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Anti-Diabetic Potential of Silver (AgNPs) and Gold (AuNPs) Nanoparticles Synthesized Using an Aqueous Extract of *Opuntia ficus indica* Cladodes in Wistar Rats

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ABSTRACT

Diabetes mellitus (DM) disease has become an increasingly important public health concern, due to its global occurrence and consequences. The study evaluated the anti-diabetic potential of silver (AgNPs) and gold (AuNPs) nanoparticles synthesized using an aqueous extract of *Opuntia ficus indica* (OFI) cladodes. The antidiabetic potential of OFI-extract, OFI-AgNPs, and OFI-AuNPs were investigated using sixty-three male Wistar rats consisting of seven (7) rats per group. Diabetes mellitus was induced by a single intraperitoneal injection of Streptozotocin (65 mg/kg b.w.) in groups DT5-DT9, while groups DT1-DT4 served as non-diabetic control groups. Glibenclamide (0.6 mg/kg b.w.) was used as a standard drug for twenty-eight days of treatment. OFI-AgNPs and OFI extract increased the body weight significantly ($P \leq 0.05$) in diabetic-treated rats and decreased the fasting blood glucose compared to DT5. The malondialdehyde levels of the liver and kidney (DT6 & DT8) were decreased compared with DT5. The activities of the enzymes were enhanced significantly ($P<0.05$) in diabetic rats treated with OFI-AgNPs and OFI-extract (DT6 & DT8) in comparison with DT5.
This finding demonstrated that OFI-AgNPs and OFI-extract protected the animals from diabetic complications associated with REDOX imbalances. Results showed that *O. ficus indica* can synthesize nanoparticles with potential as an anti-diabetic agent.

Keywords: Diabetes mellitus, Streptozotocin, *Opuntia ficus indica*, Albino rats, Nanoparticles.

Introduction

Diabetes mellitus (DM) is a metabolic disorder marked by persistent high blood sugar. This metabolic disorder affects a large number of people all over the world. The symptoms include increased urinary output, increased thirst, ketonuria, and ketonemia which result from the irregularities in the body metabolism, hence, immediate proper treatment should be implemented to prevent other diabetic complications.[1] Diabetes is of two types which include, Type 1 and Type 2. Type 1 diabetes is insulin-dependent while Type 2 diabetes is non-insulin-dependent.[2,3] Remarkable morbidity and mortality, as a result of microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke, and peripheral vascular disease) impediments, are initiated by diabetes mellitus. [3] Diabetes incidence is a sequel to the effect of harmful lifestyle, urbanization, and aging. Hyperglycaemia is the characteristic of diabetes mellitus, which enhances reactive oxygen species (ROS), and induces lipid peroxidation, and membrane destruction. ROS play a vital role in diabetes mellitus by the development of secondary complications such as cataracts, neuropathy, and nephropathy. [2] Diabetes is occasioned by a deficiency of the pancreas, in the production of insulin or body cells unable to react properly to the insulin produced. [4]

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Prevention and management involve a healthy lifestyle (diet), physical exercise, sustaining a normal body weight, and avoiding smoking tobacco. Monitoring blood pressure, and maintaining proper foot care is important for those who have contracted the disease. Type 1 DM, is a lifelong insulin-dependent therapy, [5] while type 2 DM, may be cured with medications, coupled with or without insulin. [2,4] Another rare type of diabetes is gestational diabetes, which is usually overcome after a child's birth. [6]
Insulin and some oral pills can lower hyperglycemia. [7] People with type 2 DM can be treated by weight loss surgery, especially people with overweight (obesity). [8] The threatening signs of untreated diabetes are polydipsia (increased thirst), weight loss, polyuria (increased urination), and polyphagia (increased hunger). [9] Blurry vision, headache, fatigue, delayed healing of cuts, and itchy skin is additional indications. Persistent high blood glucose can cause glucose accumulation in the lens of the eye, which leads to differences in its shape, bringing about vision variations. Diabetic dermadromes are skin rashes that occur severally in diabetes patients. [10] Some hypoglycemic agents such as rosiglitazone, phenformin, tolbutamide, troglitazone, repaglinide, metformin, Sulfonylureasis, and insulin are effective in treating diabetes and controlling hyperglycemia, however, they have harmful side-effect and sometimes resulted in diabetic complications. [11,12] Hence, there is a need to search for a natural cure for diabetes. Herbs taken are more suitable as there are no dietary limitations, like in taking biomedical drugs.[3] This study focused on the efficacy of *Opuntia ficus-indica* extracts and its biomediated nanoparticles in the treatment of diabetes. Pharmacological activities of *O. ficus-indica* in terms of oxidative damage protection, antioxidant activity, lipid peroxidation reduction, radical scavenging activities, and glutathione (GSH) levels increases have been reported. [14]

