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Biogenic Silver Nanoparticles from Antidiabetic Plants: Dual Evaluation of Insulin-Mimetic and Antibacterial Activities

Rashida Shafaat (Corresponding Author)
M.Phil. Scholar, Department Of Biotechnology, Women University Bagh Azad Kashmir Email: rashidakhan800@yahoo.com
Bismillah
National Center Of Excellence In Analytical Chemistry University Of Sindh Jamshoro Email: bismillahabbasi1996@gmail.com
Rimsha Saleem
Division Of Science And Technology, University Of Education Lahore, Pakistan
Email: rimshasaleem453@gmail.com
Keziah Shaheen
Faculty of Pharmacy, Hamdard University, Islamabad Campus
Email: keziah.shaheen@hamdard.edu.pk
Muhammad Sarib
Department Of Chemistry, University Of The Engineering And Technology Lahore
Email: muhammadsarib84@gmail.com
Talha
University of Makran Email: talha@uomp.edu.pk

Author Details

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Corresponding E-mail & Author*:

Rashida Shafaat
M.Phil. Scholar, Department Of Biotechnology, Women University Bagh Azad Kashmir
Email: rashidakhan800@yahoo.com

Abstract

Type 2 diabetes mellitus and associated secondary complications, such as impaired wound healing and multidrug-resistant bacterial infections, pose severe global health challenges. While conventional oral hypoglycemic therapies manage hyperglycemia, their clinical utility is frequently compromised by poor bioavailability, non-targeted distribution, and systemic side effects. Nanomedicine offers a transformative alternative; however, traditional chemical and physical nanoparticle synthesis methods introduce toxic residues and high environmental costs. This review comprehensively examines the green synthesis, biophysical characterization, and multifaceted therapeutic evaluation of biogenic silver nanoparticles (AgNPs) functionalized with extracts from antidiabetic medicinal plants. Phyto-synthesis represents a rapid, sustainable, and economically viable "one-pot" approach in which plant secondary metabolites including polyphenols, flavonoids, and terpenoids simultaneously act as reducing, capping, and stabilizing agents. These natural biomolecules form an organic bio-corona that provides long-term colloidal stability and suppresses particle agglomeration. Analytically, successful AgNP formation is validated by visible color transitions driven by localized surface plasmon resonance (LSPR), with face-centered cubic crystalline phases confirmed through X-ray diffraction. Biologically, these biogenic nanoformulations demonstrate potent dual-action efficacy. They mitigate metabolic

dysregulation via the robust in vitro inhibition of carbohydrate-digesting enzymes (α-amylase and α-glucosidase) and the activation of downstream insulin-mimetic signaling cascades. Concurrently, they exhibit broad-spectrum bactericidal and anti-biofilm activities by inducing membrane rupture, deactivating respiratory enzymes, and generating reactive oxygen species. Consequently, plant-mediated biogenic AgNPs bridge the gap between traditional herbal medicine and nanotechnology, offering a highly synergistic, biocompatible, and multi-targeted therapeutic platform capable of simultaneously managing metabolic dysregulation and secondary microbial infections.

Introduction

Type 2 diabetes mellitus is a highly prevalent, chronic metabolic disorder characterized by persistent hyperglycemia, peripheral insulin resistance, and progressive pancreatic \beta -cell dysfunction. Globally, the prevalence of this disorder continues to rise, with estimates predicting that the diabetic population will reach approximately 640 million individuals by 2040 (Ogurtsova et al., 2017). Pathophysiologically, diabetes is closely associated with chronic oxidative stress, where excessive production of reactive oxygen species (ROS) triggers cellular apoptosis and impairs pancreatic beta -cell maturation and insulin secretion (Wang & Wang, 2017).

