ejpmr, 2025, 12(3), 193-208

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

"EMERGING NANOTECHNOLOGIES IN DIABETES CARE: ENHANCING DRUG DELIVERY AND THERAPEUTIC EFFICACY"

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Article Received on 01/01/2025 **Article Revised on 21/01/2025** **Article Accepted on 10/02/2025**

ABSTRACT

Diabetes mellitus is a growing global health concern with significant socioeconomic burdens. Conventional therapies like insulin and oral hypoglycemic agents have limitations, including side effects, poor efficacy, and patient non-adherence. Nanotechnology offers innovative solutions for diabetes management through advanced drug delivery systems such as polymeric, lipid-based, inorganic micelles, exosome-generated, and hybrid nanoparticles. Among these, plant-derived silver nanoparticles (AgNPs) stand out due to their biocompatibility, antioxidant activity, and glucose-regulating properties. Green synthesis using plant extracts provides a sustainable and less toxic approach, leveraging bioactive compounds like polyphenols, flavonoids, alkaloids, and terpenoids to enhance insulin sensitivity and reduce complications. Medicinal plants like Jasminum sambac, Syzygium cumini, Momordica charantia, and Curcuma longa have shown promising results in nanotechnology-based diabetes treatment. However, challenges such as regulatory hurdles, safety concerns, and scalability remain. Future research should focus on improving nanoparticle formulations, ensuring biocompatibility, and integrating plant-based and synthetic nanotechnologies for a multi-targeted therapeutic approach. These advancements highlight the potential of nanotechnology in revolutionizing diabetes care with novel treatment strategies.

KEYWORDS: Nanotechnology, Diabetes mellitus, Drug delivery, Plant-derived nanoparticles, Silver nanoparticles, Antidiabetic effects.

1. INTRODUCTION

Diabetes continues to be a major global health challenge, with the International Diabetes Federation (IDF) reporting that approximately 537 million adults were living with diabetes in 2021. This number is projected to escalate to 783 million by 2045, underscoring the urgent need for effective public health strategies. According to the Global Burden of Disease Study, diabetes was the eighth leading cause of death and disability worldwide in 2021, contributing significantly to healthcare costs, which were estimated at $966 billion in that year and are expected to rise to over $1 trillion by 2045.[1,2] The prevalence of undiagnosed diabetes is particularly concerning, with nearly 44.7% of individuals unaware of their condition in 2021. This issue is most pronounced in regions such as Africa and Southeast Asia, where rates of undiagnosed diabetes exceed 50%.[3]

Diabetes is associated with a range of acute and chronic complications that significantly impact morbidity and mortality:

- Cardiovascular Diseases: Individuals with diabetes are at heightened risk for cardiovascular events. A study found that about 19.7% of chronic complications among diabetic patients were related to cardiovascular issues.[4]
- Nephropathy: Diabetic kidney disease remains a critical complication, contributing to increased morbidity. The prevalence of end-stage renal disease is on the rise due to prolonged diabetes duration and inadequate management.[5]
- Neuropathy: Neuropathy affects approximately 50% of individuals with diabetes, leading to significant functional impairment and an increased risk for foot ulcers and amputations.[4]
- Retinopathy: Diabetic retinopathy remains a leading cause of blindness among working-age adults, affecting nearly 5.2% of diabetic patients.[4]

Recent studies have also highlighted emerging complications linked to diabetes, such as cognitive decline and certain cancers, which are becoming increasingly recognized as significant contributors to the overall burden of diabetes-related morbidity.[6]

Existing practices for diabetes (primarily insulin and oral hypoglycemics) have a lot of limitations. While insulin is critical for the management of Type 1 diabetes and frequently needed in advanced Type 2 diabetes because

of its life-saving effects, it can also lead to complications like severe hypoglycemia and weight gain from usage. Insulin does not help with Type 2 diabetes, and the improvement of insulin resistance remains suboptimal over time. Limitations have been found with oral hypoglycemic agents, including sulfonylureas and thiazolidinediones. Common side effects of these medications include weight gain and increased cardiovascular risks, which can reduce adherence in patients. Furthermore, the risk of drug resistance in Type 2 diabetes arises, ultimately leading patients to develop a reliance on these techniques as they become less effective over time. This indicates an urgent need for personalized medicine that takes into account clinical differences such as comorbidities and the risk of treatment-related adverse effects, as highlighted in recent studies.[7,8] Conventional diabetes treatments have many side effects that are non-negligible hurdles in the management of diabetes. Sulfonylureas cause the highest rates of hypoglycemia and weight gain, while thiazolidinediones are responsible for causing fluid retention and doubling the risk of heart failure. These side effects can substantially impair the quality of life in patients, and in some cases, patients discontinue therapy. Additionally, the inefficiency of these medications is evident, as a significant number of patients are unable to reach target glycated hemoglobin (HbA1c) levels despite guideline-directed therapy. This inefficacy is particularly true for older antihyperglycemic therapies, which generally have not shown a reduction in macrovascular complications or mortality. Therefore, there is an increasing focus on newer pharmacologic agents that may be more efficacious and have a better safety profile.[7,8]

This review focuses on the role of plants and nanoscale technologies as potential strategies for improved management of Type 2 diabetes. It will explore the promising applications of phytochemicals and plant-derived nanoparticles, particularly silver nanoparticles (AgNPs), in enhancing glycemic control and addressing diabetes-related complications, as well as the current treatment requirements. By examining the mechanisms of action of these emerging therapies, this review aims to suggest safer and more effective alternatives to traditional diabetes treatments, while also considering future directions in this field.

2. DIABETES MELLITUS: PATHOPHYSIOLOGY AND TREATMENT CHALLENGES

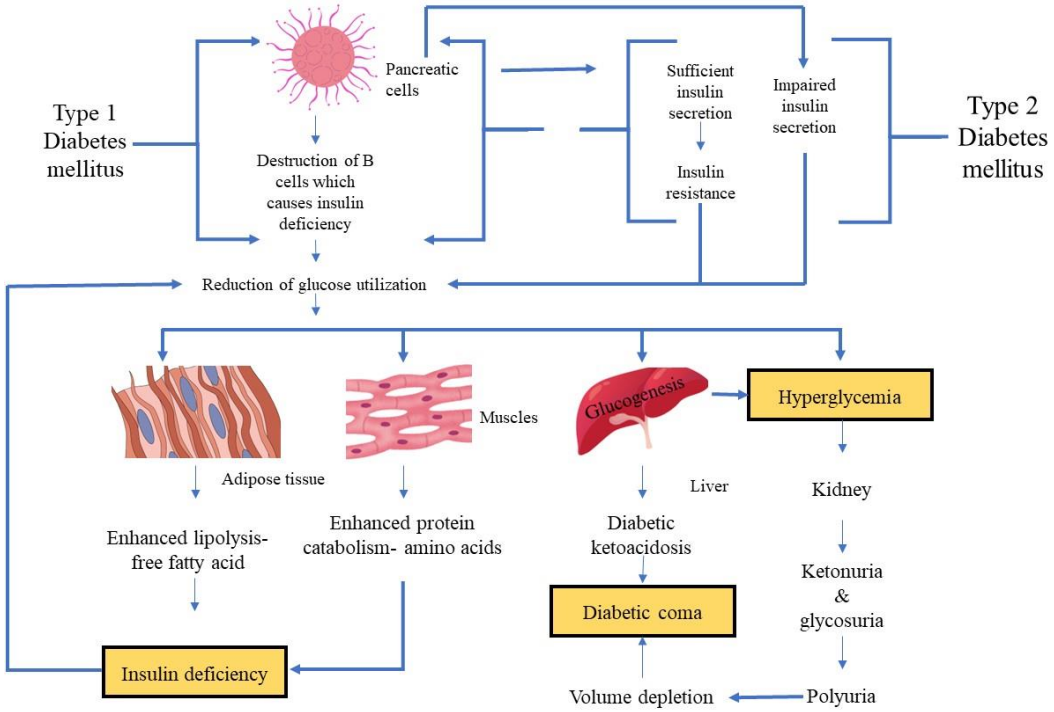

Figure 1: Pathophysiology of diabetes mellitus.