Materials and Methods

Biosynthesis and Characterization of nanoparticles (OFI-AgNPs and OFI-AuNPs)

Biosynthesized nanoparticles (OFI-AgNPs and OFI-AuNPs) used in this study were obtained from *Opuntia ficus-indica* (OFI) aqueous extracts mediated nanoparticles. *O. ficus-indica* was collected from Offa, Kwara State, Nigeria (8.14910N,4.72070E). The identity of the plant material was confirmed and authenticated at the Pure and Applied Biology Department, LAUTECH, Ogbomoso with the voucher number LHO 584. The spines were separated, clean, and dried at 40℃ inside an oven. It was pulverized using an electrical blender (Euro premium, 750 watts) for 10 s. Ten grams (10 g) of the powdery *O. ficus-indica* was obtained and suspended in 150 mL of distilled water inside the tightly closed container for 24 h in the dark cupboard. The mixture was filtered and centrifuged at 4000 rpm for 20 min. The supernatant was collected and stored for use.[15] OFI-AgNPs and OFI-AuNPs were mediated by *O. ficus-indica* extracts and characterized as reported by Adebayo *et al.*[15] The nanoparticles were fully characterized using a UV-visible spectrophotometer, Transmission Electron Microscopy (TEM) Micrograph, Fourier Transform Infrared (FTIR) spectroscopy, X-ray Diffraction (XRD), Energy Dispersive X-ray (EDX) Spectroscopy and Selected Area Electron Diffraction (SAED).[15]

Experimental design and Experimental animals

The rats were provided with basic feed for a week following the initiation of the experiments. The animals were divided into nine (9) different groups (DT1 – DT9; Different treatments), with seven animals in each group as shown in Table 1. The experimental protocols and procedures followed laboratory animal care guidelines and principles[16]. Sixty-three (63) male Wistar rats (120 - 200 g) were procured from the College of Health Sciences Animal House of LAUTECH, Ogbomoso, Nigeria. Rats were separately housed in standard environmental conditions of 50±10 % for relative humidity and a 12 h dark cycle was maintained throughout the experiment. All rats were acclimatized for a week before the commencement of the study.

Table 1: Distribution of animals into different treatment (DT) groups

Distribution of Animal	Different Treatments on animals
DT1	Non-induced given water and feeds only (Positive control).
DT2	Non-induced given water, feeds, and OFI- extract (Positive control).
DT3	Non-induced given water, feeds and OFI-AgNPs (Positive control).
DT4	Non-induced given water, feeds and OFI-AuNPs (Positive control).
DT5	Diabetic-induced rats, given water and feed (non-treated negative control)
DT6	Diabetic-induced rats, given water, feeds and OFI-AgNPs (10 mg/kg b. w)
DT7	Diabetic-induced rats, given water, feeds and OFI-AuNPs (10 mg/kg b. w)
DT8	Diabetic-induced rats, given water, feeds and OFI-extract (10 mg/kg b. w)
DT9	Diabetic-induced rats given water, feeds, and Glibenclamide (0.6 mg/kg b. w)

Rodent pellet feed was used in feeding the rats under hygienic conditions with access to water *ad libitum*. [17,18] The rats were randomly allocated into nine groups of seven rats per group.

