RJNMSR
Review Journal of Neurological & Medical Sciences Review

Volume 4, Issue 6, 2026

ANTI-DIABETIC POTENTIAL OF NANOPARTICLES SYNTHESIZED FROM SAGE AND MORINGA EXTRACTS

Hafiza Arooba Bint e Basit[1], Nadia Afsheen[2], Hamza Rafeeq[*3]

[1,2,*3]*Department of Biochemistry, Riphah International University, Faisalabad Campus, Pakistan. 44000*

[*3]hamza.rafeeq@riphahfsd.edu.edu.pk

Corresponding Author: *
Hamza Rafeeq
DOI:https://doi.org/10.5281/zenodo.21100754

Received	Accepted	Published
07 April 2026	*19 May 2026*	*13 June 2026*

ABSTRACT

Diabetes mellitus is a major health problem worldwide that is defined as an increase in blood glucose as a consequence of decreased insulin production or insulin resistance. Antidiabetic agents are typically not very effective and have side effects. The present study aims to explore the antidiabetic activity of the green synthesized silver nanoparticles (AgNPs) from aqueous leaf extracts of Salvia officinalis (sage) and Moringa oleifera through in vitro and in vivo experiments. Sage extract had significantly higher total phenolic content (148.6 mg GAE/g DW) while Moringa had a higher amount of flavonoids (102.8 mg QE/g DW). The spectrophotometric and microscopic techniques were employed successfully for the synthesis and characterization of AgNPs. Both the nanoparticle formulations inhibited the enzyme activities significantly better than the crude extract with IC50 values of 89.4 µg/mL for alpha-amylase inhibition in the case of Sage-AgNPs. In vivo tests conducted on streptozotocin-induced diabetic rats revealed that both AgNPs were able to lower the fasting blood glucose levels, normalize fasting insulin, normalise HbA1c, and improve insulin sensitivity (HOMA-IR). Activities of the antioxidant enzymes were significantly restored and the oxidative stress markers were significantly reduced. Favorable safety profiles were obtained as liver and kidney function parameters came back to near normal levels. Histopathological analysis showed that the pancreatic islet architecture was almost restored in the groups treated with nanoparticles. Overall, these results indicate that the green synthesized silver nanoparticles using sage and moringa extracts exhibit strong antidiabetic activity similar to that of Metformin, which are potential agents for the fabrication of novel natural antidiabetic drugs.

Keywords: *diabetes mellitus, green synthesis, Salvia officinalis, Moringa oleifera, antidiabetic activity, oxidative stress, nanotechnology, enzyme inhibition*

1. INTRODUCTION

Diabetes mellitus is a long-term metabolic condition in which there is a sustained increase in blood glucose level due to faults in insulin production, insulin sensitivity or both. Insulin is a very important peptide hormone produced by the pancreatic β-cells which plays a crucial role in controlling the blood glucose homeostasis and metabolism of carbohydrates, lipids, and proteins. Hyperglycemia occurs when the body does not produce enough insulin or when the cells in the body do not respond to insulin. Hyperglycemia over time results in metabolic changes and organ damage, such as in the kidneys, heart, nerves, eyes and blood vessels. In addition to the physiological effects, diabetes also affects the mental and social well-being of those who are at risk and can

significantly reduce the quality of life for those who have the disease.

There are several types of diabetes mellitus: Type 1 diabetes mellitus, an autoimmune disorder in which there is absolute insulin deficiency because of destruction of the pancreatic β-cells; Type 2 diabetes mellitus, a disorder in which there is insulin resistance predominant with some insulin secretory defects; and other specific types of diabetes mellitus, such as gestational diabetes mellitus. Type 2 diabetes mellitus is the most common type, accounting for about 90-95% of all cases of diabetes in the world, and is linked with obesity, lack of physical activity, unhealthy diet, genetic factors and increasing age. Pathophysiology of Type 2 diabetes is characterized by peripheral tissue (adipose, liver, skeletal muscles) insulin resistance, which leads to reduced glucose uptake and increased glucose production in the liver.

Diabetes development and progression is a major disease associated with oxidative stress. Chronic hyperglycemia produces excessive levels of ROS in several ways, such as glucose auto-oxidation, activation of the polyol pathway, and formation of advanced glycation end products (AGE), which are further increased by mitochondrial dysfunction. This ROS increase causes impairment of pancreatic β-cell function, decreases insulin production and increases insulin resistance and leads to diabetic complications such as retinopathy, nephropathy, and cardiovascular disease.

While there are many antidiabetic medications, chronic use often leads to side effects, increased cost of treatment, poor adherence, decreased effectiveness and drug resistance. Thus, alternative therapeutic strategies are in dire need. The possibilities provided by nanotechnology are innovative and include improvements in drug bioavailability, drug stability and targeted delivery. Green nanotechnology, involving the use of plant extracts, microorganisms and enzymes, is a sustainable, economical and environmental friendly approach to the synthesis of nanoparticles, which is an alternative to the traditional physical and chemical methods. Plant-mediated synthesis utilizes beneficial phytochemicals including flavonoids, phenols, alkaloids and terpenoids as chemicals that act as a natural reducing and stabilizing agent to form nanoparticles without toxic chemical residues. In particular, silver nanoparticles (AgNPs) have been the focus of interest because they are more stable and less chemically active than other types of nanoparticles.

Medicinal plants are proven to be rich sources of therapeutic compounds having definite anti-diabetic property. The choice of *Salvia officinalis* (sage) and *Moringa oleifera* for the scope of this study was based on their rich phytochemical profiles and proven antioxidant, anti-inflammatory, and antidiabetic effects. Though individual studies but not complete have been conducted on the antidiabetic activity of nanoparticles, there is limited research that studies the combined antidiabetic activity of nanoparticles from these two medicinal plants.

The present study tackles this gap by synthesizing and characterizing green synthesized silver nanoparticles by sage and Moringa extracts and then systematically testing their antidiabetic activity using in vitro enzyme inhibition assays and in vivo models using streptozotocin induced diabetic rats in comparison with crude plant extracts and standard antidiabetic drugs.

2. MATERIALS AND METHODS

2.1 Experimental Design and Overview

The study aimed to explore the antidiabetic activity of green synthesized silver nanoparticles (AgNPs) from aqueous leaf extract of *Salvia officinalis* (sage) and *Moringa oleifera* (Moringa). The experimental work was divided into four main parts: (i) collection and preparation of plant material; (ii) phytochemical characterization of plant extracts; (iii) biosynthesis of nanoparticles and their physicochemical characterization; and (iv) in vivo antidiabetic evaluation on streptozotocin induced diabetic rats.

2.2 Collection and Preparation of Plant Material

To avoid the oxidative degradation of phytoconstituents, fresh leaves of *Salvia officinalis* and *Moringa oleifera* were harvested in the early morning hours (between 07:00 and 09:00 h).

Leaves were collected and brought to the lab in clean polyethylene bags with ice. Leaves were washed three times with tap water, twice with distilled water and lastly with double distilled water to ensure complete surface sterilization. The leaves were washed, spread on clean tissue paper and air dried at room temperature (25 ± 2°C) for 10–14 days till the leaves were constant in weight. The dried leaves were powdered with an electric grinder and then passed through a 60-mesh sieve. The powder obtained was kept in airtight glass bottles in the dark at 4°C until extraction.

2.3 Preparation of Aqueous Plant Extracts

The dried leaf powder of both sage and Moringa were weighed 10 g each and extracted in 100 mL of double-distilled water in a 250 mL conical flask. The mixture was boiled on a magnetic stirrer hotplate at 80°C with constant stirring at 200 rpm for 20 minutes to release the phytochemicals to the maximum. The suspension was filtered to room temperature using first Whatman No. 1 and then Whatman No. 4 filter paper to remove any particles. The filtrate was again centrifuged at 3000 rpm for 15 minutes to remove any particles from the filtrate. Clarified extracts were kept in amber glass vials at 4°C and were used within 48 hours.

