Antidiabetic Potential of Biosynthesized Silver Nanoparticles with Fresh Guava Leaf

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Received: 31:03:2025 Accepted: 24:07:2025 Published: 24:07:2025

Abstract:
Current diabetes medications have been associated with varying degrees of adverse effects and prolonged toxicity, further complicating morbidity and mortality. This necessitates the search for less toxic alternatives, such as nanoparticles. Hence, this research aimed to assess the hypoglycemic capabilities of biosynthesized silver nanoparticles (AgNPs) with fresh guava leaves. Twenty-five (25) albino Wistar rats weighing 120-230 g were obtained and allowed to acclimatize for 7 days in a well-ventilated room with a standard temperature of 29 ºC, relative humidity of 70%, and a 12:12-hour photoperiod. The experimental rats were fed food and water as appropriate and were divided into five (5) groups. Group I: (NC) non-diabetic rats, given water (reconstitution solvent); Group II: (DC) non-treated diabetic rats, given distil water; Group III: (MET) Standard control: diabetic rats administered 200 mg/kg BW Metformin; Group IV: treated animals given AgNPs and guava leaves, regular feed, and water, and Group V: treated with guava extract and induced intraperitoneally with STZ at 60 mg/kg for 48hrs to induce diabetes before treatment. The dose regimens were administered once per day for twenty-one (21) days. The results obtained revealed a significant increase ($p<0.05$) in mean plasma glucose relative to diabetic control groups and a substantial increase ($p<0.05$) in mean serum insulin when compared to diabetic control groups. Mean plasma glucose in albino Wistar rats in Table 1 displayed a significant decrease in glucose levels of rats administered AgNPs from day 1 to 14 at $p<0.05$. Additionally, serum insulin was significantly elevated in the AgNPs group when compared to the Metformin group at $p<0.05$, and this was also seen in the experimental group administered guava leaf extracts. Essentially, silver nanoparticles and guava extract showed antidiabetic activity by reducing glucose levels and synergistically enhancing the production of beta cells for glucose uptake to peripheral tissues.

Keywords: **Antidiabetic, Biosynthesis, Guava Leaf, Silver Nanoparticles, Therapeutic Potential.**

1. Introduction

Diabetes mellitus is considered a long-term metabolic disorder that results from impaired insulin secretion, the absence of insulin, or both. This causes persistent rise in blood sugar levels and disruption in lipid, protein, and carbohydrate metabolism [1]. This condition disrupts glucose homeostasis, leading to serious complications affecting several body organ systems, such as the brain, renal, and cardiovascular systems. The pathophysiology of diabetes mellitus primarily involves resistance to insulin, pancreatic β-cell dysfunction, or a combination of both, which results in impaired glucose uptake and metabolism [2]. The disorder is classified into type 1 and type 2 diabetes, with a third class being gestational diabetes. Type 1 diabetes is caused by an autoimmune response that destroys pancreatic β-cells, resulting in a complete lack of insulin production. Type 2 diabetes (T2DM) is characterized by insulin resistance and progressive β-cell dysfunction, and this accounts for about 90% of diabetes cases worldwide. Gestational diabetes mellitus (GDM) is a condition characterized by elevated sugar levels during pregnancy, especially during the second (weeks 13-26) and third trimesters (week 27-delivery). Other rare forms of diabetes include the monogenic form, which occurs as a result of a single genetic alteration in an autosomal dominant gene, while secondary diabetes is due to complications of other diseases of the pancreas, such as pancreatitis. This further contributes to the heterogeneity of this disease [2, 3].

Globally, diabetes has reached alarming epidemic proportions, posing a significant threat to healthcare systems around the world [3]. In 2021, the International Diabetes Federation (IDF) reported that over 537 million individuals, between the age range of 20 to 79 years, had diabetes. If current trends continue, this frequency is tipped to rise to about 643 million by 2030 and 783 million by 2045. T2DM accounts for around 90% of all confirmed cases, primarily driven by sedentary lifestyles, obesity, and unhealthy dietary patterns that may cause a decline in glucose mobilization to peripheral tissues that bring about resistance. [2]. The highest impact of diabetes is often felt in low- and middle-income economies, with limited access to healthcare exacerbating disease outcomes. Diabetes has a significant economic impact globally,

with global healthcare costs associated with the menace reaching about USD 966 billion in 2021, an increase of 316% in the last 15 years [4].