To manage this condition, clinical practice relies on oral hypoglycemic therapies categorized into several major classes: biguanides and thiazolidinediones that act as insulin sensitizers; sulfonylureas and glinides that serve as insulin secretagogues; and carbohydrate-digesting enzyme inhibitors. However, these conventional drugs are often limited by slow action, poor bioavailability, non-targeted distribution, and drug resistance (Stein et al., 2012). Furthermore, they frequently cause undesirable side effects, such as gastrointestinal distress, abdominal distension, flatulence, diarrhea, significant weight gain, peripheral edema, and acute hypoglycemia (Ganesan, 2018).

Nanomedicine offers a promising alternative to overcome these therapeutic limitations. Nanoparticles, which range in size from subnanometers to several hundred nanometers ($1 \text{ nm} = 1 \times 10^{-9} \text{ m}$), possess unique physical and chemical characteristics. Their high surface-area-to-volume ratio facilitates cellular endocytosis, tissue penetration, systemic distribution, and favorable retention and elimination profiles within biological fluids (Khodashenas & Ghorbani, 2019). Historically, the application of metallic nanostructures spans from iron and chromium nanoparticles used in ancient Mayan pigments at Chichen Itza to 19th-century photochemistry and glass molding. In modern medicine, silver nanoparticles (AgNPs) are of particular interest due to their outstanding optical, electrical, catalytic, and biological properties (Iravani, 2014). Conventional physical and chemical methods for synthesizing AgNPs such as laser ablation, arc-discharge, or chemical reduction using ethylene glycol at 140–180 °C, hydrazine under basic conditions, or sodium borohydride at 0–5 °C require high energy consumption, specialized equipment, and toxic organic solvents or synthetic capping agents like polyvinylpyrrolidone (PVP). These processes often leave hazardous chemical residues on the nanoparticle surface, causing systemic toxicity and limiting their biomedical utility (Almatroudi, 2020).

In contrast, biological synthesis, or phyto-synthesis, is a rapid, cost-effective, and sustainable "one-pot" method that aligns with the core principles of green chemistry. Phyto-synthesis uses aqueous extracts of medicinal plants, fungi, or algae as nanofactories to reduce silver ions under mild temperature and pressure conditions (Aloke et al., 2022). The biomolecules present in these extracts act as both reducing agents and natural capping layers. This organic bio-corona prevents nanoparticle aggregation, provides long-term colloidal stability, and enhances biocompatibility. When AgNPs are synthesized using antidiabetic medicinal plants, the biological properties of the plant secondary metabolites are integrated directly onto the nanoparticle surface, creating a synergistic therapeutic system (Chaudhury et al., 2017). This dual-action approach is highly effective for managing both core metabolic dysregulation and secondary diabetic complications, such as impaired wound healing and multidrug-resistant bacterial infections (Sati, 2025).

Chemical Kinetics and Biophysical Mechanisms of Phyto-Synthesis

The biological transformation of silver ions (Ag^+) into zero-valent, crystalline metallic silver nanoparticles (Ag^0) is a multi-step process involving the reduction, nucleation, growth, and stabilization of the metal core. Plant extracts derived from antidiabetic species are rich in secondary metabolites, such as polyphenols, flavonoids, alkaloids, terpenoids, glycosides, tannins, and proteins, which drive this bioreduction (Shah et al., 2025). During the activation phase, ionic silver from a precursor salt, typically silver nitrate ($AgNO_3$), is introduced to the aqueous plant extract (Khan et al., 2023). Phenolic compounds and flavonoids containing active hydroxyl groups (–OH) act as electron donors. These compounds readily ionize, releasing free electrons and hydrogen ligands that reduce the cationic silver while being oxidized into quinones or other oxidized structures (Jha, 2025). This fundamental redox process can be represented by the following chemical equations:

$$\mathrm{Ag^+(aq)} + e^- \rightarrow \mathrm{Ag^0(s)}$$
$$\mathrm{Ag^+(aq)} + \mathrm{Phytochemical_{(reduced)}} \rightarrow \mathrm{Ag^0(s)} + \mathrm{Phytochemical_{(oxidized)}}$$

Thermodynamically, plant polyphenols (such as catechol and gallic acid) exhibit redox potentials in the range of +0.3 to +0.5 V versus the standard hydrogen electrode (SHE). Because the standard reduction potential of the Ag^+/Ag^0 half-reaction is +0.80 V vs. SHE, the reaction is thermodynamically favorable and proceeds spontaneously at ambient or moderate temperatures (Siakavella et al., 2020).