2.1 Insulin Resistance and β-Cell Dysfunction: Characterization of the pathology of Type 2 Diabetes Mellitus (T2DM) is primarily comprised of insulin resistance and β-cell failure of the pancreas (the effects of some pathogens may vary). Insulin resistance is a state in which insulin-stimulated uptake does not occur in tissues such as the liver, muscle, and adipose tissue due to a lack of sensitivity. Several factors predispose individuals to this condition, such as obesity, lack of physical activity, and genetic makeup.

One of the biggest risk factors is obesity, which induces metabolic dysfunction and insulin resistance, particularly central adiposity. Adipose tissue secretes free fatty acids (FFA) and inflammatory cytokines, which disturb the milieu of free fatty acids, leading to decreased insulin sensitivity by impairing insulin signaling pathways

mechanistically. The pancreatic β-cells cannot adequately compensate for insulin resistance, ultimately leading to impaired insulin secretion. Under chronic high glucose stimulation, β-cell dysfunction occurs through multiple pathways such as oxidative and endoplasmic reticulum (ER) stress. This leads, over time, to protein misfolding, which accumulates in β-cells and eventually causes apoptosis and a decrease in the pancreatic beta-cell insulin secretion capacity. It is also established that elevated levels of reactive oxygen species (ROS) further aggravate β-cell dysfunction by inducing inflammation and cell death.[9,10]

2.2 Limitations of Current Treatments: With so many different treatment options available, there is a greater need now than ever for new, effective, and safe therapies in diabetes management. Most of the treatments being prescribed are insulin and oral antihyperglycemic agents. Nonetheless, these therapies are also quite constrained. Using insulin is a critical tool in controlling Type 1 diabetes and often more severe forms of Type 2 diabetes; however, it comes with an array of side effects — most notably weight gain and hypoglycemia. In addition, oral medications (such as sulfonylureas and thiazolidinediones) may lead to adverse effects such as gastrointestinal disturbances and vascular risks. Furthermore, most patients develop resistance to treatment over time, driven by the natural progression of T2DM. Drug resistance among Type 2 diabetic patients is also reaching new heights. The disease typically worsens, often requiring greater and more numerous drug regimens as patients' responses to standard therapies decrease. Unfortunately, sometimes these combinations do not work and can also be risky, underscoring the critical need for novel therapeutic approaches to improve glycemic control by addressing core components of insulin resistance and β-cell dysfunction.[11]

3. ROLE OF PLANTS IN DIABETES MANAGEMENT

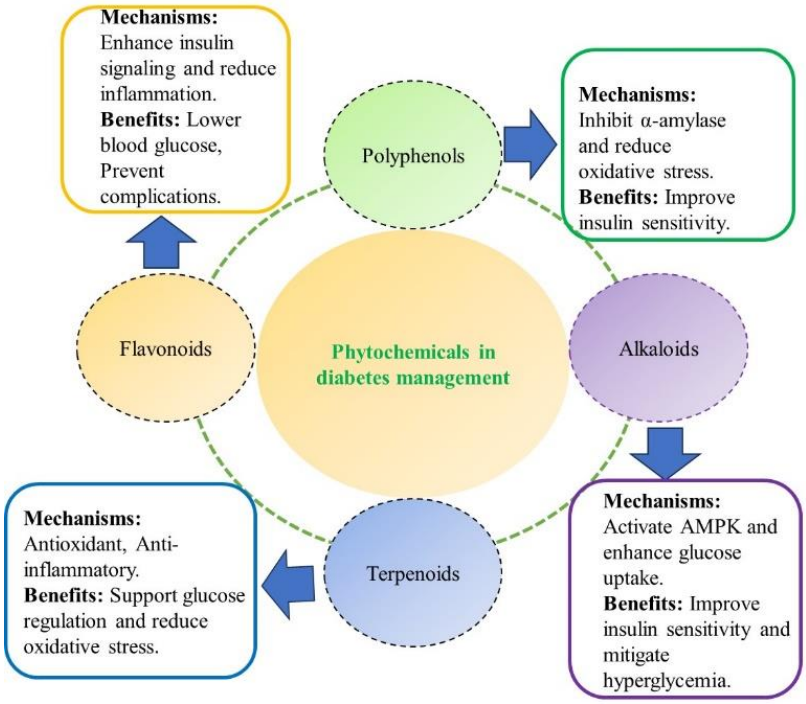

Figure 2: Role of phytochemicals in diabetes management.

3.1 Phytochemicals with Antidiabetic Effects: Plants have phytochemicals that are bioactive compounds with multiple health benefits and vast potential in diabetes management. Polygenic compounds target several components of glucose metabolism, oxidative stress, and insulin pathways. Some of the major classes of phytochemicals that are associated with antidiabetic properties are.

3.1.1 Polyphenols: Polyphenols are most known as antioxidants and insulin-sensitizing compounds. These compounds hinder carbohydrate-degrading enzymes (α-amylase and α-glucosidase) in the intestine, minimizing the amount of glucose absorbed by the gut. A meta-analysis has shown that polyphenols from medicinal plants markedly enhance insulin sensitivity and decrease glucose-induced oxidative stress in diabetes.[12]

3.1.2 Flavonoids: Widespread evidence suggests that flavonoids (e.g., quercetin and catechins) may decrease blood glucose levels and improve glycemic regulation. These compounds affect glucose metabolism through insulin signaling pathways and possess anti-inflammatory properties. Flavonoids may protect against diabetic complications by acting through antioxidant, anti-inflammatory, and immunomodulatory mechanisms.[13,14]

3.1.3 Alkaloids: Antidiabetic plants, phenolics, and alkaloids from various medicinal plants also display beneficial properties. Berberine (from Berberis aristata), an alkaloid, has been reported to activate AMP-activated protein kinase (AMPK), consequently enhancing insulin sensitivity. Studies indicate that acid stimulants improve glucose uptake and glycogen synthesis, thereby normalizing hyperglycemia.[15]

3.1.4 Terpenoids: Terpenoids are widely used due to their wide range of biological activities, including anti-inflammatory and antioxidant properties. The compounds are also effective in enhancing glucose metabolism and reducing oxidative stress in diabetic models, suggesting their potential as diabetes combat agents.[12]

3.2 Notable Plants with Antidiabetic Potential

Table 1: The antidiabetic potential of various plants.

