Anti-glycemic potential of *Abelmoschus caillei* (A. Chev.) Stevels Pod aqueous and methanol extract on streptozotocin-induced diabetic rats.

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Abstract

Diabetes mellitus is a lingering disease associated with pancreatic malfunctioning unable to synthesize sufficient insulin, or the insulin produced by the body cannot be effectively utilized, resulting in the accumulation of glucose in the body. This study evaluates the anti-diabetic activity of the aqueous and methanol extracts of *Abelmoschus caillei* in Streptozotocin-induced diabetic rats. Thirty male rats were administered with 45 mg/kg Streptozotocin (STZ) to induce-diabetes for 3 days and thereafter treated with graded oral doses of 200 and 400 mg/kg of aqueous and methanol pod extracts of *A. caillei* for 28 days. Hematological analysis, biochemical analysis and histopathology of the heart, were carried out using standard procedures. The results from this study showed a significant reduction in the elevated blood glucose levels at day 28 of the aqueous and methanol extracts (67.37; 130 mg/dL and 173.0; 140.0 mg/dL) with percentage reduction of (68.29; 56.3% and 30.7; 45.8%) respectively when compared with glibenclamide group and diabetes control (220.7 mg/dl; 43.98 % and 418.7 mg/dl; 0%). The hematological, lipid profile and liver function test had a slight significant difference specifically at 400 mg/kg of the extracts when compared with the control $p > 0.05$. The architectural frame work of the organ's histopathology elicited no deformities in liver, kidney, pancreases, lungs, and heart the treated groups when compared with the diabetic control. This study showed that *A. caillei* extracts possess anti-diabetic potentials, thereby supporting the claims in the management of diabetes from the traditional folk's report.

Keywords: *Abelmoschus caillei;* hyperglycemia; histopathology; hematology; biochemistry

Introduction

Diabetes mellitus (diabetes) is a chronic condition which occurs when the pancreas does not produce enough insulin, or when the body cannot use the insulin it produces

effectively, resulting in the accumulation of underutilized glucose in the body (Kumaran *et al.* 2014; Dey *et al.* 2002). Elevated blood sugar (Hyperglycemia), leads to serious damage to many of the body's systems, especially the nerves and blood vessels evident in complications such as cataract, retinopathy, nephropathy and neuropathy (Kumaran *et al.* 2014). Diabetes is also characterized by disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The general causes and risk factors associated with diabetes are obesity, physical inactivity, insulin resistance, and abnormal glucose production by the liver, high blood pressure, high levels of low density lipoproteins and triglycerides with low levels of high density lipoprotein, history of cardio vascular disease and family history of diabetes. Classic signs and symptoms of diabetes include polyuria (increased urine frequency), polydipsia (extreme thirst), polyphagia (extreme hunger), unexplained weight loss, headache, pain in the feet, weakness and tiredness, severe nausea and vomiting, palpitations and blurred vision. According to World Health Organization's (WHO) estimates in 2014, 347 million people worldwide have diabetes and more than 80% of people with diabetes live in low- and middle- income countries (WHO 2015). Diabetes was reported to be the sixth leading cause of death in India and United States of America (Saha *et al.* 2011) and WHO projects that death as a result of diabetes will double between 2005 and 2030. Diabetes is rapidly emerging as a major public health problem in Nigeria. Close to a decade ago, the prevalence rate of type-2 diabetes, according to the International Diabetes Foundation/WHO reports, was estimated to be over 3.4% of 24 million Nigerian diabetes sufferers between the ages of 20-79 years and with projected estimate of 3.9% rise in 2025 (Ojiako and Chikezie, 2014; Chikezie *et al.* 2015). Ethno-pharmacological surveys indicate that more than 1,200 plants are used in traditional medicine systems for the management of diabetes (Andrew *et al.* 2018), but only a small number of these excluding *Abelmoschus caillei* pods have received scientific and medical evaluation.

Abelmoschus caillei (A. Chev.) Stevels, family Malvaceae is commonly known as West Africa Okra (English), Ohukpo or Omonupkogbe (in Bini), Abukpa (in Igbo), Ilagidi (in Yoruba) and Ikhiawhornekhua (in Etsako) (Osawaru and Dania-ogbe 2010). It is a stout, erect herb which is often woody at the base. *Abelmoschus caillei* is used as a seasonal indicator, medicinally (during child labour and birth and as throat clearer), as fuel, in rope making, sponge making, and mythical belief by some tribes of South Western Nigeria. The extracted mucilage has been reported as plasma replacement or blood volume expander and the leaves used as a basis for poultice, as an emollient, sudorific, antiscorbulic and to treat dysuria (Osawaru *et al.* 2010). Alcohol extract from leaves has been reported to eliminate oxygen free radicals, alleviate renal tabular-interstitial diseases, improve renal function and reduce proteinuria (Siemonsma and Hamon 2002). It has been reported to prevent cancer and heart disease (Idu 2010) and the mucilage is used in midwifery and in trado-medicinal practices to ward off evil spirits (Obire 2002). No scientific data is available on the anti-diabetic activity of *Abelmoschus caillei*. Hence, this study was conducted to test the aqueous and methanol extracts of *A. caillei* for anti-diabetic activities in STZ-induced diabetic rats at different doses, to justify its use scientifically.

Materials and Method

Plant Material Collection

Fresh fruits of *Abelmoschus caillei* were purchased from Okpella market in Akoko-Edo Local Government Area of Edo State, Nigeria in December, 2014. The plant material was identified and authenticated by Dr. M.E. Osawaru of the Department of Plant Biology and Biotechnology, University of Benin, Nigeria and voucher specimen number was obtained from the herbarium (UBW-T14).

Preparation of Extracts

The fruit pods were washed to get rid of dirt and debris under flowing tap water. They were then cut transversely into smaller bits and shade dried. The dried plant materials were pulverized to coarse powdered form using an electric laboratory mill. The powder was divided into two equal parts of about 600 g each. The first part was extracted with methanol using Soxhlet apparatus at 60 °C. The methanol extract was concentrated by freeze-drying using an FD10M freeze dryer at 4 °C for two days in the National Centre for Energy and Environment, Energy Commission of Nigeria in Benin City, Nigeria. The second part was extracted with distilled water by cold maceration. The extract was filtered using a fine mesh muslin cloth then concentrated by freeze drying. Both extracts were refrigerated at 4 °C prior to use.