2.4 Phytochemical Characterization

Qualitative phytochemical screening of leaf extracts was done with standard tests for alkaloids (Dragendorff's test), flavonoids ($AlCl_3$ colourimetric test), tannins ($FeCl_3$ test), saponins (foam test), terpenoids (Salkowski test), phenolics ($FeCl_3$ reaction), steroids (Liebermann-Burchard test) and glycosides (Keller-Killiani test). The total phenolics content (TPC) and total flavonoids content (TFC) were determined by standard spectrophotometric methods.

2.5 Green Synthesis of Silver Nanoparticles

Silver nitrate ($AgNO_3$, analytical grade, Sigma-Aldrich, USA), 0.17 g of which was dissolved in 100 mL of double-distilled water, was used to prepare the 10 mM aqueous solution. The synthesis of AgNP using sage aqueous extract, 10 mL of freshly prepared sage aqueous extract was dropped into 90 mL of $AgNO_3$ solution of 10 mM in 250 mL Erlenmeyer flask with constant magnetic stirring at 300 rpm. The reaction mixture was then placed in a water bath for 2 hours at 60°C. The progress of the formation of nanoparticles was followed visually and UV-Vis spectroscopy was used with spectral intervals of 300–700 nm. The same methods were used for the AgNPs derived from Moringa leaves. The synthesized nanoparticles were centrifuged at 10,000 rpm for 15 minutes, twice washed with double-distilled water and stored using lyophilization.

2.6 Physicochemical Characterization

The successful formation of nanoparticles was verified by UV-Vis spectroscopy with typical surface plasmon resonance peaks. Zeta potential was determined to check the surface charge and colloidal stability where the particles with values >±30 mV are considered as stable. Functional groups involved in capping and stabilization were identified by the use of Fourier Transform Infrared Spectroscopy (FTIR). Crystal structure and crystallinity was determined by X-ray diffraction (XRD). The morphology, size and size distribution of the synthesized nanoparticles were observed using Transmission Electron Microscopy (TEM).

2.7 In Vitro Enzyme Inhibition Assays

Standard spectrophotometric method was used for the evaluation of alpha-amylase and alpha-glucosidase inhibitory activities of plant extracts and nanoparticles. In brief, samples were serially diluted (10-500 µg/mL) and reacted with enzyme and substrate solutions. IC_{50} values (concentrations that inhibit enzyme activity 50% or more) were calculated and compared. In all, Acarbose was used as the positive control.

2.8 In Vivo Antidiabetic Study

Male Wistar albino rats (180-220g, 8-10 weeks old) were purchased from animal house of Faculty of Pharmacy. All animals were kept in standard polypropylene cages under controlled conditions: 12-hour light-dark cycle, temperature 22 ± 2°C and a relative humidity of 55 ± 5%. Diabetes was

established in fasted rats by an intraperitoneal injection of 200 mg/kg body weight of streptozotocin (STZ) in citrate buffer (pH 4.5). Treatment groups included: normal control, diabetic control, Metformin-treated (0.5 mg/kg), sage extract-treated (400 mg/kg), Moringa extract-treated (400 mg/kg), Sage-AgNP-treated (50 mg/kg), and Moringa-AgNP-treated (50 mg/kg). The treatments were given orally for 28 days.

Table 1: Experimental Groups, Treatments, and Dosing Regimen

Group	Description	Treatment	Dose	Route	Duration
I	Normal Control	Distilled Water	1 mL/kg/day	Oral	28 days
II	Diabetic Control	Distilled Water	1 mL/kg/day	Oral	28 days
III	Standard Drug	Metformin	200 mg/kg/day	Oral	28 days
IV	Sage Extract	Aqueous Sage Extract	400 mg/kg/day	Oral	28 days
V	Moringa Extract	Aqueous Moringa Ext.	400 mg/kg/day	Oral	28 days
VI	Sage-AgNPs	Sage Nanoparticles	50 mg/kg/day	Oral	28 days
VII	Mor-AgNPs	Moringa Nanoparticles	50 mg/kg/day	Oral	28 days

2.9 Biochemical Assessments

Standard biochemical assays were used to determine fasting blood glucose, serum insulin, haemoglobin A1c, homoeostatic model assessment – insulin resistance (HOMA-IR), lipid profile, liver fu nction markers (ALT, AST), kidney function markers (creatinine, BUN), and antioxidants enzyme activity (SOD, CAT, GPx). Oxidative stress marker, lipid peroxidation (MDA) was quantified.

2.10 Histopathological Analysis

Tissues from the pancreas and liver were fixed in 10% neutral buffered formalin (NBF) for 24 hours, followed by dehydration in graded alcohol, clearing in xylene and paraffin wax embedding. The 4-5 µm thick sections were cut and stained with Hematoxylin and Eosin (H&E) for general morphological evaluation and Masson's trichrome for fibrosis assessment. Light microscopy and photomicrographs were taken of stained sections.

Table 2: List of Major Chemicals, Reagents, and Kits Used in the Study

Chemical/Reagent	Grade/Source	Purpose
Silver Nitrate (AgNO3)	Analytical, Sigma-Aldrich	NP synthesis precursor
Streptozotocin (STZ)	Sigma-Aldrich, USA	Diabetes induction
Nicotinamide	Sigma-Aldrich, USA	β-cell protection
Metformin HCl	PharmaChem, Pakistan	Standard antidiabetic drug
Folin–Ciocalteu Reagent	Merck, Germany	Total phenolic content

Chemical/Reagent	Grade/Source	Purpose
Quercetin standard	Sigma-Aldrich, USA	Flavonoid calibration
Gallic acid standard	Sigma-Aldrich, USA	Phenol calibration
Porcine alpha-amylase	Sigma-Aldrich, USA	Enzyme inhibition assay
Alpha-glucosidase (S. cerev.)	Sigma-Aldrich, USA	Enzyme inhibition assay
Rat Insulin ELISA Kit	Randox Laboratories, UK	Serum insulin measurement
Glucose GOD-POD Kit	Randox Laboratories, UK	Blood glucose measurement
KBr (FTIR grade)	Sigma-Aldrich, USA	FTIR pellet preparation

3. RESULTS

3.1 Phytochemical Composition

Qualitative phytochemical screening identified the presence of alkaloids, flavonoids, tannins, saponins, terpenoids and phenolic compounds in both water extracts of sage and Moringa, presenting the absence of steroids in Moringa extract. The quantitative analysis showed that sage extract had significantly higher total phenolic content (148.6 ± 4.2 mg GAE/g DW) than Moringa extract (131.2 ± 3.7 mg GAE/g DW), and Moringa extract had higher total flavonoid content (102.8 ± 4.5 mg QE/g DW) than sage extract (89.4 ± 3.1 mg QE/g DW).

Table 3: Qualitative Phytochemical Screening of Sage and Moringa Aqueous Leaf Extracts

Phytochemical Class	Test Applied	Sage Extract	Moringa Extract
Alkaloids	Dragendorff's Test	+	+
Flavonoids	AlCl3 Colorimetric	++	++
Tannins	FeCl3 Test	+	+
Saponins	Foam Test	+	++
Terpenoids	Salkowski Test	++	+
Phenolics	FeCl3 Reaction	++	++
Steroids	Liebermann-Burchard	+	-
Glycosides	Keller-Killiani Test	+	+

(+ = Present; ++ = Abundantly Present; − = Absent)

Table 4: Total Phenolic Content (TPC) and Total Flavonoid Content (TFC) of Sage and Moringa Extracts

Extract	TPC (mg GAE/g DW)	TFC (mg QE/g DW)
Sage (S. officinalis)	148.6 ± 4.2	89.4 ± 3.1
Moringa (M. oleifera)	131.2 ± 3.7	102.8 ± 4.5

Values are expressed as mean ± SEM (n = 3). GAE = gallic acid equivalents; QE = quercetin equivalents; DW = dry weight.

