

Facile green synthesis of Silver nanoparticles using ventilago maderaspatana leaf extract, physicochemical properties and evaluation of antidiabetic potential against streptozotocin induced diabetic albino rats

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Abstract

The Silver nanoparticles (NPs) had been bio-synthesized using *Ventilago maderaspatana* leaf extract. The chemical and physical properties of the biosynthesized Silver NPs had been analyzed by XRD, FE-SEM, TEM, EDAX, FTIR and UV – visible absorption. The diffraction pattern confirmed the cubic structure of the synthesized NPs. The average crystallite size had been calculated by the Debye Scherrer's method and W-H plot as 11.7 and 9.3 nm, respectively. The FESEM and TEM images confirmed the sized distribution around this range. The antidiabetic efficiency of the biosynthesized Silver NPs were assessed in a group of rats for 10 mg/ kg b.w and 20 mg/kg b.w. Injection of streptozotocin in experimental rat showed elevated level of biochemical parameters such as serum blood glucose, total protein, albumin and HbA1c. Meanwhile, serum insulin (2.50 ± 0.55) and activity of glucokinase (64.50 ± 8.66) levels were diminished. Treatment with silver nanoparticles decreased levels blood glucose, total protein, albumin and HbA1c to normal in dose dependent manner. On the other hand, insulin level (7.55 ± 0.63) and activity of glucokinase (121.50 ± 4.60) level were increased. It was due to the antidiabetic potential of *V. maderaspatana* mediated silver nanoparticles.

1 Introduction

Diabetes mellitus is a metabolic disorder caused by the insulin deficiency or inefficiency of insulin usage by the body. Diabetes is one of the top five causes of death worldwide. Uncontrolled diabetes damages vital organs, including the kidneys, eyes, liver, heart, nerves and blood vessels, over time. These complications can result in death [1, 2]. Diabetes currently affects more than 150 million people worldwide, and this figure is expected to double in the next 20 years [3]. According to the latest report of International Diabetic Federation (IDF), 592 million people will be affected in next 25 years [4].

Diabetes mellitus can be treated with drugs such as biguanides sulphonyl ureas, alpha-glucosidase inhibitors (acarbose, miglitol), and thiazolidinediones, insulin, etc. However, they have undesirable side effects like hypoglycemia and/or gastrointestinal complications due to drug toxicity [5]. As a result, the researcher around the world are working on new therapeutic method and new drugs with less side effects [6]. The biocompatibility of nanomedicine drew a lot of attention from the research community. Biocompatible nanomaterials have been extensively researched for biomedical applications such as antidiabetic, anticancer, antimicrobial, antioxidants, wound healing, bioimaging, and so on. [7–9]. In this regard, the metal and metal oxide nanoparticles such as silver, gold, copper, CuO, TiO₂, ZnO, etc. have been extensively studied due to their potential biomedical applications with less side effects [5, 10–14]. Amongst others, the silver nanoparticles have been extensively investigated because of their superior physical, chemical and biological properties [15–18]. The higher degree of biocompatibility of Silver than conventional medicines makes them a suitable candidate material for therapeutic application, diagnosis and bio-imaging.

A number of chemical and physical synthesis process had been used to synthesis the silver nanoparticles [19]. But the traditional synthesis methods includes the usage of hazardous chemicals and cost of production is high. Green synthesis of nanoparticles is currently a focused area of research in order to obtain biocompatible nanomaterial at a low cost without hazardous wastage [20–23]. The synthesis of NPs using plant extracts is most promising because of its low cost and environmental friendliness, which opens up significant opportunities in green chemistry [24]. Bio macromolecules/phytochemicals derived from the extracts of plant have been continued, because of their antibiotic, antitumor, and anthelmintic properties. The plant extracts also lessens the use of hazardous chemicals, works as a potential stabilizer and capping agent in the synthesis of NPs[25, 26]. *Ventilago maderaspatana* is

traditional medicinal plant used to treat the various diseases, including diabetes. Thus the present study focused on evaluating antidiabetic activity of bio-synthesized silver nanoparticles derived using *Ventilago maderaspatana* leaf against streptozotocin induced diabetic albino rats.

2 Materials And Methods

2.1 Materials

Medicinal plant *V. maderaspatana* was derived from Kolli Hills, Namakkal, Tamil Nadu, India and the collected plant was authenticated as *V. maderaspatana* (Gaertn.) belonging to the family Rhamnaceae by Department of Botany, St. Joseph College, Trichy, Tamil Nadu (Specimen access No. SJCBT2112). The leaves of the *V. maderaspatana* were collected, shade-dried, and powdered. Using this powder, extracts were prepared by Soxhlet extraction method using ethyl acetate solvent and stored at 4°C for further study.

2.2 Preparation of Silver nanoparticles

Biological mediated silver nanoparticle was synthesized using *V. maderaspatana* leaf ethyl acetate extract. The required amount of silver nitrate was dissolved in double distilled water. Then, the 10 ml of ethanolic extract of *V. maderaspatana* leaves was added slowly to 90 ml of silver nitrate solution under continuous stirring for 30 minutes. While the temperature of the reaction mixture was maintained at 50°C. This mixture incubated in dark place at room temperature for 24 hrs. The white color silver nitrate solution changed to brown indicated formation of silver nanoparticles. This colour change confirmed the reduction of silver nanoparticles [27, 28]. The reduction of silver nitrate is due to the antioxidant metabolites like phenolics, flavonoids etc. present in the plant extract[29, 30].

2.5 Characterization of nanoparticles

The XRD (Rigaku Ultimalll) analysis was carried out to confirm the polymeric nature of Silver NPs. FT-IR spectroscopy was used to investigate the presence of functional groups and the type of bonds in the NPs (Model: Perkin Elmer, Make: Spectrum RX I). The surface morphology of the synthesized NPs has been assessed by FE-SEM (Carl Zeiss Ultra 55 FESEM) micrographs with EDX (model: Inca). Transmission Electron Microscopy (TEM) (JEOLJEM-2010UHR) was used to analyze the size and morphology of the NPs. The spectral absorption was measured with a UV-Visible Spectrometer (Model: lambda 35, Make: Perkin Elmer) in the wavelength range of 300 to 600 nm.