Experimental animals

Healthy male and female Wistar albino rats weighing between 180 to 205 g were used for the experiment. The animals were purchased from the Department of Biochemistry Animal House, University of Benin, Benin City and kept in plastic animal cages (which were regularly cleaned and disinfected). The cages and animals were housed in the Animal and Environmental Biology Department Animal House, Faculty of Life Science, University of Benin, Benin City, Nigeria, and maintained under standard laboratory conditions (temperature: 28-31 °C; humidity: 50-55%; and 12:12 h day: night cycle). The animals were allowed unrestricted access to water and standard laboratory diet, and allowed to acclimatize to the new environment for a period of two weeks. They were handled according to standard protocols for the use of laboratory animals' source from Life Sciences ethical committee, University of Benin, for the use of animals issued an ethical number (LS17462).

Induction of Diabetes

Diabetes was induced in overnight fasted rats by a single intraperitoneal injection of 45 mg/kg body weight of streptozotocin (STZ). STZ was dissolved in 0.1M cold sodium citrate buffer, pH 4.2 and the control rats were injected with vehicle alone. To prevent STZ-induced hypoglycaemia, rats received 5% dextrose solution after STZ administration and for the next 24 h. Diabetes was verified after 72 h by measuring blood glucose level with strips using glucometer (Accu-Chek®) Active, Roche Diagnostic Corporation, Germany) and the diabetic rats confirmed as those having blood glucose level greater than 200 mg/dL (Djomeni *et al.* 2006) and were grouped for the experiment.

Experimental Protocol

The effect of the extracts was studied in STZ induced diabetic rats for 4 weeks. The rats were divided into 6 groups (n=5). The choice of doses were determined from previous acute study, then pilot study was established before the commencement of this present study Group I: Diabetic negative control received STZ and 1 mL distilled water (DW). Group II: Positive diabetic control animals were administered Glibenclamide (10 mg/kg body weight orally). Glibenclamide served as the standard drug and the dose (10 mg/kg body weight/day) was adopted based on a

previous study by Sheikh *et al.* (2013)**.** Group III: Diabetic Rats administered aqueous extract of *Abelmoschus caillei*-200 mg/kg b.w. orally. Group IV: Diabetic rats administered aqueous extract of *A. caillei* 400 mg/kg b.w. orally. Group V: Diabetic rats administered 200 mg/kg b.w. methanol extract of *A. caillei* orally. Group VI: Diabetic rats administered 400 mg/kg b.w. methanol extract of *A. caillei* orally. The various treatments were administered orally using an oral-gastric gavage for 28 days. The glibenclamide, aqueous and methanol extract of *A. caillei* were triturated with distilled water just before oral administration. The acute effect of the treatments on the diabetic rats was studied by determining the fasting blood glucose level for the first 4 h after treatment at intervals of 1, 2 and 4 h. For the sub-acute study, the fasting body weight and fasting blood glucose level were estimated at the end of every week for a period of 28 days.

Haematological Analysis

On the 28th day, the rats were fasted overnight and anaesthetized with chloroform in a chamber. The animals where then sacrificed and 3 mL of blood was collected by cardiac puncture into 5 mL EDTA (ethylenediaminetetra acetic acid) bottles and estimated for concentration of various hematological parameters. The parameters considered were white blood cell count (WBC), lymphocytes (LYP), monocytes (MO), granulocytes (GR), red blood cell count (RBC), hemoglobin concentration (Hgb), packed cell volume (PCV) and platelet count (PLT). The hematological parameters were analyzed using automatic hematology analyzer (Model BC-2800) within 24 h of blood collection (Malomo *et al.* 2002).

Biochemical Assay

The blood sample for biochemical assays also collected via cardiac puncture were placed in lithium heparin sample bottles and centrifuged at 3000 revolutions per min (rpm) and plasma was separated using Pasteur pipettes into clear labeled bottles. The samples were stored in deep freezer at -20°C until analyses were carried out (Bagul *et al.* 2005). The blood plasma was used for the evaluation of the following biochemical parameters cholesterol (CHOL), triglycerides (TRIGS), aspartate aminotransferase (AST), albumin (ALB), total protein (TP), total bilirubin (T BIL), direct bilirubin (D BIL), alanine aminotransferase (ALT) alkaline phosphate (ALP), high density lipoprotein (HDL) and low density lipoprotein (LDL). The biochemical parameters were evaluated using commercial kits obtained from Randox Laboratories, UK.

Histopathological Studies

The experimental animals were sacrificed on the 28th day of the experiment and vital organs were isolated, fixed in 10% formal saline for 24 hours, dehydrated in an alcohol-xylene series and embedded in paraffin. Sections were stained with hematoxylin and eosin for histological examination and photomicrographs were taken. The organs considered include liver, heart, lungs, kidney, and pancreas (Drury and Wallinton 2013).

Statistical Analysis

Data were subjected to one-way analysis of variance (ANOVA), followed by Dunnett's test for multiple comparisons using Graph-pad prism software (version 6.01). Results are expressed as Mean ± SEM. Values of $P < 0.05$ were considered as statistically significant.