The disease is also credited as being one of the most prevalent pediatric disorders, having an annual incidence rate ranging from 2% to 5%. [5]. Despite advances in pharmacological treatments, including insulin analogues, GLP-1 receptor agonists, and SGLT2 inhibitors, diabetes continues to be a cause of morbidity and mortality. Complications like diabetic nephropathy, retinopathy, neuropathy, and cardiovascular diseases significantly diminish the quality of life of patients. Early detection, lifestyle interventions, and emerging therapeutic strategies, including regenerative medicine and precision diabetes care, are crucial in mitigating disease progression [6]. Nanotechnology, a prominent field within material science, has gained attention for its unique physicochemical properties and extensive use in several fields, including electronics, catalysis, and targeted drug delivery [7]. Metal nanoparticles, with sizes ranging between 1 and 100 nm, have garnered significant scientific interest because of their exceptional optical, biological, and electrical properties [8].

Among these, silver nanoparticles (SNPs) have shown remarkable potential in various scientific fields because of their distinctive optical characteristics. Advances in nanobiotechnology have enabled the synthesis of plant-based silver nanoparticles, which function as potent inhibitors of glucosidase and amylase enzymes crucial for carbohydrate metabolism. These SNPs hold promise as therapeutic agents for diabetes management, especially in severe cases [9]. Plant-based SNPs offer several advantages, including cost-effectiveness, environmental sustainability, non-toxicity, and suitability for biomedical applications [10]. Studies have demonstrated that plant-based SNPs effectively inhibit amylase activity, helping to regulate postprandial glucose levels, a key aspect of diabetes treatment [11]. Medicinal plants in therapy are increasingly favored because of their wide distribution and reduced toxicity compared to synthetic alternatives [12]. Notably, around 25% of currently approved pharmaceuticals are derived from plant-based compounds, highlighting their importance in modern medicine and supporting the development of plant-based nanotherapeutics for diabetes [13, 14]

Often called guava, *Psidium guajava* is a popular medicinal plant from the *Myrtaceae* family, and it is traditionally used in various cultures owing to its therapeutic potential. Native to regions such as Indonesia, South America, Bangladesh, India, and Pakistan, guava has been employed to treat diabetes, gastrointestinal disorders, and other conditions. Different species of the guava tree have been employed in traditional medical practice, reflecting their diverse pharmacological advantages. Scientific studies have identified numerous bioactive phytochemicals in *P. guajava* leaves, which contribute to their anti-diabetic, antioxidant, hepatoprotective, antibacterial, lipid-lowering, and antidiarrheal properties [14, 15]. Fresh guava leaves, in particular, have attracted significant scientific interest for their potential to modulate glucose metabolism and aid glycemic regulation, making them promising candidates in the management of diabetes [16]. The integration of traditional knowledge with modern scientific research underscores the capabilities of *P. guajava* as a valuable resource for innovative therapeutic approaches in diabetes treatment.

II. MATERIALS AND METHODS

I. MATERIALS

Grower's mash, ceramic plates, plastic rubber, cages, oral cannulas, plastic water bottles, syringes (different sizes), dissecting sets, distilled water, clean water, hand gloves, cotton wool, disinfectant, morning fresh, toilet roll, laboratory coat, glass stirrers, beakers, ceramic crucibles, separating funnels, rotary sets, conical flasks, desiccators, Whatman No.1 filter paper (24 cm), chloroform, picric acid, EDTA bottles, plain sample bottles, test tubes, masking tape, cardboard paper, measuring cylinder, retort stand, thumb pins, spatulas.

Equipment

Dry oven (model 362), micropipette (1000 µl), electric weighing balance (Denver, model: IR-30, USA.), Thermocool freezer (model TH 170, China), one-touch fine-test auto coding premium blood glucose coding centre.

Drugs

Metformin (purchased from Fidelity Medical Stores Igoli Ogoja). AgNPs were obtained from Sigma Aldrich USA.

Plant material collection

Fresh *P. guajava* leaves were harvested from a farm in Okuku town, Yala LGA, Cross River State, Nigeria.

Preparation of the plant extract

Collected leaves of *P. guajava* were washed 2-3 times with sterile distilled water, and 20 g were diced into sizeable pieces and boiled in 100 ml of sterile distilled water at 70^0C using a water bath for five (5) minutes.

Synthesis of Silver Nanoparticles (AgNPs)

The formation of silver nanoparticles (AgNPs) was confirmed visually by a color change from pale yellow to dark brown, indicating surface plasmon resonance. To validate this, UV-Visible spectrophotometry was conducted, revealing a peak at 400 nm. This confirms the formation of AgNPs. Further structural and morphological confirmation was performed using X-ray Diffraction (XRD) and Scanning Electron Microscopy (SEM), which identified characteristic crystalline silver peaks and spherical particle morphology, respectively.

