INTRODUCTION

Diabetes mellitus has been implicated in the causes of morbidity and mortality worldwide. Its prevalence is increasing at an alarming rate with a global estimation of 463 million individual are diabetes in 2019, predicted to rise to 578million by 2030 and 700million by 2045. 

Diabetes mellitus refers to a group of metabolic disease characterized by chronic hyperglycemia with abnormalities in carbohydrate, fat and protein metabolism, primarily as a result of deficiency in insulin secretion from beta-cell of pancreas or ineffectiveness of insulin in target tissues (insulin action) or both leading to micro-vascular and macro-vascular complications such as retinopathy, neuropathy, nephropathy, myocardial infarction, heart failure and stroke. These metabolic derangements cause dyslipidemia which contribute to high cardiovascular disease risk.

Chronic hyperglycemia in diabetes mellitus induced oxidative stress which releases excessive free radicals from reactive oxygen species (ROS) and a diminution in antioxidant defense status. Alterations in endogenous antioxidant defense system by extreme free radicals cause oxidative damage and progression of diabetes mellitus-related complications. Intervention for prevention and treatment of diabetes is urgently needed.

Present conventional treatment for diabetes mellitus involves insulin therapy and oral synthetic antidiabetic drugs. However, most synthetic anti-diabetic drugs have their own limitations and deleterious side effects. Due to these toxicities, scientists’ attention has been focused on phyto-herbal medicine sources as alternative therapy for diabetes. Most of these plants contain classes of chemical compounds with hypoglycemic effect.

Anacardium occidentale Linn (family Anacardiaceae) alternatively known as cashew tree originated from Brazil. Different parts of this plant such as stem bark, fruits, and leaf extract are ethno-medicinally used for management of diseases such as diabetes, infection, diarrhea, hemorrhage, and as well as antimicrobial activity. Also, Anacardium occidentale nut has been reported to attenuate dyslipidemia in rats. Phytochemical analysis of this plant revealed the presences of high levels of secondary metabolites such as tannins, flavonoids, phenols, saponins, and alkaloids, as well as derivatives such as anacardic acid, which are used as raw...
material for herbal medicines formulation. There has been experimental report on the hypoglycemic activity of *Anacardium occidentale* leaf, stem bark, and nut extracts separately. Nevertheless, none of these data validate the specific efficacious part of *Anacardium occidentale* plant for diabetes therapy. This study therefore investigated the antidiabetic comparative effects of *Anacardium occidentale* methanolic leaf, stem bark and nut extracts.

**MATERIALS AND METHODS**

**Drugs and Chemicals:** Glimepiride (GMP), Streptozotocin (STZ), Ketamin and Xylazine.

**Plant Materials Collection**

Fresh nut, leaves and stem bark of *Anacardium occidentale* were harvested from Agricultural Science Plant Research Farm, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria. The plant was identified, authenticated and assigned a voucher specimen number LH0533 by Dr. A. T. J. Ogunkunle at Biology Department Laboratory of the institution.

**Extraction of the Plant Materials**

*Anacardium occidentale* leaves, stem bark and nuts were thoroughly washed. The leaves was air-dried at room temperature, while the nut and stem bark were sun-dried. The outer coated layer of the nut was removed to obtain the pure plant nut. The leaves, stem bark and nut were separately ground into fine powder forms using electric blender and stored in air-tight container. 500g of each fine powder forms were also extracted separately in a Soxhlet apparatus with a methanol solvent (95%). The extracts were concentrated using rotary evaporator under reduced pressure and the dried methanolic extracts obtained were kept in air-tight container at 4°C until used.

**Experimental Animals**

Ninety (90) adult male Wistar rats weighing (200±20g) were used and obtained from Physiology Department Research Animal Breeding House, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria. The animals were housed in a plastic cage (10rats/cage) and acclimatized for 14 days under free-pathogen environment at constant room temperature of (25 ±2°C), relative humidity (45±5%) and natural 12:12hours light/dark cycle with free access to commercial rat pellet feed and water *ad libitum*. All experimental procedures and handling of animals were performed according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals for Biomedical Research and were approved by the Institutional Animals Care and Use Committee of Ladoke Akintola University of Technology.