Following initial reduction, the zero-valent silver atoms (Ag^0) serve as nucleation centers, colliding and aggregating to form stable metallic nuclei. During the growth phase, these nuclei expand as additional silver ions are reduced onto their surfaces. To limit particle size and prevent agglomeration, other biomolecules, such as proteins, polysaccharides, organic acids, and flavonoids, adsorb onto the high-energy crystalline facets of the growing nanoparticles (Salayová et al., 2021). This capping process creates a protective organic shell that provides steric and electrostatic stabilization, ensuring excellent colloidal dispersion (Melkamu & Bitew, 2021).

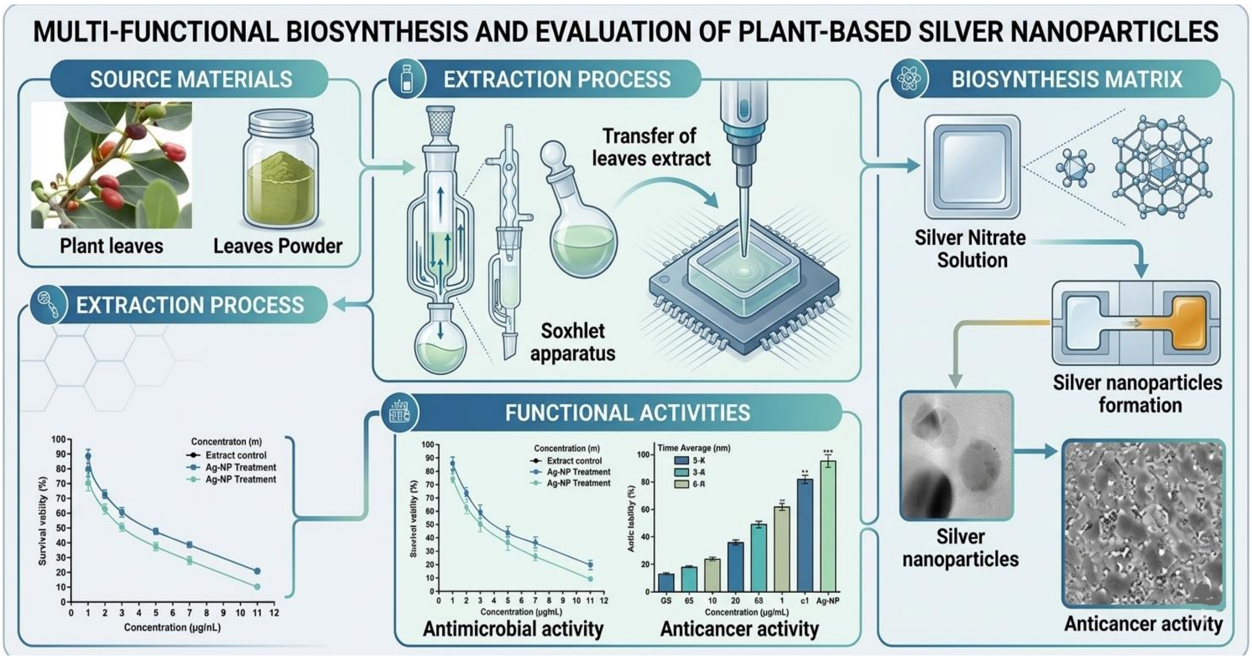
This synthesis process is monitored macroscopically by a color change in the reaction mixture from colorless or pale yellow to a deep, reddish-brown color. This color change is caused by surface plasmon resonance (SPR), where the conduction band electrons of the metallic silver nanoparticles undergo collective, coherent oscillations when excited by incident light of specific wavelengths. This SPR absorption peak, typically detected via UV-visible spectrophotometry between 390 nm and 450 nm, serves as a key indicator of successful nanoparticle formation (Shahzadi et al., 2025).