Characterization of Silver Nanoparticles (AgNPs)

Comprehensive characterization of the synthesized AgNPs was conducted using Fourier Transform Infrared Spectroscopy (FTIR) to identify functional groups responsible for capping and stabilization. XRD analysis confirmed the crystalline structure of the nanoparticles, while SEM imaging revealed their morphology and size distribution. These techniques collectively validated the successful synthesis of AgNPs.

Silver Nanoparticles formation

XRD analysis of the synthesized AgNPs revealed prominent peaks at $2\theta = 38.2°$, $44.4°$, and $64.5°$, which correspond to the (111), (200), and (220) planes of face-

centered cubic (fcc) silver. This confirms that the silver nanoparticles were formed in the crystalline phase.

Dosage of Plant Extract

The dose of the plant extract administered was 20 mL/kg body weight.

Animals condition

Twenty (20) male Wistar rats with a weight range of 120-230 g were purchased from the Medical Biochemistry Department, Cross River University of Technology, Okuku Campus animal house. Experimental animals were then acclimatized for seven days under standard conditions of room temperature of 29 °C and relative humidity of 29ºC, following a 12:12-hour natural light-dark cycle. The animals were fed water and food *ad libitum*, with proper hygiene being maintained by cleaning and removing faeces and pills from their cages.

Animal experimentation and drug administration

The actual amount of drug needed by the animals was collected using the formula.

Y (mg) = D × w/1000 g

Where D – dose of metformin (mg/kg)

w - Body weight of animal (g)

Y- Actual amount of drug needed (16g)

A stock solution (50 mg/ml) was made when 500 mg of metformin was dissolved in 10 ml of distilled water.

Experimental design

In the experiment, a total of 25 Wistar rats were used, including 20 diabetic rats and 5 normal control rats. They were evenly divided into five groups, each having five rats.

Group I: Non-diabetic rats fed water

Group II: Non-treated diabetic rats, given distilled water

Group III: Standard control diabetic rats administered 200 mg per kilogram body weight of Metformin (MF).

Group IV: treated animals were given AgNPs, guava leaves, normal feed, and water.

Group V: administered guava extract.

Plant extract administration and standard drug lasted seven days while the entire experiment was twenty-one (21) days, and experimental animals were sacrificed exactly 24 hours after the last administration, and blood was collected via cardiac puncture.

Induction of diabetes

Diabetes mellitus was experimentally induced in Twenty (20) female Wistar rats following an overnight fast. Each rat received a single intra-peritoneal injection of streptozotocin (STZ) at a dosage of 60 mg/kg body weight. The STZ was freshly reconstituted in cold citrate buffer to ensure stability and activity. To prepare the STZ stock solution, 1 gram (1000 mg) of STZ was dissolved in 20 ml of cold citrate buffer, yielding a concentration of 50 mg/ml. Based on the required dosage, 1.2 ml of this solution was administered to a rat weighing 1 kg (i.e., 60 mg ÷ 50 mg/ml = 1.2 ml).After 48 hours post-STZ administration, fasting blood glucose (FBS) levels were measured using a One-touch FINE-TEST Advantage glucometer. Blood samples were collected by puncturing the tail vein of each rat. Only rats with FBS levels ranging between 200–600 mg/dL were considered diabetic and included in the experimental group. The estimation of fasting blood sugar in the selected rats was conducted using the Glucose Oxidase-Peroxidase (GOD-POD) enzymatic method. In this method, glucose oxidase catalyzes the oxidation of β-D-glucose to D-gluconic acid and hydrogen peroxide (H_2O_2). In the presence of peroxidase, the hydrogen peroxide then reacts with phenol and 4-Aminoantipyrine (4-AAP) to form a colored quinoneimine dye. The intensity of the resulting color is directly proportional to the glucose concentration in the sample and was measured spectrophotometrically.

Reaction Equation

β-D-glucose + H_2O + O_2 → (Glucose oxidase) → D-gluconic acid + H_2O_2

H_2O_2 + Phenol + 4-AAP → (Peroxidase) → Quinoneimine dye + 4 H_2O.