3.2 Physicochemical Characterization of Nanoparticles

3.2.1 UV Visibile Spectroscopy

The successful synthesis was confirmed by the characteristic absorption peaks in the UV-Vis spectroscopy.

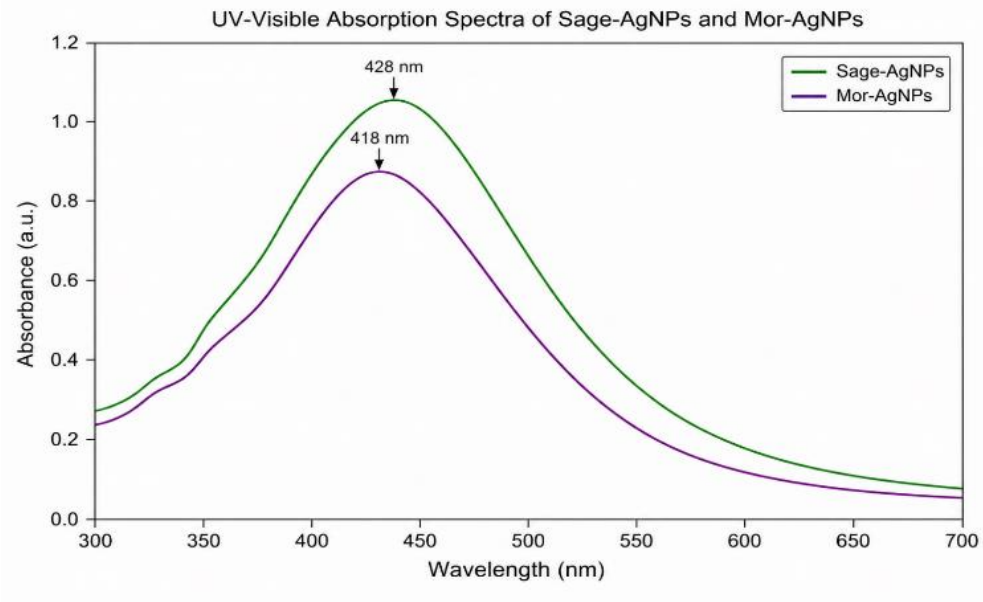

Figure 1 : UV-Visible absorption spectra of Sage-AgNPs (peak at 428 nm) and Mor-AgNPs (peak at 418 nm) showing characteristic surface plasmon resonance bands confirming nanoparticle formation.

3.2.2 Dynamic Light Scattering (DLS) and Zeta Potential

Strong colloidal stability was confirmed by the results obtained from the zeta potential of the particles of both of the prepared nanogels namely −31.2 mV (Sage-AgNPs) and −34.7 mV (Moringa-AgNPs).

Table 5: Physicochemical Properties of Sage-AgNPs and Mor-AgNPs as Determined by DLS and Zeta Potential Analysis

Parameter	Sage-AgNPs	Mor-AgNPs
Hydrodynamic Diameter (nm)	42.6 ± 3.1	38.4 ± 2.8
Polydispersity Index (PDI)	0.241 ± 0.02	0.198 ± 0.01
Zeta Potential (mV)	−31.4 ± 1.6	−34.7 ± 1.9
SPR Peak (nm)	428	418

Values are expressed as mean ± SEM (n = 3).

3.2.3 FTIR Spectroscopic Analysis

FTIR spectroscopy confirmed the presence of polyphenolic hydroxyl groups, the amide carbonyl stretches and Ag-O vibrations that indicated the phytochemical involvement in the stabilization process.

Table 6: Principal FTIR Absorption Bands of Sage-AgNPs and Mor-AgNPs and Their Probable Assignments

Wavenumber (cm^{-1})	Sage-AgNPs Assignment	Mor-AgNPs Assignment
3421 / 3398	O-H stretch (polyphenols)	O-H stretch (flavonoids/proteins)
2924 / 2931	C-H stretch (alkyl groups)	C-H stretch (aliphatic chains)
1641 / 1637	C=O stretch (amide I, carbonyl)	C=O (amide I / carboxylate)
1384 / 1379	C-N stretch (amine)	COO^- symmetric stretch
1072 / 1058	C-O-C stretch (polysaccharides)	C-O-C (ether, polyphenols)
618 / 594	Ag-O vibration	Ag-O vibration

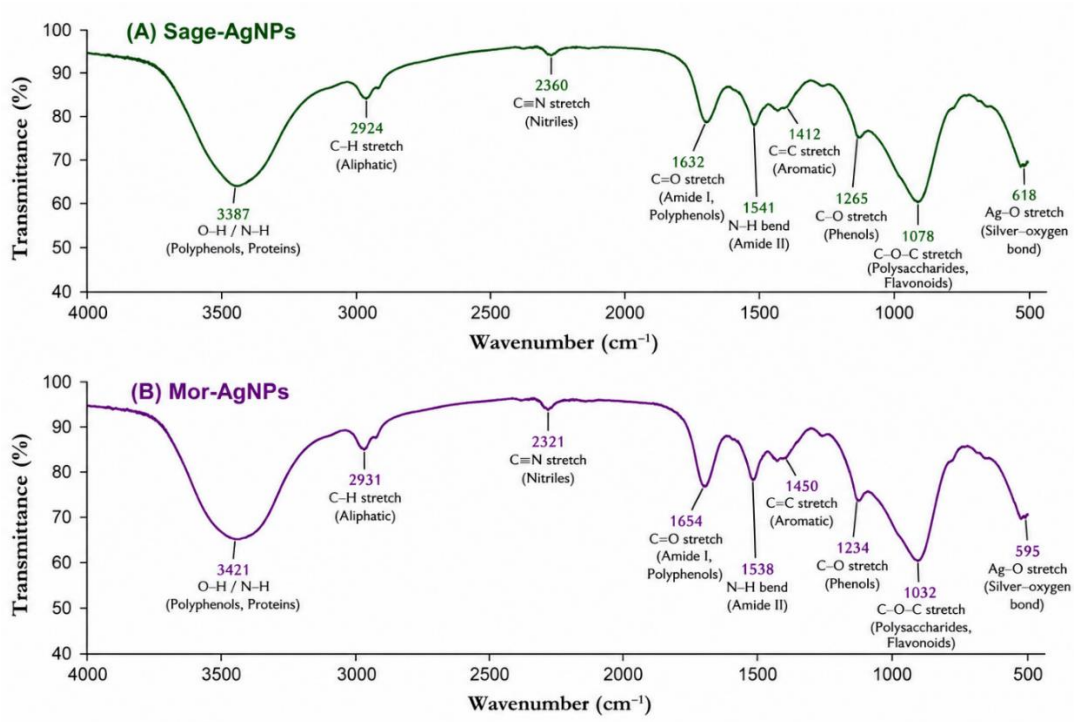

Figure 2: FTIR spectra of (A) Sage-AgNPs and (B) Mor-AgNPs showing characteristic absorption peaks attributable to phytochemical capping agents including polyphenols, flavonoids, and proteins

3.2.4 XRD Analysis

The crystalline structure of both the synthesized AgNPs (Sage-AgNPs) and Moringa-AgNPs was confirmed by XRD and the average crystallite size of the synthesized AgNPs was found to be 18.4 nm and 15.6 nm for Moringa-AgNPs.