Characterization and Biophysical Optimization of Biogenic Silver Nanoparticles

A comprehensive characterization of biogenic silver nanoparticles (AgNPs) is essential to understand their physical and chemical properties, optimize synthesis parameters, and evaluate their potential clinical applications. Various analytical techniques are used to determine nanoparticle size, morphology, surface charge, elemental composition, crystalline structure, and the nature of the organic capping layer (Sekar et al., 2022).

The crystalline nature of biogenic AgNPs is typically confirmed by powder X-ray diffraction (XRD) analysis, which regularly reveals distinct diffraction peaks corresponding to the face-centered cubic (FCC) lattice structure of metallic silver (Ali, 2023). The average crystallite size can be calculated from the XRD patterns using the Scherrer equation. Energy-dispersive X-ray analysis (EDX) is used to confirm the presence of elemental silver, showing a characteristic optical absorption peak at approximately 3 keV, which is typical for metallic silver nanocrystals (Labulo et al., 2022).

Figure 1. Green synthesis cascade of bio-functionalized silver nanoparticles from Soxhlet plant extraction to dual antimicrobial and anticancer applications.



The organic capping layer on the nanoparticle surface is analyzed using Fourier transform infrared (FTIR) spectroscopy. FTIR spectra identify functional groups such as hydroxyl (–OH), carbonyl (C=O), and amine ($-NH_2$) groups derived from the plant proteins, flavonoids, and phenolics. These functional groups bind to the metallic silver core, protecting the nanoparticles from aggregation and enhancing their biological activity (Almayouf et al., 2024).

Table 1: Green Synthesis Parameters and Biophysical Characteristics of Plant-Derived AgNPs

Plant Species and Extract Source	**Optimal Precursor and Synthesis Parameters**	**Key Capping and Stabilizing Biomolecules (FTIR)**	**Crystalline Structure and Crystallite Size (XRD)**	**Hydrodynamic Size, Core Size, and Surface Charge (DLS/TEM)**	**Optical Properties and Localized Surface Plasmon Resonance (LSPR)**
Moringa oleifera (aqueous leaf extract)	1 mL extract + 100 mL of 1 mM $AgNO_3$, heated at	Amino acids, vitamins, enzymes, structural proteins	Crystalline face-centered cubic (FCC); ~7 nm	Spherical morphology; core size 10–25 nm	SPR peaks at 415–439 nm

	60–80°C for 1 h				
Coffea arabica (green coffee aqueous extract)	1 mM $AgNO_3$ precursor under biological conditions	Alkaloids, terpenoids, glycosides, polyphenols	FCC lattice; crystallite size ~7.2 nm	Well-dispersed nanospheres; core 8.6 ± 3.5 nm; capped 29.9 ± 4.3 nm	SPR bands at 329 nm and 425 nm
Fagonia cretica (aqueous plant extract)	Phyto-mediated aqueous synthesis	Polyphenols, flavonoids, organic acids	Highly crystalline FCC phase	Spherical clustered morphology; 20–50 nm	Visible-range plasmon band
Stenocereus queretaroensis (flower extract)	Aqueous flower extract + $AgNO_3$ precursor	Phenolics, flavonoids (sinapic acid, p-coumaroyl tyrosine, procyanidin dimer β1, dihydroquercetin)	Crystalline phase confirmed	Rough spherical particles; ~99.5 nm	Stable plasmon resonance band
Thymus serpyllum (aqueous leaf extract)	Phyto-reduction of $AgNO_3$ precursor	Phenolic monoterpenes, organic acids, flavonoids	FCC crystalline structure	Uniform spherical nanoparticles; ~42 nm	Well-defined SPR peak in visible range
Gymnema sylvestre (aqueous leaf extract)	10 mL extract + 90 mL of 1 mM $AgNO_3$, 24 h reaction	Gymnemic acids, saponins, phenolics	Highly crystalline metallic Ag	Spherical particles; 30–100 nm	SPR peak at 390–400 nm
Centella asiatica (leaf and stem extract)	Aqueous extraction; alkaline pH 11–12 synthesis	Alkaloids, flavonoids, glycosides, terpenoids	FCC crystallinity	Highly spherical; 20 nm (leaf), 19 nm (stem)	SPR peaks at 405 nm and 408 nm