2.6. Antidibetic activity

2.6.1. Experimental animals

Healthy adult male Wistar albino rats (*Rattus norvegicus*) with a body weights in the range of 150 to 200 g have been used as the test model for the present study. The rats were procured from Tamilnadu Veterinary and Animal Science University, Chennai and kept in controlled conditions. The rats have been grouped into control and experimental groups and kept in various plastic cages (Tarsons made 43 x 27 x 15cm cages). The rats were fed with standard pellet feed (Sai Durga Feeds and Foods, Bangalore) and provided water ad libitum. During the experimental period, the standards of animal care were followed, and the Institutional Animal Ethical Committee gave its approval to the experimental protocols used in this study (Ethical Committee's Approval No. BDU/IAEC/2014/NE/31/).

2.6.2. Induction of diabetes

Diabetes mellitus was induced in overnight fasted albino rats by a single intraperitoneal injection of streptozotocin (50 mg/kg body weight in double distilled water) [31, 32]. By measuring the blood glucose level only 48 hours after streptozotocin injection, the diabetes in streptozotocin-induced rats was assessed. The rats with fasting blood glucose level more than 250 mg/dl were considered as diabetic [31].

2.6.3. Experimental protocol

After being given a 12-hour fast, the male albino rats had been divided into five groups of six rats, and each group was subsequently housed in its own cage. Group I was treated as the control group (non-diabetic rats). A single intraperitoneal injection of STZ was used to induce diabetes in rats from groups II, III, IV and V. Group II rats were employed as the diabetic control group (Hyperlipidemic control). 10 mg/kg b.w and 20 mg/kg b.w of Ag NPs were administered to rats in Groups III and IV, respectively. On the other hand, the group V rats were treated with Standard drug (glibenclamide). The duration of treatment was extended to 30 days. The body weights, water intake and food consumption of both the control and experimental rats were monitored daily in the morning. Rats were sacrificed after 30 days, and their blood was obtained via cardiac punching; the serum was then separated and used in biochemical analysis. The antidiabetic activity have been assessed by examining abnormalities in the serum blood glucose levels, glycosylated haemoglobin levels, serum insulin levels, serum total protein, serum albumin and liver glucokinase level in the experimental diabetic rats.

Week wise blood glucose level was estimated early morning using Accu-Chek Active glucometer at one week interval. Serum blood glucose level, glycosylated haemoglobin (HbA1c), serum total protein, serum albumin, liver glucokinase level and serum insulin were analyzed for estimation of antidiabetic activity. Above mentioned parameters except insulin were analysed using Semi-Automatic Auto analyzer (Star 21plus, Manufactured by Aspen Diagnostics Pvt., Ltd., New Delhi) and insulin was analyzed using CLIA (Chemiluminescence Immune Assay) kit (Science Medical solutions Diagnostics Ltd., USA) using Centaur Immuno Assay Instrument, USA. Vital organ pancreas was removed and stored in normal saline for histological examinations.

2.9. STATISTICAL ANALYSIS

The parameters were statistically analysed using the SPSS statistical package (Version. 21). The results were expressed as mean $\pm$ SD. One-way Analysis of Variances (ANOVA) and SNK post hoc test were made for examining the influence of treatment of *V. maderaspatana* mediated silver nanoparticles on diabetic rat models[33].

3 Results And Discussion

3.1 X-ray diffraction analysis (XRD)

Figure 1a shows the X-ray diffraction pattern of Silver NPs. The structure, phase purity and crystallite size of the bio synthesized Silver NPs have been analyzed using diffraction pattern. The sharp diffraction peaks at the diffraction angle of 38.23°, 44.38°, 64.56° and 77.57° are corresponding to the (111), (200), (220) and (311) planes of face-centered cubic (FCC) Silver NPs, respectively (JCPDS card No.: 87-0720) [34]. These results were consistent with the earlier work done by the various authors[34, 35]. There is no extra peaks related to the impurity phases in the XRD pattern and this implies the phase purity of the bio-synthesized Silver NPs.

The Debye Scherrer's formula is used to calculate the average crystallite size of the synthesized Silver NPs [36]. The calculated average crystallite size of the bio-synthesized Silver NPs is found to be 11.7 nm and the lattice parameter has been calculated as 4.0768 Å. The Williamson and Hall (W-H) plot is plotted between the 4sin θ and

$\beta\cos\theta$ as shown in Fig. 1b. The average crystallite size has been calculated from intercept as 9.3 nm using W-H plot[11]. The negative strain ($\epsilon = -2.5 \times 10^{-3}$) is because of the lattice compression of the Silver NPs.

3.2. Morphological and compositional analysis

The FESEM and TEM micrographs have been used to analyze the morphological characteristics and size distribution of the synthesized Silver NPs as shown in the Fig. 2a and c, respectively. The morphological characterization of Silver NPs made clear that the particles were in spherical shape and size was around the range of 6–15 nm (Fig. 2d). The chemical purity and elemental compositions of Silver NPs have been verified by EDX spectrum as seen in Fig. 2b.

3.3. FTIR analysis

The infra-red absorption studies disclose the existence of various functional groups and bonding structures in the synthesized NPs. FT-IR spectra of Silver NPs revealed the IR absorptions of hydroxyl and carboxyl functional groups (Fig. 3). The broad absorption bands at 3632 and 1636 cm^{-1} correspond to the stretching and bending vibrations of hydroxyl molecules which exist in the Silver NPs, respectively [36]. A weak absorption and a sharp absorption are noticed at 2068 and 1379 cm^{-1} analogous to the carboxyl group [37]. The strong absorption 800 to 400 cm^{-1} indicates the formation of Silver-Silver framework[38].

3.4. Optical absorption properties

The UV-visible spectra of bio-synthesized Silver NPs is shown in Fig. 4a. The absorption covers the entire visible region and the absorption is maximum at 434 nm . The absorption spectrum is very consistent with earlier works and it confirms synthesis of Silver NPs[39, 40]. The broad absorptions is because of the nano sized particles. The absorption of nanoparticles is expected to be affected by a number of factors, including band gap, defects, and impurity centres.

