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IDOSR JOURNAL OF EXPERIMENTAL SCIENCES 12(2): 33-40, 2026 ISSN: 2579-0781

https://doi.org/10.59298/IDOSR/JES/06/1223340 IDOSRJES12206

Green Nanotechnology in Diabetes Therapy: Biogenic Nanoparticles from Medicinal Plants as Therapeutic Agents

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ABSTRACT

Green nanotechnology has emerged as an innovative and sustainable approach in diabetes therapy, utilizing plant-derived biomolecules for the synthesis of biogenic nanoparticles with intrinsic therapeutic activity. Unlike conventional chemically synthesized nanoparticles, green-synthesized nanoparticles employ medicinal plant extracts as reducing, stabilizing, and capping agents, thereby minimizing toxic residues and enhancing biocompatibility. These biogenic nanoparticles commonly gold, silver, zinc oxide, selenium, and iron oxide nanoparticles, often exhibit synergistic antidiabetic effects derived from both the metallic core and phytochemical corona. Mechanistically, they modulate insulin signaling pathways, improve glucose uptake, suppress oxidative stress, inhibit carbohydrate-digesting enzymes, and protect pancreatic β-cells from apoptosis. Their nanoscale size enhances cellular uptake, tissue distribution, and interaction with metabolic targets. Preclinical studies demonstrate improved glycemic control, antioxidant status, lipid profiles, and islet preservation in diabetic models compared with crude extracts or chemically synthesized counterparts. However, concerns remain regarding long-term toxicity, biodistribution, standardization of synthesis protocols, and regulatory classification. This review explores the principles of green nanoparticle synthesis, mechanistic insights into their antidiabetic actions, therapeutic evidence, safety considerations, and translational challenges. Biogenic nanoparticles represent a promising intersection of phytotherapy, sustainability, and precision nanomedicine in diabetes management.

Keywords: green nanotechnology; biogenic nanoparticles; medicinal plants; diabetes therapy; β-cell protection

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia due to impaired insulin secretion, insulin resistance, or both. Type 2 diabetes (T2DM), the most prevalent form, involves progressive insulin resistance in peripheral tissues accompanied by pancreatic β-cell dysfunction[1–3]. The disease imposes substantial global health and economic burdens, contributing to cardiovascular disease, nephropathy, neuropathy, and retinopathy. Although pharmacological therapies have advanced considerably, challenges remain, including adverse effects, limited durability of response, therapeutic resistance, high cost, and restricted accessibility in low-resource settings.

Traditional medicinal plants have long been used in the management of diabetes. Numerous botanicals contain bioactive phytochemicals polyphenols, alkaloids, terpenoids, saponins, and flavonoids that improve glucose homeostasis through multiple mechanisms[4, 5]. These include inhibition of α-amylase and α-glucosidase, enhancement of insulin receptor signaling, activation of AMP-activated protein kinase (AMPK), suppression of oxidative stress, and attenuation of inflammatory pathways such as NF-κB. Despite promising preclinical and limited clinical evidence, translation of phytotherapy into standardized and highly effective treatments has been constrained by poor solubility, instability, rapid metabolism, and inconsistent bioavailability[6, 7].

Nanotechnology has introduced novel strategies for improving drug delivery and therapeutic efficiency. Conventional nanoparticle synthesis often involves hazardous chemicals, high energy input, and toxic stabilizers, raising environmental and safety concerns[8–10]. In contrast, green nanotechnology applies eco-friendly synthesis methods using biological entities including plant extracts, bacteria, fungi, and algae as

reducing and stabilizing agents. Among these, plant-mediated synthesis has gained significant attention due to its simplicity, scalability, and intrinsic therapeutic potential[11].

In plant-based green synthesis, phytochemicals serve dual roles: they reduce metal ions to form nanoparticles and cap or stabilize the resulting structures. This process generates biogenic nanoparticles characterized by a metallic or metal-oxide core surrounded by a phytochemical corona[12]. The corona may enhance stability, modulate biological interactions, and confer additional therapeutic properties. For diabetes therapy, such nanoparticles combine the metabolic effects of the plant extract with nanoscale advantages including improved cellular uptake, increased surface reactivity, and targeted tissue interaction[12].