Dual In Vitro Evaluation: Carbohydrate-Digesting Enzyme Inhibition and Cellular Glucose Uptake

Biogenic silver nanoparticles (AgNPs) exhibit dual therapeutic efficacy, functioning as both potent inhibitors of key carbohydrate-digesting enzymes and active facilitators of cell glucose transport. This dual action offers a comprehensive approach to managing blood glucose levels by slowing down intestinal carbohydrate breakdown and promoting glucose clearance from the bloodstream (Majeed et al., 2022). The primary therapeutic target for managing postprandial blood glucose is the inhibition of pancreatic α-amylase and intestinal α-glucosidase. Pancreatic α-amylase cleaves internal α-1,4-glucosidic bonds in starch and complex dietary carbohydrates, converting them into oligosaccharides and maltose (Rahman et al., 2023). Intestinal α-glucosidase then hydrolyzes this terminal, non-reducing α-1,4-glucosidic residues to release free glucose, which is absorbed into the bloodstream. Inhibiting these enzymes delays carbohydrate digestion, prolongs overall absorption time, and blunts postprandial blood glucose spikes (González-Garibay, 2026).

Molecular Signaling Pathways of Insulin-Mimetic Activity

sequestered in the cytoplasm, and glucose transport is severely impaired.

To understand the insulin-mimetic mechanisms of biogenic silver nanoparticles (AgNPs), it is necessary to examine the downstream intracellular signaling cascades that regulate glucose homeostasis under both normal and diabetic conditions (Nouri et al., 2020).

In healthy cells, insulin binds to the extracellular α-subunits of the heterodimeric insulin receptor (IR), activating the tyrosine kinase domain within the intracellular β-subunits. This autophosphorylation recruits and phosphorylates insulin receptor substrate (IRS) proteins, primarily IRS-1 and IRS-2 (Hopkins et al., 2020). Phosphorylated IRS recruits' phosphoinositide 3-kinase (PI3K), which converts membrane phosphatidylinositol 4,5-bisphosphate (PIP_2) into phosphatidylinositol 3,4,5-trisphosphate (PIP_3) (Kearney et al., 2021).

In type 2 diabetes, this signaling cascade is severely disrupted. Epigenetic modifications, such as DNA methylation and histone acetylation, suppress the transcription of insulin, adiponectin, and the insulin-responsive GLUT4 gene. Chronic, low-grade systemic inflammation releases inflammatory cytokines that block insulin receptor phosphorylation, rendering the classical PI3K/Akt pathway inactive. As a result, GLUT4 vesicles remain sequestered in the cytoplasm, and glucose transport is severely impaired (Khalid et al., 2021)

In Vivo Hypoglycemic Effects and Histopathological Restoration

The therapeutic efficacy of biogenic silver nanoparticles (AgNPs) has been evaluated in vivo using various animal models of drug-induced diabetes, primarily streptozotocin (STZ)-induced diabetic mice and rats. Streptozotocin is a glucosamine-nitrosourea compound that selectively destroys insulin-producing pancreatic β-cells, inducing severe insulinopenia, hyperglycemia, and hyperlipidemia (Lambe, 2026).