RESULTS

Anti-diabetic Study

Table 1 shows the hypoglycemic effect of aqueous and methanol extracts of *Abelmoschus caillei* in STZ-induced diabetic

rats after 1, 2 and 4 (acute study) of the experiment. Although the administration of glibenclamide (10 mg/kg body weight) reduced the blood glucose level from 394.04 ± 45.17 (mg/dL) to 324.71 ± 47.51 (mg/dL) the 0 and 4 h of the experiment, when these values were compared to the diabetic control, there was no statistical significance. Aqueous extracts of *Abelmoschus caillei* at doses 200 and 400 mg/kg body weight reduced the blood glucose level from 212.33 ± 42.19 to 193.04 ± 45.52 mg/dL and 297.73 ± 46.04 to 225.70 ± 30.85 mg/dL with percentage reduction of 9.09% and 24.19% respectively between 0 and 4 h of the experiment. Methanol extracts of *Abelmoschus caillei* at both doses did not reduce the blood glucose of the diabetic experimental animals in the first 4 h of the experiment when compared to the initial blood glucose level. Table 2 shows the hypoglycemic effect of aqueous and methanol extracts of *Abelmoschus caillei* in STZ-induced diabetic rats (sub-acute study). In the sub-acute study, the various treatments significantly reduced the blood glucose level of the diabetic experimental animals when compared to the diabetic control. Glibenclamide (10 mg/kg body weight) produced a reduction that was statistically significant ($p<0.05$) when compared to the diabetic control group, with 43.98% reduction on the 28th day of the experiment. Aqueous extract of *Abelmoschus caillei* at 200 mg/kg body weight produced a highly significant reduction ($p<0.001$) when compared to the diabetic control, with a percentage reduction of 68.29%, making this treatment the most effective in reducing hyperglycemia in this study. At 400 mg/kg body weight, aqueous extract of *Abelmoschus caillei* also caused a highly significant reduction ($p<0.001$) in the blood glucose level when compared to the diabetic control and the percentage reduction was 56.3% at the end of the experiment. At 200 and 400 mg/kg of the extract with glibenclamide elicited a significant decrease ($p < 0.01$) when compared with untreated control, with percentage reduction of 30.7% and 45.8% respectively.

Table 1: Hypoglycemic effect of aqueous and methanol extracts of *Abelmoschus caillei* in STZ-induced diabetic rats

Groups	**Dose (mg/kg)**	**Mean change of blood glucose (mg/dl) in hours after treatment**				**% Reduction**
		0 hour	1 h	2 h	4 h	
Streptozotocin	40	303.02±30.12[a]	350.00±9.02[a]	343.31±12.41[a]	314.02±11.24[a]	No decrease
Glibenclamide	10	394.04±45.17 [a]	311.70±22.70[a]	318.71±7.86[a]	324.71±47.51[a]	17.56
Aq. *A. caillei*	200	212.33±42.19 [a]	215.74±32.97[b]	208.72±36.36[b]	193.04±45.52[b]	9.09
Aq. *A. caillei*	400	297.73±46.04 [a]	284.02±56.35[a]	264.34±36.71[a]	225.70±30.85[a]	24.2
Meth. *A. caillei*	200	249.50±39.55 [a]	280.02±30.02[a]	279.02±22.52[a]	289.03±17.32[a]	No decrease
Meth. *A. caillei*	400	258.32±8.97 [a]	287.71±16.17[a]	280.71±13.69[a]	267.71±9.06[a]	No decrease

Values are expressed as Mean ± SEM, P<0.05; n=5, Aq: Aqueous extract; Meth: Methanol extract; DW: distilled water * Significant values at P<0.05; ** significant values at P<0.01 both compared to the diabetic control group

Table 2: Hypoglycemic effect of aqueous and methanol extracts of *Abelmoschus caillei* in STZ-induced diabetic rats

Treatment Groups	Dose (mg/kg)	Mean change of blood glucose (mg/dl) weeks after treatment					% reduction
		Initial	1st week	2nd week	3rd week	4th week	
Streptozotocin	40	303.0±30.20[a]	320.0±14.00[a]	344.0±27.54[a]	379.0±57.30[a]	418.7±93.81[a]	No decrease
Glibenclamide	10	394.0±45.17	330.3±32.05[a]	314.3±24.91[a]	295.0±12.06[a]	220.7±34.20[b]	43.98 %
Aq. *A. caillei*	200	212.3±42.19	142.3±33.01[c]	116.0±33.14[c]	102.7±28.76[c]	67.33±7.36[c]	68.29 %
Aq. *A. caillei*	400	297.7±46.04	183.3±36.33[b]	167.3±35.14[b]	143.7±28.99[c]	130.0±17.39[c]	56.3 %
Meth. *A. caillei*	200	249.5±39.55	269.0±21.94[a]	229.0±38.68[a]	190.0±45.03[b]	173.0±17.32[b]	30.7 %
Meth. *A. caillei*	400	258.3±8.97	472.7±47.76[a]	291.3±93.60[a]	127.0±19.09[c]	140.0±24.34[b]	45.8 %

Values are expressed as Mean ± SEM, P<0.05; n=5, Aq: Aqueous extract; Meth: Methanol extract; DW: distilled water, * Significant values at P<0.05; ** significant values at P<0.01; *** significant values at P<0.001, when compared to diabetic control group

Hematological Analysis

Hematological indices analyzed after 28 days oral treatment of STZ-induced diabetic rats with aqueous extract of *A. caillei* (200 and 400 mg/kg body weight), methanol extract of *A. caillei* (200 and 400 mg/kg body weight) and the standard drug (10 mg/kg body weight glibenclamide) compared with the normal and untreated control are presented in Table 3. The composition in white blood cell count, red blood cell count, hemoglobin concentration, packed cell volume and platelet count where not significantly altered by the treatments when compared with the normal and diabetic control groups. Whereas the percentage lymphocytes, monocytes and granulocytes where significantly altered in groups treated with aqueous extract of *A. caillei* (400 mg/kg body weight) and methanol extract of *A. caillei* (400 mg/kg body weight).

Table 3: Effect of aqueous and methanol extracts of *Abelmoschus caillei* on haematological parameters in STZ induced diabetic rats.