Ethical Permission

The study was approved by the Ethical Committee on the use of Laboratory Animals of the Faculty of Basic Medical Sciences, LAUTECH with approval number LTH2018-16. The experimental protocols adopted in this study are in tandem with Laboratory Animal Care guidelines and Principles.[16]

Induction with Streptozotocin

Diabetes was induced in Wistar rats by intraperitoneal injection of streptozotocin (65 mg/kg b), dissolved in acidified normal saline (pH 4.5) after a 12 h fast. The diabetes situation was established by measuring the glucose level of the blood after 72 h of streptozotocin injection using Accu check sensor comfort glucometer (Roche, Mexico City) to measure the fasting blood sugar (FBS) via tail tip sampling. Rats with blood sugar levels of more than 120 mg/dL, were considered to be diabetic and used for further studies. Rats with blood sugar levels less than 80 mg/dL are hypoglycaemic. [18,19,20] The fasting blood sugar was also monitored on the 0, 7th, 10th, 14th, 21st, and 28th days.

Body Weight Assessment

The body weights of the rats were recorded regularly by using a weighing balance from the beginning until the expiration of the study (0, 7^{th}, 14^{th}, $21^{st,}$ and 28^{th} day) at the interval of seven days. The change in body weight of rats was observed and recorded

Sample Preparation

At the termination of the experiment on the 28th day, the rats were sacrificed under mild anesthetic conditions. The rat was sacrificed and blood samples were withdrawn by cardiac puncture from the rat's heart into lithium heparinized bottles, the liver and kidney were also removed, and their weight was determined. Portions of liver and kidney were sliced, rinsed in normal saline solution, and immediately stored in sterile bottles placed in ice until ready for homogenization.

Biochemical assays

The blood samples collected from the rats were centrifuged at 5000 rpm for 10 min, and the serum obtained was stored in the refrigerator until further use. The liver and kidney samples were sliced and homogenized with pestle and mortar in an equal volume of chilled 10 mM phosphate buffer (pH 7), over ice cubes. The homogenates were centrifuged at 5000 rpm for 20 min. The supernatants were used for the biochemical assays to determine the concentrations of, Catalase (CAT),[21] Glutathione-s-transferase (GST), Superoxide dismutase (SOD),[22] Glutathione peroxidase (GPX), Reduced Glutathione (GSH) and Malondialdehyde (MDA). [23]

Statistical analysis

All data collected were expressed using Graph Pad Prizm 6. Data were expressed as mean $\pm$ Standard error of the mean (mean ± S.E.M), and the statistical significance between the groups was analyzed using a one-way analysis of variance (ANOVA) followed by turkey's post hoc test (t-test), and $P \leq 0.0\,5$ was considered significant.

Results and Discussion

Bodyweight loss and gain in rats

The results in Table 2 show that induction of diabetes resulted in a progressive reduction of rat body weight as observed in group DT5. The weight loss in DT5 was found to be significant when compared with normal control rats. However, treatment with OFI-AgNPs, OFI-AuNPs, and OFI extract lower the diabetic-related weight loss in the groups of animals when compared with the diabetic group (DT5). The reduction of weight loss by the nanoparticles and extract was found to be comparable with the effect of the standard drug Glibenclamide. Streptozotocin (STZ) is a naturally occurring compound of glucosamine nitrosourea used to induce diabetes mellitus in experimental models.

Table 2: Body Weight of experimental rats (g)

Group/Time	Day 0	Day 7	Day 14	Day 21	Day 28
DT_1	169 ± 1.45^{aa}	176 ± 3.73^{ab}	186 ± 1.64^{aa}	200 ± 1.46^{aa}	214 ± 1.66^{aa}
DT_2	167 ± 3.00^{aa}	173 ± 2.29^{ab}	182 ± 1.70^{ab}	195 ± 2.10^{aa}	211 ± 2.21^{ab}
DT_3	166 ± 4.06^{ab}	175 ± 3.39^{aa}	184 ± 5.6^{ab}	201 ± 5.61^{ab}	217 ± 4.85^{ab}
DT_4	166 ± 2.98^{ab}	172.0 ± 2.69^{aa}	181 ± 2.81^{aa}	182 ± 4.37^{aa}	172 ± 1.0^{aa}
DT_5	167.9 ± 1.23^{aa}	138.6 ± 5.42^{aa}	145.7 ± 5.61^{bc}	128.6 ± 3.89^{ab}	120 ± 2.23^{ab}
DT6	168.9 ± 1.4aa	164.4 ± 9.04^{ab}	163.4 ± 8.50^{cd}	174.9 ± 1.17^{abc}	185.3 ± 8.12^{ab}
DT_7	169.3 ± 8.5^{aa}	140.0 ± 8.24^{ab}	142.9 ± 1.58^{ab}	122.1 ± 9.05^{ab}	107.1 ± 1.74^{ab}
DT_8	167.0 ± 1.97^{ab}	162.4 ± 1.48^{aa}	165.6 ± 1.87^{aa}	172.3 ± 3.78^{abc}	182.7 ± 3.29^{ab}
DT_9	166.6 ± 7.38^{ab}	161 ± 3.14^{aa}	168.1 ± 1.15^{aa}	173.7 ± 1.71^{bc}	180.3 ± 1.31^{ac}