II. BIOCHEMICAL ASSAY

Determination of Serum Insulin concentration using assay kits from Monobind Inc (Eastham, 1985)

The needed number of coated wells was fastened in a holder. Specimens, 50 µl of standards, and controls were distributed into designated wells. Each well received 100 µl of estradiol biotin reagent, which was carefully mixed for about 20-30 seconds before being covered with the use of plastic wraps. The entire mixture was kept under standard ambient temperature (20-27°C) for about 2 hours. After removing the contents of the microplate using a decantation method, an absorbent paper was used to blot the plates dry. After adding 350 µl of wash buffer to each well, it was decanted using blotting and tapping. For a total of three washes, this process was carried out twice. In each well, 100 µl of the working substrate solution was added. This entire mixture was then left under incubation for 15 minutes at standard room temperature. Each well received 50 µl of stock solution, which was gently stirred for 15-20 seconds. Absorbance was taken at 450 nm using the microplate reader (with a reference wavelength between 620-630 nm) in 30 minutes.

Statistical analysis

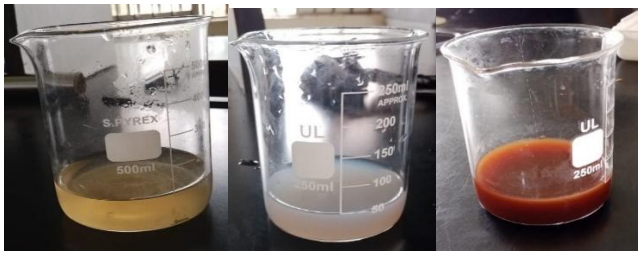
All collected data were subjected to analysis and presented as mean ± SEM**.** One-way Analysis of variance (ANOVA) was done to establish the statistical difference between the means using SPSS version 23, where statistical significance set at $p<0.05$.

III. RESULTS

Colour change and UV-Visible Spectroscopy

The UV-Vis absorption peak observed at 400 nm corresponds with findings in previous studies where biosynthesized silver nanoparticles showed peaks within the 380–450 nm range, confirming successful nanoparticle formation [7,12]. This alignment with existing literature supports the reliability of the synthesis method. As shown in Figure 1a. The surface Plasmon resonance showed a rise as

detected by the UV-visible spectrum, showing a rise starting at 350 nm and having its peak at 400 nm, as shown in Figure 1b.



(a) (b) (c)

Figure 1: (a) Boiled leaves of Guava, (b) Aqueous $AgNO_3$ solution, (c) Guava and AgNPs after 5 minutes

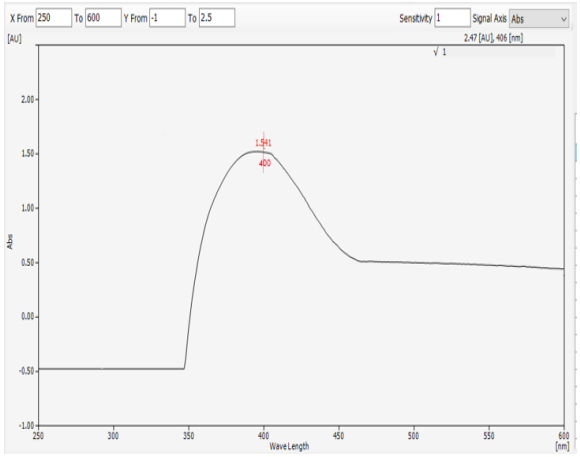


Figure 2: UV-Vis spectrum of *Psidium guajava* silver nanoparticles.

The formation of silver nanoparticles was confirmed through the visible change in color to dark brown, as seen in Figure 1c. This is indicative of nanoparticle formation through surface plasmon resonance. The detection was validated using the UV-Visible spectrophotometer with a specific peak at 400 nm, which correlates with the localized surface plasmon resonance of silver nanoparticles.

Results of mean plasma glucose and serum insulin

Mean plasma glucose and mean serum insulin levels after the administration of $AgNO_3$ and Guava extract in Wistar rats are presented in Table 1. This displayed a significant decrease in glucose levels of the AgNPs from the 1st to the 14th day at $p<0.05$. Although it was not significantly different in guava extract from days 1 to 7, the glucose levels decreased in the guava extract on day 14 when compared to days 1 and 2.