Parameters	Streptozotocin (40 mg/kg)	Glibenclamide (10 mg/kg)	AQ AC (200 mg/kg)	AQ AC (400 mg/kg)	Meth. AC (200 mg/kg)	Meth. AC (400 mg/kg)
WBC($X10^3$/UL)	9.53±1.56[a]	14.37±3.78[b]	12.00±1.96[a]	8.57±2.44[a]	13.05±1.65[b]	14.00±4.65[b]
LYP (%)	90.43±3.61[a]	80.07±11.19[a]	76.00±9.30[a]	45.40±6.41[b]	64.80±0.16[a]	44.17±16.02[b]
MO (%)	3.93±1.92[a]	8.07±4.42[c]	9.30±3.23[c]	17.17±0.41[c]	11.50±2.43[c]	20.37±3.15[d]
GR (%)	5.63±1.92[a]	11.87±6.77[b]	14.70±6.06[b]	37.43±6.61[c]	23.70±2.31[c]	35.47±13.07[c]
RBC ($X10^6$/UL)	6.86±0.37[a]	8.11±0.39[a]	7.77±0.18[a]	7.33±0.16[a]	7.39±0.11[a]	8.12±0.65[a]
Hgb (g/dl)	12.60±0.91[a]	14.13±0.56[a]	14.55±0.09[a]	14.43±0.54[a]	14.20±0.35[a]	15.30±0.46[b]

PVC (%)	42.23±2.86[a]	43.73±1.43[a]	45.20±1.67[a]	46.83±2.53[b]	44.70±0.06[a]	48.60±1.44[b]
PLT ($X10^3$/UL)	457.30±87.27[a]	123.30±36.63[a]	447.00±114.90[a]	311.30±74.31[a]	211.00±41.57[a]	364.00±173.50[a]

Values are expressed as Mean ± SEM, P<0.05; n=5, WBC: White blood cell count; LYP: Lymphocytes; MO: Monocytes; GR: Granulocytes; RBC: Red blood cell count; Hgb: Haemoglobin concentration; PVC: Packed cell volume; PLT: Platelet count, AQ AC: Aqueous extract of *Abelmoschus caillei* Meth. AC: Methanol extract of *Abelmoschus caillei* * Significant values at P<0.05; ** Significant values at P<0.01 when compared to normal and diabetic control.

Biochemical analysis

Table 4 shows the effect of aqueous and methanol extracts of *A. caillei* on biochemical parameters in STZ-induced diabetic rats. The values for the cholesterol, triglycerides and low density lipoprotein (mg/dL) in the different treatment groups were not statistically different when compared to the normal control group. While the value for the high density lipoprotein was significantly lower ($p<0.05$) in the untreated control when compared to the normal control group. There was a decrease in total protein of the animals without treatment as (untreated control), although this was not statistically significant when compared to the normal control group and the groups treated with glibenclamide and aqueous and methanol extracts of *A. caillei.* The values for the aspartate aminotransferase, alanine aminotransferase and alkaline phosphate (U/L) were not significantly different in all treatment groups when compared with the normal and untreated control. However, the value for the albumin was significantly higher ($p<0.01$) in the group treated with aqueous extract of *A. caillei* (200 mg/kg body weight) when compared with the untreated control. The levels of the total and direct bilirubin were not significantly altered in all treatment groups when compared with untreated control.

Table 4: Effect of aqueous and methanol *Abelmoschus caillei* extracts on lipid profile and liver function indices in STZ induced diabetic rats.

Parameters	**Streptozotocin (40 mg/kg)**	**Glibenclamide (10 mg/kg)**	**AQ AC (200 mg/kg)**	**AQ AC (400 mg/kg)**	**Meth. AC(200 mg/kg)**	**Meth. AC (400 mg/kg)**
CHOL (mg/dl)	60.15±7.81[a]	105.80±38.13[b]	88.72±25.18[a]	41.10±12.65[a]	60.90±0.43[a]	112.80±31.07[b]
TRIGS (mg/dl)	48.42±25.02[a]	92.35±22.13[b]	81.54±2.85[b]	44.66±6.53[a]	66.30±30.28[b]	76.84±35.80[b]
HDL (mg/dl)	20.83±2.90[a]	37.15±2.73[b]	33.86±0.60[b]	37.15±3.31[b]	34.12±1.65[b]	33.68±1.06[b]
LDL (mg/dl)	29.63±2.24[a]	50.14±35.03[a]	38.56±24.01[a]	4.98±14.64[b]	13.53±7.27[b]	63.73±29.27[a]
AST (U/L)	14.27±0.99[a]	3.50±0.00[c]	23.15±3.26[a]	16.83±1.51[a]	10.85±4.24[b]	13.42±1.72[a]
ALT (U/L)	21.00±2.01[a]	20.00±2.11[a]	16.50±0.17[b]	18.77±3.27[a]	18.55±0.72[a]	18.40±1.14[a]
ALP (U/L)	85.81±19.51[a]	101.3±23.55[a]	31.53±2.30[c]	49.58±4.65[b]	55.35±14.59[b]	52.05±12.92[b]
TP (mg/dl)	6.15±0.22[a]	7.07±0.30[a]	7.24±0.60[a]	7.12±0.12[a]	6.59±0.47[a]	6.59±0.17[a]
ALB (mg/dl)	4.67±0.28[a]	5.24±0.12[a]	7.50±0.16[b]	4.89±0.20[a]	5.44±0.70[a]	4.37±0.69[a]
TBIL (mg/dl)	1.11±0.28[a]	1.30±0.23[a]	2.15±0.60[b]	2.08±0.50[b]	1.60±0.04[a]	1.16±0.05[a]

DBIL (mg/dl)	0.96±0.24[a]	0.74±0.02[b]	1.06±0.16[a]	1.04±0.14[a]	2.14±0.61[a]	0.88±0.25[a]

Values are expressed as Mean ± SEM, P<0.05; n=5, AQ AC: Aqueous extract of *Abelmoschus caillei;* Meth. AC: Methanol extract of *Abelmoschus caillei*, * significant values at P<0.05 when compared to normal control; ** significant values at P<0.01 when compared to diabetic control; CHOL: Cholesterol; TRIGS: Triglycerides; HDL: High density lipoprotein; LDL: Low density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphate; TP: Total protein; ALB: Albumin; T BIL: Total bilirubin; D BIL: Direct bilirubin

Changes in Body Weight

During the experimental study, it was observed that the animals in the normal control group remained healthy and active while the animals in the groups induced with diabetes using STZ at 40 mg/kg body weight experienced severe weight loss and were ill looking. Table 5 shows the mean body weight (in g) of the animals treated with aqueous and methanol extracts of *A. caillei* at different doses (200 and 400 mg/kg body weight for both extracts), as well as the animals that served as normal control, untreated control and standard (given 10 mg/kg body weight glibenclamide) during the 4-week period of the experiment. The changes in body weight were not statistically significantly when the different treatment groups were compared to each other. However, there was a steady rise in the mean body weight of animals from the beginning of the experiment to the 3rd week and then a slight decline by the 4th week in the normal control group, and a continuous decline in the mean body weight of the animals in the groups induced with diabetes until the 2rd week from when there was slight increase in the mean body weight of the animals in the groups treated with glibenclamide and both aqueous and methanol extracts of *A. caillei* at the different doses, while the mean body weight of the untreated control continued to decline.