Data were expressed as X ± SD (n=7) mean followed by different superscripts within the same row are significantly (P<0.05) different.
DT_1: Non-induced given water and feeds only (Positive control); DT_2: Non-induced given water, feeds and OF extract (Positive control).
DT_3: Non-induced given water, feeds and OF-AgNPs (Positive control); DT_4: Non-induced given water, feeds and OF-AuNPs (Positive control).
DT_5: Diabetic-induced rats, given water and feeds (non-treated negative control); DT_6: Diabetic-induced rats, given water, feeds and OF-AgNPs
DT_7: Diabetic-induced rats, given water, feeds and OF-AuNPs ; DT_8: Diabetic-induced rats, given water, feeds and OF extract
DT_9: Diabetic-induced rats given water, feeds and Glibeclamide

Table 3: Fasting Blood sugar of experimental rats (mg/dL)

Group	Day 0	Day 7	Day 14	Day 21	Day 28
DT_1	87.00 ± 1.22^{aa}	85.40 ± 3.682^{ab}	86.00 ± 2.098^{ab}	85.60 ± 2.015^{ab}	89.60 ± 1.965^{aa}
DT_2	82.20 ± 3.967^{aa}	84.60 ± 2.943^{bc}	89.20 ± 1.391^{ab}	87.80 ± 2.35^{ab}	87.00 ± 1.304^{aa}
DT_3	88.80 ± 5.928^{ab}	85.60 ± 3.219^{aa}	89.40 ± 2.676^{ab}	88.80 ± 1.772^{aa}	86.20 ± 3.693^{ab}
DT_4	87.40 ± 5.446^{ab}	85.80 ± 2.437^{ab}	86.40 ± 2.249^{ab}	80.20 ± 2.888^{ab}	82.00 ± 1.550^{ab}
DT_5	88.00 ± 4.658^{ab}	275.80 ± 5.295^{aa}	282.4 ± 9.605^{aa}	311.6 ± 2.950^{ab}	378.6 ± 3.385^{aa}
DT_6	89.20 ± 3.071^{ab}	233.4 ± 3.410^{ab}	126.0 ± 2.710^{ab}	94.20 ± 7.248^{ab}	87.2 ± 4.130^{ab}
DT_7	85.00 ± 5.670^{ab}	283.20 ±1.769^{ab}	260.8 ± 2.530^{ab}	155.2 ± 2.870^{aa}	139.2 ± 2.020^{ab}
DT_8	80.00 ± 1.761^{ab}	231.6 ± 1.680^{aa}	147.8 ± 2.670^{aa}	89.80 ± 3.865^{ab}	87.44 ± 2.83^{ab}
DT_9	85.20 ± 1.772^{aa}	202.6 ± 2.610^{aa}	157.0 ± 3 .590^{ab}	111.6 ± 1.200^{aa}	89.60 ± 2.940^{ab}

Data were expressed as X ± SD (n=7) mean followed by different superscripts within the same row are significantly (P<0.05) different.
DT_1: Non-induced given water and feeds only (Positive control); DT_2: Non-induced given water, feeds and OF extract (Positive control).
DT_3: Non-induced given water, feeds and OF-AgNPs (Positive control); DT_4: Non-induced given water, feeds and OF-AuNPs (Positive control).
DT_5: Diabetic-induced rats, given water and feeds (non-treated negative control); DT_6: Diabetic-induced rats, given water, feeds and OF-AgNPs
DT_7: Diabetic-induced rats, given water, feeds and OF-AuNPs ; DT_8: Diabetic-induced rats, given water, feeds and OF extract
DT_9: Diabetic-induced rats given water, feeds and Glibeclamide