**Experimental Diabetes Induction**

The rats were fasted overnight (12hrs fasting) on the last day of acclimatization prior to diabetes induction. A single dose of freshly prepared streptozotocin (50mg/kgb.w) dissolved in 0.1M citrate buffer (pH4.5) was injected intraperitoneally to induced diabetes. The animals were allowed to drink a 20% glucose solution overnight to forestall initial drug induced hypoglycemic death. Fasting blood samples were withdrawn from the rats’ tail after 72hours of streptozotocin injection to determine the blood glucose levels using one-touch Accu-Chek glucometer and animals with fasting plasma blood glucose level above 200 mg/dl were selected as diabetic and used for this study.

**Experimental Design and Treatment**

The ninety (90) rats were randomly selected and grouped into 9 groups (10 rats/group). The diabetic induced rats were allotted into 8 groups in addition to the normal group. The groupings were as follow:

Group I: Control (non-diabetic rats)

Group II: Diabetic (untreated rats)

Group III: Diabetic rats treated with 100mg/kgb.w AOMNE

Group IV: Diabetic rats treated with 200mg/kgb.w AOMNE

Group V: Diabetic rats treated with 100mg/kgb.w AOMLE

Group VI: Diabetic rats treated with 200mg/kgb.w AOMLE

Group VII: Diabetic rats treated with 100mg/kgb.w AOMSBE

Group VIII: Diabetic rats treated with 200mg/kgb.w AOMSBE

Group IX: Diabetic rats treated with 2.0mg/kgb.w p.o Glimepiride (GMP)

The extracts and Glimepiride were administered orally using oral cannula for 28days with feed and water *ad libitum*. During treatment phase, food and water intake were measured each day.

**Body weights Measurement and Fasting Plasma Glucose level Determination**

The body weights and fasting plasma glucose levels were taken on day 1 of acclimatization and each week throughout the entire treatment period. The body weights were measured with a digital weighing scale and glucose oxidase-peroxidase (GOD-POD) method was used to determine the fasting plasma glucose levels from the blood samples obtained from the tail puncture of the rats using Accu-Chek glucometer.

**Sample Collection and Biochemical Assays**

After the last dose of treatment, the rats were fasted overnight (12hours fasting), anesthetized with ketamin (45mg/kgb.w) and xylazine (20mg/kgb.w) injected intraperitonealy and sacrificed by cervical dislocation. The fasting plasma blood samples were withdrawn from the rats’ heart via cardiac puncture into heparinized tubes, centrifuge at 3500rpm for 5minutes and clear supernatant plasma were retrieved for estimation of biochemical parameters. Levels of triglycerides (TG), total cholesterol (TC) and high density lipoprotein-cholesterol (HDLC) were determined using enzymatic colorimetric method with a commercial kit Diagnostic Kit (Genzyme Diagnostics, MA, USA) followed the manufacturers’ protocol. The level of low density lipoprotein-cholesterol (LDLC) was calculated according to Friedewald et al. formula; LDLC = TC - (HDLC - TG/5).18

Marker of oxidative stress malondialdehyde (MDA) level and antioxidant superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) levels were measured by enzyme linked immunosorbent assay (ELISA) methods using Rat MDA, SOD, GPx and CAT commercial Elisa Kit (Elabscience, China) according to manufacturer’s instruction. Glutathione reductase (GSH) was measured based on the Gupta and Gupta method.19

Plasma hepatic enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels were measured spectrophotometrically using standard automated techniques based on the instruction of the manufacturer. Kidney function markers urea, uric acid and creatinine levels were determined using a commercial assay kit obtained from Siemens Health Care Diagnostics.

**Statistical Analysis**
Data were analyzed using statistical package for social sciences (SPSS version, 21.0). The data were expressed as standard error of mean (mean ± SEM) and statistical difference comparison between groups was evaluated using one-way analysis of variance (ANOVA) followed by Tukey’s post-hoc test. Data were considered statistically significant at p<0.01, p<0.05.

RESULTS

Effects of *Anacardium occidentale* methanolic nut, leaf, and stem bark extracts on body weight, food and water intake in streptozotocin-induced diabetic rats.