Botanical Name	Common Name	Part Used	Antidiabetic Potential	Reference
Jasminum sambac	Arabian Jasmine	Leaves, Flowers	Restores fasting glucose levels, mitigates oxidative stress, improves lipid profile	[16].
Syzygium cumini	Jamun	Seeds, Bark	Enhances glucose utilization, reduces insulin resistance, and improves carbohydrate metabolism	[17].
Momordica charantia	Bitter Melon	Fruits	Stimulates insulin secretion, improves glucose uptake, and reduces blood glucose levels	[18].
Tinospora cordifolia	Giloy	Stem, Leaves	Enhances insulin sensitivity, promotes beta-cell regeneration	[19].
Trigonella foenum-graecum	Fenugreek	Seeds	Delays glucose absorption, improves insulin sensitivity and reduces fasting blood glucose levels	[20].
Cinnamomum cassia	Cinnamon	Bark	Increases insulin receptor activity and improves glycogen synthesis	[21].
Ocimum sanctum	Holy Basil, Tulsi	Leaves	Reduces fasting blood glucose, improves antioxidant enzyme activity	[22].
Gymnema sylvestre	Gurmar	Leaves	Suppresses glucose absorption in the intestine, promotes beta-cell repair	[23].
Aloe vera	Aloe Vera	Gel, Leaves	Improves glucose uptake, increases insulin secretion, and reduces oxidative stress	[24].
Curcuma longa	Turmeric	Rhiome	Reduces blood glucose levels, improves insulin resistance, and mitigates inflammation	[25].

3.3 Mechanisms of Action: Several medicinal plants have antidiabetic properties through multiple modes of action. The mechanisms include the inhibition of important enzymes, increased insulin secretion and sensitivity to insulin, and regulation of glucose metabolism, as described below. The following is a detailed elucidation of these modes based on recent literature.

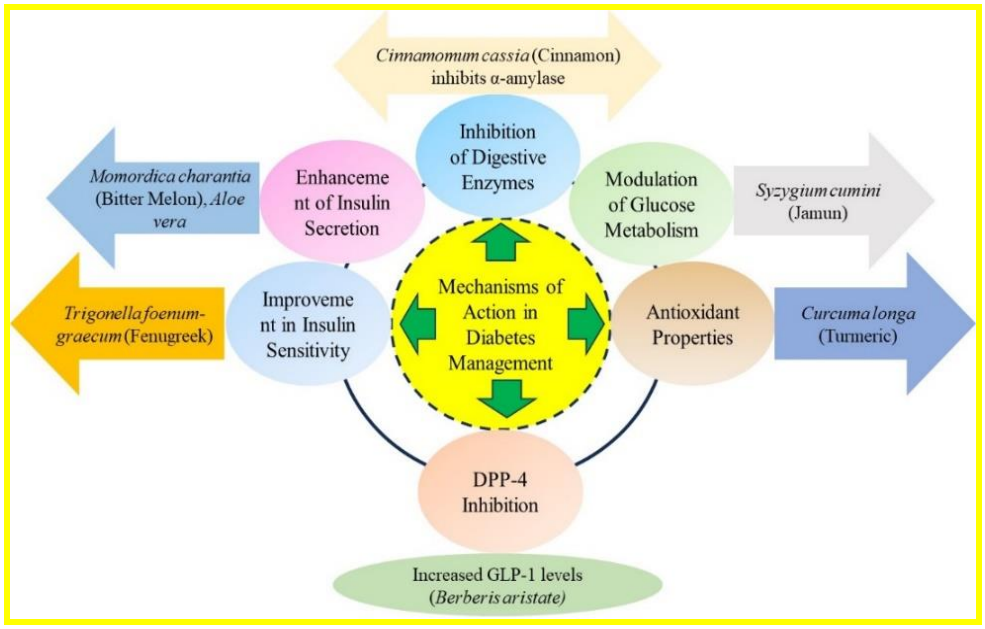

Figure 3: Mechanism of action of various plants in diabetes management.

3.3.1 Inhibition of Digestive Enzymes: Plants inhibit the enzymes (α-amylase and α-glucosidase) that are important for carbohydrate digestion and absorption. These plants prevent these enzymes from degrading carbohydrates into glucose, thus reducing postprandial blood glucose levels by slowing down the process.

Example: Cinnamomum cassia (cinnamon) has been found to block the activity of α-amylase, resulting in a reduced uptake of glucose in the intestines.[12]

3.3.2 Enhancement of Insulin Secretion: Some plants enhance pancreatic β-cells by triggering insulin secretion, the result of which is decreased blood glucose levels.

Example: Momordica charantia (Bitter Melon) has already shown itself capable of increasing insulin secretion and cell glucose uptake.[26] Additionally, Aloe vera has been reported to increase insulin secretion, contributing to better blood glucose control.[27]

3.3.2 Improvement in Insulin Sensitivity: Insulin-sensitive plants (e.g., Trigonella foenum-graecum - Fenugreek) improve the hypothalamus's response to ingested carbohydrate signaling insulin. This is an important mechanism for ameliorating insulin resistance commonly observed in type 2 diabetes mellitus.

Example: Fenugreek seeds have been found to increase fasting blood glucose and insulin sensitivity through some bioactive compounds that modulate metabolic pathways in the following ways.[28]

3.3.4 Modulation of Glucose Metabolism: Several plants impact glucose homeostasis by increasing muscle and adipose tissue glucose uptake or by decreasing hepatic glucose output. Syzygium cumini (Jamun), for instance, increases glucose utilization and enhances carbohydrate metabolism, resulting in blood sugar regulation.[29]

3.3.5 Antioxidant Properties: Oxidative stress is a significant contributor to diabetes complications. Many medicinal plants possess antioxidant properties that help mitigate oxidative damage to pancreatic β-cells.

Example: Curcuma longa (Turmeric) exhibits strong antioxidant effects that protect pancreatic cells from oxidative stress, improving overall metabolic health.[30]

3.3.6 DPP-4 Inhibition: Dipeptidyl peptidase-4 (DPP-4) inhibitors enhance incretin hormone levels, which stimulate insulin secretion and inhibit glucagon release.
Example: Compounds from Berberis aristata have been shown to inhibit DPP-4 activity, leading to increased GLP-1 secretion and improved glycemic control.[12]

4. NANOTECHNOLOGY IN DIABETES MANAGEMENT

4.1 Types of Nanoparticles in Diabetes Management: Nanotechnology has introduced many nanoparticles (NPs) for managing diabetes, including differently functionalized nanoparticles. These nanoparticles improve drug delivery systems, increase therapeutic effects, and relieve metabolic diseases stemming from diabetes. Below is a complete description of various types of nanoparticles in diabetes care, detailing their types, benefits, and research studies.

Table 2: Description, benefits, and applications in diabetes of various types of nanoparticles.