Biogenic nanoparticles typically range from 10 to 100 nm in size, facilitating enhanced permeability and cellular internalization via endocytosis. Their physicochemical properties such as size, shape, surface charge, and composition can be tuned by modifying extraction conditions, pH, temperature, and precursor concentration[13]. Importantly, the use of medicinal plant extracts introduces antioxidant and anti-inflammatory molecules that may reduce nanoparticle-induced toxicity compared with chemically synthesized counterparts[14].

Metallic nanoparticles synthesized via green methods include gold (AuNPs), silver (AgNPs), zinc oxide (ZnO NPs), selenium (SeNPs), and iron oxide (Fe_3O_4 NPs). Each exhibits distinct biological properties[14]. Gold nanoparticles are valued for biocompatibility and stability, silver nanoparticles for antimicrobial and enzyme-modulating activity, selenium nanoparticles for antioxidant and insulin-mimetic effects, and zinc oxide nanoparticles for modulation of glucose metabolism and insulin signaling[15].

In the context of diabetes, oxidative stress and chronic inflammation play central roles in insulin resistance and β-cell dysfunction. Hyperglycemia promotes reactive oxygen species (ROS) generation, mitochondrial dysfunction, and cytokine release, all of which impair insulin signaling pathways[16, 17]. Biogenic nanoparticles often display strong antioxidant capacity, scavenging ROS and upregulating endogenous antioxidant enzymes such as superoxide dismutase and catalase. Additionally, nanoscale size enhances interaction with cellular signaling pathways, potentially improving glucose uptake and preserving β-cell integrity[18].

Green nanotechnology therefore represents more than a manufacturing approach; it integrates phytotherapy and nanomedicine into a unified therapeutic platform[19]. However, challenges persist. Variability in plant extract composition may affect nanoparticle reproducibility. Long-term biodistribution and toxicity profiles remain incompletely characterized. Regulatory frameworks for biogenic nanoparticles are still evolving, particularly when nanoparticles themselves function as therapeutic agents rather than drug carriers[19]. This review examines the principles and methodologies of green synthesis, the mechanistic basis of biogenic nanoparticle antidiabetic activity, preclinical therapeutic evidence, safety considerations, and translational prospects. By harnessing sustainable synthesis and intrinsic plant bioactivity, green nanotechnology may contribute to safer and more accessible innovations in diabetes therapy.

2. Principles and Methods of Green Synthesis

Green synthesis of nanoparticles relies on plant extracts as natural reducing and stabilizing agents. The process typically involves mixing an aqueous or hydroalcoholic plant extract with a metal salt precursor such as chloroauric acid (for gold nanoparticles) or silver nitrate (for silver nanoparticles)[20]. Phytochemicals including flavonoids, phenolics, terpenoids, sugars, and proteins donate electrons to reduce metal ions into zero-valent or metal-oxide nanoparticles. The reaction is influenced by pH, temperature, concentration, and extraction method. Alkaline conditions often accelerate reduction, while temperature modulates particle size and shape. Rapid color change in the reaction mixture indicates nanoparticle formation due to surface plasmon resonance[21]. Characterization techniques include UV–visible spectroscopy, dynamic light scattering, transmission electron microscopy, X-ray diffraction, and Fourier-transform infrared spectroscopy to confirm particle size, morphology, crystallinity, and phytochemical capping. Green synthesis offers several advantages: reduced environmental toxicity, cost-effectiveness, and elimination of hazardous reagents. Additionally, phytochemical capping enhances colloidal stability and biocompatibility[22]. However, variability in plant extract composition may affect reproducibility. Standardization of extraction and synthesis parameters is therefore critical for therapeutic development.

3. Types of Biogenic Nanoparticles in Diabetes Therapy

Biogenic nanoparticles represent a unique class of therapeutic nanomaterials that integrate the intrinsic physicochemical properties of metals with the bioactivity of plant-derived phytochemicals, creating multifunctional platforms for diabetes therapy. Among these, gold nanoparticles (AuNPs) have attracted significant attention due to their strong antioxidant and anti-inflammatory properties[23]. Biogenically synthesized AuNPs exhibit the ability to modulate insulin signaling pathways, enhance glucose uptake in skeletal muscle and adipose tissue, and reduce oxidative stress in metabolically active organs. Their phytochemical coatings further contribute to redox balance and cellular protection, amplifying their metabolic benefits[24-27].