In untreated diabetic group rats, body weight and food intake were significantly (p<0.05) reduced whereas, water intake significantly increased. The body weight and food intake were increased after administration of *Anacardium occidentale* methanolic nut, leaf and stem bark extracts along with significantly reduction in water intake. The low and high doses of nut extract greatly improved the body weight. Also, high dose of the stem bark slightly improves the body weight but effectively reduced the water intake.

Effects of *Anacardium occidentale* methanolic nut, leaf, and stem bark extracts on fasting plasma blood glucose levels and lipids profiles in streptozotocin-induced diabetic rats.

Diabetic untreated rats demonstrated significant (p<0.01) increase in plasma fasting blood glucose levels in comparison with non-diabetic rats. *Anacardium occidentale* methanolic nut, leaf and stem bark extracts administrations significantly decreased the elevated fasting blood glucose levels compared with untreated diabetic rats. High dose of *Anacardium occidentale* stem bark extract distinctly lowered the fasting plasma blood glucose levels of diabetic rats than other extracts (fig. 2a).

The triglycerides (TG), total cholesterol (TC) and low density lipoprotein-cholesterol (LDL-C) levels of untreated diabetic induced rats were significantly (p<0.05) higher and high density lipoprotein-cholesterol (HDL-C) level was significantly lowered compared with the non-diabetic rats. Administration of methanolic nut, leaves and stem bark extracts of *Anacardium occidentale* to the diabetic rats significantly reduced the TG, TC, and LDL-C levels and increased the HDL-C level in comparison with untreated diabetic induced rats. Low and high doses of *Anacardium occidentale* nut extract were the most effective in diminishing the TG, TC, and LDL-C levels. Furthermore, the nut extract high dose remarkably enhanced the HDL-C level with fair effect by the leaves extract high dose (fig. 2b).

Effects of *Anacardium occidentale* methanolic nut, leaf, and stem bark extracts on marker of oxidative stress and antioxidant enzymes activity in streptozotocin-induced diabetic rats.

Malondialdehyde (MDA) level, a biomarker of oxidative stress in untreated diabetic rats significantly (p<0.05) increased compared with non-diabetic rats. The *Anacardium occidentale* methanolic leaves, stem bark and nut extracts supplement to the diabetic rats attenuate the MDA level when compared with the untreated diabetic rats. Among these extracts, *Anacardium occidentale* nut extract high and low doses exhibited reasonable diminution in MDA level. Further, the levels of superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and reduced glutathione (GSH) were significantly (p<0.05) decreased in untreated diabetic rats in comparison to the non-diabetic rats. SOD, GPx, CAT, and GSH levels were increased after administration of *Anacardium occidentale* methanolic leaves, nut and stem bark extracts to the diabetic rats compared with untreated diabetic rats. Specifically, *Anacardium occidentale* nut extract high and low doses extremely elevated SOD, GPx, CAT and GSH levels followed by stem bark and leaves extract high doses (table 2).

Effects of *Anacardium occidentale* methanolic nut, leaf, and stem bark extracts on hepatic enzymes and kidney function parameters in streptozotocin-induced diabetic rats.

There were significant (p<0.01) elevation in hepatic plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) levels in untreated diabetic induced rats compared with the non-diabetic rats. Administration of *Anacardium occidentale* methanolic nut, leaf and stem bark extracts lessen the elevated AST, ALT and ALP levels in comparison to the untreated diabetic rats. The nut extract high dose radically reduced the ALT, AST, and ALP levels (table 3).

Furthermore, kidney function parameters urea, uric acid and creatinine levels were significantly (p<0.01) higher in untreated diabetic rats compared with the non-diabetic rats. Treatment of the diabetic rats with high and low doses of *Anacardium occidentale* methanolic nut, leaf and stem bark extracts lowered the urea, uric acid and creatinine levels compared with untreated diabetic. All the extracts drastically lowered these parameters (table 3).

