion, elevating endoplasmic reticulum (ER) workload and proinsulin misfolding[27,81-87]. Chronic ER stress activates the unfolded protein response; when adaptive capacity is exceeded, pro-apoptotic signaling pathways are engaged. High glucose and lipid exposure increases oxidative stress, impairs mitochondrial coupling, and promotes β-cell dedifferentiation, reducing the expression of key transcription factors and glucose-sensing machinery[27,88-93]. Islet inflammation, driven by resident macrophages and cytokine spillover, further accelerates apoptosis. In humans, islet amyloid deposition can add mechanical and inflammatory stress to β-cells.

Insulin resistance is also heterogeneous: some patients show predominant hepatic resistance with fasting hyperglycemia, whereas others show marked muscle resistance with exaggerated postprandial excursions[2, 28,94-100]. This heterogeneity helps explain variable responses to the same agent and highlights the value of tissue-directed delivery. β-cells, for their part, rely on balanced autophagy and mitochondrial dynamics to maintain insulin granule homeostasis; disruption of these quality-control systems increases susceptibility to glucolipotoxic stress. Moreover, α-cell dysregulation and elevated glucagon can worsen hepatic glucose output, adding another inflammatory and metabolic loop that therapies may need to modulate in practice.

From a therapeutic design perspective, insulin resistance and β-cell protection share several actionable nodes. Enhancing AMPK activity can increase glucose uptake and fatty acid oxidation while reducing hepatic glucose production. Restoring PI3K/Akt signaling can normalize GLUT4 trafficking and suppress gluconeogenesis[29,101-106]. Reducing ceramide accumulation, inhibiting stress kinases, and dampening NF-κB–mediated cytokine production can simultaneously improve insulin sensitivity and reduce islet inflammatory injury. Finally, boosting endogenous antioxidant defenses (for example, via Nrf2 signaling) can protect both insulin-responsive tissues and β-cells from ROS-driven damage[29,107-110]. Phytochemicals can hit many of these targets, but achieving adequate exposure in the right tissues is often the limiting step providing a strong rationale for nanocarrier-based delivery.

3. Antidiabetic Phytochemicals for Insulin Sensitization and Islet Protection

Phytochemicals relevant to insulin resistance and β-cell protection span several chemical families, and many converge on a small set of metabolic and stress-response pathways. Among polyphenols, curcumin is frequently studied for its capacity to suppress NF-κB signaling, reduce oxidative stress, and improve insulin sensitivity through AMPK activation and modulation of adipokines[30,111-114]. Resveratrol can promote mitochondrial biogenesis via SIRT1 and PGC-1α signaling, improve endothelial function, and dampen inflammatory cytokine production, effects that collectively support insulin action in muscle and liver [30, 115-120]. Flavonols such as quercetin and kaempferol enhance glucose uptake, inhibit stress kinases, and reduce lipid peroxidation; catechins such as epigallocatechin gallate (EGCG) can modulate glucose absorption, improve insulin signaling, and reduce hepatic fat accumulation.

Alkaloids provide another important class. Berberine improves glycemic control in many preclinical models by activating AMPK, suppressing hepatic gluconeogenic enzymes, improving lipid metabolism, and influencing gut microbiota-derived metabolites that affect insulin sensitivity[31–33]. Other alkaloids and related nitrogen-containing compounds can inhibit carbohydrate-digesting enzymes or modulate incretin pathways, thereby reducing postprandial glucose burden and indirectly lowering β-cell demand. Phenolic acids such as chlorogenic acid can reduce intestinal glucose transport and inhibit key hepatic enzymes that contribute to glucose output.

Terpenoids and saponins are prominent in ethnomedicinal antidiabetic plants. Ginsenosides have been reported to improve insulin sensitivity, reduce adipose inflammation, and protect β-cells against oxidative injury by modulating antioxidant defenses and apoptosis regulators[34, 35]. Thymoquinone and related terpenoid quinones can reduce ROS production, stabilize mitochondrial function, and attenuate cytokine signaling, contributing to improved insulin action and β-cell survival. Saponins may influence membrane microdomains and receptor signaling while also reducing intestinal glucose absorption.

For β-cell protection specifically, several phytochemicals act on oxidative and ER stress, two dominant drivers of β-cell failure. Activation of Nrf2-regulated antioxidant programs increases expression of enzymes such as heme oxygenase-1 and glutathione-related defenses, limiting ROS-mediated DNA and membrane damage[36]. Some polyphenols and terpenoids also modulate autophagy, helping β-cells clear misfolded proteins and damaged mitochondria. Anti-apoptotic effects are often reflected in shifts in Bcl-2 family balance, reduced caspase activation, and improved mitochondrial membrane potential. Because β-cells have relatively low baseline antioxidant capacity, even modest improvements in redox homeostasis can be functionally meaningful[36].