Type of Nanoparticles	Description	Benefits	Applications in Diabetes	Reference
Polymeric Nanoparticles	Biodegradable polymers such as PLGA, chitosan, and polycaprolactone encapsulate drugs like insulin.	Enhanced oral bioavailability, slow drug release, targeted delivery, decreased dosing frequency.	Protects insulin from degradation, controlled GI release, and tissue-specific drug concentration.	[31].
Lipid-Based Nanoparticles	Includes SLNs, NLCs, and liposomes for hydrophobic and hydrophilic drugs.	Improved solubility, bioavailability, stability, and controlled release of antidiabetic drugs.	Targeted insulin delivery, and enhanced drug stability.	[32].
Inorganic Nanoparticles	Nanoparticles such as silver, gold, silica, and iron oxide.	Multifunctional properties: antimicrobial activity, real-time imaging, combination therapies.	Diabetic wound healing, targeted delivery, therapeutic and diagnostic applications.	[33].
Micellar Nanoparticles	Self-assembled amphiphilic copolymers forming micelles for encapsulating hydrophobic drugs.	Improved drug solubility, targeted delivery, and better cellular uptake.	Delivery of hydrophobic drugs to tissues related to glucose metabolism.	[34].
Exosomes	Natural nano-sized extracellular vesicles for	Cross biological barriers, personalized medicine,	Delivery of therapeutic agents, and alteration of	[35].

	cell-to-cell communication.	non-immunogenic.	biological events for diabetes treatment.	
Hybrid Nanoparticles	Engineered systems combining two or more types of nanoparticles.	Multifunctional capabilities, combining therapy and diagnostics.	Potential for drug delivery and imaging in diabetes care.	[36].
Smart Nanoparticles	Advanced nanocarriers that respond to biological stimuli or environmental changes.	Targeted delivery, improved efficacy, controlled release based on stimuli like pH, temperature, and enzymes.	Precision-based diabetes therapy and drug delivery systems.	[37].

4.1.1 Polymeric Nanoparticles: Biodegradable polymeric nanoparticles, such as poly (lactic-co-glycolic acids) (PLGA), chitosan, and polycaprolactone, are biocompatible and can be tailored for slow drug release. They encapsulate antidiabetic pro-drugs like insulin to protect them from degradation and are aimed at the controlled release of the drug in the gastrointestinal tract. This results in enhanced oral bioavailability and decreased dosing frequency. Additionally, they enable targeted concentration toward specific tissues.[31]

4.1.2 Lipid-Based Nanoparticles: SLNs/NLCs liposomes for hydrophobic and hydrophilic drugs include solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and liposomes, which contain both hydrophobic and hydrophilic drugs. These nanoparticle conjugates in lipids are expected to improve the solubility and bioavailability of poorly water-soluble antidiabetic drugs, leading to better bioavailability along with controlled release. There is an improvement in the stability and bioavailability of insulin among other antidiabetic agents, allowing for targeted delivery to various tissues.[32]

4.1.3 Inorganic Nanoparticles: Inorganic nanoparticles consist of silver, gold, silica, and iron oxide. These nanoparticles possess special physical and chemical properties that could be utilized for therapeutic applications. In addition to their roles as delivery agents or imaging agents, inorganic nanoparticles can be multifunctional. They may also exhibit antimicrobial properties to promote the healing of diabetic wounds. Improved targeting and the possibility for real-time imaging, along with combination therapies, enhance therapeutic benefits.[33]

4.1.4 Micellar Nanoparticles: Micellar nanoparticles are obtained from self-assembling amphiphilic copolymers into micelles, which serve to encapsulate hydrophobic drugs. Micelles improve the solubility of hydrophobic drugs that are hardly soluble in water and enhance their delivery to target sites in the human body. The increase in drug solubility, breast cancer cell uptake, and targeted delivery to specific cells or tissues related to glucose metabolism is provided by the targeting moiety.[34]

4.1.5 Exosomes: Natural, nano-sized extracellular vesicles are released by cells that package proteins, lipids, or RNAs for use in cell-to-cell communication. Exosomes can be programmed to deliver therapeutic agents into target cells and alter biological events associated with diabetes treatment. They can act as non-covalent carriers to limit immunogenicity; they can cross biological barriers, offering the possibility for personalized medicine in diabetes treatment.[35]

4.1.6 Hybrid Nanoparticles: Hybrid nanoparticles are synthetic systems that combine two or more different nanoparticles to form a multifunctional platform with potential applications in medicine, etc. Nanoparticles can have therapeutic and/or diagnostic functionalities that are suited for cancer treatment and imaging. The generation of hybrid nanostructures with more than one type of nanostructure (e.g., liposomes, micelles, magnetic nanoparticles) is essential for their design and synthesis. This underscores the ability of these systems to serve as both drug carriers and imaging agents.[36]

4.1.7 Smart Nanoparticles: Smart nanoparticles are specific biological stimuli or environmentally responsive advanced nanocarriers. These are designed to facilitate drug delivery by targeting certain cells or tissues, thus providing better effectiveness and safety for applications. Recent progress in smart nanoparticles has focused on their response to stimuli such as pH, temperature, and enzymes. Smart nanoparticles include polymeric nanoparticles and mesoporous silica nanoparticles assessed against the target therapy in cancer.[37]

4.2 Mechanisms of Nanoparticle Action in Diabetes: Nanoparticles (NPs) have recently emerged as a disruptive approach for diabetes management by improving drug delivery and therapeutic efficacy, among other benefits. This section will discuss the interaction of nanoparticles with biological systems, specifically for diabetes treatment.

4.2.1 Cellular Uptake and Intracellular Transport: s The cellular uptake of therapeutic agents, such as insulin, is significantly improved by nanoparticles. They enter target cells via a variety of endocytic routes, including the following mechanisms.

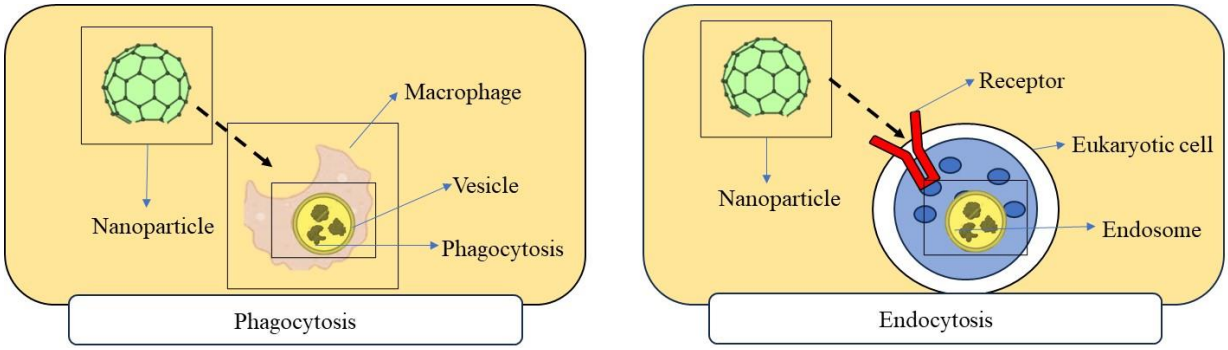

Figure 4: Mechanism of Cellular Uptake and Intracellular Transport (Phagocytosis), and (Endocytosis).