<table>
<thead>
<tr>
<th>S/N</th>
<th>METABOLITES</th>
<th>NUT</th>
<th>LEAVES</th>
<th>STEM BARK</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saponins</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>Flavonoids</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Tannins</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Phlobatanins</td>
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<td>+</td>
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<td>5</td>
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<tr>
<td>6</td>
<td>Terpenoids</td>
<td>+</td>
<td>+</td>
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<td>7</td>
<td>Cardiac Glycosides</td>
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<td>8</td>
<td>Anthraquinones</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>Alkaloids</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>Reducing Sugar</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

(+) means detected, (-) means not detected.
Figure 1: Effects of *Anacardium occidentale* methanolic nut, leaf, and stem bark extracts on (a) body weight (b) food intake (c) water intake in streptozotocin (STZ)-induced diabetic rats. *Values are expressed as mean ± SEM (n=10).* *#significant at p<0.05 compared with control; *significant at p<0.05 compared with untreated diabetic group.
Figure 2: Effects of *Anacardium occidentale* methanolic nut, leaf, and stem bark extracts on (a) fasting blood glucose levels (b) lipids profiles in streptozotocin (STZ)-induced diabetic rats. *Values are expressed as mean ± SEM (n=10).* *'significant at p<0.05 compared with control; *'significant at p<0.05 compared with untreated diabetic group.*
### Table 2: Effects of *Anacardium occidentale* methanolic nut, leaf and stem bark extracts on oxidative stress marker and antioxidant enzymes activities in streptozotocin-induced diabetic rats

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>MDA (µM)</th>
<th>SOD (µ/ml)</th>
<th>GPx (U/L)</th>
<th>CAT (mol/ml/min)</th>
<th>GSH (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (non-diabetic)</td>
<td>6.74 ± 0.08</td>
<td>1.83 ± 0.20</td>
<td>51.02 ± 1.91</td>
<td>24.63 ± 0.64</td>
<td>2.63 ± 0.13</td>
</tr>
<tr>
<td>Diabetic (untreated)</td>
<td>11.75 ± 0.58*</td>
<td>0.79 ± 0.01*</td>
<td>24.01 ± 2.07*</td>
<td>12.40 ± 0.32*</td>
<td>1.53 ± 0.03*</td>
</tr>
<tr>
<td>Diabetic + 100mg/kgb.w AOMNE</td>
<td>4.01 ± 0.04*</td>
<td>1.62 ± 0.05*</td>
<td>60.01 ± 0.26*</td>
<td>27.18 ± 1.79*</td>
<td>2.49 ± 0.29*</td>
</tr>
<tr>
<td>Diabetic + 200mg/kgb.w AOMNE</td>
<td>3.47 ± 0.19*</td>
<td>1.78 ± 0.22*</td>
<td>63.39 ± 3.51*</td>
<td>34.05 ± 1.94*</td>
<td>3.35 ± 0.18*</td>
</tr>
<tr>
<td>Diabetic + 200mg/kgb.w AOMLE</td>
<td>6.73 ± 0.61*</td>
<td>1.42 ± 0.03*</td>
<td>55.14 ± 2.43*</td>
<td>26.10 ± 2.78*</td>
<td>2.60 ± 0.53*</td>
</tr>
<tr>
<td>Diabetic + 100mg/kgb.w AOMLE</td>
<td>5.09 ± 0.15*</td>
<td>1.55 ± 0.02*</td>
<td>56.27 ± 2.43*</td>
<td>24.34 ± 1.95*</td>
<td>3.12 ± 0.73*</td>
</tr>
<tr>
<td>Diabetic + 100mg/kgb.w AOMSBE</td>
<td>6.37 ± 0.78*</td>
<td>1.47 ± 0.07*</td>
<td>57.02 ± 3.13*</td>
<td>27.44 ± 0.23*</td>
<td>2.39 ± 0.31*</td>
</tr>
<tr>
<td>Diabetic + 200mg/kgb.w AOMSBE</td>
<td>5.66 ± 0.85*</td>
<td>1.35 ± 0.09*</td>
<td>59.27 ± 1.40*</td>
<td>29.65 ± 2.28*</td>
<td>2.92 ± 0.32*</td>
</tr>
<tr>
<td>Diabetic + 2mg/kgb.w Glimepiride</td>
<td>3.37 ± 0.06*</td>
<td>1.68 ± 0.13</td>
<td>66.02 ± 2.27*</td>
<td>31.13 ± 0.85*</td>
<td>2.30 ± 0.17*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM (n=10). *significant at p<0.05 compared with control; **significant at p<0.01 compared with untreated diabetic group.

### Table 3: Effects of *Anacardium occidentale* methanolic nut, leaf and stem bark extracts on hepatic enzymes biomarkers and kidney function parameters in streptozotocin-induced diabetic rats.