Silver nanoparticles (AgNPs) synthesized using medicinal plant extracts display potent inhibitory activity against carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, thereby reducing postprandial hyperglycemia[25,28-32]. These enzyme-modulating effects slow glucose absorption and improve glycemic

stability. Importantly, the presence of antioxidant phytochemicals on the nanoparticle surface helps mitigate the cytotoxicity traditionally associated with silver, enhancing biocompatibility and therapeutic safety.

Selenium nanoparticles (SeNPs) play a crucial role in metabolic regulation through their involvement in antioxidant defense systems, particularly glutathione peroxidase activity and redox homeostasis[26,33-37]. SeNPs exhibit insulin-mimetic properties, improve insulin sensitivity, and protect pancreatic β-cells from oxidative damage and inflammatory injury. Their dual antioxidant and metabolic regulatory functions make them particularly valuable in diabetes therapy[26,38-43].

Zinc oxide nanoparticles (ZnO NPs) contribute to glycemic control through zinc's essential role in insulin synthesis, storage, and secretion. ZnO nanoparticles enhance pancreatic insulin release, stabilize insulin granules, and improve systemic glucose regulation in diabetic models[27,44-50].

Iron oxide nanoparticles (Fe_3O_4 NPs) offer multifunctionality by supporting targeted drug delivery, imaging, and metabolic modulation, enabling both therapeutic and diagnostic applications. Collectively, these nanoparticle systems combine metallic bioactivity with phytochemical synergy, creating integrated therapeutic platforms for precision diabetes management.

4. Mechanisms of Antidiabetic Action

Biogenic nanoparticles exert their antidiabetic effects through multilevel and synergistic biological mechanisms that target core metabolic pathways involved in glucose homeostasis. A primary mechanism involves the enhancement of insulin signaling, where nanoparticles activate key intracellular pathways such as PI3K/Akt and AMPK, leading to improved glucose uptake, increased insulin sensitivity, and enhanced cellular energy metabolism[28,51-57]. These signaling cascades promote GLUT4 translocation in skeletal muscle and adipose tissue, facilitating efficient glucose clearance from circulation. Another critical mechanism is enzyme inhibition, particularly the suppression of α-amylase and α-glucosidase, which reduces carbohydrate digestion and glucose absorption in the gastrointestinal tract. This effect directly contributes to the control of postprandial hyperglycemia and glycemic variability[29,58-60].

Antioxidant activity represents a central therapeutic pathway, as biogenic nanoparticles effectively scavenge reactive oxygen species (ROS), reduce lipid peroxidation, and restore redox balance in insulin-sensitive tissues and pancreatic β-cells. By mitigating oxidative stress, these systems protect cellular structures and preserve metabolic function[30,61-63].

In parallel, anti-inflammatory effects play a major role through the downregulation of NF-κB signaling pathways and suppression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. This anti-inflammatory modulation improves insulin sensitivity and reduces chronic low-grade inflammation associated with diabetes[30,64-66].

Importantly, β-cell protection is achieved through the reduction of oxidative injury, inflammatory damage, and apoptotic signaling, preserving insulin synthesis and secretory capacity. The phytochemical corona surrounding biogenic nanoparticles synergizes with the nanoparticle core, amplifying metabolic regulation, antioxidant defense, and signaling modulation, resulting in enhanced therapeutic efficacy across multiple biological pathways.

5. Preclinical Evidence and Therapeutic Outcomes

A substantial body of preclinical evidence supports the therapeutic potential of plant-mediated biogenic nanoparticles in diabetes management. Animal studies consistently demonstrate significant reductions in fasting blood glucose levels, improved lipid profiles, enhanced antioxidant enzyme activity, and restoration of metabolic homeostasis following treatment with green-synthesized nanoparticles[31]. These effects are accompanied by improvements in insulin sensitivity, reduced inflammatory biomarkers, and protection of pancreatic tissue architecture.

Gold and selenium nanoparticles frequently exhibit superior β-cell preservation compared to crude plant extracts, highlighting the added value of nanoparticle-based delivery systems[32]. These nanoplatforms enhance intracellular delivery, prolong bioactivity, and improve cellular retention of phytochemicals, leading to stronger disease-modifying effects. Zinc oxide nanoparticles have been shown to significantly improve insulin levels, stabilize glycemic control, and enhance glucose tolerance in diabetic animal models, reflecting zinc's essential role in pancreatic endocrine function[32].

Comparative studies further indicate that green-synthesized nanoparticles demonstrate reduced toxicity and enhanced therapeutic efficacy relative to chemically synthesized counterparts[33]. The phytochemical surface coatings not only improve biocompatibility but also contribute additional antioxidant and anti-inflammatory bioactivity, creating synergistic therapeutic effects.