The Tauc's relation is used to calculate the optical band gap [11]:

$$h\nu = A(h\nu - E_g)^n \quad (5)$$

where A and E_g are the constant and band gap, respectively. The exponent n is determined by the type of transition, and in this case, n is set to $\frac{1}{2}$ for direct allowed transition. The Tauc's plot is plotted to find the optical band gap of the material as seen in Fig. 4b. The band gap value is obtained by extrapolating a straight line to the x-axis. The optical band gap of the biosynthesized nanoparticle is 2.36 eV .

3.5. ANTIDIABETIC ACTIVITY

Streptozotocin (STZ) is anticancer agent that produces diabetes mellitus by destroying selectively pancreatic β -cells[41]. The present study focused on post intraperitoneal injection of STZ in experimental rats induced diabetes by destruction of pancreatic beta cells. It was confirmed by elevated level of blood glucose and wane of serum insulin level. It was due to the cellular metabolic oxidative mechanisms of streptozotocin[42]. Blood glucose level was hiked (326.00 ± 16.06) in diabetic control rats throughout experimental period due to the impact of STZ. This increased blood glucose level could be due to glycogenolysis or glyconeogenesis. Zhang et al. also discovered an increase in glucose levels in the urine of STZ-induced diabetic rats due to gluconeogenesis and glycogenolysis [43]. Blood glucose levels began to fall after the treatment with Silver NPs in the first week and normalized in the final week of treatment (Table 1 and Fig. 5). This is due to the antidiabetic activity of plant extract and plant mediated

silver nanoparticles. Serum blood glucose level have been found to be high in untreated diabetic rats (330.75 ± 24.49 mg/dl) and treatment of Silver NPs remarkably reduced near to the normal level (Table 2 and Fig. 6). It is due to the antidiabetic activity of biosynthesized Silver NPs and this result also was previously proved various authors[44–46].

Table 1

Effect of *V.maderapatana* mediated silver nanoparticles treatment on blood glucose level of STZ induced diabetic albino rats. Values within the parentheses are range of respective mean.

Blood Glucose mg/dl					
Groups	Week 1	Week 2	Week 3	Week 4	Week 5
Group I	102.25 ± 10.78	110.50 ± 13.48	105.75 ± 11.44	110.25 ± 9.18	104.00 ± 14.49
Group II	293.25 ± 21.72	320.25 ± 20.60	333.25 ± 8.42	327.00 ± 22.70	326.00 ± 16.06
Group III	288.25 ± 24.92^a	$266.25 \pm 10.24^{a,b}$	$244.50 \pm 12.68^{a,b,c}$	$153.75 \pm 11.62^{a,b}$	141.75 ± 12.07^b
Group IV	299.50 ± 14.53^a	$274.25 \pm 13.30^{a,b}$	$210.50 \pm 13.63^{a,b}$	$142.50 \pm 10.08^{a,b}$	133.50 ± 10.50^b
Group V	309.00 ± 21.94	263.50 ± 26.49	210.75 ± 21.93	138.50 ± 13.18	125.00 ± 5.72

Groups

Group I - Normal control

Group II – Diabetic control

Group III – Treated with 10mg/ kg b.w. of silver nanoparticles Group IV – Treated with 20mg/kg b.w. of silver nanoparticles

Group V – Treated with standard drug (Glibenclamide 5mg/kg b.w.)

a = $p < 0.05$ versus control rats

b = $p < 0.05$ versus diabetic control rats

c = $p < 0.05$ versus glibenclamide treated diabetic rats.

Table 2

Effect of *V.maderapatana* mediated silver nanoparticles treatment on biochemical parameters of STZ induced diabetic albino rats. Values within the parentheses are range of respective mean.

Groups	Blood glucose (mg/dl)	Serum Insulin (μIU/ml)	HbA1c (%)	Glucokinase	Total Protein (g/dl)	Albumin (g/dl)
Group I	112.00±12.24	8.2±0.70	7.30±1.44	120.00±49.13	8.83±0.79	8.23±0.79
Group II	330.75±24.49	2.5±0.55	13.8±1.80	64.50±8.66	24.23±1.35	19.23±1.50
Group III	154.25±7.59 ^{a,b,c}	4.7±0.62 ^{a,b,c}	10.0±0.74 ^{a,b}	89.75±7.89	16.53±1.62 ^{a,b,c}	14.70±2.22 ^{a,b,c}
Group IV	125.25±6.24 ^b	7.5±0.63 ^{a,b,c}	8.8±1.01 ^{a,b}	121.50±4.6 ^b	11.13±1.12 ^b	10.23±0.94 ^b
Group V	124.75±5.68	7.6±0.68	8.5±0.62	125.50±5.45	10.30±1.34	10.30±1.19

Groups

Group I - Normal control

Group II – Hyperlipidemic control

Group III – Treated with 10mg/ kg b.w. of silver nanoparticles Group IV – Treated with 20mg/kg b.w. of silver nanoparticles

Group V – Treated with standard drug (Glibenclamide 5mg/kg b.w.)

a = p<0.05 versus control rats

b = p<0.05 versus diabetic control rats

c = p<0.05 versus glibenclamide treated diabetic rats

Insulin level was statistically ($p < 0.05$) diminished in STZ-induced rats due to the selective destruction of pancreatic beta cells and it was recovered to normal after the treatment with Silver NPs (Table 2 and Fig. 6). It is due to the antidiabetic activity and partial regenerative properties of *V. maderapatana* and plant mediated Silver NPs. Oral administration of *P. sapota* leaf extract and its Silver NPs could be involved in the release of insulin from the beta cells as every bit, and resultant in significant rise in the level of insulin. It is believed that antioxidants in the leaf extract and plant mediate the mechanism of action, which results in curing the disease [44–46]. Daisy et al. found that dihydroxygymnemic triacetate increased insulin levels in diabetic rats by 50%, which could be attributed to the stimulation of insulin secretion from regenerated or residual B-cells [47]. Our results are very consistent with this finding.