#### HEPATIC ENZYMES BIOMARKERS

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>ALP (mol/ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (non-diabetic)</td>
<td>117.92 ± 11.27</td>
<td>43.75 ± 3.88</td>
<td>326.85 ± 15.65</td>
</tr>
<tr>
<td>Diabetic (untreated)</td>
<td>300.70 ± 19.53**</td>
<td>95.67 ± 1.62**</td>
<td>584.56 ± 52.37**</td>
</tr>
<tr>
<td>Diabetic + 100mg/kgb.w AOMNE</td>
<td>122.34 ± 6.84**</td>
<td>37.55 ± 1.29**</td>
<td>221.77 ± 40.54**</td>
</tr>
<tr>
<td>Diabetic + 200mg/kgb.w AOMNE</td>
<td>113.99 ± 6.97**</td>
<td>28.08 ± 2.05**</td>
<td>208.70 ± 21.43**</td>
</tr>
<tr>
<td>Diabetic + 100mg/kgb.w AOMLE</td>
<td>148.39 ± 8.17**</td>
<td>36.90 ± 3.03**</td>
<td>275.24 ± 43.59**</td>
</tr>
<tr>
<td>Diabetic + 200mg/kgb.w AOMLE</td>
<td>142.49 ± 21.99**</td>
<td>45.71 ± 2.66**</td>
<td>254.47 ± 21.90**</td>
</tr>
<tr>
<td>Diabetic + 100mg/kgb.w AOMSBE</td>
<td>138.56 ± 12.0**</td>
<td>36.24 ± 2.88**</td>
<td>245.38 ± 17.29**</td>
</tr>
<tr>
<td>Diabetic + 200mg/kgb.w AOMSBE</td>
<td>123.32 ± 13.11**</td>
<td>32.65 ± 3.36**</td>
<td>288.87 ± 18.17**</td>
</tr>
<tr>
<td>Diabetic + 2mg/kgb.w Glimepiride</td>
<td>174.43 ± 9.89**</td>
<td>34.61 ± 5.37**</td>
<td>135.67 ± 24.55**</td>
</tr>
</tbody>
</table>

#### KIDNEY FUNCTION PARAMETERS

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>Urea (mg/dL)</th>
<th>Uric acid (mg/dL)</th>
<th>Creatinine (µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (non-diabetic)</td>
<td>20.76 ± 0.24</td>
<td>6.98 ± 0.28</td>
<td>83.03 ± 9.14</td>
</tr>
<tr>
<td>Diabetic (untreated)</td>
<td>66.68 ± 5.31**</td>
<td>11.97 ± 0.74**</td>
<td>157.16 ± 13.75**</td>
</tr>
<tr>
<td>Diabetic + 100mg/kgb.w AOMNE</td>
<td>30.63 ± 0.49**</td>
<td>7.19 ± 0.36**</td>
<td>56.34 ± 5.55**</td>
</tr>
<tr>
<td>Diabetic + 200mg/kgb.w AOMNE</td>
<td>23.46 ± 2.77**</td>
<td>7.68 ± 0.01**</td>
<td>65.23 ± 5.55**</td>
</tr>
<tr>
<td>Diabetic + 100mg/kgb.w AOMLE</td>
<td>23.32 ± 1.26**</td>
<td>8.74 ± 0.19**</td>
<td>59.30 ± 2.10**</td>
</tr>
<tr>
<td>Diabetic + 200mg/kgb.w AOMLE</td>
<td>23.25 ± 1.14**</td>
<td>6.52 ± 0.23**</td>
<td>65.23 ± 2.10**</td>
</tr>
<tr>
<td>Diabetic + 100mg/kgb.w AOMSBE</td>
<td>26.20 ± 0.66**</td>
<td>6.78 ± 0.11**</td>
<td>53.37 ± 3.63**</td>
</tr>
<tr>
<td>Diabetic + 200mg/kgb.w AOMSBE</td>
<td>25.84 ± 1.47**</td>
<td>7.85 ± 0.25**</td>
<td>53.37 ± 3.63**</td>
</tr>
<tr>
<td>Diabetic + 2mg/kgb.w Glimepiride</td>
<td>23.03 ± 0.29**</td>
<td>8.94 ± 0.31**</td>
<td>41.51 ± 4.19**</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SEM (n=10). **significant at p<0.01 compared with control; ***significant at p<0.01 compared with untreated diabetic group.
**DISCUSSION**