Polysaccharides and oligosaccharide-rich fractions, although not "small molecules," can contribute by slowing gastric emptying, reducing glucose diffusion, and shaping microbiota fermentation toward short-chain fatty acids that improve insulin sensitivity[37]. Some phytochemicals inhibit digestive enzymes (α-amylase and α-glucosidase), lowering postprandial spikes and easing β-cell workload. In practice, the most promising candidates are those with multi-pathway activity and wide safety margins for chronic administration.

Despite this mechanistic richness, phytochemicals can suffer from poor target engagement in vivo. Many are extensively metabolized, and the active species may be metabolites rather than the parent compound. Additionally, complex extracts may contain both synergists and antagonists, making standardization essential. These realities favor formulation strategies that (i) increase effective exposure of validated actives or bioactive metabolite precursors, (ii) enable co-delivery of complementary compounds to address multiple nodes of insulin resistance and β-cell stress, and (iii) reduce variability through controlled manufacturing and marker-based quality control.

4. Nanocarrier Platforms and Formulation Design Principles

Nanocarrier selection for phytochemicals is driven by the physicochemical properties of the payload (polarity, stability, dose), the intended route of administration, and the target tissue[38, 39]. Polymeric nanoparticles, commonly based on biodegradable polyesters or polysaccharides, are versatile for encapsulating hydrophobic polyphenols and terpenoids while providing sustained release through matrix erosion or diffusion. Natural polymers such as chitosan add mucoadhesion and transient tight-junction modulation, which can increase oral uptake of poorly permeable compounds. Crosslinked nanogels made from chitosan, alginate, or other biopolymers can be engineered to swell or degrade in response to pH, ionic strength, or enzymatic cues, supporting region-specific release along the gastrointestinal tract[40].

Lipid-based systems are particularly effective for lipophilic phytochemicals. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) increase apparent solubility and protect cargo from oxidation while enabling controlled release from a lipid matrix. Nanoemulsions and self-emulsifying systems increase interfacial surface area and can enhance dissolution and lymphatic transport, potentially reducing first-pass metabolism[40]. Classical liposomes provide a bilayer structure that accommodates both hydrophilic and hydrophobic molecules and can be modified with polyethylene glycol or other coatings to improve stability and circulation time.

Smaller supramolecular carriers such as polymeric micelles and cyclodextrin inclusion complexes are useful when the goal is rapid solubilization rather than long-term sustained release[41]. Dendrimers and other highly branched macromolecules offer high loading capacity and many surface groups for conjugation of targeting ligands, but they require careful control of charge-related toxicity.[41] Inorganic and hybrid nanocarriers, including mesoporous silica or metal-based nanoparticles produced by green synthesis, can add imaging or catalytic functions; however, their long-term clearance profiles must be explicitly characterized for chronic metabolic diseases.

Formulation design must also anticipate the biological barriers that shape exposure. Oral systems must survive gastric acidity, bile salts, and digestive enzymes, then interact appropriately with intestinal mucus and epithelium[42]. For some phytochemicals, preserving local intestinal activity is desirable, so mucoadhesive retention and limited systemic absorption may be beneficial. For systemic insulin sensitization or β-cell protection, absorption enhancement and protection from first-pass metabolism become priorities. Particle size, surface charge, and hydrophilicity influence mucus penetration, uptake by enterocytes, and capture by the mononuclear phagocyte system[42].

Co-delivery is often advantageous because insulin resistance involves parallel pathways. Nanocarriers can encapsulate combinations (for example, an AMPK activator plus an antioxidant) or pair a phytochemical with a conventional drug to reduce dose requirements[43]. Release kinetics can be tuned by polymer composition, lipid crystallinity, or responsive crosslinkers, allowing intestinal release or slow systemic exposure. Surface chemistry must be optimized to prevent aggregation and preserve activity during storage[43].

Across platforms, robust characterization is essential: particle size distribution, zeta potential, morphology, encapsulation efficiency, chemical stability of marker compounds, and in vitro release in biorelevant media. Scalable manufacturing methods (high-pressure homogenization, microfluidics, solvent evaporation, spray drying, or lyophilization) should be considered early, because batch-to-batch reproducibility is a common translational failure point[44]. For phytochemical products, quality-by-design approaches that link carrier attributes to pharmacokinetics and pharmacodynamics help ensure that improvements in insulin resistance and β-cell markers reflect purposeful engineering rather than uncontrolled variability.