Glycosylated haemoglobin (HbA1C) is used to assess the level of oxidative stress in diabetics [48]. Increased blood glucose levels stimulate non-enzymatic protein glycation, which can result in irreversible changes as seen in the characterization of glycosylated haemoglobin [49]. High content of HbA1c was observed in diabetic control group and reduced to normal level after the treatment with Silver NPs (Table 2 and Fig. 6). The elevated level of glycosylated haemoglobin in STZ-induced diabetic rats suggested a poor glycemic control mechanism due to the

impact of streptozotocin. STZ injection in normal rat destroyed the pancreatic beta cells effectively and reduced synthesis of insulin. It leads to the impaired glycemic mechanisms. In the current study, treatment with Silver NPs significantly reduced HbA1C levels in experimental rats. This is due to the good antidiabetic activity of plant extract and its silver nanoparticles. HbA1c levels were reduced during diabetes treatment, and microvascular complications were significantly reduced. Some authors reported that the treatment with Silver NPs reduced the HbA1c level and prevent the micro vascular complications [50].

Glucokinase (GK) activity was increased in Silver NPs treated groups compared to diabetic groups (Table 2 and Fig. 6). Low level of activity of glucokinase in diabetic control group indicating the GK gene expression may decrease due to the development of diabetes. After the treatment with Silver NPs and standard drug might be induce the expression of GK gene and it was regulate the activity of glucokinase. Therefore, GK gene is a strong marker for diabetic therapy[51]. Protein and albumin levels were increased in STZ-induced diabetic rats. Then, it was statistically ($p < 0.05$) declined to normal level by the treatment of Silver NPs (Table 2 and Fig. 6).

Histoarchitecture of Silver Nps treated pancreas, liver and kidney:

After treatment with Silver NPs, the damaged pancreatic tissues were partially restored. Furthermore, the Silver NPs preserved the islet cells with increased β cells (Fig. 7). This result was previously proved by many authors[27, 44, 52]. Histopathological analysis of Silver NPs used here may reduce the effect of inflammation, which is believed to be causative for insulin resistance [52]. This was similar to our results. Biologically synthesized Silver NPs effectively reduced blood glucose level, as well as increased pancreas function in animal models [27, 44].

4 Conclusion

In this study leaf extract of *Ventilago maderaspatana* possessed capacity to synthesis silver nanoparticles. The XRD pattern proven that the synthesized NPs were in FCC structure with phase purity. EDAX and FTIR spectra confirmed the chemical purity and the presence of various functional groups. The band gap of the Silver NPs had been found to be 2.36 eV and it was very consistent with the earlier results. The *V. maderapatana* mediated silver nanopartilces effectively reduce the blood glucose, glycosylated haemoglobin level total protein and albumin level, and also potentially increased the level of insulin, and glucokinase in streptozotocin induced diabetic rats. Hence, the bio-synthesized silver NPs using *V. maderaspatana* have been proposed as a potential biocompatible materials for the treatment of diabetics.

Declarations

Ethical Approval

Institutional Animal Ethical Committee gave its approval to the experimental protocols used in this study (Ethical Committee's Approval No. BDU/IAEC/2014/NE/31/)

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions:

P. Karuppannan: Validation, Formal analysis, Investigation; **Dr.K. Saravanan:** Supervision, Conceptualization, Investigation, Writing - Original Draft; **M. Ashokkumar:** Investigation, Writing - Original Draft; **Chukwaebuka Egbuna:** Formal analysis, Investigation