Humans have been using various plants species as alternative therapy for different ailments including diabetes due to their own efficacy 20. Here in the present study, antidiabetic comparison effects of *Anacardium occidentale* methanolic nut, leaf, and stem bark extracts were investigated in streptozotocin induced-diabetic rats. Streptozotocin is commonly used as diabetogenic agent in animal model of diabetes due to its ability to induce pancreatic cells necrosis that consequences in loss of insulin secretion, leading to hyperglycemia and diabetic complications 21,22.

Diabetes is associated with excessive body weight loss due to imbalance of metabolic pathways 23. In this study, diabetes induced rats demonstrated obviously reduction in body weight and this is in line with the report of Abbasi et al. 24. The body weight reduction observed in this study could be due to muscle wasting and tissue protein loss. In addition, severe reduction in food intake in this study could also contribute to body weight loss. The bodyweight was improved after treated the diabetic rats with *Anacardium occidentale* methanolic nut, leaf, and stem extracts, indicating that these extracts restored the normal metabolic pathways and prevent the tissue proteolysis thereby inhibit the muscle wasting induced by hyperglycemia condition, which is parallel with the findings of Rines et al. 25.

Additionally, chronic exposure to hyperglycemia in diabetes is the main etiology of diabetic complications and vasculopathy which promote atherosclerosis 26. Elevated blood glucose levels were also observed in untreated diabetic rats in this study. This finding corroborates the result of Dakam et al. 27 who also reported substantial increase in blood glucose level of streptozotocin-induced diabetic rats. This rise in the blood glucose levels maybe as a result of reduced glucose uptake by peripheral cells due to insensitivity to insulin action or diminutive insulin secretion from damage pancreatic beta cells 28. Many phytochemicals such as saponins, tannins, alkaloids, flavonoids and terpenoids have been reported to possess anti- hyperglycemic effect 29. Administration of methanolic leaves, stem bark and nut extracts of *Anacardium occidentale* plant diminished the elevated blood glucose levels. The observed anti-hyperglycemia activity of these extracts may be attributed to the presences of one or more phytochemicals capable of stimulating glucose uptake in peripheral tissues, inhibition of α-amylase and α-glucosidase enzyme activities to slow down intestinal glucose absorption, restoration of damage pancreatic beta cell to secrete sufficient insulin and prevention of hepatic gluconeogenesis. These extracts were compared with glibenpiride, the stem bark extract high dose lowering the elevated blood glucose level proficiently.

The major metabolic disorder associated with diabetes is dyslipidemia 30. The diabetic untreated rats in this study showed the main features of diabetic dyslipidemia: elevated triglycerides (TG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and a decrease in the high density lipoprotein-cholesterol (HDL-C). This observation is in consonance with the finding of Abdel-Azim Assi et al. 31. The observed elevated TG, TC and LDL-C could be partly due to increased intestinal biosynthesis of cholesterol because diabetes shifted the major site of cholesteroegenesis from the liver to the small intestine leading to hypercholesterolemia 32. However, on treatment of diabetic rats with *Anacardium occidentale* methanolic nut, leaf and stem bark extracts, this altered lipid profile was reversed noticeably with reduction in TG, TC, and LDL-C levels while HDL-C level increased and this result support the data of Sharma et al. 33. on the lipid lowering effect of stevia extract on humans. This improvement in HDL level will be helpful in preventing several cardiovascular disease complications induced by diabetic dyslipidemia. Saponins, one of the active phyto-chemical have been reported to possess ability to reduce hyperlipidemia by effectively reducing absorption of fats after digestion by pancreatic lipases thereby inhibiting adipogenesis 34. This anti-hyperlipidemic action of *Anacardium occidentale* methanolic nut, leaf and stem bark extracts might be due to the presence of phyto-constituent saponins. A light effect was observed in diabetic rats treated with leaf extract high dose (200mg/kgb.wt) while a more noticeable effect was observed in rats treated with high dose (200mg/kg/b.wt) of *Anacardium occidentale* nut extract than other extracts.