- Phagocytosis: Immune cells ingest large particles mainly through this process.
- Endocytosis: In this pathway, the binding of nanoparticles to specific receptors on the cell surface leads to internalization, known as 'receptor-mediated endocytosis.

Insulin-loaded nanoparticles with a high uptake can potentially overcome insulin resistance in the target tissue. For example, polymeric nanoparticles have been reported to maintain insulin bioactivity and uptake, thus exerting improved blood glucose control in diabetic models.[38,39]

4.2.2 Targeted Drug Delivery

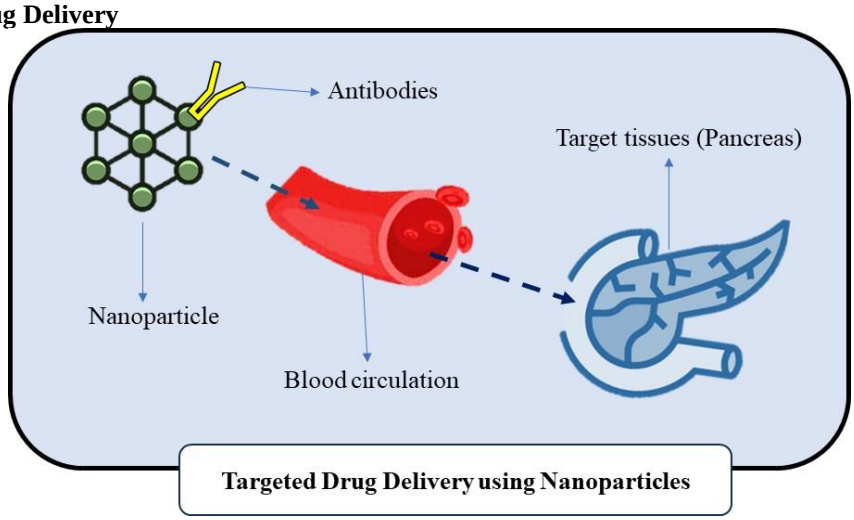

Figure 5: Mechanism of target drug delivery of nanoparticles.

Nanoparticles may be functionalized with targeting ligands like antibodies or peptides to achieve specific drug delivery to particular tissues or cells. This laser-targeted method provides a better therapeutic effect, while the safety of side effects is improved.

Targeting insulin-sensitive tissues (e.g., skeletal muscle and adipose tissue) in diabetes management is particularly advantageous. Research has shown that nano-functionalized nanoparticles can restore insulin sensitivity and provide efficient regulation of blood glucose levels.[34,40] For instance, the intended improvements in oral bioavailability of insulin and other antidiabetic drugs are being pushed towards lipid nanoparticle-based carriers, directly leading to the liver and pancreas tissue.[39]

4.2.3 Immune Modulation: There are some nanoparticles in particular (especially the metallic ones) with immune-modulatory behavior that can be beneficial for the treatment of complications of diabetes. Activating or dampening the function of immune cells makes nanoparticles either trigger another inflammation or reduce inflammatory levels.

One of the most common side effects of diabetes is chronic inflammation, which results in slow wound healing and contributes to diabetes complications. For instance, immune-modulatory nanoparticles that alleviate inflammation could serve a dual benefit of healing while reducing infection and promoting repair. New research has shown that these immune-based nanoparticles improve diabetic wound healing by attenuating inflammatory responses and promoting the repair of tissues.[38,40]

4.3 Recent Advances in Nanotechnology for Diabetes Care: Nanomedicine continues to bring excitement to diabetes management in an entirely new way that changes drug delivery. Some key advancements and their applications are listed as follows.

4.3.1 Nanoparticles in Insulin Resistance Treatment: Engineered to target insulin-resistant tissues, nanoparticles are very effective at reversing glucose metabolism. One of the latest breakthroughs is a hollow nano scavenger based on biodegradable Pt nanoparticles and a mitochondrial uncoupler drug delivery system. The scavengers lower the levels of reactive oxygen species (ROS) in liver cells, which restores insulin sensitivity and normalizes hyperglycemia in diabetic mice.[41] Likewise, polymeric nanoparticles loaded with anti-inflammatory agents were shown to increase glucose uptake in human liver cells and therefore represent a possible route for the chronic treatment of diabetes with these polymeric nano-systems.[40,41]

4.3.2 Nanotechnology in Diabetes-induced Complications

Nanoparticles are addressing complications like retinopathy and nephropathy by targeting oxidative stress and inflammation.

- Suppression of retinal neovascularization by gold nanoparticles in the VEGF signaling pathway is necessary for treating diabetic retinopathy.[42]
- Silver nanoparticles (AgNPs) alleviate oxidative damage in hyperglycemia-mediated diabetic tissues, thus contributing to the repair of neuropathy and nephropathy.[40,43]
- Eprosartan mesylate in nanoliposomes reduces diabetic nephropathy fibrosis markers and has renal-protective effects.[42]

4.3.3 Nanoparticles in Diabetic Wound Healing

Silver-based nanoparticles in diabetes wound care: Silver nanoparticles promote tissue regeneration, delay infection development, and accelerate healing in chronic diabetic ulcers.[43] Clinical studies also validate the superiority of SilvrSTAT Gel (AgNP-based) over conventional dressings and faster healing rates. However, long-term efficacy data are lacking, and combination therapies (e.g., with growth factors) are being studied.[44]

4.4 Properties of Nanoparticles

The effectiveness of nanoparticles in diabetes care stems from their unique physicochemical properties.

4.4.1 Size and Surface Area

- Nanoparticles (1–100 nm) penetrate biological membranes efficiently, reaching insulin-sensitive tissues like the liver and pancreas.[45]
- Optimal size (10–100 nm) balances tissue penetration and circulation time, avoiding rapid renal clearance.[45]

4.4.2 Surface Functionalization

- PEGylation (coating with polyethylene glycol) reduces immunogenicity, prolonging nanoparticle circulation in the bloodstream.[46]
- Ligands (e.g., antibodies, peptides) enable targeted delivery to specific cells, improving drug efficacy while minimizing off-target effects.[45,46]

4.4.3 Biodegradability and Biocompatibility

- PLGA nanoparticles degrade into lactic and glycolic acid, naturally occurring metabolites, ensuring safety and minimal immune response.[47]
- Biodegradable systems like hollow nanoscavengers break down after delivering therapeutic payloads, reducing toxicity risks.[41,47]

4.6 Role of Nanoparticles in Diabetes Management: Nanoparticles have recently been suggested as a potential way to treat diabetes, especially by promoting insulin delivery, providing antioxidant properties, and improving glucose monitoring systems. This is followed by specific advances and applications of nanoparticles in the focus areas below.

Oral Insulin Delivery

Meanwhile, new advancements in oral insulin delivery have gone beyond the conventional poly (lactic-co-glycolic acid) (PLGA) nanoparticle. Some relevant examples are.