5. Targeted and Stimuli-Responsive Delivery to Insulin-Sensitive Tissues and Islets

Targeted delivery seeks to concentrate phytochemicals in tissues that drive insulin resistance or in pancreatic islets where β-cell loss occurs. For hepatic insulin resistance, nanoparticles can exploit hepatocyte receptors, such as the asialoglycoprotein receptor, by displaying galactose-like motifs on the surface[45]. Such designs can increase hepatic exposure of AMPK activators or gluconeogenesis suppressors while limiting off-target distribution. Adipose tissue targeting often focuses on inflamed depots enriched in activated macrophages; carriers decorated with mannose or other ligands that favor macrophage uptake can deliver anti-inflammatory polyphenols to reduce cytokine production and improve adipokine signaling[45]. Because skeletal muscle is responsible for most insulin-stimulated glucose disposal, improving muscle exposure is attractive, but it remains challenging; approaches include tuning particle size for capillary transport and using peptides that bind muscle-associated receptors or extracellular matrix components.

β-cell protection adds additional constraints. Islets are highly vascularized but small, and nonspecific nanoparticles may be cleared by the liver and spleen before reaching endocrine tissue. Strategies under

exploration include ligand-mediated targeting to receptors expressed on β-cells or islet endothelium, as well as exploiting the enhanced permeability of inflamed islets in experimental models[46]. Once internalized, subcellular targeting may matter because mitochondrial dysfunction and ER stress are key drivers of β-cell apoptosis. Mitochondria-targeting moieties and redox-sensitive linkers can enrich antioxidant release near mitochondrial ROS sources, while ER-stress–modulating phytochemicals benefit from sustained intracellular availability[46].

Stimuli-responsive nanoformulations aim to synchronize release with metabolic cues, improving safety and efficacy. Glucose-responsive systems can release cargo when glucose is elevated by using reversible boronate–diol interactions or glucose oxidase–mediated local acidification that triggers polymer swelling[47, 48]. While initially developed for insulin delivery, the same logic can be applied to phytochemicals that modulate insulin signaling or inflammation, providing higher exposure during hyperglycemic periods and lower exposure during normoglycemia. Reactive oxygen species (ROS)-responsive carriers degrade in oxidative environments typical of insulin-resistant adipose tissue and stressed islets, releasing antioxidants and anti-inflammatory agents precisely where ROS is high. pH-sensitive systems can exploit differences between stomach, intestine, and intracellular endosomes to protect cargo and enhance cytosolic delivery[49].

Successful targeting is ultimately measured by functional outcomes improved insulin sensitivity indices, reduced inflammatory biomarkers, preserved β-cell mass, and lower glycemic variability, rather than by particle accumulation alone. Therefore, head-to-head studies that compare targeted versus non-targeted formulations, and that quantify both biodistribution and pathway engagement, are essential to demonstrate that sophisticated designs translate into clinically meaningful advantages.

6. Evidence Base: Preclinical Outcomes and Emerging Human Signals

Preclinical research consistently shows that nanoformulation can amplify the metabolic impact of phytochemicals by improving exposure, stability, and tissue delivery. In rodent models of diet-induced insulin resistance, phytochemical nanoparticles frequently reduce fasting glucose and insulin, improve oral glucose tolerance, and lower indices such as HOMA-IR relative to equivalent doses of free compounds[50]. Mechanistic readouts often align with improved insulin signaling: increased Akt phosphorylation, enhanced GLUT4 translocation in muscle and adipose tissue, reduced hepatic expression of gluconeogenic enzymes, and increased AMPK activation. Inflammatory and oxidative stress markers commonly improve as well, including lower TNF-α and IL-6 levels, reduced lipid peroxidation products, and higher activity of antioxidant enzymes[50].

Curcumin is a widely used example because its free form is poorly bioavailable. Lipid nanoparticles, polymeric nanoparticles, and nanoemulsions have all been reported to enhance curcumin exposure and produce stronger improvements in insulin sensitivity and adipose inflammation than non-formulated curcumin[51–53]. Resveratrol nanoformulations have shown enhanced mitochondrial and endothelial benefits, with reductions in hepatic steatosis and improvements in insulin signaling at lower doses than free resveratrol[54, 55]. Berberine nanoformulations are similarly attractive because berberine has limited oral bioavailability; nanoparticle delivery can increase systemic levels and may strengthen effects on hepatic glucose production and lipid metabolism. Quercetin and EGCG nanoemulsions or nanogels have been used to improve stability and intestinal absorption, often translating into improved antioxidant status and β-cell preservation in streptozotocin or diet-based diabetes models.

Where measured, pharmacokinetic studies show higher Cmax, longer half-life, and greater area under the curve for nanoformulated phytochemicals, supporting dose reduction. Clinical translation may benefit from continuous glucose monitoring, imaging-enabled biodistribution, and stratification by insulin-resistance phenotype to reduce response heterogeneity in trials[56].