Table 5: Effect of aqueous and methanol extracts of *Abelmoschus caillei* on the body weight (grams) of STZ induced diabetic rats.

Groups	**Treatment Dose (mg/kg)**	**Mean weight of animals (grams) during experiment**				
		Initial	**1st week**	**2nd week**	**3rd week**	**4th week**
Streptozotocin	40	191.77±23.33	158.36±1.67	156.74±8.82	163.32±10.93	165.03±12.58
Glibenclamide	10	180.00±10.00	158.31±10.14	158.32±13.64	161.75±16.67	161.72±19.22
AQ *A. caillei*	200	171.57±16.91	150.00±5.00	186.71±8.82	190.07±5.77	168.31±4.41
AQ *A. caillei*	400	203.37±1.67	178.34±6.01	190.00±10.00	203.37±14.24	183.33±16.67
Meth. *A. caillei*	200	180.09±15.28	156.77±14.53	158.30±8.33	168.34±13.33	151.72±11.67
Meth. *A. caillei*	400	203.38±14.24	145.00±18.03	160.00±5.00	171.76±12.02	151.70±7.27

Values are expressed as Mean ± SEM, P<0.05; n=5, There is no significant difference between treatments when compared to normal and diabetic control groups. AQ: Aqueous extract; Meth: Methanol extract.

Organ to Body Weight Ratio

The mean values of the weight of heart were 0.65±0.06, 0.58±0.07, 0.62±0.03, 0.62±0.02, 0.76±0.07, 0.63±0.01 and 0.67±0.03, in the normal control, untreated control, and groups treated with glibenclamide (10 mg/kg body weight), aqueous extract of *A. caillei* (200

mg/kg body weight), aqueous extract of *A. caillei* (400 mg/kg body weight), methanol extract of *A. caillei* (200 mg/kg body weight) and methanol extract of *A. caillei* (400 mg/kg body weight) respectively as shown in Table 6. The heart to body weight ratio was not significantly altered in the treatment groups when compared to the normal and untreated control as shown in table 7. The mean values of the weight of the liver for the different groups is represented in Table 6. The liver to body weight ratio in the untreated control and group treated with methanol extract of *A. caillei* at 400 mg/kg body weight (43.26±1.07 and 43.34±0.16 gram/kg respectively) were significantly higher ($p<0.05$) than the normal control group (33.52±1.62 gram/kg) as shown in Table 7. The mean values of the weight of the kidney for the different groups is represented in Table 6. The kidney to body weight ratio in the untreated control (4.99±0.53 gram/kg) was highly significant ($p < 0.01$) than the normal control (3.23±0.06 gram/kg). The groups treated with methanol extract of *A. caillei* at doses of 200 and 400 mg/kg body weight (4.41±0.03 and 4.44±0.02 gram/kg groups is represented in Table 6. The pancreas to body weight ratio in the treatment groups were not significantly altered in all groups.

respectively) and glibenclamide at a dose of 10 mg/kg body weight (4.49±0.12 gram/kg) were significantly higher ($p<0.05$) than the normal control group (33.52±1.62 gram/kg) as shown in Table 7. While the group treated with aqueous extract of *A. caillei* at 400 mg/kg body weight had a significantly lesser ratio ($p<0.05$) when compared to the untreated control. The mean values of the weight of the lungs for the different groups is represented in Table 6. The lung to body weight ratio in the treatment groups were not significantly altered but the untreated control had the lowest value (8.77±1.58 gram/kg). The mean values of the weight of the gonads for the different groups is represented in table 6. The gonad to body weight ratio in the treatment groups were not significantly altered in all groups when compared to the normal control group but the group treated with 400 mg/kg body weight methanol extract of *A. caillei* had a significantly higher ($p<0.05$) gonad to body weight ratio when compared to the untreated control. The mean values of the weight of the pancreas for the different

Table 6: Effect of aqueous and methanol extracts of *Abelmoschus caillei* on the organ weight

Groups	Doses	Mean weight of animals at sacrificial time (grams)	Mean weight of organs (grams)					
			Heart	Liver	Kidney	Lungs	Gonads	Pancreas
Streptozotocin	40	165.03±12.58	0.58±0.07	6.51±0.85	0.73±0.05	1.29±0.22	0.50±0.32	0.37±0.07
Glibenclamide	10	161.72±19.22	0.62±0.03	5.16±0.01	0.58±0.02	1.72±0.38	0.73±0.35	0.32±0.01
AQ AC (200 mg/kg)	200	168.31±4.41	0.62±0.02	5.84±0.15	0.71±0.04	1.91±0.10	1.06±0.41	0.32±0.00
AQ AC (400 mg/kg)	400	183.33±16.67	0.76±0.07	7.41±0.36	0.78±0.04	2.15±0.11	0.24±0.01	0.46±0.06
Meth. AC (200 mg/kg)	200	151.72±11.67	0.63±0.01	6.72±0.46	0.70±0.05	1.74±0.27	0.37±0.16	0.31±0.07
Meth. AC (400 mg/kg)	400	151.70±7.27	0.67±0.03	7.52±1.25	0.76±0.06	1.75±0.05	1.68±0.32	0.40±0.04

Values are expressed as Mean ± SEM, $P<0.05$; n=5, AQ AC: Aqueous extract of *Abelmoschus caillei*, Meth. AC: Methanol extract of *Abelmoschus caillei*