- **Lipid-Core Micelles:** These nanomedicines entrap insulin in a lipid core, which protects the drug from being degraded during its digestion in the gastrointestinal tract. This approach enhances the absorption of insulin through intestinal membranes for successful oral delivery.
- **Solid Lipid Nanoparticles (SLNs):** Insulin-loaded SLNs have significantly decreased blood glucose concentrations in diabetic animals, as demonstrated by our studies and others. For example, SLNs with palmitoyl cetyl ester have been found to have an insulin association efficiency of up to 43%, providing a strong hypoglycemic effect even 24 hours after oral dosage.[48,49]
- **Poly(Styrene-co-Maleic Acid) Micelles SMA Micelles:** A study reported the oral delivery of insulin that involved the use of SMA micelles, which were able to facilitate intestinal diffusion of insulin and stimulate liver glucose uptake, pointing towards possible clinical applications for diabetes therapy.[48]

Antioxidant Properties

Due to their conspicuous antioxidant capacity, nanoparticles also have the properties to counteract oxidative stress, such as in diabetic conditions.

- **Copper Nanoparticles (CuNPs):** proving to be efficient antioxidants with remarkable free radical scavenging activity, inhibiting α-amylase and α-glucosidase enzyme-related anti-diabetic effects.[50]
- **Platinum Nanoparticles:** They are broad-spectrum antioxidants with the ability to mimic different enzyme antioxidant activities, consequently minimizing oxidative stress and inflammation caused by diabetes in various tissues. They have been demonstrated to significantly lower reactive oxygen species (ROS) production in cellular systems.[51]

Glucose Monitoring

The most recent advances in glucose-sensitizing nanoparticles are substantially transforming CGM systems and insulin delivery devices for diabetes diagnostics.[1,2] With the current advances in smart co-formulated nanoparticles and glucose-responsive smart nanotechnology, these innovations bring more patient-centric approaches for effective delivery.

Smart nanotechnology

- **Nanoparticles responsive to Glucose:** A study in ACS Nano reports that the authors designed and synthesized nanoparticles capable of releasing insulin according to glucose levels. By altering the degree of acetalation in dextran polymers, researchers developed protein profiles for rapid and sustained insulin release. Diabetic mouse models showed significantly increased insulin concentrations in these nanoparticles, illustrating their capacity to achieve effective glycemic control with one dose for up to 16 hours.[52]

Coformulated Nanoparticles

- **Recent Findings from Con A systems:** A review of the 2024 report on a study of hydrogel using Con A (Con A) to modulate insulin release in a glucose-responsive manner. Hydrogel swells in hyperglycemic conditions for insulin delivery and shrinks at lower glucose levels, which leads to decreased release rates. Smart insulin delivery systems: A Promising Approach via this mechanism.[53]
- **Continuous monitoring modalities:** Nanosensorics were envisioned, reviewed, and their importance in enhancing glucose monitoring capabilities is apparent. To this end, nanoscale sensors are conceived as effective electrodes for catalytic enhancement that enable more sensitive and precise glucose quantification than conventional processes.[54]

4.7 Challenges in Nanoparticle Applications

4.7.1 Regulatory and Clinical Trials

Due to the unique technology and its associated risks, nanoparticle-based drug regulation is challenging. Regulatory authorities and bodies such as the FDA and EMA only allow clinical trials after a very high level of safety data has been established. The intricate design of the nanoparticles impairs the standardization of safety assessments, which is driving the time delays in obtaining clinical licenses. For example, new developments in glucose-controlling insulin delivery systems demonstrate current obstacles in translating from bench to bedside, especially regarding precise insulin release and the stability of entrapped proteins.[32]

4.7.2 Economic Barriers: The massive expense of advanced materials and manufacturing technologies means that commercial-level production of nanoparticles is still economically out of reach. The complexity of the manufacturing process may be a barrier to scaling nanoparticle-based therapies and could therefore present challenges for clinical relevance at a large scale. However, there is evidence that scalability should be optimized in order to facilitate the wider adoption of these technologies into healthcare facilities.[55,56]

4.7.3 Toxicity and Safety: The toxicity is a significant problem in the field of nanomedicine applications. Nanoparticles are expected to have a host of unusual bioactivities that were not accounted for in their general safety over the long term. Currently, studies are aimed at ensuring the biocompatibility and toxicity of the different nanomaterial formulations, particularly those intended for gene/drug delivery.[52]

4.7.4 Scalability: One of the biggest bottlenecks in the commercial scaling of nanoparticles is their manufacturing. The complex manufacturing processes for synthesizing and encapsulating nanoparticles are typically not amenable to high-volume, low-cost production, which can ensure availability. The challenges in scaling these nanoparticle technologies to reach routine clinical practice must be resolved.[55]

4.7.5 Regulatory Approvals: The regulatory approval for nanoparticle-based therapeutics is a lengthy process that requires well-completed preclinical studies and phases of clinical trials. The newness of these materials demands thorough assessment to guarantee patient safety and efficacy, which can lengthen the time required to get new products approved. Current literature highlights the challenges in obtaining clear regulatory pathways specific to nanomedicine so that it can be approved promptly while ensuring safety.[32,57]

4.8 Silver Nanoparticles (AgNPs) in Diabetes: Silver nanoparticles (AgNPs) have recently been targeted by the scientific community for their applications in diabetes through nanomedicine. These properties are well-suited for their potential use in the management of diabetes as well as the complications it causes, due to their antimicrobial, antioxidant, and anti-inflammatory effects.

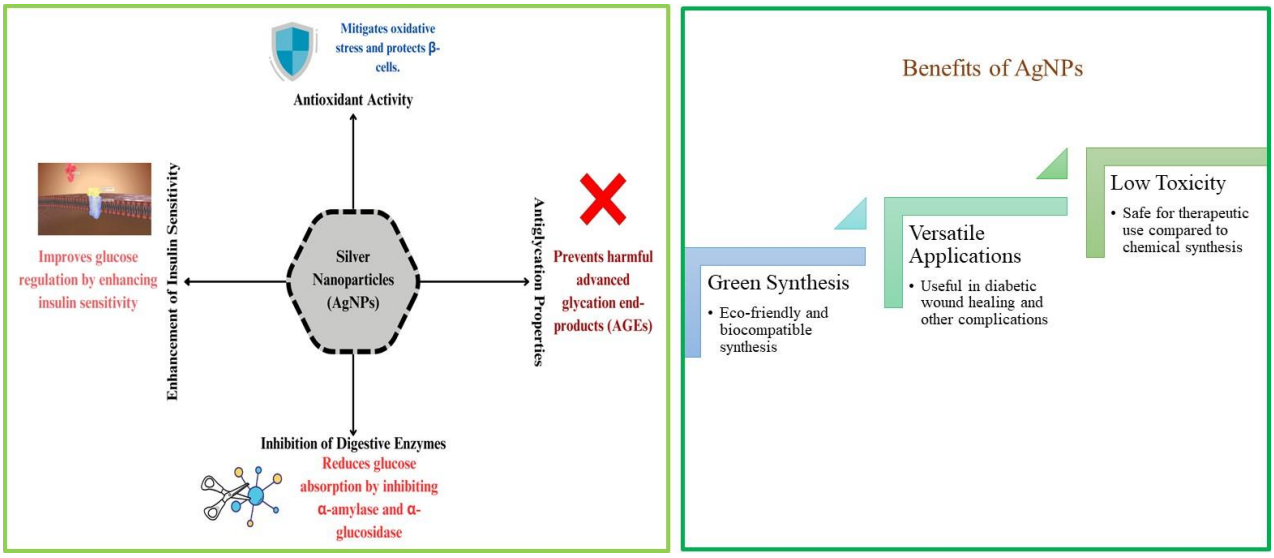

Figure 5: Mechanisms and Benefits of Silver Nanoparticles in Diabetes Management.