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

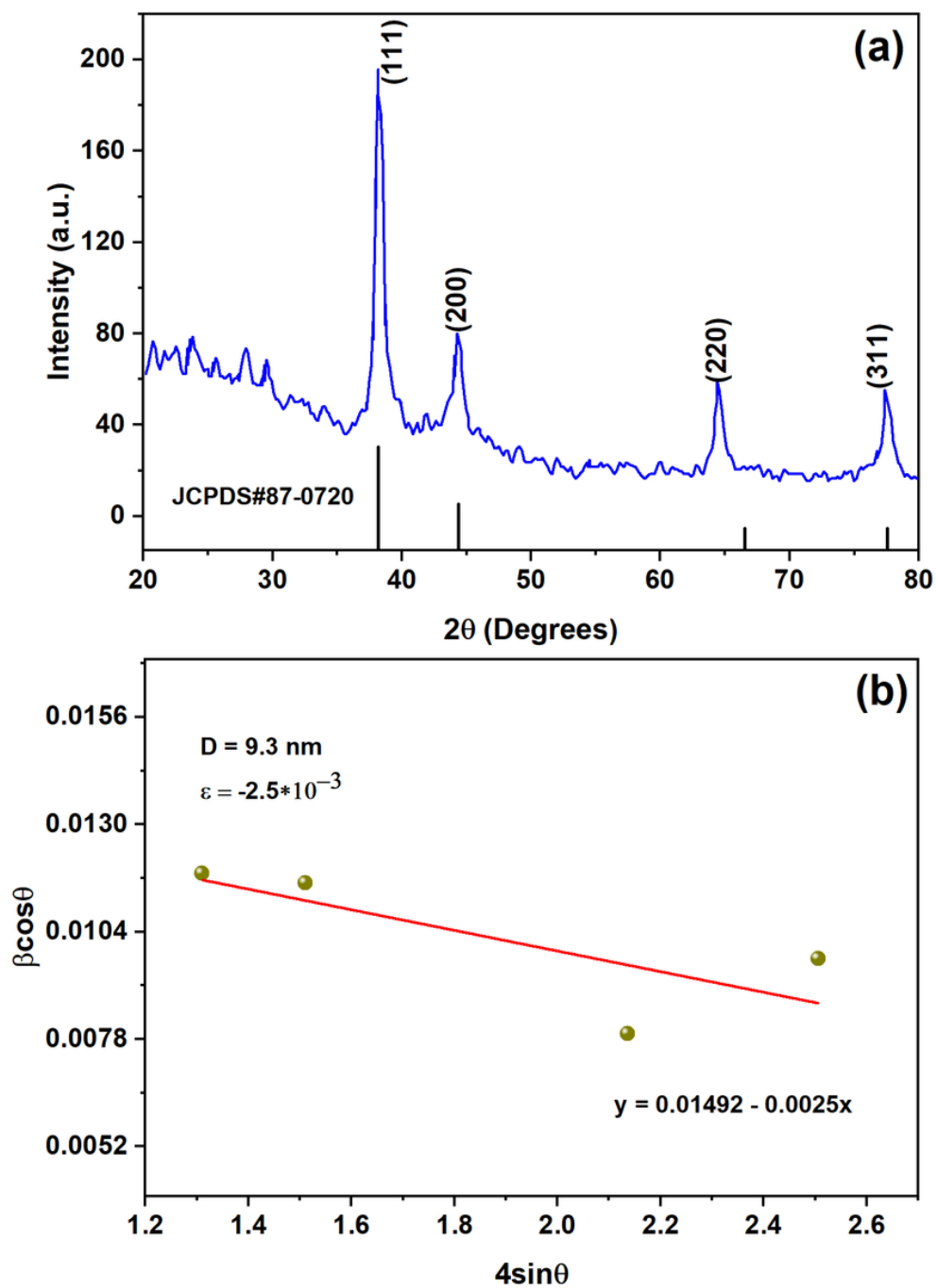


Figure 1

a) XRD pattern and b) W-H Plot of Silver NPs

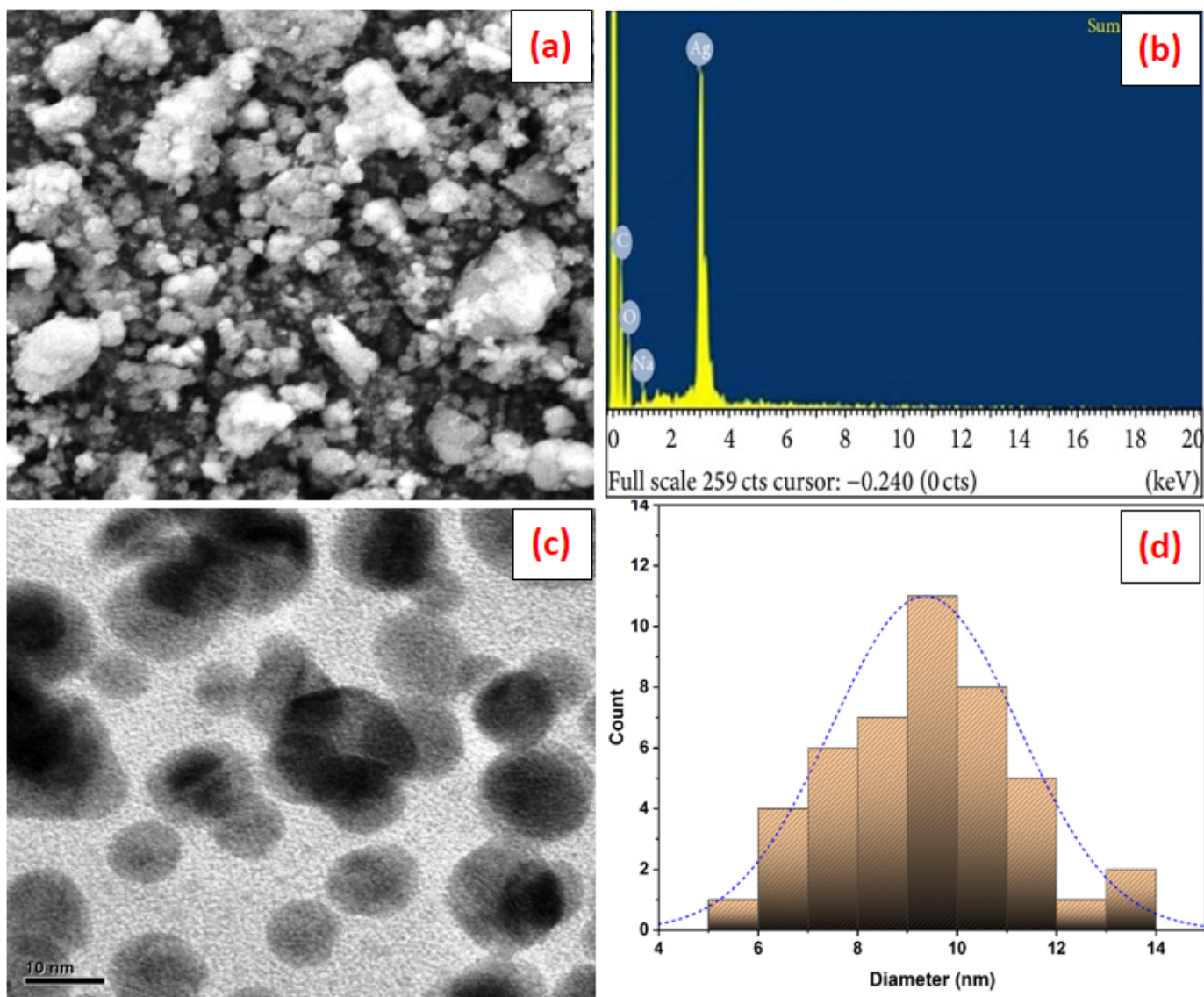


Figure 2

a) SEM, b) EDX, c) TEM and d) Particle size Histogram of Silver NPs