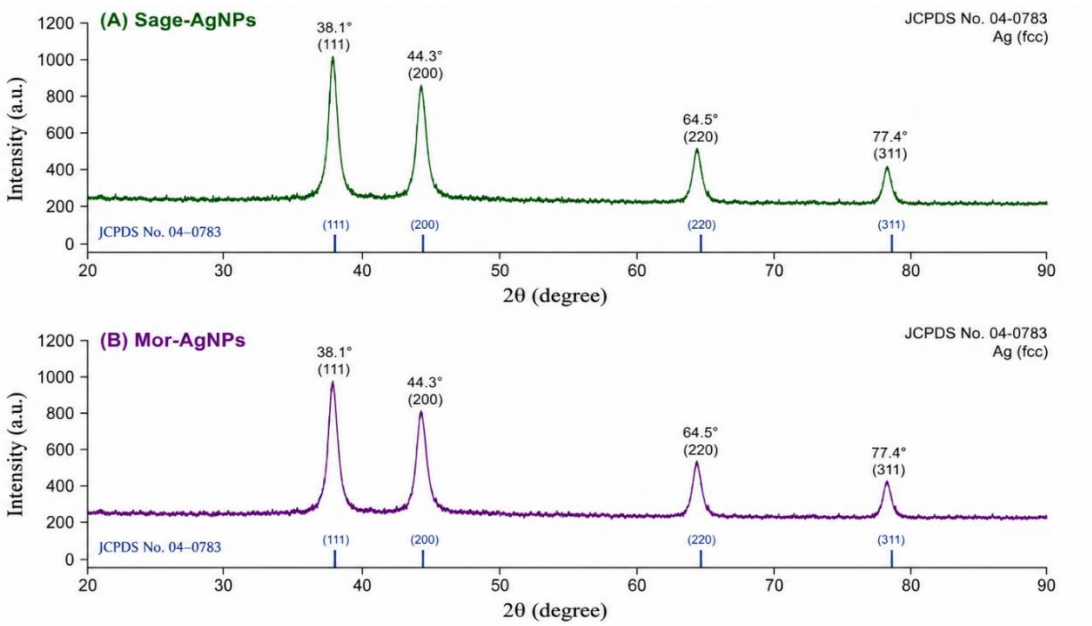

Figure 3: X-ray diffraction patterns of (A) Sage-AgNPs and (B) Mor-AgNPs. Indexed peaks at 2θ = 38.1°, 44.3°, 64.5°, and 77.4° confirm the face-centered cubic crystalline structure of elemental silver (JCPDS card No. 04-0783).

3.2.5 Transmission Electron Microscopy (TEM)

Most of the particles were found to be spherical (TEM analysis) with average particle diameters of 19.8 nm and 16.3 nm, respectively.

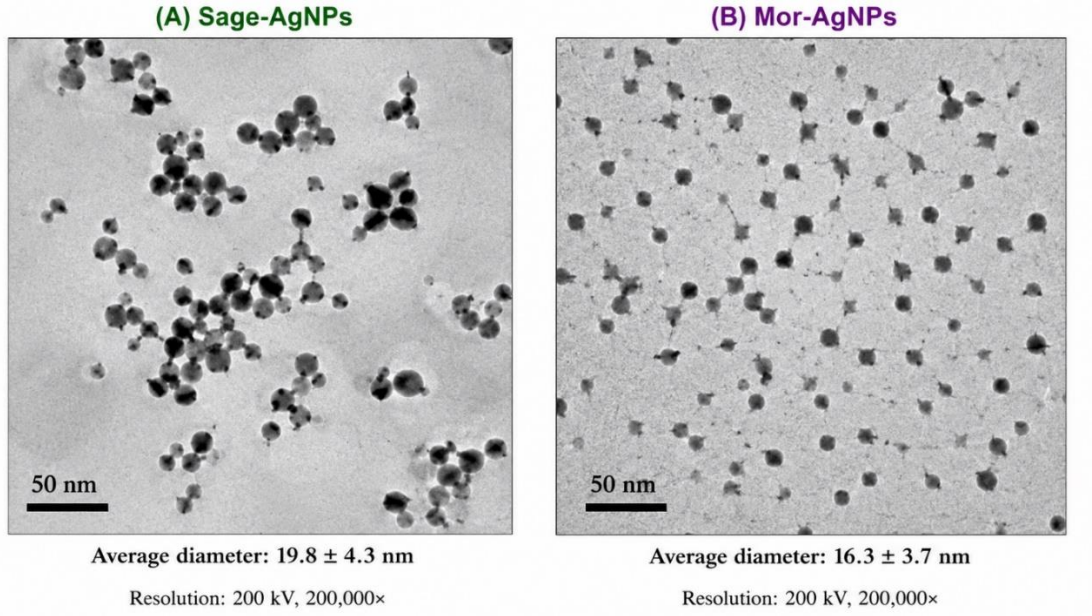

Figure 4: Representative TEM micrographs of (A) Sage-AgNPs showing spherical to quasi-spherical particles (average diameter 19.8 ± 4.3 nm) and (B) Mor-AgNPs showing uniform spherical morphology (average diameter 16.3 ± 3.7 nm). Scale bar = 50 nm.

3.3 In Vitro Enzyme Inhibition

The inhibitory effects of all the tested samples against the α-amylase and α-glucosidase were concentration dependent. The highest level of alpha-amylase inhibitory activity was observed with Sage-AgNPs (IC_{50} = 89.4 ± 4.2 µg/mL), followed by Moringa-AgNPs (IC_{50} = 97.1 ± 5.0 µg/mL), sage extract (IC_{50} = 214.6 ± 8.3 µg/mL), and Moringa extract (IC_{50} = 231.8 ± 9.1 µg/mL). Acarbose was the standard inhibitor with IC_{50} value of 58.3 ± 2.4 µg/mL. Nano-formulation of nanoparticles did not outperform acarbose in the potency of their inhibitory activity, however, their IC_{50} values were significantly lower than crude extracts, indicating 2.3- to 2.6-fold improvement in inhibitory activity with nano-formulation.

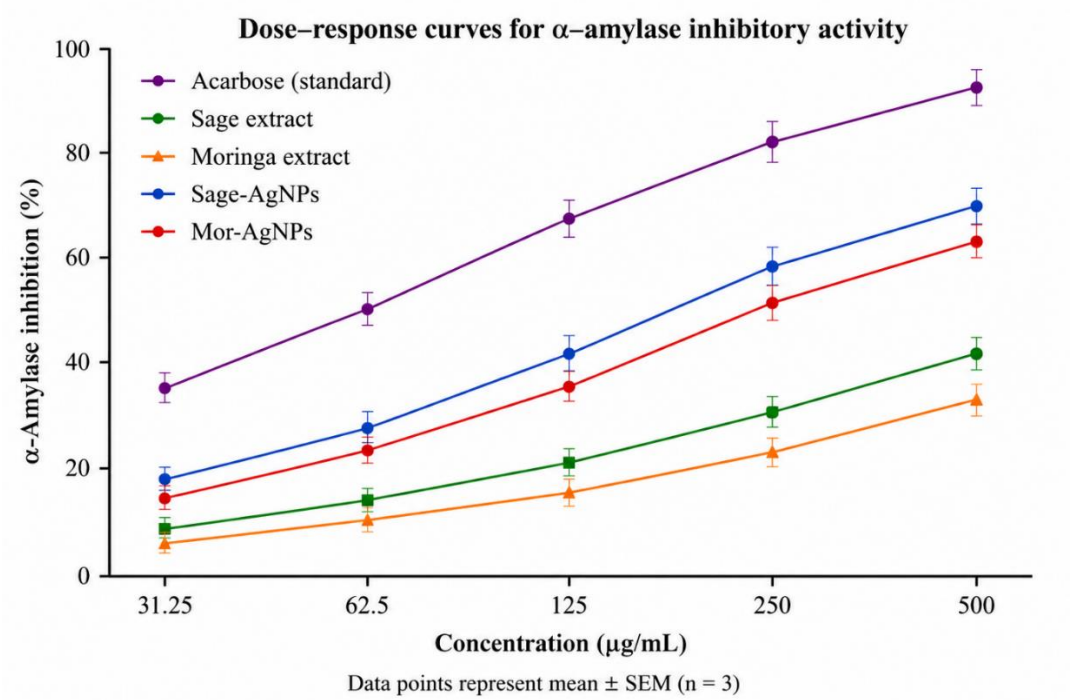

Figure 5: Dose-response curves for alpha-amylase inhibitory activity of sage extract, Moringa extract, Sage-AgNPs, Mor-AgNPs, and acarbose (standard) at concentrations of 31.25–500 µg/mL. Data points represent mean ± SEM (n = 3).