It causes a selective cytotoxicity effect on the pancreas leading to damage of pancreatic beta cells and consequently hindering the synthesis of insulin.[24] Streptozotocin-induced diabetic animals show symptoms of increased water intake, polyuria, dehydration, excessive hair loss, weight loss, muscle wasting, diarrhea, cataracts, and increased food intake like diabetic human patients.[25,26] The disruption of β-cells by diabetes eventually leads to physico-metabolic abnormalities, such as a decrease in body weight gain, and an increase in food and water intake.[27,28]

Levels of Fasting Blood Sugar (FBS) in Rats

Levels of FBS in treated and untreated diabetic rats are presented in Table 3. The untreated diabetic group (DT5) shows a significant (P<0.05) elevation of the FBS level when compared with the normal control group from the second week of the experiment. The treatment of diabetic animals with OFI-AgNPs and the OFI extract (DT6 and DT8) prompted a sharp decrease in FBS levels by the second week. The treatment of diabetic rats with OFI-AuNPs (DT7) was not effective as observed for DT6 and DT7. The influence of both the OFI-AgNPs and the OFI extract on blood sugar reduction is comparable with Glibenclamide. Reports are available on green synthesized nanoparticles with their *in vitro* anti-diabetic activities.[29,30]. The effect of the biosynthesized OFI-AgNPs, OFI-AuNps, and aqueous extract of *Opuntia ficus indica* was evaluated *in vivo* using streptozotocin-induced diabetic rats. The administration of the biosynthesized OFI-AgNPs and OFI-AuNPs and OFI extract lowered the blood glucose level in diabetic rats. The excessive-high blood glucose of the diabetic rats was significantly reduced in OFI-AgNPs and OFI extract which suggests their insulin stimulatory effects which may be due to partial regeneration of the pancreatic β-cell.[28,31] The reduction in the blood glucose level of treated diabetic rats attested to a corrective measure orchestrated by the administration of OFI-AgNPs and OFI extract. The partial protection of animals from a decreased body weight of the treated diabetic rats with OFI-AgNPs and OFI extract could be due to improved glucose utilization and subsequently decreased glycogen, protein degradations, and muscle wasting.[32] These effects could be credited to improved glucose usage in the body, as evidenced by the decrease of fasting blood sugar, which retreated the weight loss by structural protein degradation.

The liver and kidney antioxidant enzymes activities and other oxidative stress markers in diabetic rats

Antioxidant activities of the liver and kidney were determined by evaluating the activities of catalase (CAT), glutathione peroxidase (GPx), glutathione-s-transferase (GST), and superoxide dismutase (SOD) in the liver (Figures 1 a, b, c, and d) and kidney (Figures 2 a,b,c, and d).

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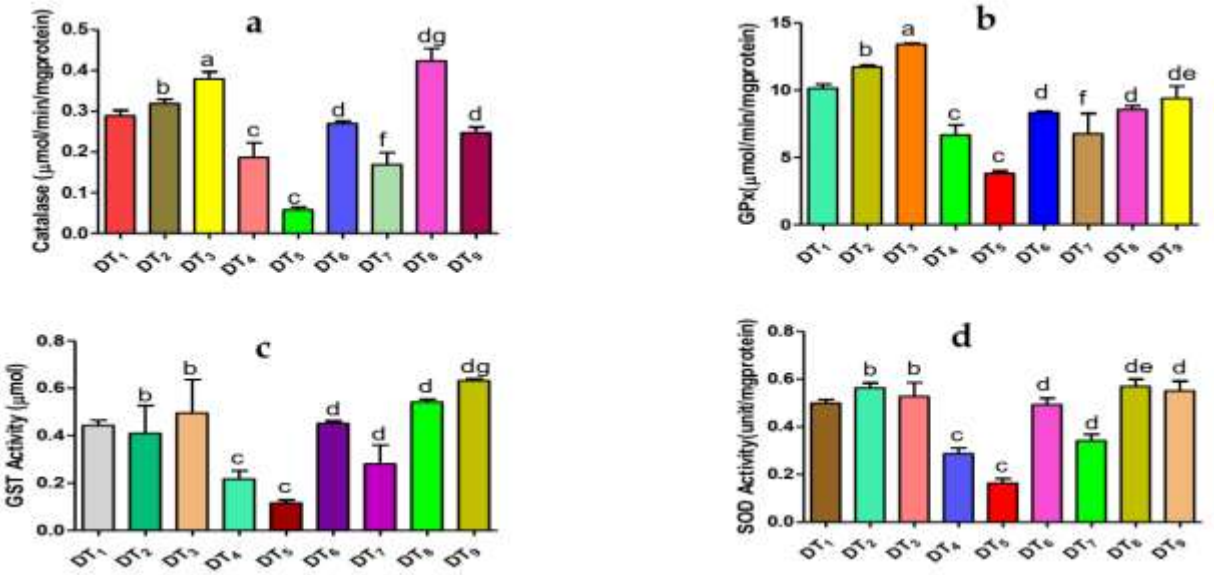