Table 7: Effect of aqueous and methanol extracts of *Abelmoschus caillei* comparing the ratios of weight of organ to the weight of animal

Groups		Organ to body weight ratio (g/kg)					
	Dose (mg/kg)	H: BW	L: BW	K: BW	LG: BW	G: BW	P: BW
Streptozotocin	40	3.87±0.13	43.26±1.07*	4.99±0.53**	8.77±1.58	2.95±1.53	2.59±0.25
Glibenclamide	10	4.84±0.57	40.21±2.79	4.49±0.12*	13.96±3.84	5.14±2.37	2.48±0.28
AQ AC	200	3.72±0.20	34.97±1.78	4.24±0.37	11.44±0.87	6.12±2.31	1.88±0.03
AQ AC	400	3.75±0.32	36.61±2.01	3.86±0.23*[a]	10.63±0.62	1.18±0.05	2.24±0.26
Meth. AC	200	4.00±0.17	42.64±0.16	4.41±0.03*	10.81±1.05	0.89±0.14	1.87±0.34
Meth. AC	400	4.29±0.20	43.34±0.16*	4.44±0.02*	10.38±0.40	9.60±1.23*[a]	2.30±0.10

Values are expressed as Mean ± SEM, P<0.05; n=5, AQ AC: Aqueous extract of *Abelmoschus caillei* Meth. AC: Methanol extract of *Abelmoschus caillei* [a] Significant values at P<0.05; ** Significant values at P<0.01 when compared to normal control *[a] Significant values at P<0.05 when compared to diabetic control H: Heart; L: Liver; K: Kidney; LG: Lungs; G: Gonad; BW:

The results for the histopathology of various organs considered are shown below. Plates 1-5 represents the photomicrographs of the stained sections of the liver, heart, kidney, lungs, and pancreas in the different experimental groups.

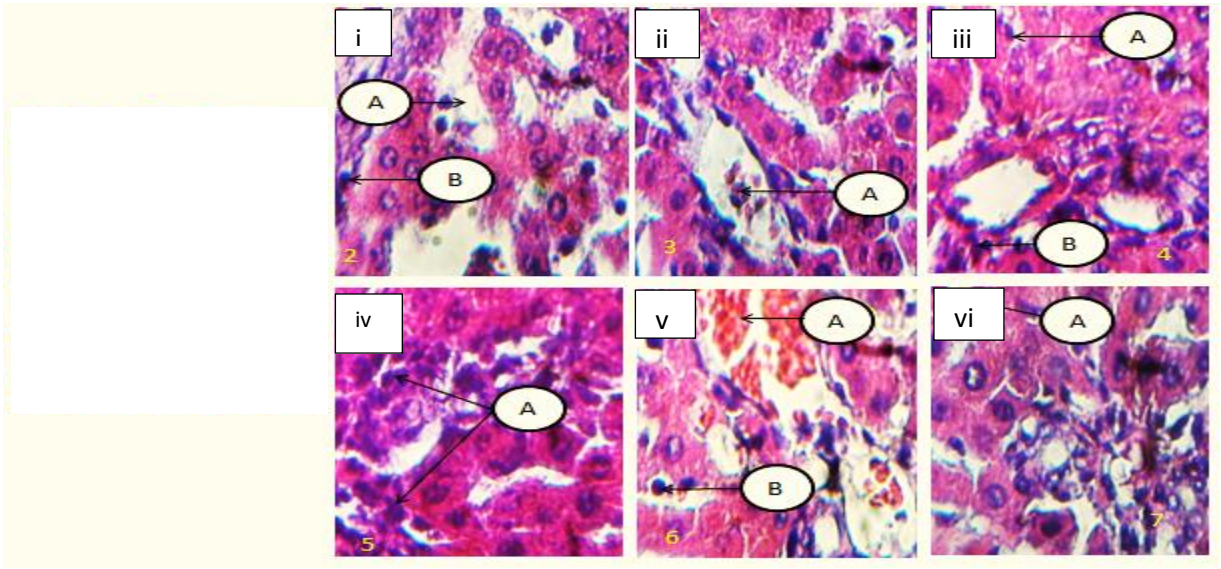

Plate 1: Effect of aqueous and methanol extracts of *Abelmoschus caillei* on the hepatic cells of rats

(i) Rat liver induced with STZ (Diabetes) showed A, patchy macrovesicular steatosis and B, mild periportal infiltrates of lymphocytes, (ii) Rat liver induced with STZ and given Glybenclamide showing A, mild portal vascular congestion, (iii) Diabetic rat liver given 200 mg/kg aqueous extract showing A, mild kupffer cell activation and B, mild periportal infiltrates of lymphocytes, (iv) Diabetic rat liver given 400 mg/kg aqueous extract showing A, mild periportal infiltrates of lymphocytes, (v) Diabetic rat liver given 200 mg/kg Methanol extract showing A, mild vascular congestion and B mild Kupffer cell activation, (vi) Diabetic rat liver given 400 mg/kg methanol extract showing A, mild kupffer cell activation (H&E x 400).

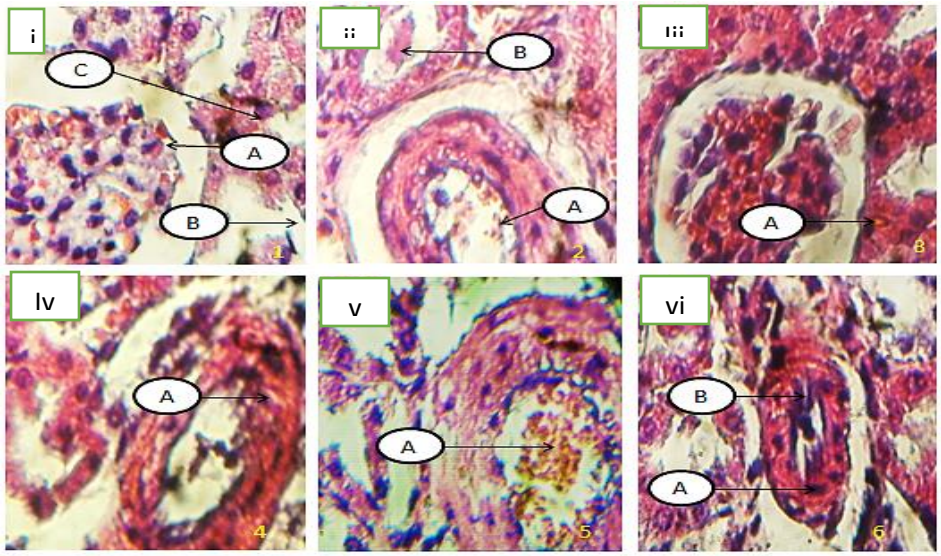

Plate 2: Effect of aqueous and methanol extracts of *Abelmoschus caillei* on the cardiac cells of rats