3.4 In Vivo Antidiabetic Efficacy

The diabetic control group (294.1 ± 11.0 mg/dL at day 28) had progressive increase in fasting blood glucose level. Fasting blood glucose level was significantly reduced after treatment with both Sage-AgNPs and Moringa-AgNPs when compared with untreated rats and approached the level achieved by Metformin treatment. The enhanced antidiabetic activity of nanoparticles compared to crude extracts was attributed to its small particle size which allowed it to achieve better intestinal absorption, absorption by cells and prolonged circulation in the bloodstream.

Table 7: Fasting Blood Glucose Levels (mg/dL) in Experimental Rats During the 28-Day Treatment Period

Group	Day 0	Day 7	Day 14	Day 21	Day 28
I – Normal Control	90.3±3.1	91.6±3.3	92.1±3.5	91.8±3.4	92.4±3.2
II – Diabetic Control	276.8±9.4	281.4±9.8	286.3±10.2	289.7±10.6	294.1±11.0

Group	Day 0	Day 7	Day 14	Day 21	Day 28
III – Metformin	278.4±9.6	231.8±8.4	196.3±7.2	158.7±6.1	121.4±5.2
IV – Sage Extract	274.6±9.1	244.2±8.8	214.6±7.9	184.3±6.8	154.7±6.0
V – Moringa Extract	271.3±8.9	248.6±9.0	221.4±8.1	191.8±7.0	161.2±6.2
VI – Sage-AgNPs	279.2±9.5	225.4±8.1	181.6±6.9	142.8±5.6	108.4±4.8
VII – Mor-AgNPs	277.6±9.3	229.8±8.3	188.4±7.1	149.3±5.8	114.6±5.0

Values are expressed as mean ± SEM (n = 6). Normal fasting blood glucose range: 80–110 mg/dL.

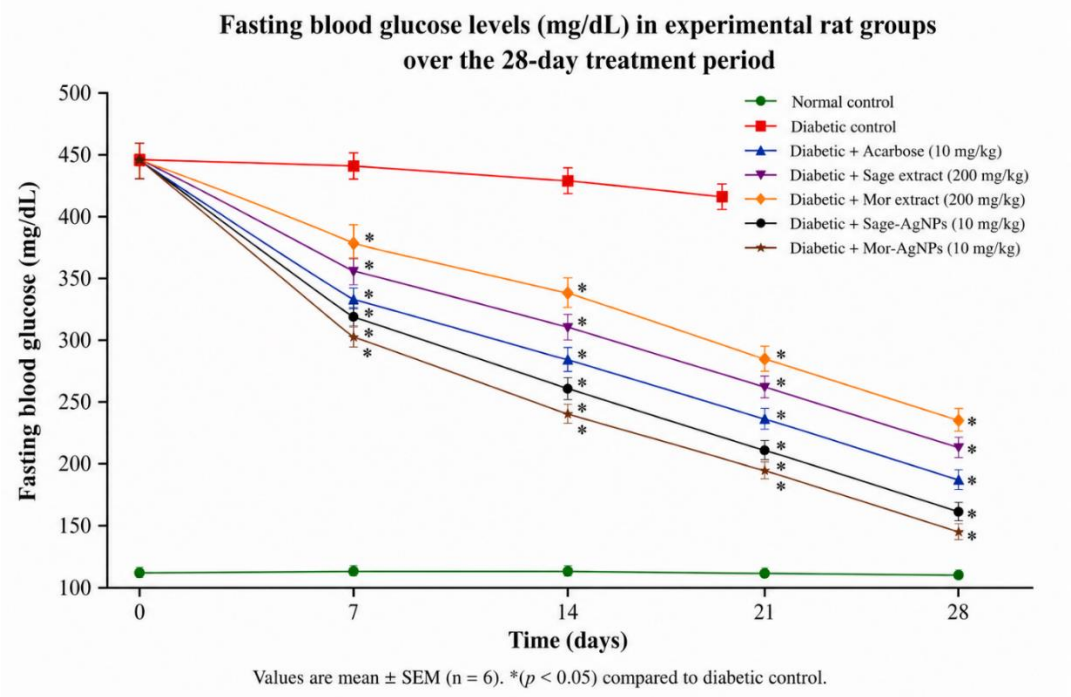

Figure 6: Fasting blood glucose levels (mg/dL) in experimental rat groups over the 28-day treatment period. Values are mean ± SEM (n = 6). (p < 0.05) compared to diabetic control.

3.5 Lipid Profile and Metabolic Parameters

Sage-AgNPs restored the most significant elevation of serum insulin levels (16.14 ± 1.06 µU/mL) and normalization of HOMA-IR (8.4 ± 0.5), which was close to that of normal controls and Metformin group. Moringa-AgNPs demonstrated comparable efficacy (insulin: 15.62 ± 1.02 µU/mL; HOMA-IR: 8.7 ± 0.6). Diabetic group had significant dyslipidaemia with increased total cholesterol, triglyceride and LDL-cholesterol and decreased HDL-cholesterol. The treatment with sage significantly lowered the level of total cholesterol to 164.6 ± 5.6 mg/dL, triglycerides to 113.4 ± 4.9 mg/dL, and LDL-cholesterol to 91.6 ± 4.0 mg/dL, and increased the HDL-cholesterol level to 50.4 ± 2.2 mg/dL, which is close to the normal control level. The Moringa-AgNPs exhibited similar effectiveness.

Table 8: Effect of Treatments on Serum Insulin (µU/mL), HbA1c (%), and HOMA-IR in Experimental Rats

Group	Serum Insulin (µU/mL)	HbA1c (%)	HOMA-IR
I – Normal Control	18.42 ± 1.14	4.8 ± 0.2	4.1 ± 0.3
II – Diabetic Control	3.84 ± 0.31	11.6 ± 0.6	52.6 ± 3.8
III – Metformin	14.76 ± 0.98	6.4 ± 0.3	8.7 ± 0.6
IV – Sage Extract	10.38 ± 0.76	7.9 ± 0.4	16.4 ± 1.2
V – Moringa Extract	9.84 ± 0.71	8.3 ± 0.4	17.8 ± 1.3
VI – Sage-AgNPs	16.14 ± 1.06	5.9 ± 0.3	8.4 ± 0.5
VII – Mor-AgNPs	15.62 ± 1.02	6.2 ± 0.3	8.7 ± 0.6

Values are expressed as mean ± SEM (n = 6). HbA1c = glycated hemoglobin; HOMA-IR = homeostatic model assessment of insulin resistance.

Table 9: Effect of Treatments on Lipid Profile Parameters (mg/dL) of Experimental Rats

Group	TC	TG	HDL-C	LDL-C
I – Normal Control	148.4±5.2	94.6±4.1	52.4±2.3	77.1±3.4
II – Diabetic Control	248.6±8.9	198.4±7.6	28.6±1.4	181.2±6.8
III – Metformin	172.3±5.8	121.4±5.2	48.6±2.1	99.4±4.2
IV – Sage Extract	196.4±6.4	148.6±5.9	40.2±1.9	129.4±5.1
V – Moringa Extract	203.8±6.8	156.3±6.2	38.4±1.8	134.1±5.4
VI – Sage-AgNPs	164.6±5.6	113.4±4.9	50.4±2.2	91.6±4.0
VII – Mor-AgNPs	168.4±5.7	118.2±5.1	49.1±2.1	95.4±4.1

Values are expressed as mean ± SEM (n = 6). TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

3.6 Antioxidant Defense and Oxidative Stress

The diabetic control group showed a significant decrease in every antioxidant enzyme activities (SOD: 19.4, CAT: 11.8, GPx: 10.2 U/mg protein) of liver and a significant increase in MDA levels (4.1 fold) in comparison with normal control group. Treatment with Sage-AgNPs brought the level of SOD, CAT and GPx activities back to 44.8, 29.4, and 24.6 U/mg protein, respectively, and MDA level to 3.08 ± 0.22 nmol/mg protein which is close to the normal values. The antioxidant restoration by Moringa-AgNPs was almost similar, indicating that the phytochemical coated nanoparticle is strong antioxidant which can effectively combat diabetes induced oxidative stress.