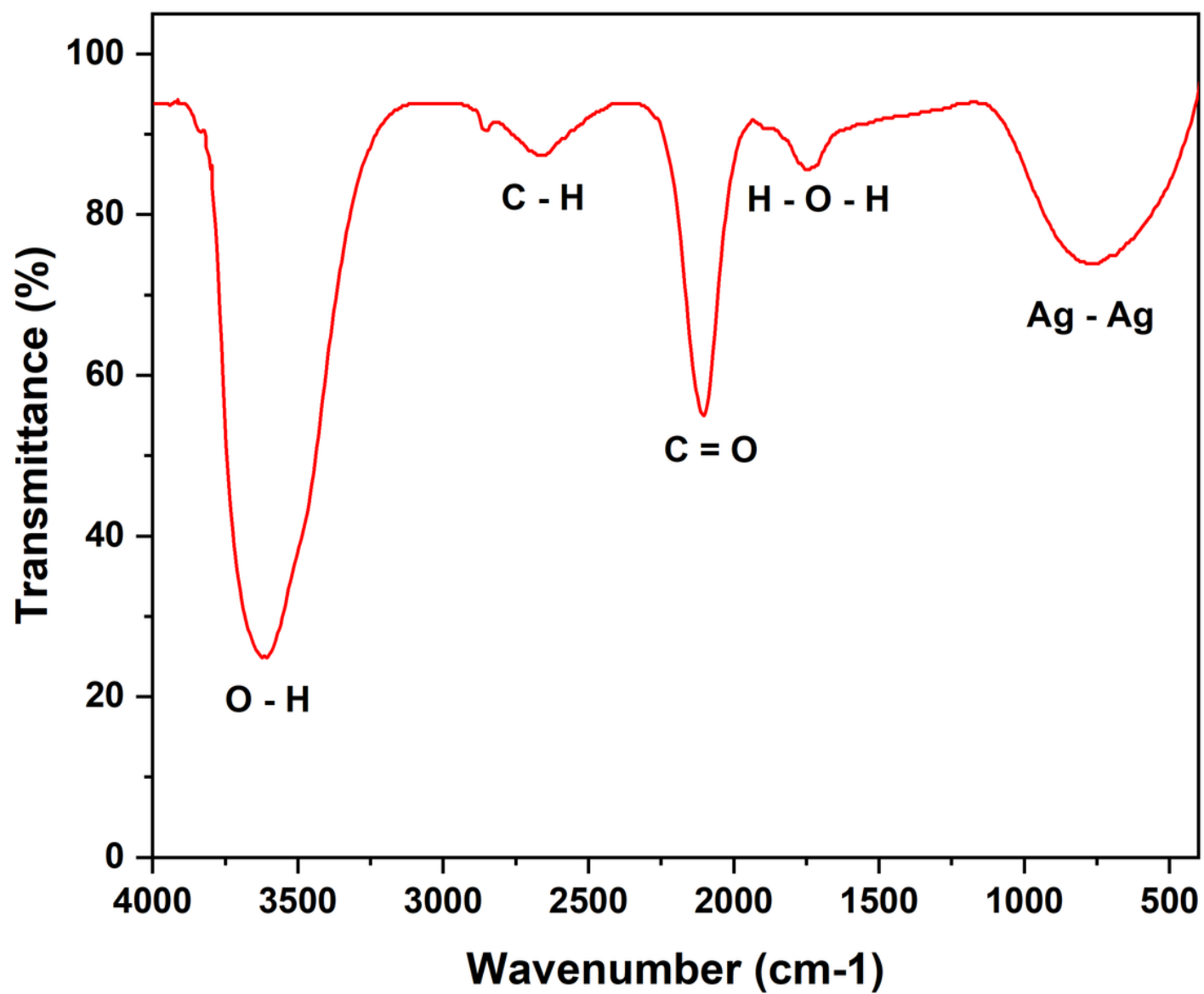


Figure 3

FT-IR spectrum of Silver NPs

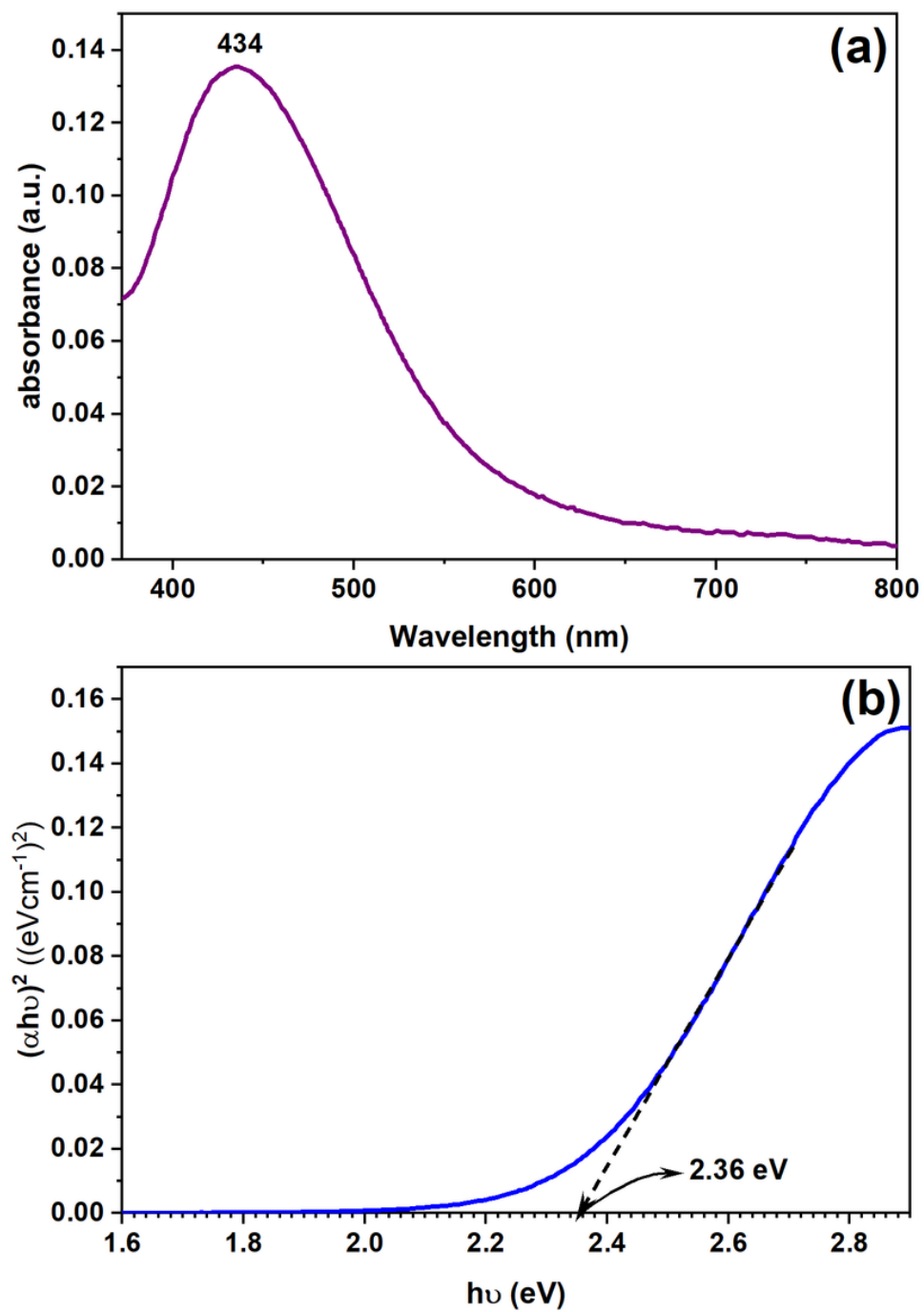


Figure 4

a) UV-Visible spectra and b) Tauc's Plot of silver NPs

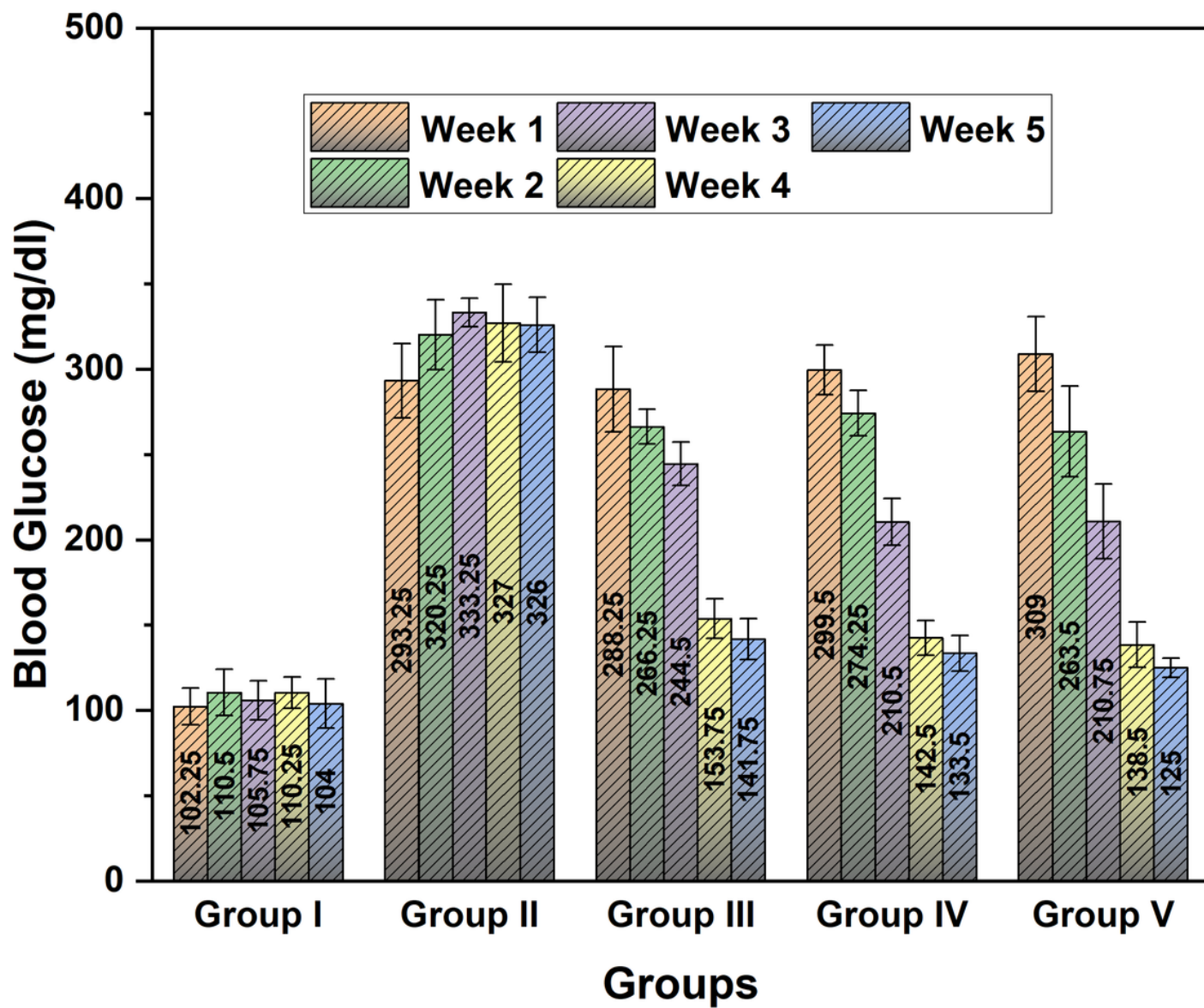


Figure 5