(i). Diabetic rat heart showed A, patchy coronary intimal ulceration A, (ii) Diabetic rat heart given Glibenclamide showing A, focal vascular intimal erosion and B, asymmetric medial hypertrophy, (iii) Diabetic rat heart given 200 mg/kg aqueous extract showing A, focal intimal erosion and B, asymmetric medial hypertrophy, (iv) Diabetic rat heart given 400 mg/kg aqueous extract showing A, patchy intimal erosion and B, asymmetric medial hypertrophy, (v) Diabetic rat heart given 200 mg/kg methanol extract showing A, mild vascular congestion and B., mild vascular dilatation, (vi) Diabetic rat heart given 400 mg/kg methanol extract showing A, mild medial hypertrophy (H&E x 400).

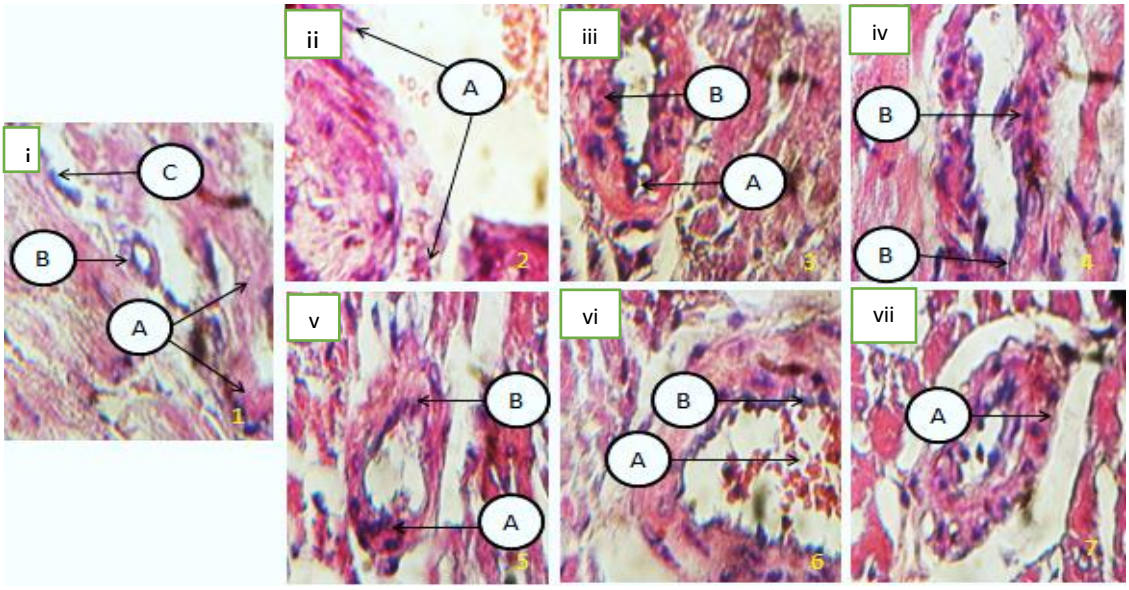

Plate 3: Effect of aqueous and methanol extracts of *Abelmoschus caillei* on the renal cells of rats

(i) Control: Rat kidney composed of A, glomerulus, B, tubules and C, interstitial space, (ii) Diabetic rat kidney given Glybenclamide showing A, mild vascular congestion and B, proteinaceous material, (iii) Diabetic rat kidney given 200 mg aqueous extract showing

A, mild interstitial congestion, (iv) Diabetic rat kidney given 400 mg aqueous extract showing A, mild medial hypertrophy, (v) Diabetic rat kidney given 200 mg Methanolic extract showing A, mild vascular congestion, (vi) Diabetic rat kidney given 400 mg Methanolic extract showing A, mild vascular hypertrophy and B, patchy intimal erosion (H&E x 400)

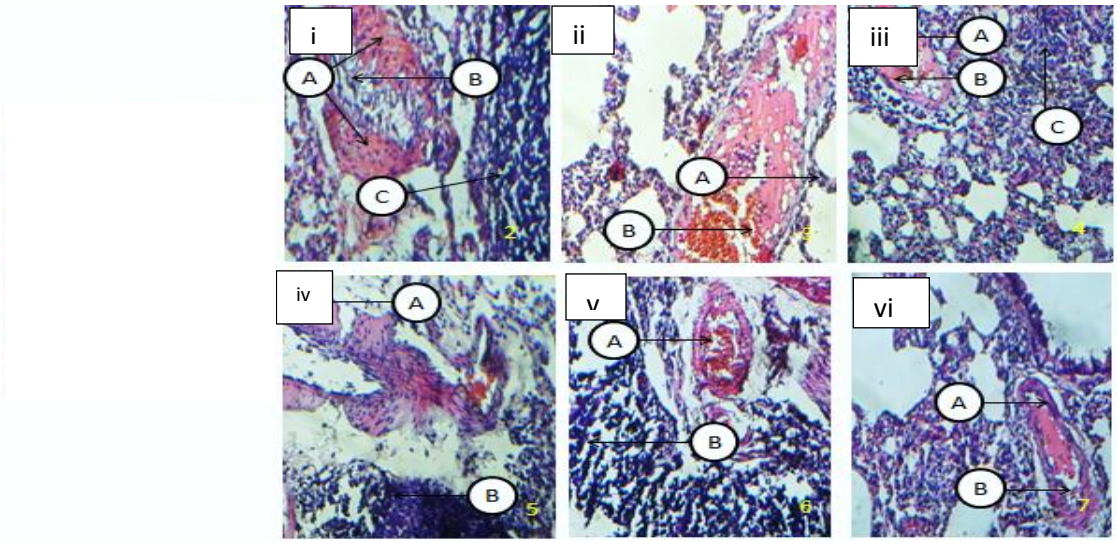

Plate 4: Effect of aqueous and methanol extracts of *Abelmoschus caillei* on the lungs cells of rats