Figure 1: Enzymes [CAT (a), GPX (b), GST (c) and SOD (d)] activities in liver of rats treated with AgNPs, AuNPs and OFI extract.

a Level of significance was taken at P<0.05 for six rats per group.
'a' signifies significant(P<0.05) increase when compared with control group
'b' signifies no significant increase when compared with control group.
'c' signifies significant(P<0.05) decrease when compared with control group
'd' signifies significant (P<0.05) increase when compared with diabetes only group.
'f' signifies no significant increase when compared with diabetes only group
'g' signifies significant increase when compared to Diab.+ AgNPs, Diab.+ AuNPs and Diab.+ Glib. group

b Level of significance was taken at P<0.05 for six rats per group.
'a'signifies significant increase at P<0.05 when compared with control group
'b' signifies no significant increase when compared with control group.
'c' signifies significant (P<0.05) decrease when compared with control group
'd'signifies significant (P<0.05) increase when compared with diabetes only group.
'e' signifies no significant increase when compared with Diab.+ AgNPs, Diab.+ AuNPs and Diab.+ Ext. group
'f' signifies no significant increase when compared with diabetes only group

c Level of significance was taken at P<0.05 for six rats per group.
'b'signifies no significant increase when compared with control group.
'c' signifies significant (P<0.05) decrease when compared with control group.
'd' signifies significant (P<0.05) increase when compared with diabetes only group.
'f' signifies s no significant increase when compared with diabetes only group
'g' signifies significant (P<0.05) increase when compared with Diab.+ AgNPs and Diab.+ AuNPs.

d Level of significance was taken at P<0.05 for six rats per group.
'b' signifies no significant increase when compared with control group.
'c' signifies significant (P<0.05) decrease when compared with control group.
'd' signifies significant (P<0.05) increase when compared with diabetes only group.
'e' signifies no significant increase when compared with Diab.+ AgNPs and Diab.+ Glib.group.

The induction of diabetes caused a significant (P<0.05) decrease in the activities of all antioxidant enzymes in both the liver and the kidney. The treatment of diabetic rats with the OFI-AgNPs and the extract consistently ameliorated the activities of the deranged enzyme better than the OFI-AuNPs treatment. The reversed activities of both OFI extract (DT8) and OFI-AgNPs (DT6) on the effects of STZ-induced diabetes can well be compared with the effect of the standard drug group (DT9). Reduced Glutathione (GSH) and the Malondialdehyde (MDA) of the Liver (Figures 3 a and b) and Kidney (Figures 3 a and b) are the markers of oxidative stress. The GSH level of the untreated diabetic group (DT_5) showed a significant (P<0.05) reduction while significant MDA levels were observed when compared with the normal control group. Application of OFI-AgNPs, OFI-AuNPs, OFI extract, and standard drugs (DT_6, DT_7, DT_8, and DT_9) significantly increased reduced GSH levels and decreased elevated MDA levels. Overall, the order of the activity follows; OFI-AgNPs (DT_6) > OFI extract (DT_8) > Glibenclamide (DT_9) > OFI-AuNPs (DT_9). Persistent high blood glucose is toxic to macrovascular and microvascular systems a condition termed glucotoxicity. Glucotoxicity contributes to the release of radicals that overwhelm the inbuilt antioxidant defense system leading to oxidative stress in diabetic conditions.[33] Oxidative stress has been shown to play a major role in the etiology of diabetic complications.[34] Antioxidant enzymes such as GST, CAT, GPx, SOD, and other oxidative stress markers like GSH and MDA are known to be altered during diabetes.[34] The decreased activities of enzymatic and non-enzymatic antioxidant and significantly high level of lipid oxidation product (MDA) in untreated diabetic rats observed in this study is consistent with that reported in the previous studies.[35] The ability of the OFI-AgNPs and the OFI extract in ameliorating the effect of diabetes on these biomarkers shows that they can be used as antidiabetic agents. The elevated oxidation in diabetic rats caused a significant (P<0.05) reduction in the level of catalase, GPx, GST, and superoxide dismutase enzymes, which are responsible for scavenging free radicals in the diabetes disease state.[36]