Week wise blood glucose level of *V. maderaspatana* mediated silver

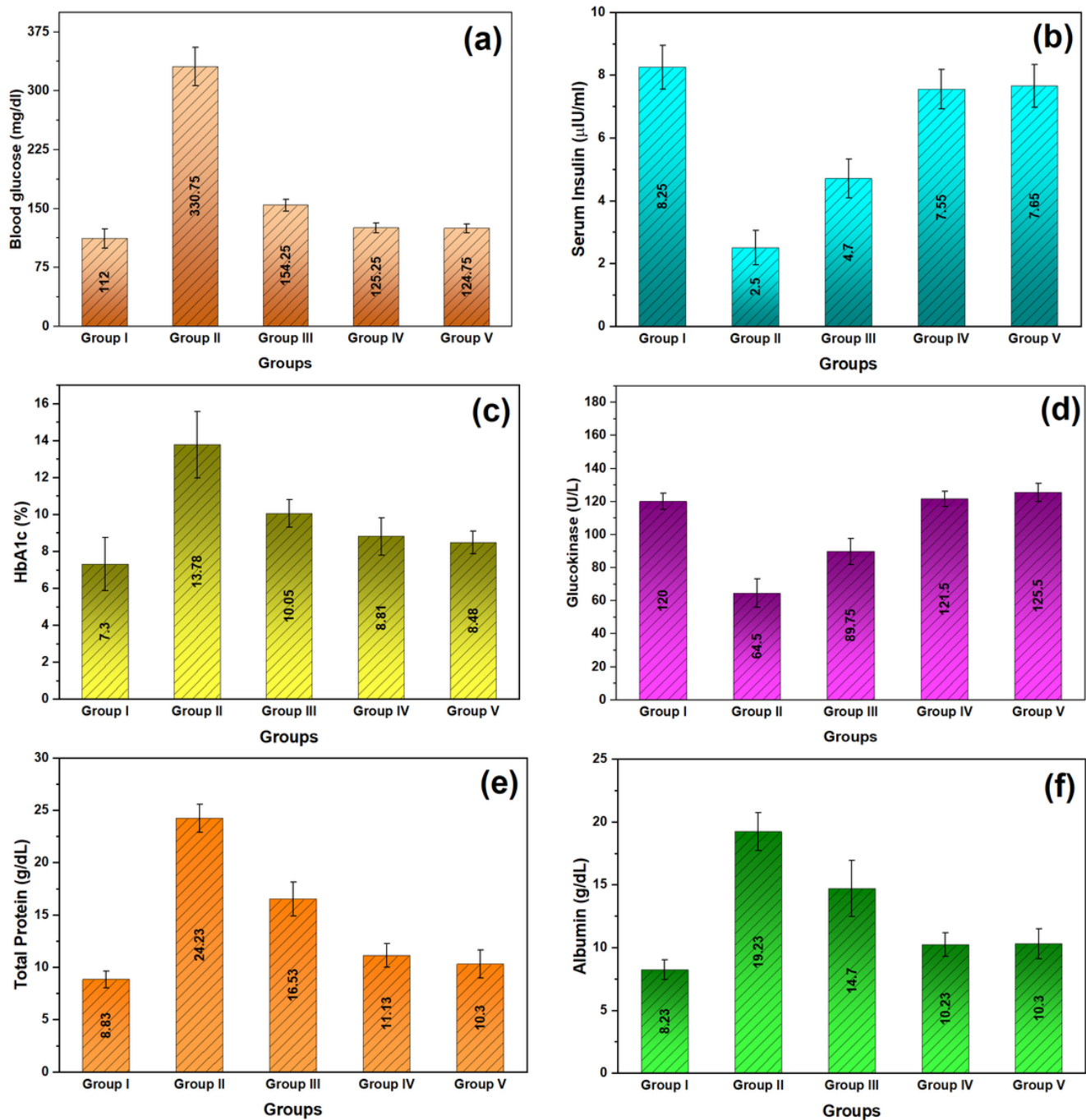


Figure 6

a) Glucose, b) Insulin, c) HbA1c, d) Glucokinase, e) Total protein and f) Albumin levels of Control rats, Diabetic control rats, Glibenclamide treated diabetic