TABLE 1: MEAN PLASMA GLUCOSE (mg/dL)

Group	1st day	7th day	14th day
NC	87.50±7.32^{a}	87.50±7.32^{a}	86.75±12.17^{a}
DC	600.00±0.00^{b}	500.75±114.76^{b}	600.00±0.00^{b}
MET	600.00±0.00^{c}	413.00±156.61^{d}	393.00±174.03^{d}
AgNPs	385.00±112.74^{e}	425.00±203.65^{e}	91.75±10.43^{f}
GV	600.00±0.00^{g}	600.00±0.00^{g}	523.25±153.50^{g}

Values are expressed as Mean ± S.D, n=4, NC= Normal Control, DC= Diabetic Control, Met = Metformin, $AgNO_3$, GV = Guava. Means with different superscript letters across rows (from left to right) were significantly different, while means with the same superscripts were not at $p<0.05$.

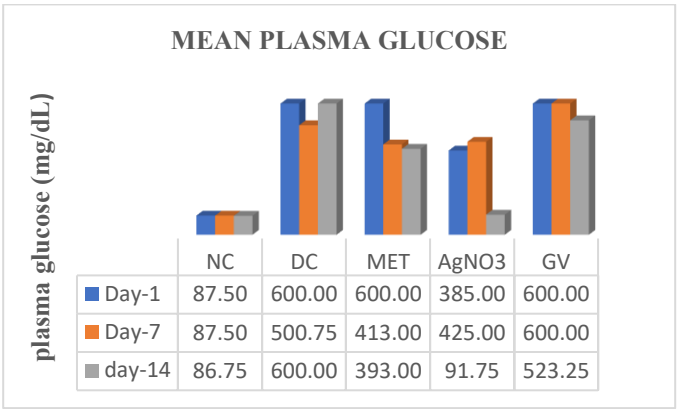


Figure 3: Mean serum glucose

The results of mean serum insulin in albino Wistar rats revealed a significant increase in the insulin level of the AgNPs groups when compared to the Metformin group at $p<0.05$. It also showed a significant increase in insulin levels of the guava leaf extract (GV) group relative to the metformin group.

TABLE 2: MEAN SERUM INSULIN (mIU/ml)

	INS (mIU/ml)
NC	87.09±2.65^{a,c}
DC	133.34±5.3^{b}
MET	86.80±13.57^{c,a}
AgNPs	112.18±4.40^{d}
GV	104.15±7.60^{e,a,d}

Values are expressed as Mean ± S.D, n=4, NC= Normal Control, DC= Diabetic Control, Met = Metformin, $AgNO_3$, GV = Guava. Means with different superscript letters across rows (from left to right) were significantly different, while means with the same superscripts were not at $p<0.05$.

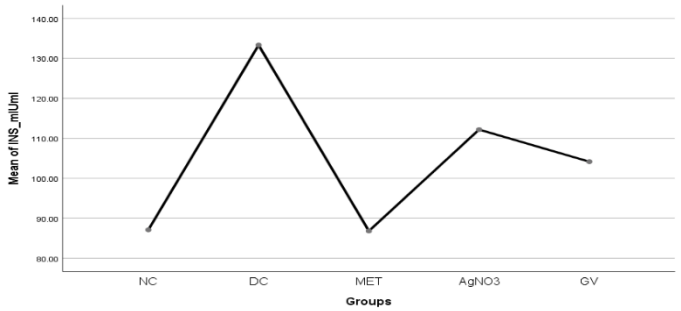


Figure 4: Graphical representation of mean serum insulin (mIU/ml).

IV. DISCUSSION

Chronic hyperglycemia and metabolic irregularities in proteins, lipids, and carbohydrates are defining features of diabetes mellitus, a disease marked by decreased insulin production, insulin resistance, or both [1]. This disorder throws off glucose homeostasis, which leads to serious problems that impact cardiovascular, renal, and neurological systems, among other organ systems. Oxidative stress, which results from an imbalance between the body's antioxidant defense systems and the generation of reactive oxygen species (ROS), is closely linked to type 2 diabetes mellitus (T2DM). This oxidative imbalance contributes to cellular dysfunction, progressive β-cell apoptosis, impaired β-cell maturation, and a decline in insulin synthesis and secretion. The chronic overproduction of ROS worsens insulin resistance and induces oxidative damage

to pancreatic β-cells, which are particularly vulnerable due to their limited antioxidant capacity. This oxidative stress-driven pathophysiology underscores the delicate role of redox homeostasis in the progression of diabetes, positioning T2DM as a disorder intricately linked to oxidative stress. Hyperglycemia in diabetes is associated with several metabolic disorders [15].