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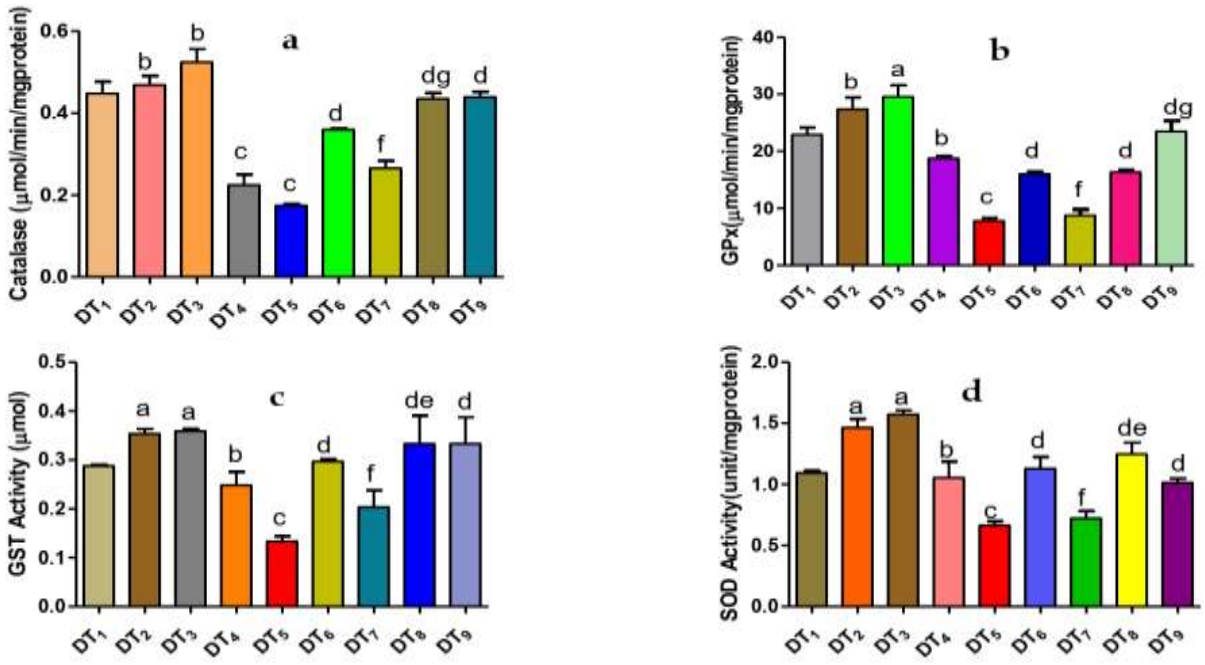

Figure 2: Enzymes [CAT (a), GPX (b), GST (c) and SOD (d)] activities in kidney of rats treated with AgNPs, AuNPs and OFI extract.

a Level of significance was taken at P<0.05 for six rats per group.
b. Represents no significant increase when compared with control group.
c. Represents significant (P<0.05) decrease when compared with control group.
d. Represents significant (P<0.05) increase when compared with diabetes only group.
f. Represents no significant increase when compared with diabetes only group.
g. Represents significant (P<0.05) increase when compared with Diab.+ AgNPs and Diab.+ AuNPs.