4.8.1 Mechanisms of Action

4.8.1.1 Antioxidant Activity: Due to their high antioxidant activity, AgNPs reduce oxidative stress levels in diabetes. Diabetes is a disease where many complications, such as neuropathy and retinopathy, occur due to oxidative stress. AgNPs can mitigate oxidative stress and protect pancreatic β-cells, thereby promoting better metabolic health.[58]

4.8.1.2 Inhibition of Digestive Enzymes: Silver nanoparticles can inhibit essential digestive enzymes like α-amylase and α-glucosidase. The inhibition lowers glucose absorption from the intestines and subsequently achieves lower postprandial blood glucose levels. This works almost exclusively on blood sugar surges after a meal — a mechanism.[59]

4.8.1.3 Antiglycation Properties

AgNPs were found to prevent the production of advanced glycation end products (AGEs), which are harmful byproducts that lead to diabetic complications. Inhibition of glycation processes by AgNPs is expected to help decrease the chances of long-term diabetic complications.[59]

4.8.1.4 Enhancement of Insulin Sensitivity: Some studies suggest that silver nanoparticles may improve insulin sensitivity, aiding in better glucose regulation and potentially reducing the need for exogenous insulin.[60]

4.9 Benefits of Silver Nanoparticles

4.9.1 Biogenic Synthesis: Green synthesis of silver nanoparticles using plant extracts is a less toxic and eco-friendly technique compared to conventional chemical methods. This method contributes to higher biocompatibility and can thus be used in therapeutic AgNPs.[59]

4.9.2 Versatile Applications: AgNPs can be used not only for direct antidiabetic activity but also as a means to enhance wound healing in diabetic patients, in part attributed to their antimicrobial properties. This is especially important in preventing infection in diabetic ulcers.[61]

4.9.3 Low Toxicity: Studies indicate that biogenic silver nanoparticles have low toxicity levels, making them safer for therapeutic applications compared to synthetic alternatives.[58]

4.10 Applications in Drug Delivery: Emerging Silver nanoparticles (AgNPs) as a delivery system for insulin and other antidiabetic agents is new and has several advantages over classical delivery approaches. The versatile properties of these systems give rise to enhanced bioavailability, controlled release, and therapeutic efficacy. Some applications of AgNPs in the field of drug delivery systems for diabetes management are centered in this section.

4.10.1 Targeted Delivery Mechanisms

Enhanced Bioavailability

The bioavailability of insulin could be enhanced through Silver Nanoparticles (AgNPs), which serve as a safeguard against enzymatic degradation in the gastrointestinal tract. This is particularly important considering that insulin is the least stable in the GI tract and is therefore administered via subcutaneous injections. On one hand, researchers are attempting to develop the oral delivery of insulin by encapsulating it in AgNPs.[60]

Controlled Release

The engineering of AgNPs can be designed to trigger a time-released insulin. This is to permit more realistic levels of blood glucose by emulating the natural release of insulin from pancreatic β-cells. This would result in a reduced frequency of administration and can still ensure proper glycemic control with controlled-release formulations.[59]

Targeting Specific Tissues: Functionalization of silver nanoparticles with targeting ligands can be used to improve drug delivery to insulin-sensitive tissues, such as skeletal muscle and adipose tissue, targeted by nanoparticles. This is a targeted strategy to reduce systemic adverse effects and improve the efficacy of effects at the intended site. [61]

5. PLANT-DERIVED NANOPARTICLES IN DIABETES THERAPY

5.1 Green Synthesis of Nanoparticles: Green synthesis of nanoparticles using plant extract is an alternative to the traditional chemical approach in nanofabrication. This strategy employs complete plant parts (leaves, roots, stems, for example) to generate nanoparticles that are free from toxic chemicals. Generally, this process involves the reduction of metal cations in solution by phytochemicals, which are compounds found in plant extracts that play both reducing and stabilizing roles.

Key advantages of green synthesis include

Simplicity and Cost-effectiveness: The methods are often straightforward and do not require expensive equipment or complex procedures.

Environmental Safety: This method minimizes environmental pollution and is considered safer for human health than traditional chemical synthesis methods.

Biocompatibility: Nanoparticles produced through green synthesis exhibit high biocompatibility, making them suitable for biomedical applications, including drug delivery systems for diabetes therapy.[62,63]

Studies indicate that plant extracts can lead to the formation of nanoparticles with well-defined sizes and shapes, which is an important aspect of their efficiency in therapeutic applications. For example, research has been published regarding the synthesis of silver nanoparticles via various plant extracts, as in vivo studies have proven their excellent antimicrobial activity and have also shown beneficial effects on diabetes management.[64,65]

5.2 Therapeutic Benefits of Plant-Based Nanoparticles: Plant-origin nanoparticles display potential therapeutic implications in diabetes owing to their superior stability and bioavailability. Nanosizing of phytochemicals (e.g., curcumin, resveratrol, quercetin) results in better pharmacokinetic properties, which are associated with enhanced absorption and efficacy in lowering blood glucose.

The therapeutic benefits include

Enhanced Stability and Bioavailability: Nanosized formulations increase the solubility and stability of bioactive compounds that are usually not water-soluble. This improvement leads to enhanced bioavailability upon administration.[66]

Glucose-Lowering Effects: Many studies have also found that plant extract-derived nanoparticles can drastically decrease blood glucose levels. For example, thymoquinone nano-carriers have shown anti-hyperglycemic effects similar to current medications like metformin.[67]

Multi-target Mechanisms: Plant nanoparticles can act on several pathways in the management of diabetes. This may aid in the restoration of β-cell function, maintain or restore insulin sensitivity, or reduce oxidative stress (all crucial in managing diabetes).[38,66]

Some of the recent reviews have compiled the capacity of these nano-formulations in treating diabetes and its related complications, focusing on the possibilities to overcome conventional therapeutic strategies. The integration of nanotechnology in diabetes treatment is an important advancement towards better pharmacokinetics, aiming for an improvement in patient outcomes.[66,67]

5.3 Mechanisms of Action of Plant-Derived Nanoparticles

Antioxidant Properties: Antioxidant activities of plant-derived nanoscale nanoparticles (particularly silver nanoparticles (AgNPs) from various plant extracts) are significant. These nanoparticles can reduce oxidative stress, which is an important factor associated with the progression of diabetes complications such as neuropathy and retinopathy. For instance, AgNPs increase the activity of endogenous antioxidant enzymes, scavenge free radicals, lower oxidative damage to pancreatic cells, and boost insulin sensitivity.[67,68]