Insulin-mediated uptake of glucose by the tissue is a key factor in maintaining glucose homeostasis. However, oral glucose-lowering drugs and synthetic insulin often exhibit significant contraindications, including severe hypoglycemia at high doses, which can lead to hepatic injury, neurological imbalances, lactic acidosis, digestive disorders, and even death. Consequently, there is a growing need for safer, cost-effective, and natural alternatives with high therapeutic potential for diabetes management. Guava (*Psidium guajava*) has emerged as a promising candidate due to its antidiabetic properties and minimal side effects [16]. This study investigates the antidiabetic potential of biosynthesized silver nanoparticles (AgNPs) using fresh guava leaf extract. In traditional medicine, guava leaves (GL) have traditionally been used to treat diabetes [14]. Their hypoglycemic qualities are ascribed to bioactive substances such as polysaccharides and flavonoids. Research has indicated that two major flavonoids present in GL extract, guaijaverin and avicularin, considerably enhance hepatocyte morphology and the β-cell function of the pancreas in hyperglycemic mouse models [14]. Avicularin prevents intracellular lipid formation by preventing glucose absorption via GLUT-4 in vitro, without harming 3T3-L1 adipose cells [17, 14], while guaijaverin increases the activity of dipeptidyl-peptidase IV, a digestive enzyme involved in blood glucose regulation [18]. Moreover, GL polysaccharides (GLPs) have exhibited antidiabetic potential in streptozotocin-induced diabetic mice subjected to a high-fat diet.

In this study, mean serum insulin levels in experimental rats revealed a considerable increase in the AgNPs-treated groups at $p<0.05$, indicating enhanced secretion of insulin and pancreatic β-cell regeneration, which facilitates glucose uptake and reduces hyperglycemia [19]. Similarly, guava leaf extract significantly increased insulin production, comparable to the effects of AgNPs, suggesting its potential to enhance β-cell regeneration. The antidiabetic and antioxidant properties of both AgNPs and guava extract are likely responsible for these effects, consistent with previous findings that highlight improvements in hepatocyte morphology and pancreatic β-cell function in diabetic mice [14]. Guaijaverin, in particular, has been shown to enhance dipeptidyl-peptidase IV activity, further supporting the therapeutic potential of guava leaves [17]. The study also underscores the effectiveness of natural antioxidants in mitigating oxidative stress [20]. Silver nanoparticles, known for their rich antioxidant content, can penetrate deep into tissues and effectively scavenge free radicals, particularly oxygen-based ones. The biosynthesis of AgNPs from plant extracts, such as guava leaves, is advantageous compared to microbial or algal methods, as it avoids the complexities of culture maintenance and reduces biohazard risks [14]. Plant-derived phytochemicals, including phenols, terpenoids, and flavonoids, are potent stabilizing, reducing, and capping agents, enhancing the biomedical properties of nanoparticles [21]. They exhibit hypoglycemic properties by inhibiting intestinal enzymes like α-amylase and α-glucosidase, thereby reducing postprandial blood glucose levels [21].

In this study, the guava leaf extract and AgNPs significantly decreased plasma glucose levels relative to diabetic controls and metformin at $p<0.05$. This evaluation is attributed to the therapeutic effects of AgNPs, which enhance insulin secretion and glucose utilization. The mechanism of action involves the regeneration of pancreatic β-cells, which boosts the immune system and prevents cytokine-induced inflammation and β-cell destruction. Although the current study demonstrates the antidiabetic potential of biosynthesized AgNPs, the biocompatibility and systemic toxicity of these nanoparticles were not assessed. Future research should focus on conducting cytotoxicity assays, histopathological evaluations, and long-term exposure studies to determine safety and suitability for therapeutic applications. The study demonstrates that both AgNPs and guava extract can counteract the autoimmune destruction of pancreatic cells, a hallmark of type 1 diabetes.

V. CONCLUSION

The present study provides compelling evidence supporting the antidiabetic capabilities of silver nanoparticles and fresh guava leaf extracts. Not only that the synthesized nanoparticles significantly reduce blood glucose levels in experimental models, but they also exert a synergistic effect with guava phytochemicals in aiding pancreatic β-cell regeneration, to yield improved glucose uptake. These dual advantages indicate a promising therapeutic avenue for the management of hyperglycemia and the restoration of glycemic control in diabetic conditions. It also offers a sustainable and eco-friendly option to conventional diabetes treatment. However, further studies are recommended to ascertain the detailed mechanism, and long-term toxicity of the biosynthesized compound to validate their safety and efficacy for translational therapeutic use.

ACKNOWLEDGEMENT

In memory of late Mrs. Christiana Edonmi Edun.

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