b Level of significance was taken at P<0.05 for six rats per group.
'a' signifies significant (P<0.05) increase when compared with control group
'b' signifies no significant increase when compared with control group.
'c' signifies significant (P<0.05) decrease when compared with control group
'd' signifies significant (P<0.05) increase when compared with diabetes only group.
'e' signifies no significant increase when compared with Diab. + Ext.
'f' signifies no significant increase when compared with diabetes only group
'g' signifies significant(P<0.05) increase when compared withDiab.+AgNPs, Diab + AuNPs and Diab.+ Extract group.

c Level of significance was taken at P<0.05 for six rats animals per group.
'a' signifies significant (P<0.05) increase when compared with control group
'b' signifies no significant increase when compared with control group.
'c' signifies significant (P<0.05) decrease when compared with control group
'd' signifies significant (P<0.05) increase when compared with diabetes only group.
'e' signifies no significant increase when compared with Diab.+AgNPs and Diab. + Glib.
'f' signifies no significant increase when compared with diabetes only group

d Level of significance was taken at P<0.05 for six rats per group.
'a' signifies significant (P<0.05) increase when compared with control group
'b' signifies no significant increase when compared with control group.
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'd' signifiessignificant (P<0.05) increase when compared with diabetes only group.
'e' signifies no significant increase when compared with Diab.+ AgNPs and Diab. +Glib.
'f' signifiess no significant increase when compared with diabetes only group

Diabetes mellitus is linked with oxidative stress. However, this resulted in a reduction of the enzymatic and non-enzymatic antioxidant defense system activities. The *in vivo* antioxidant defense parameters examined in this study are catalase, GPx, GST and superoxide dismutase, MDA, and GSH. SOD protects tissues against oxidative damage as a result of reactive oxygen species (ROS) by converting superoxide radicals into molecular oxygen and hydrogen peroxide. [37] Catalase breakdown hydrogen peroxide and safeguards tissues from highly reactive hydroxyl radicals.[38] MDA is the major oxidative product of lipid peroxidation. Determination of serum thiobarbituric acid reactive substances (TBARS) was utilized as a sign of lipid peroxidation and it helps to determine the extent of tissue damage.[39] Several studies have revealed an elevation of TBARS and hydroperoxides in the liver and kidney of experimental diabetes mellitus.[38] In this research, the elevated MDA content in diabetic rats was significantly lowered by the administration of biosynthesized OFI-AgNPs and OFI extract for 28 days. The observed reduction in the MDA content of the treated diabetic rats could be a result of the antioxidant potential of the biosynthesized OFI-AgNPs and OFI extract.

GSH, a tripeptide non-enzymatic antioxidant presents in the liver, eliminates free radical species such as hydrogen peroxide, superoxide radical, and thus sustaining membrane protein thiols. GSH scavenges the free radicals as well as a co-substrate for peroxide detoxification by glutathione Peroxidase (GPx).[26,39] In a diabetic condition, the plasma and tissues decline GSH concentration due to increased utilization caused by oxidative stress,[40] which was observed in the current study. The administration of OFI-AgNPs and OFI extract significantly ($P< 0.05$) elevate the GSH and its associated enzyme in diabetic rats. This implies that the OFI-AgNPS and OFI extract can regulate the redox status of the membrane protein thiols.[37] Anomalies in lipid profiles are common impediments in diabetes mellitus. Such abnormality characterizes the risk factors for coronary heart diseases.[41] Stimulation of hormone-sensitive lipase during insulin shortage causes an increase in free fatty acid mobilization from adipose tissue. [42] The outcome of this research work displayed the potential of OFI-AgNPs and OFI extract in reducing oxidative stress due to high levels of antioxidants. Kidney and liver tissue could be protected from oxidative stress damage with the capability of OFI-AgNPs and OFI extract by quenching free radicals inside cells.

OFI-AgNPs and OFI extract showed compelling protective potential against diabetes complications. The ability of these agents may be linked to the reduction of oxidative stress occasioned by persistent high blood sugar levels in diabetic rats

Conclusion

The nanoparticles with outstanding antioxidant and antidiabetic properties could make *O. ficus indica* extract to be used in nanodrug formulation for the treatment of diabetes and different medical purposes due to its ability to protect tissues against oxidative stress and glycemic properties.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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