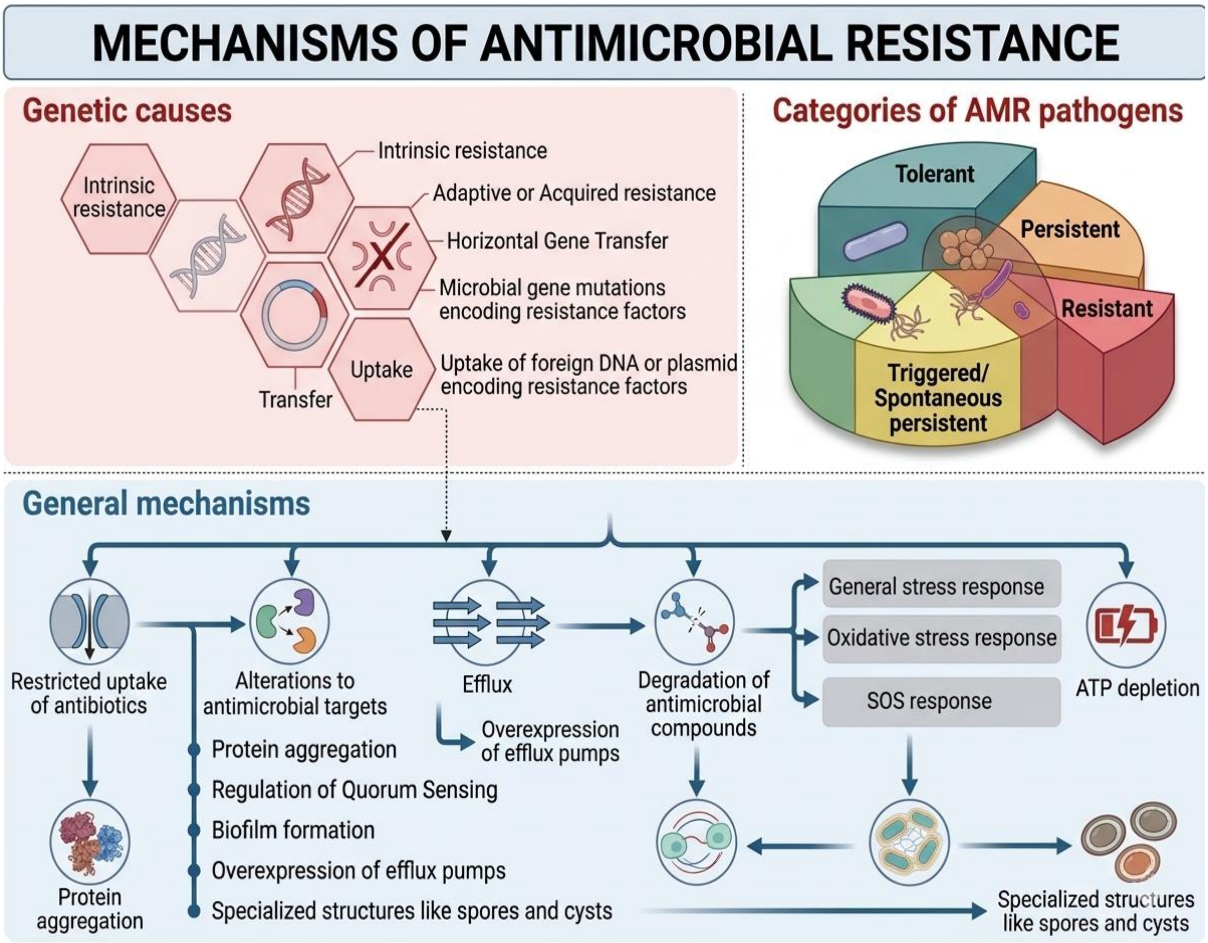
In these models, treatment with biogenic AgNPs has demonstrated significant hypoglycemic effects, normalized lipid profiles, and promoted tissue repair. For instance, in STZ-induced diabetic BALB/c mice, oral administration of *Thymus serpyllum*-mediated AgNPs at a dose of 10 mg/kg led to a significant drop in fasting blood glucose (FBG) levels, as confirmed by intraperitoneal glucose tolerance tests (IPGTT) and insulin tolerance tests (ITT) (Khan et al., 2023). Histological analysis using hematoxylin and eosin (H&E) staining showed morphological restoration of pancreatic islets, liver, and kidney tissues, reversing the structural damage caused by diabetic oxidative stress (Wahab et al., 2022).