Despite these encouraging patterns, important translational caveats remain. Many studies use high doses, short durations, or small sample sizes, and they may not include rigorous comparators such as optimized free-drug formulations. Measuring only glucose endpoints can obscure whether improved glycemia reflects insulin sensitization, β-cell preservation, or reduced caloric intake due to formulation effects on appetite[57]. Nanocarrier components themselves may contribute to bioactivity, especially when using natural polymers with mucoadhesive or immunomodulatory properties, complicating attribution.

Human evidence is emerging but still limited. Small trials of enhanced-bioavailability formulations of certain polyphenols suggest improvements in inflammatory markers and modest glycemic benefit, but robust demonstrations of improved insulin resistance and β-cell preservation remain scarce[58]. Future clinical studies will need standardized phytochemical markers, validated nanoparticle characterization, and mechanistic endpoints (insulin sensitivity clamps or secretion tests) to confirm that the advantages seen in animal models translate to patients.

7. Safety, Manufacturing, and Translational Priorities

Because diabetes requires chronic therapy, safety and manufacturability are as important as efficacy for phytochemical nanoformulations. Nanocarriers can alter absorption and biodistribution, potentially increasing systemic exposure to constituents that were previously confined to the gut. Key safety questions include acute cytotoxicity, immune activation (complement and cytokine responses), long-term organ accumulation, and interactions with concomitant antidiabetic drugs[38, 38]. Particle size, surface charge, and composition influence uptake by the mononuclear phagocyte system and deposition in liver and spleen. Biodegradable

polymers and physiological lipids generally offer more predictable clearance than some inorganic carriers, but even "biocompatible" materials may cause issues if they aggregate, carry residual solvents, or trigger hypersensitivity.

Manufacturing translation often fails when formulations cannot be produced reproducibly at scale. Methods such as high-pressure homogenization, solvent evaporation, microfluidics, and spray drying can be scaled, but they require tight control of temperature, shear, solvent removal, and sterilization or microbial limits[59]. Quality-by-design approaches define critical quality attributes—particle size distribution, encapsulation efficiency, release profile, and chemical stability of marker compounds- and link them to clinical performance. For complex botanicals, standardization requires validated analytical fingerprints and marker quantification, with specifications for degradation products.

Regulatory pathways for nanoformulated phytochemicals can be ambiguous because products may be viewed as dietary supplements, botanical drugs, or nanomedicines depending on claims and jurisdiction[60]. Regardless of category, regulators increasingly expect clear identity, purity, potency, stability, and evidence of safety, along with documentation of nanomaterial characterization. Developers should plan for comparability studies when manufacturing changes occur, because small shifts in particle properties can alter exposure. Transparent labeling and evaluation of herb–drug interactions are critical given real-world co-administration with standard therapies[61].

Cost and access considerations should not be overlooked. Formulations that require rare excipients, cold-chain storage, or complex sterile processing may be impractical in many settings. Developers should also evaluate environmental impact, particularly for persistent inorganic materials and solvent-intensive manufacturing. Open reporting of negative results and standardized protocols will reduce publication bias and speed field-wide learning for patients.

Future innovation is likely to emphasize precision and practicality. Glucose- and ROS-responsive carriers could reduce hypoglycemia risk and maximize benefit in inflamed tissues. Biomimetic carriers, including plant-derived vesicles and membrane-coated nanoparticles, may improve tolerability. Combination formulations that pair phytochemicals with complementary mechanisms, or integrate them with low-dose conventional drugs, may provide durable insulin sensitization while protecting β-cells. Finally, clinical trials should incorporate mechanistic endpoints (insulin sensitivity and secretion testing), continuous glucose monitoring, and stratification by phenotype to identify who benefits most, accelerating responsible translation.

CONCLUSION

Phytochemical nanoformulations offer a practical route to address two core defects in type 2 diabetes: insulin resistance and progressive β-cell failure. By improving solubility, protecting labile compounds from degradation, and enabling controlled or stimuli-responsive release, nanocarriers can increase effective target engagement at liver, muscle, adipose tissue, and pancreatic islets. Preclinical studies repeatedly show stronger improvements in insulin signaling, inflammatory tone, oxidative stress, and islet survival than equivalent free phytochemicals, and early clinical signals suggest that enhanced-bioavailability formulations may translate into modest metabolic benefit. However, the field must move beyond proof-of-concept by standardizing botanical markers, performing head-to-head comparators, and integrating mechanistic endpoints that distinguish insulin sensitization from β-cell protection. Because diabetes therapy is lifelong, rigorous nanotoxicology, scalable manufacturing, and clear regulatory positioning are essential. With phenotype-stratified trials and rational carrier design, phytochemical nanomedicine could become a credible adjunct for durable glycemic control. Affordable formulations could expand access to metabolic therapies worldwide.

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