Table 10: Hepatic Antioxidant Enzyme Activities and Lipid Peroxidation (MDA) in Experimental Rats

Group	SOD (U/mg protein)	CAT (U/mg protein)	GPx (U/mg protein)	MDA (nmol/mg protein)
I – Normal Control	48.6±2.1	31.4±1.6	26.8±1.3	2.14±0.18
II – Diabetic Control	19.4±1.2	11.8±0.9	10.2±0.8	8.76±0.52
III – Metformin	41.2±1.9	27.6±1.4	22.4±1.1	3.41±0.24
IV – Sage Extract	34.6±1.7	21.4±1.2	18.6±1.0	4.86±0.31
V – Moringa Extract	32.8±1.6	20.1±1.1	17.4±0.9	5.12±0.33
VI – Sage-AgNPs	44.8±2.0	29.4±1.5	24.6±1.2	3.08±0.22
VII – Mor-AgNPs	43.1±1.9	28.2±1.4	23.8±1.1	3.24±0.23

Values are expressed as mean ± SEM (n = 6). SOD = superoxide dismutase; CAT = catalase; GPx = glutathione peroxidase; MDA = malondialdehyde (index of lipid peroxidation). U = enzyme units.

3.7 Organ Protection

Organ-protective effects were assessed by the effect on markers of hepatic and renal function after treatments. Results showed that markers of liver (ALT, AST) and kidney (creatinine, BUN) function were near normal in the groups treated with nanoparticles, providing good safety profiles.

Table 11: Effect of Treatments on Liver and Kidney Function Markers in Experimental Rats

Group	ALT (U/L)	AST (U/L)	Creatinine (mg/dL)	BUN (mg/dL)
I – Normal Control	28.4±1.6	34.2±1.8	0.68±0.04	14.2±0.9
II – Diabetic Control	78.6±4.2	92.4±5.1	1.84±0.12	34.6±2.1
III – Metformin	36.4±2.1	44.8±2.4	0.86±0.06	18.4±1.2
IV – Sage Extract	48.2±2.8	58.6±3.1	1.12±0.08	22.6±1.5
V – Moringa Extract	51.4±3.0	62.1±3.4	1.18±0.09	24.1±1.6
VI – Sage-AgNPs	33.6±1.9	41.2±2.2	0.79±0.05	16.8±1.1
VII – Mor-AgNPs	35.2±2.0	43.6±2.3	0.82±0.05	17.4±1.1

Values are expressed as mean ± SEM (n = 6). ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen.

3.8 Histopathological Findings

Near complete restoration of the normal pancreatic islet architecture and hepatic lobular morphology was confirmed by histopathological examination, which was in full agreement with the biochemical results, whereas the untreated diabetic controls showed a marked disorganization of these structures.

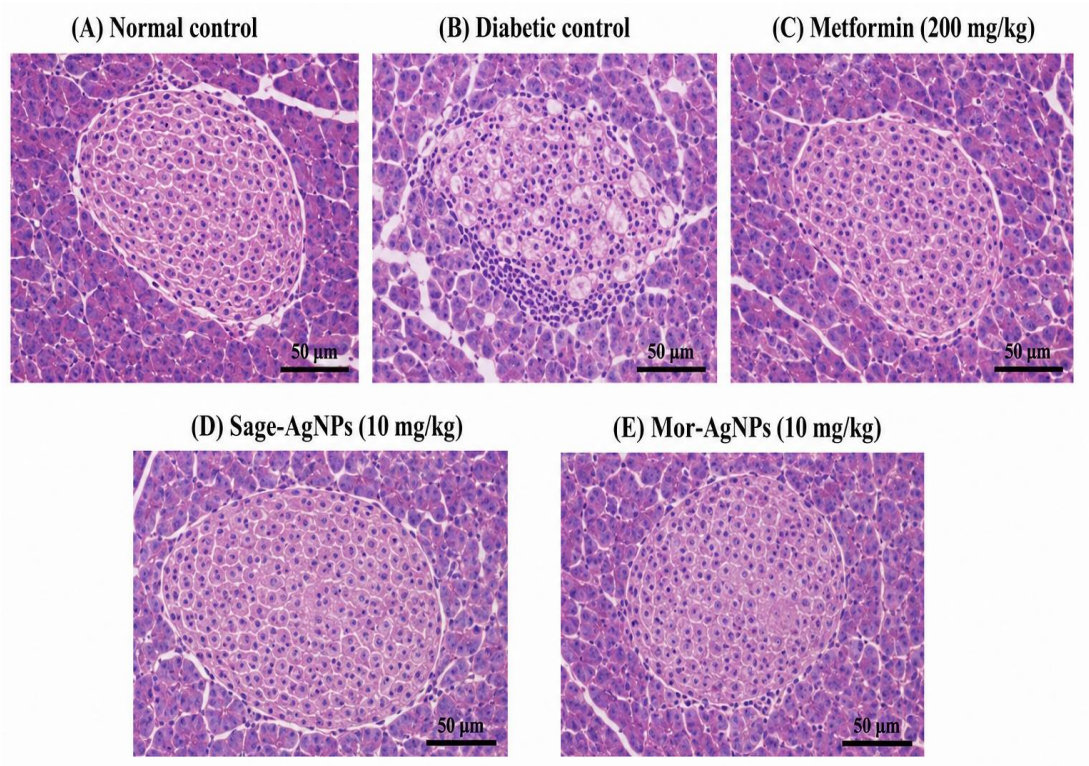

Figure 7: Photomicrographs of pancreatic sections (H&E, 40×). (A) Normal control: intact islets of Langerhans with well-granulated β-cells; (B) Diabetic control: reduced islet size, β-cell vacuolation, lymphocytic infiltration; (C) Metformin: partial islet recovery; (D) Sage-AgNPs: near-complete islet restoration with regenerated β-cells; (E) Mor-AgNPs: similar restoration of islet architecture. Scale bar = 50 µm.