Anti-Inflammatory Effects: Inflammation at the molecular level plays a major role in the progression of diabetic complications. Nanoparticles from plants have been shown to affect the pro-inflammatory cytokine profile by downregulating the expression of TNF-α and IL-6 (junk proteins) and upregulating anti-inflammatory markers. This action aims to subdue the long-standing inflammation observed in diabetes, which could prevent outcomes such as cardiovascular diseases and diabetic nephropathy.[67]

Gene Modulation: Some plant-derived nanoparticles have been reported to regulate gene expression in insulin signaling and glucose metabolic pathways. Indeed, these nanoparticles have been shown to upregulate glucose transporter proteins (e.g., GLUT4) in order to presumably augment glucose entry into cells, thus demonstrating an improvement in glycemic control in diabetic models.[67,68]

5.4 Characterization of Plant-Based Nanoparticles

Size and Morphology: Optimization of the size and shape of nanoparticles is essential for their therapeutic efficacy, especially in applications related to drug delivery. For targeted delivery, nanoparticles of size ~1-100 nm are usually efficient, as they can bypass biological barriers and augment cellular uptake. Smaller nanoparticles typically have a large surface area-to-

volume ratio, which may allow for enhanced interactions with biological systems.[67,69]

Surface Charge: An important parameter that controls nanoparticles stability and interaction with biological membranes is the zeta potential. The absolute zeta potential means that particles are likely to be more stable in suspension, but also changes the charge may change cellular uptake, being positively charged nanoparticles usually have a stronger interaction with negatively charged cell membranes. Essential for maximized drug delivery w/o cytotoxicity.[70,71]

Structural Integrity: Since the stability and integrity of plant-based nanoparticles in a biological environment are prerequisites for their use in diabetes treatment, nanoparticle stability is affected by environmental pH, ionic strength, and the presence of biomolecules. UV-Vis spectroscopy, FTIR, and electron microscopy (used primarily to confirm morphology) are employed for the characterization of these properties.[69,70]

5.5 Plant-Based Nanoparticles in Diabetic Wound Healing

Wound Healing Mechanisms: Plant-derived nanoparticles play an important role in improving wound healing in the diabetic population, especially in cases of advanced ulcers. They are antimicrobial to prevent infection, anti-inflammatory to reduce swelling and pain, and possess tissue healing and regenerative capabilities.

Some examples include certain silver nanoparticles extracted from plants such as Carica papaya (baby pawpaw), which have been found effective in inducing collagen synthesis and enhancing the wound closure rate in diabetic models. Moreover, these nanoparticles can be used to modulate growth factors for angiogenesis and tissue repair, leading to better healing outcomes.[66,72]

5.6 Future Directions and Clinical Applications

Clinical Trials and Translational Research: Plant-based nanoparticles are being integrated into diabetes care, with several clinical trials in progress to evaluate their safety and effectiveness. A couple of examples include AgNPs for wound healing, which have demonstrated beneficial effects in terms of reduced runoff times when compared to conventional treatments.[71,72]

Regulatory Considerations: Evolution of the nanomedicine regulatory landscape. Agencies such as the FDA mandate complete safety assessments that include biocompatibility evaluations and long-term systemic toxicity studies for regulatory approval for clinical use. Being able to navigate these regulatory frameworks is essential for commercializing a successful product.[71,72]

Commercialization Challenges: Making large-scale plant-based nanoparticle production scalable (both economically and by streamlining the manufacturing processes) as well as overcoming regulatory hurdles is essential. For the therapeutic use of these nanoparticles, establishing steady production protocols to guarantee consistent quality in nanoparticle formulations is paramount.[71,72]

5.7 Comparison of Synthetic vs. Plant-Derived Nanoparticles for Diabetes Therapy

Table 3: Comparison of the Advantages, Limitations, and Applications of Plant-Derived Nanoparticles (PDNPs) vs. Synthetic Nanoparticles in Diabetes Treatment.

Aspect	Plant-Derived Nanoparticles (PDNPs)	Synthetic Nanoparticles	Significance	Reference
Biocompatibility	High biocompatibility, reducing immune reactions.	May trigger immune responses due to synthetic materials.	PDNPs are more compatible with biological systems, reducing potential immune issues.	[66], [73].
Toxicity	Naturally low toxicity, leads to fewer side effects.	Potential toxicity concerns depend on material composition.	PDNPs are safer, offering fewer side effects for diabetic treatments.	[66], [74].
Synthesis Method	Environmentally friendly, green synthesis using plant extracts.	Chemical and physical methods often involve toxic reagents.	PDNPs offer a sustainable approach with minimal environmental impact.	[67], [74].
Production Cost	Cost-effective at a small scale but challenging for large-scale production.	More scalable and cost-efficient for industrial manufacturing.	PDNPs are cost-effective in research but face challenges for large-scale production.	[73], [75].
Standardization	Variability in plant sources makes standardization difficult.	Highly standardized with controlled synthesis.	Standardization of PDNPs is challenging, limiting consistent production.	[67], [74].
Stability	Depends on the plant extract composition.	Generally, more stable due to optimized formulations.	PDNP stability can vary, affecting consistency in diabetes treatment.	[73], [75].
Drug Delivery	Functionalized for targeted	Designed for precise drug	PDNPs can target specific	[67], [74].

Efficiency	drug delivery, especially to pancreatic β-cells.	targeting and controlled release.	tissues for enhanced therapeutic outcomes.	
Combination Therapy	Can be combined with synthetic nanoparticles for enhanced bioavailability.	Often used in combination therapies to optimize treatment.	Combining PDNPs with synthetic nanoparticles can improve the efficacy of diabetes treatment.	[66], [67].
Application in Diabetes	Modulates metabolic pathways, improves insulin sensitivity, and enhances glucose uptake.	Used for insulin delivery, controlled drug release, and glucose monitoring.	PDNPs target multiple pathways in diabetes treatment for better results.	[67], [75].

6. CONCLUSION

Today, nanotechnology opens a new dawn in diabetes management, where the finite capabilities of conventional therapies are challenged to offer a solution. Several kinds of nanomaterials such as polymeric, lipid carriers, inorganic, micellar, and exosome-derived nanoparticles have remarkable applications to improve drug delivery bioavailability and targeting towards specific cells/tissues, and also modulate the host immune response. Among these, plant silver nanoparticles (AgNPs) are enticed with their biocompatibility benefits and antioxidant properties, aiding in glycemic control. Plant extract-based green synthesis further enriches their therapeutic potency by providing a greener and more sustainable option. Besides nanotechnology, plant-based bioactive compounds (polyphenols, flavonoids, alkaloids, and terpenoids) and the antidiabetic capabilities of various plant species have significant effects on the improvement of certain diabetic pathophysiologies, e.g., insulin resistance, re-establishment of glucose homeostasis, and reduction of oxidative stress. While progress has been made, multiple hurdles remain to be tackled, such as regulatory approval, large-scale manufacturing, safety concerns, and clinical translation. Research should target the optimization of nanoparticle formulations, stability, and bioavailability improvement, as well as extensive preclinical and clinical studies to achieve future validation of their effectiveness and safety.

The integration of nanotechnology with plant-based treatments offers an efficient approach toward future antidiabetic interventions and, hopefully, personalized therapeutic strategies in diabetes care, surpassing the existing options.

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