Similarly, in healthy mouse models, AgNPs synthesized using *Stenocereus queretaroensis* flower extract administered at 100 mg/kg significantly reduced postprandial blood glucose levels. This effect was attributed to the delayed digestion of dietary carbohydrates, supported by the strong in vitro inhibition of α-glucosidase and α-amylase (González-Garibay, 2025).

Broad-Spectrum Antibacterial Activity and Anti-Biofilm Mechanics

Patients with diabetes mellitus are highly susceptible to chronic, non-healing skin infections, such as diabetic foot ulcers. These wounds are frequently infected by opportunistic, multidrug-resistant (MDR) bacterial pathogens, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* (Jebril et al., 2021). A major clinical barrier to healing is the formation of bacterial biofilms. Within these biofilms, bacteria are embedded in an Extracellular Polymeric Substance (EPS) matrix that restricts antibiotic penetration, making the infection highly resistant to standard clinical therapies (Dagher, 2025).

Figure 2. Mechanisms of Antimicrobial Resistance and Pathogen Classification



A powerful solution to this challenge, exhibiting broad-spectrum bactericidal and anti-biofilm activities through multiple, simultaneous mechanisms of action that prevent the development of bacterial resistance (Keskin, 2025) These mechanisms target several bacterial components:

Electrostatic binding and membrane rupture: Due to electrostatic attraction, positively charged biogenic AgNPs and Ag^+ bind readily to the negatively charged cell walls and cytoplasmic membranes of bacteria. This interaction causes localized structural damage, forming "pits" and pores that denature the membrane, disrupt the electrochemical gradient, and cause the leakage of essential cytoplasmic contents, leading to cell lysis (More et al., 2023).

Inhibition of cellular respiration and ATP production: Once inside the membrane, silver ions target and bind to thiol (–SH) groups on respiratory enzymes, such as NADH dehydrogenase. This deactivates the electron transport chain, halting adenosine triphosphate (ATP) synthesis and depriving the bacterial cell of energy (Mateo & Jiménez, 2022).

ROS-mediated oxidative stress: The disruption of cellular respiration induces the overproduction of reactive oxygen species (ROS), such as superoxide radicals ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($OH^\bullet$) (Komazec et al., 2023). This massive oxidative stress depletes intracellular glutathione (GSH) and causes lipid peroxidation, protein denaturation, and oxidative DNA damage (Paciorek et al., 2020).

Interference with nucleic acids and translation: Silver ions and small AgNPs bind readily to sulfur- and phosphorus-rich structures, including the phosphate backbone of bacterial DNA. This interaction induces DNA condensation, halting transcription and replication. Concurrently, silver denatures bacterial ribosomes, blocking protein translation (Mateo & Jiménez, 2022).

Disruption of cellular signaling: Bacterial growth and adaptation rely on phosphotyrosine-mediated signaling cascades. Biogenic AgNPs can dephosphorylate tyrosine residues on bacterial peptides, disrupting cell signaling and triggering apoptosis-like cell death (More et al., 2023).