rats, Silver nanoparticles treated diabetic rats nanoparticles treated diabetic albino rats

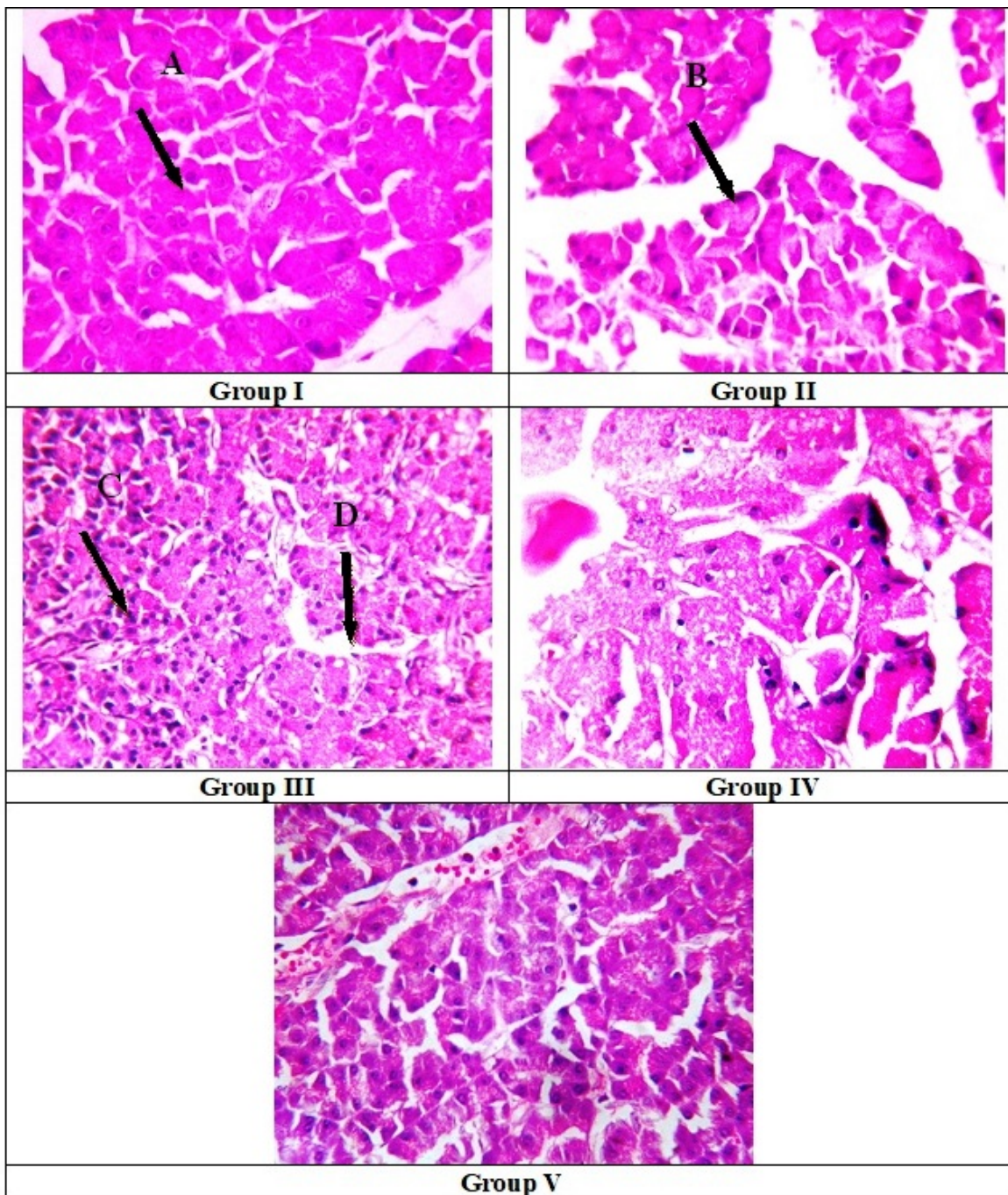


Figure 7

Effect of *V. maderapatana* mediated silver nanoparticle treatment on histoarchitecture of pancreas of STZ induced diabetic rats