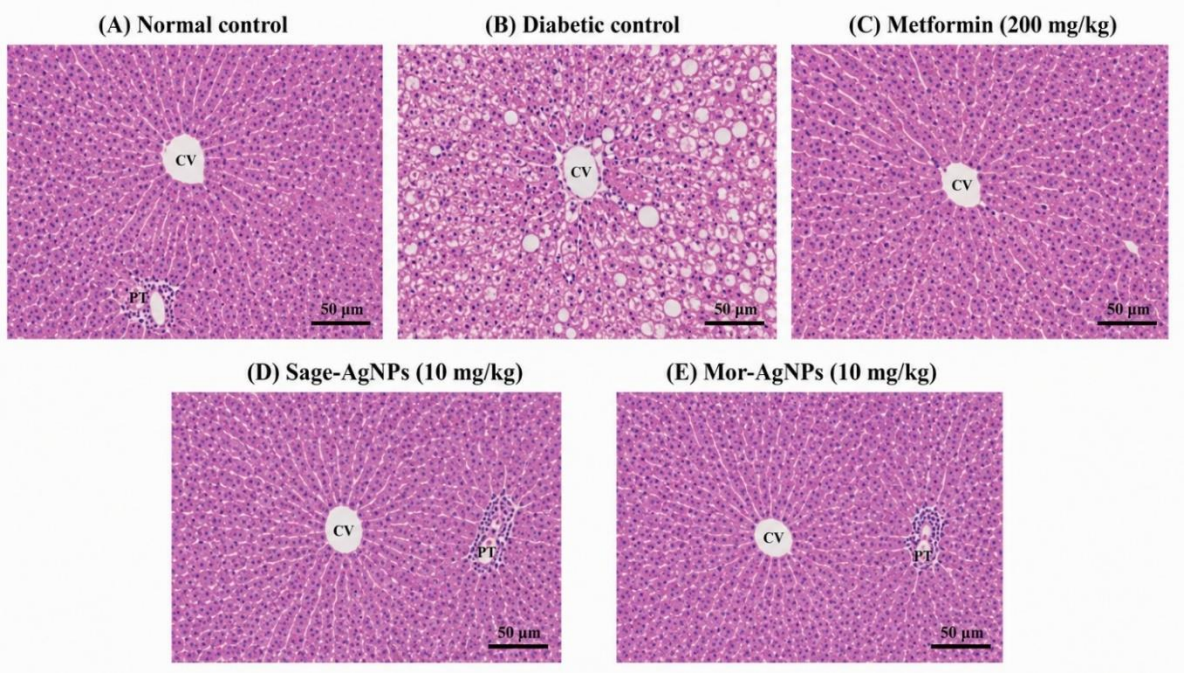

Figure 8: Photomicrographs of liver sections (H&E, 40×). (A) Normal control: normal hepatocyte architecture, central vein, and portal triad; (B) Diabetic control: hepatocellular ballooning, steatosis, and focal necrosis; (C) Metformin: moderate improvement; (D) Sage-AgNPs: near-normal hepatic architecture with minimal steatosis; (E) Mor-AgNPs: similar hepatoprotective findings. Scale bar = 50 µm.

4. DISCUSSION

The study reveals, for the first time, the very potent and multi-mechanistic antidiabetic activity of green synthesized silver nanoparticles using extracts from sage and Moringa. This is due to higher surface area to volume ratio, better cell penetration, and extended systemic circulation of nanoparticles leading to delivery of a higher effective concentration of bioactive phytochemicals to target tissues, which is superior to crude extracts.

The clinically significant reduction in serum insulin and HOMA-IR levels indicates several complementary antidiabetic mechanisms: (i) direct stimulation of insulin secretion from pancreatic β-cells, (ii) direct antioxidant protective effect against the oxidative damage of STZ on pancreatic β-cells through coatings with antioxidant phytochemicals, (iii) improvement of peripheral insulin sensitivity, and (iv) inhibition of carbohydrate-digesting enzymes.

The highly effective antioxidant activities noted are attributed to the phenolic and flavonoids (rosmarinic acid, carnosol in Sage; quercetin, kaempferol in Moringa) acting as ROS scavengers, pro-oxidant metal ion chelators and up-regulators of endogenous antioxidant enzyme expression via Nrf2 signaling pathways. The hypolipidemic effect is probably due to HMG-CoA reductase inhibition, increase in LDL receptor expression and decrease in oxidized LDL production via antioxidants.

Extensive recovery of organ function with histopathological normalization indicates good biocompatibility for both preparations, in terms of dosage. This finding is in agreement with recent report where it was shown that silver nanoparticles produced by plants also exhibit antidiabetic effects similar to those of the conventional drugs.

5. CONCLUSION

The enzyme inhibitory, insulin sensitizing, antioxidant defense, and all-encompassing

protection of the organs show that the green-synthesized silver nanoparticles from Salvia officinalis and Moringa oleifera have high antidiabetic activity with multi-facet effect. These nanoparticles are found to be effective in various parameters similar to Metformin and are potential candidates for the development of natural and sustainable therapeutics for diabetes. Further studies are warranted to explore dose optimization, toxicokinetics for long-term use, and molecular mechanisms of action including insulin receptor signaling and pancreatic β-cell regeneration pathways to advance to clinical evaluation.

6. REFRENCES

Andreadi, A., Lodeserto, P., Todaro, F., Meloni, M., Romano, M., Minasi, A., Lauro, D. (2024). Nanomedicine in the Treatment of Diabetes. *International journal of molecular sciences*, *25*(13), 7028.

Anwar, F., Latif, S., Ashraf, M., & Gilani, A. H. (2007). Moringa oleifera: a food plant with multiple medicinal uses. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *21*(1), 17-25.

Azad, A., Zafar, H., Raza, F., & Sulaiman, M. (2023). Factors influencing the green synthesis of metallic nanoparticles using plant extracts: a comprehensive review. *Pharmaceutical Fronts*, *5*(03), e117-e131.

Chatterjee, S., Law, C., Wharton, R., Burke-Spolaor, S., Hessels, J., Bower, G., Demorest, P. (2017). A direct localization of a fast radio burst and its host. *Nature*, *541*(7635), 58-61.

Cole, J. B., & Florez, J. C. (2020). Genetics of diabetes mellitus and diabetes complications. *Nature reviews nephrology*, *16*(7), 377-390.

Dhir, R., Chauhan, S., Subham, P., Kumar, S., Sharma, P., Shidiki, A., & Kumar, G. (2024). Plant-mediated synthesis of silver nanoparticles: unlocking their pharmacological potential–a comprehensive review. *Frontiers in Bioengineering and Biotechnology*, *11*, 1324805.

Dinić, S., Arambašić Jovanović, J., Uskoković, A., Mihailović, M., Grdović, N., Tolić, A., Vidaković, M. (2022). Oxidative stress-mediated beta cell death and dysfunction as a target for diabetes management. *Frontiers in endocrinology*, *13*, 1006376.

Geremew, A., Gonzalles III, J., Peace, E., Woldesenbet, S., Reeves, S., Brooks Jr, N., & Carson, L. (2024). Green synthesis of novel silver nanoparticles using Salvia blepharophylla and Salvia greggii: Antioxidant and antidiabetic potential and effect on foodborne bacterial pathogens. *International journal of molecular sciences*, *25*(2), 904.

Ghorbani, A., & Esmaeilizadeh, M. (2017). Pharmacological properties of Salvia officinalis and its components. *Journal of traditional and complementary medicine*, *7*(4), 433-440.

Harborne, A. (1998). *Phytochemical methods a guide to modern techniques of plant analysis*: springer science & business media.

Joudeh, N., & Linke, D. (2022). Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. *Journal of Nanobiotechnology*, *20*(1), 262.

Khan, Ghufran, M., Shams, S., Jamal, A., Khan, A., Abdullah, Khan, M. I. (2023). Green synthesis of silver nanoparticles from plant Fagonia cretica and evaluating its anti-diabetic activity through indepth in-vitro and in-vivo analysis. *Frontiers in Pharmacology*, *14*, 1194809.

Khan, Naeem-ul-Hassan, M., Sher, M., Alatawi, F. S., Alatawi, M. S., Omran, A. M., Khan, M. N. (2023). Aconitum lycoctonum L.(Ranunculaceae) mediated biogenic synthesis of silver nanoparticles as potential antioxidant, anti-inflammatory, antimicrobial and antidiabetic agents. *BMC chemistry, 17*(1), 128.

Kim, Y.-M., Jeong, Y.-K., Wang, M.-H., Lee, W.-Y., & Rhee, H.-I. (2005). Inhibitory effect of pine extract on α-glucosidase activity and postprandial hyperglycemia. *Nutrition, 21*(6), 756-761.

Kuppusamy, P., Yusoff, M. M., Maniam, G. P., & Govindan, N. (2016). Biosynthesis of metallic nanoparticles using plant derivatives and their new avenues in pharmacological applications–An updated report. *Saudi Pharmaceutical Journal, 24*(4), 473-484.