Despite these promising outcomes, standardized clinical trials remain limited, and most evidence is confined to experimental and preclinical models. Variability in synthesis methods, dosing strategies, and characterization protocols also limits direct comparison across studies[33]. Translational progress will therefore depend on standardized production methods, harmonized experimental designs, reproducible nanoformulation protocols, and rigorous clinical validation frameworks to support regulatory approval and clinical integration.

6. Safety, Toxicity, and Regulatory Considerations

Although green synthesis approaches significantly reduce chemical toxicity associated with conventional nanoparticle production, safety concerns remain, particularly regarding nanoparticle accumulation in vital organs such as the liver, spleen, kidneys, and lymphatic tissues. The reticuloendothelial system plays a central role in nanoparticle clearance, increasing the risk of long-term tissue retention and potential chronic toxicity[34].

Toxicological outcomes are strongly influenced by particle size, surface charge, dose, and exposure duration. Smaller particles exhibit greater tissue penetration but may pose higher cytotoxic risks, while prolonged exposure increases the likelihood of bioaccumulation[35]. These factors necessitate long-term biodistribution, chronic toxicity, and metabolic clearance studies to ensure safety.

Standardization of synthesis protocols, physicochemical characterization, and dosing regimens is essential for reproducibility, comparability, and regulatory approval. Regulatory agencies require rigorous safety documentation, including detailed pharmacokinetic profiling, immunogenicity assessment, biodistribution mapping, and long-term exposure data[36, 37].

The regulatory classification of nanomedicine remains complex, often requiring additional safety frameworks beyond conventional phytotherapy regulations. Consequently, the successful clinical translation of biogenic nanoparticles depends on the development of harmonized regulatory standards, quality control systems, and validated safety assessment pipelines, ensuring that therapeutic innovation is aligned with patient safety and regulatory compliance.

7. Future Perspectives and Translational Challenges

Future research in biogenic nanoparticle-based diabetes therapy should prioritize reproducibility, scalable synthesis, and precision targeting to enable sustainable clinical translation. Scalable green synthesis methods must be developed to ensure cost-effective production, batch consistency, and global accessibility. Precision targeting strategies will further enhance tissue specificity and therapeutic efficacy. The integration of nanotechnology with personalized medicine frameworks offers significant promise. Coupling biogenic nanoparticles with patient-specific metabolic profiling and glucose-responsive delivery systems may enable adaptive, individualized therapeutic strategies that dynamically respond to glycemic fluctuations and metabolic states.

Hybrid therapeutic systems, combining biogenic nanoparticles with conventional antidiabetic drugs, represent another promising avenue, offering synergistic benefits through multi-pathway targeting and dose reduction strategies. However, the most critical translational challenge remains the absence of large-scale, standardized clinical trials. Comprehensive clinical studies evaluating long-term safety, efficacy, biodistribution, and therapeutic durability are essential to validate preclinical success.

Ultimately, successful translation will depend on interdisciplinary collaboration between nanotechnologists, pharmacologists, clinicians, regulatory scientists, and industry stakeholders. Through coordinated translational ecosystems, biogenic nanomedicine can evolve from experimental innovation into clinically transformative diabetes therapy.

CONCLUSION

Green nanotechnology offers a sustainable and innovative platform for diabetes therapy by integrating medicinal plant bioactivity with nanoscale engineering. Biogenic nanoparticles synthesized from plant extracts exhibit multifaceted antidiabetic mechanisms, including improved insulin signaling, oxidative stress reduction, enzyme inhibition, and β-cell protection. Their eco-friendly production and potential biocompatibility make them attractive alternatives to conventional nanomaterials. Nevertheless, careful evaluation of long-term safety, reproducibility, and regulatory compliance is essential. With rigorous standardization and translational research, plant-mediated nanoparticles may become valuable therapeutic agents in precision diabetes management, particularly in resource-limited settings where medicinal plants are culturally embedded and readily accessible.

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CITE AS: Bwambale Isaac (2026). Green Nanotechnology in Diabetes Therapy: Biogenic Nanoparticles from Medicinal Plants as Therapeutic Agents. IDOSR JOURNAL OF EXPERIMENTAL SCIENCES 12(2): 33-40. https://doi.org/10.59298/IDOSR/JES/06/1223340