Oxidative stress induced by persistent hyperglycemia also contributes to the pathogenesis and progression of cellular injury in diabetes mellitus through production of reactive oxygen species that further upsurge releasing of lipid peroxidation end product malondialdehyde (MDA) level, a marker of free radicals production and dwindling in biological antioxidant defense system 35. This study also observed increase in MDA level and reduced antioxidant superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and reduced glutathione (GSH) levels in untreated diabetic rats, which are in consistent with finding of Almatroodi et al. 26. Oral supplementation of *Anacardium occidentale* methanolic nut, leaf and stem bark extracts to the diabetic rats attenuated the MDA level and ameliorates the activity of antioxidant SOD, CAT, GPx and GSH. This finding indicated that *Anacardium occidentale* nut, leaf leaves, nut and stem bark posses a strong antioxidant properties capable of neutralizing free radicals and preventing cellular damage by oxidative stress in diabetes mellitus which is in accordance with report of Domekouo et al. 37, who reported antioxidant properties of *Morinda lucida* aqueous stem bark extract in streptozotocin-induced diabetic rats. High dose (200mg/kgb.wt) and low dose (100mg/kgb.wt) of *Anacardium occidentale* nut extract were the most effective in attenuating the oxidative stress marker and elevate the antioxidant enzymes activity. The stems back extract high dose (200mg/kgb.wt) as well as the leaves extract high dose (200mg/kgb.wt) also lessen the oxidative stress and ameliorate the antioxidant enzymes but not as efficient as the nut.

The elevation in hepatic enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) is typically associated with the hyperglycemia status in diabetes mellitus. These hepatic enzymes (AST, ALT and ALP) are useful biomarkers of hepatocytes damage and the levels are usually increased in acute hepatopothy 38,39. These elevated hepatic enzymes might contribute to the development of diabetic ketogenesis and gluconeogenesis 40. Elevated levels of hepatic enzymes AST, ALT, and ALP were also observed in this current study, which revealed some levels of hepatic damage and this support the result of Shahla Rezaei 41. Furthermore, hyperglycemia in diabetes induced renal dysfunction markedly by elevation in kidney function markers urea, uric acid and creatinine levels 42. In this study, renal biomarkers urea, uric acid and creatinine levels were elevated in untreated diabetic rats, suggesting the impairment of the renal function in filtering and eliminating toxic waste product and this finding is in agreement with previous results of Rashid and Khan 43. However, in diabetic rats treated with methanolic extracts of nut, leaf and stem bark of *Anacardium occidentale* plant, a decline in the elevated markers of hepatic enzymes and renal function parameters were observed, which prove the protection of vital organs from chronic hyperglycemia damages by these extracts and this harmonize the finding of Hasan et al. 44. Also, phyto-chemical constituents such as alkaloids, tannins, and saponins in plants extract have previously reported to exhibit vital organs protective effects 45. The restoration of hepatic enzymes and renal functions of
these extracts could be attributed to possession of these bioactive compounds. Comparably, Anacardium occidentale nut extract high dose (200mg/kg bw) attenuated the elevated hepatic enzymes closely to glimepiride and (100 mg/kg bw) and (200mg/kg bw) of nut, leaf and stem bark methanolic extracts efficiently showed renal protective effects with negligible differences.

CONCLUSION

From our findings, Anacardium occidentale nut, leaf and stem bark have hypoglycemic, hypolipidemic and antioxidant therapeutic properties. The Anacardium occidentale nut possesses the most potent anti-diabetic therapeutic effects followed by the stem bark with the leaves being the least. The nut of Anacardium occidentale plant could be useful as alternative therapy for diabetes. Further, synergistic anti-diabetic effect of the nut, leaf and stem bark should be investigated.

ABBREVIATIONS

AOMNE: Anacardium occidentale methanolic nut extract; AOMLE: Anacardium occidentale methanolic leaves extract; AOMSBE: Anacardium occidentale methanolic stem bark extract.

DECLARATIONS:

Authors’ Contributions

FO conceived the original idea, designed and supervised the research. AO and MO performed the experiments with the support of FO. FO, MO and AO collected the data. MO and AO analyzed the data and prepared the manuscript. FO reviewed the manuscript. All authors have read and approved the final manuscript.

Competing Interests

No competing interests.

Funding

This research work did not receive any specific funding/financial support.

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