The antibacterial efficacy of biogenic silver nanoparticles (AgNPs) is strongly influenced by bacterial cell wall structure. Gram-negative bacteria (e.g., *E. coli*, *P. aeruginosa*) are generally more susceptible to AgNPs than Gram-positive bacteria (e.g., *S. aureus*) (Yin et al., 2020). This is because Gram-negative bacteria possess a thin peptidoglycan cell wall (2–3 nm), whereas Gram-positive bacteria have a thick, highly cross-linked peptidoglycan layer (30–80 nm) that acts as a physical barrier, slowing the penetration of nanoparticles and silver ions (More et al., 2023). Additionally, physical parameters such as size and shape play key roles in antibacterial potency: nanoparticles smaller than 10 nm or 16 nm can directly penetrate cell walls, and triangular-shaped nanoparticles often show enhanced bactericidal activity.

Numerous quantitative studies have demonstrated the high antibacterial and anti-biofilm potency of biogenic AgNPs:

Phragmanthera austroarabica extract-mediated AgNPs showed potent antibacterial activity against Gram-negative pathogens, including *Proteus vulgaris* (MIC 2.5 µg/mL) and *Pseudomonas aeruginosa* (MIC 5 µg/mL), and Gram-positive *Streptococcus mutans* (MIC 1.25 µg/mL) (Chand et al., 2020).

Rosemary-mediated AgNPs (10–50 nm) exhibited strong antibacterial effects against both standard and multidrug-resistant (MDR) strains of *B. subtilis*, *S. aureus*, *P. aeruginosa*, *E. coli*, and *K. pneumoniae*, with zones of inhibition ranging from 11.7 to 29.7 mm (Velgosova et al., 2024). For this assay, bacterial suspensions were adjusted to a 0.5 McFarland standard ($1–2 \times 10^8$ CFU/mL), introduced to agar wells (0.6 mm diameter), treated with 100 µL of a 300 µg/mL nanoformulation, and incubated at 37 °C for 24 h. The minimum inhibitory concentration (MIC) was determined using double-fold serial dilutions from 200 µg/mL to 12.5 µg/mL, with DMSO and gentamicin serving as negative and positive controls, respectively (Ogunleye, 2026).

AgNPs synthesized using gum kondagogu (5 nm) showed MIC and minimum bactericidal concentration (MBC) values that were 3.2-fold and 16-fold lower for *S. aureus* and *E. coli*, respectively, compared to standard chemically synthesized counterparts, while displaying potent anti-biofilm activity at a concentration of 2 µg/mL (González-Garibay, 2026). These studies used susceptibility assays including micro-broth dilution, cytoplasmic content leakage (to assess membrane damage), NPN (N-phenyl-1-naphthylamine) membrane permeabilization assays, and intracellular ROS measurement via H_2DCFDA fluorescence (Atanu, 2025).

Conclusion

The integration of green chemistry with nanomedicine marks a significant advancement in treating type 2 diabetes mellitus and its complex secondary pathology. This review highlights that phyto-synthesizing silver nanoparticles using antidiabetic plant extracts produces a unique, dual-action therapeutic system. Thermodynamically favorable redox reactions transform silver ions into stable, crystalline nanocrystals.

The resulting organic bio-corona avoids the toxicity issues of conventional synthetic capping agents while preserving the bioactivities of native plant metabolites directly on the nanoparticle surface. Biologically, these biogenic nanoparticles offer a comprehensive approach to managing diabetes. In vitro and in vivo studies demonstrate that they blunt postprandial blood glucose spikes by inhibiting α-amylase and α-glucosidase, while promoting tissue repair and restoring cell signaling pathways. Concurrently, their multi-targeted antibacterial mechanisms including membrane disruption and oxidative stress generation effectively combat biofilm-forming, multidrug-resistant pathogens. This dual performance makes plant-mediated AgNPs an excellent candidate for treating diabetic complications such as non-healing foot ulcers. Ultimately, moving these biogenic nanoformulations from bench to bedside will depend on standardizing synthesis protocols, evaluating long-term

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