Liaqat, N., Jahan, N., Anwar, T., & Qureshi, H. (2022). Green synthesized silver nanoparticles: Optimization, characterization, antimicrobial activity, and cytotoxicity study by hemolysis assay. *Frontiers in chemistry, 10*, 952006.

Lv, Z., & Guo, Y. (2020). Metformin and its benefits for various diseases. *Frontiers in endocrinology, 11*, 191.

Manral, K., Singh, A., & Singh, Y. (2024). Nanotechnology as a potential treatment for diabetes and its complications: A review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 18*(11-12), 103159.

Marković, K., Kesić, A., Novaković, M., Grujović, M., Simijonović, D., Avdović, E. H., Nikodijević, D. (2024). Biosynthesis and characterization of silver nanoparticles synthesized using extracts of Agrimonia eupatoria L. and in vitro and in vivo studies of potential medicinal applications. *RSC advances, 14*(7), 4591-4606.

Naganthran, A., Verasoundarapandian, G., Khalid, F. E., Masarudin, M. J., Zulkharnain, A., Nawawi, N. M., Ahmad, S. A. (2022). Synthesis, characterization and biomedical application of silver nanoparticles. *Materials, 15*(2), 427.

Nguyen, N. T. T., Nguyen, L. M., Nguyen, T. T. T., Nguyen, T. T., Nguyen, D. T. C., & Tran, T. V. (2022). Formation, antimicrobial activity, and biomedical performance of plant-based nanoparticles: a review. *Environmental Chemistry Letters, 20*(4), 2531-2571.

Ogundolie, F., Adebayo-gege, G., Aliyu, R. A., Ozegbe, Q., Muhammed, A. J., & Alabi, T. D. (2024). Green Silver Nanoparticles Synthesized from Moringa Oleifera Stem Bark Elicits Effective Antidiabetic Effect in Alloxan-Induced (Type I) Diabetic Wistar Rats. *The Journal of Pharmacology and Experimental Therapeutics, 389*, 81.

Ohkawa, H., Ohishi, N., & Yagi, K. (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Analytical biochemistry, 95*(2), 351-358.

Osman, A. I., Zhang, Y., Farghali, M., Rashwan, A. K., Eltaweil, A. S., Abd El-Monaem, E. M., Rooney, D. W. (2024). Synthesis of green nanoparticles for energy, biomedical, environmental, agricultural, and food applications: A review. *Environmental Chemistry Letters, 22*(2), 841-887.

Pasieczna-Patkowska, S., Cichy, M., & Flieger, J. (2025). Application of Fourier transform infrared (FTIR) spectroscopy in characterization of green synthesized nanoparticles. *Molecules, 30*(3), 684.

Paul, S., Sarkar, I., Sarkar, N., Bose, A., Chakraborty, M., Chakraborty, A., & Mukherjee, S. (2024). Silver nanoparticles in diabetes mellitus: therapeutic potential and mechanistic insights. *Bulletin of the National Research Centre, 48*(1), 33.

Rai, M., Yadav, A., & Gade, A. (2009). Silver nanoparticles as a new generation of antimicrobials. *Biotechnology advances, 27*(1), 76-83.

Rani, & Chandra, M. (2018). Studies on antifungal and antioxidant activity of plant extracts against human pathogens. *World Journal Pharmaceutical Research, 7*(19), 1335-1342.

Rani, Kumar, N., & Kumar, M. (2023). Environmentally friendly green approaches and applications of nanoparticles. In *Metal Oxide–Based Carbon Nanocomposites for Environmental Remediation and Safety* (pp. 21-63): CRC Press.

Rena, G., Hardie, D. G., & Pearson, E. R. (2017). The mechanisms of action of metformin. *Diabetologia, 60*(9), 1577-1585.

Romero-Carmona, C. E., Chávez-Corona, J. I., Lima, E., Cortés, H., Quintanar-Guerrero, D., Bernad-Bernad, M. J., Leyva-Gómez, G. (2024). Nanoparticle and microparticle-based systems for enhanced oral insulin delivery: A systematic review and meta-analysis. *Journal of Nanobiotechnology, 22*(1), 802.

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Ogurtsova, K. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice, 157*, 107843.

Salehi, B., Jornet, P. L., López, E. P.-F., Calina, D., Sharifi-Rad, M., Ramírez-Alarcón, K., Setzer, W. N. (2019). Plant-derived bioactives in oral mucosal lesions: a key emphasis to curcumin, lycopene, chamomile, aloe vera, green tea and coffee properties. *Biomolecules, 9*(3), 106.

Sengottaiyan, A., Aravinthan, A., Sudhakar, C., Selvam, K., Srinivasan, P., Govarthanan, M., Selvankumar, T. (2016). Synthesis and characterization of Solanum nigrum-mediated silver nanoparticles and its protective effect on alloxan-induced diabetic rats. *Journal of Nanostructure in Chemistry, 6*(1), 41-48.

Shah, M., Nawaz, S., Jan, H., Uddin, N., Ali, A., Anjum, S., Abbasi, B. H. (2020). Synthesis of bio-mediated silver nanoparticles from Silybum marianum and their biological and clinical activities. *Materials Science and Engineering: C, 112*, 110889.

Shaheen, T. I., El-Naggar, M. E., Hussein, J. S., El-Bana, M., Emara, E., El-Khayat, Z., Hebeish, A. (2016). Antidiabetic assessment; in vivo study of gold and core-shell silver-gold nanoparticles on streptozotocin-induced diabetic rats. *Biomedicine & Pharmacotherapy, 83*, 865-875.

Sharmah, B., Barman, H., Afzal, N. U., Loying, R., Kabir, M. E., Borah, A., Manna, P. (2024). Surface-functionalized nanoceria: dual action in diabetes management via glucose-responsive insulin delivery and oxidative stress mitigation. *ACS Biomaterials Science & Engineering, 10*(10), 6397-6414.

Shobhawat, M., Srivastav, S., Shukla, R. G., & Bhagat, O. L. (2025). Assessing the Impact of BMI and Glycaemic Control on Cardiac Autonomic Neuropathy in Patients with Early and Long-standing Diabetes Mellitus: A Window of Opportunity. *Annals of Neurosciences*, 09727531251384548.

Srinivasan, K., Viswanad, B., Asrat, L., Kaul, C., & Ramarao, P. (2005). Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening. *Pharmacological research, 52*(4), 313-320.

Swilam, N., & Nematallah, K. A. (2020). Polyphenols profile of pomegranate leaves and their role in green synthesis of silver nanoparticles. *Scientific Reports, 10*(1), 14851.

Trivedi, R., Upadhyay, T. K., Mujahid, M. H., Khan, F., Pandey, P., Sharangi, A. B., Alabdallah, N. M. (2022). Recent advancements in plant-derived nanomaterials research for biomedical applications. *Processes, 10*(2), 338.

Wadhwa, P., Sharma, S., Sahu, S., Sharma, A., & Kumar, D. (2022). A review of nanoparticles characterization techniques. *Current Nanomaterials, 7*(3), 202-214.

Wani, S. A., Khatoon, B. A., & Khanum, F. (2021). Antioxidant catalytic and biological activities of zinc oxide nanoparticles synthesized by using lagerstreomia specio leaves. *International Journal of Innovations in Engineering Research and Technology*, *8*(08), 182-191.

Wronka, M., Krzemińska, J., Młynarska, E., Rysz, J., & Franczyk, B. (2022). The influence of lifestyle and treatment on oxidative stress and inflammation in diabetes. *International journal of molecular sciences*, *23*(24), 15743.

Xie, Y., Ma, C., Yang, X., Wang, J., Long, G., & Zhou, J. (2021). Phytonanomaterials as therapeutic agents and drug delivery carriers. *Advanced drug delivery reviews*, *176*, 113868.

Zhishen, J., Mengcheng, T., & Jianming, W. (1999). The determination of flavonoid contents in mulberry and their scavenging effects on superoxide radicals. *Food chemistry*, *64*(4), 555-559.