(i) Diabetic rat lungs, given STZ showing A, severe vascular hypertrophy, B, luminal stenosis and C, mild lymphoid activation, (ii) Diabetic rat lungs given Glybenclamide showing A, moderate vascular congestion and B, mild vascular dilatation, (iii) Diabetic rat lungs given 200 mg Aqueous extract showing A, mild vascular congestion and B, mild dilatation and C, mild lymphoid activation, (iv) Diabetic rat lungs given 400 mg Aqueous extract showing A, mild vascular dilatation and B, mild lymphoid activation, (v) Diabetic rat lungs given 200 mg Methanolic extract showing A, moderate vasodilatation and B, moderate lymphoid activation, (vi) Diabetic rat lungs given 400 mg Methanolic extract showing A, mild vasodilatation and B, mild vascular congestion (H&E x 100)

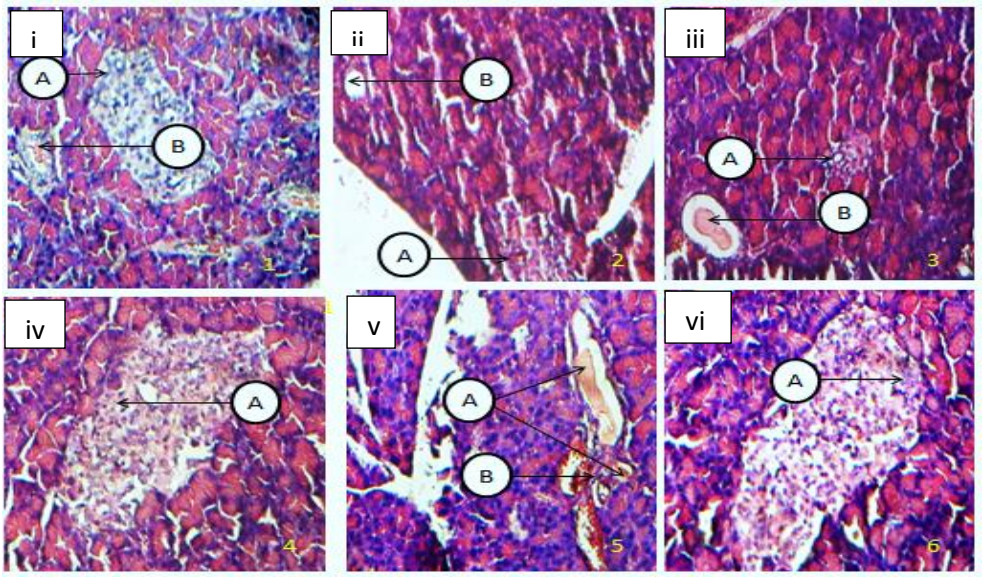

Plate 5: Effect of aqueous and methanol extracts of *Abelmoschus caillei* on the pancreatic cells of rats

(i) Diabetic rat pancreas given Glybenclamide showing A, fairly resurgent islet and B, interlobar ductal proteinaceous material, (ii) Diabetic rat pancreas given 200 mg aqueous extract showing A, faintly resurgent islets and B, fairly dilated and patent interlobar duct, (iii) Diabetic rat pancreas given 400 mg aqueous extract showing A faintly resurgent islets and B mild luminal proteinaceous material, (iv) Diabetic rat pancreas given 200 mg/kg Methanol extract showing A fairly resurgent islets, (v) Diabetic rat pancreas given STZ showing A, moderate proteinaceous luminal casts and B, patchy vascular intimal erosion, (vi) Diabetic rat pancreas given 400 mg/kg Methanol extract showing A, fairly resurgent islets (H&E x 100)

Discussion

The results obtained from acute diabetes study elicited that graded doses (200 and 400) of *Abelmoschus caillei* leaf aqueous extract and glibenclamide had a significant reduction in lowering blood sugar level at 2 hr. and 4 hr. when compared with the untreated control. More so, the extract displayed a significant increase in the percentage blood glucose level at 200 and 400 mg/kg of the aqueous extract, when compared with the untreated controls. This showed that the aqueous extract elicited and onset and potent inhibitory effect of hyperglycemia in 1, 2, and 4 hours after treatment. This agreed with the reports of Ravi *et al.* (2005); Shyam and Ganapaty (2013) that evaluation of antidiabetic activity of methanol extract from the aerial parts of *Barleria montana* in streptozotocin induced diabetic rats. Also no significant reduction in the percentage blood glucose level at 200 and 400 mg/kg of *A. caillei* methanol extract when compared with the control groups. The sub-chronic diabetes study, which lasted for a period of 28 days, showed that *A. caillei* aqueous and methanol extracts at 200 and 400 mg/kg had a significant reduction in lowering blood sugar level at weeks 1, 2, 3 and 4 when compared with the control groups. More so, the extract exhibited a significant increase in the percentage blood glucose level at 200 and 400 mg/kg of the aqueous and methanol extract when compared with the untreated controls. This is in line with the findings of Bisht and Sisoda (2011) that worked on the assessment of antidiabetic potential of *Cinnamomum tamala* leaves extract in streptozotocin-induced diabetic rats.

The results of the hemoglobin and red blood cells count across graded doses (200 and 400) of *A. caillei* leaf aqueous and methanol extract elicited a significant increase in hemoglobin and red blood cells level when compared with the control groups ($p > 0.05$). The administration of the various extracts of *A. caillei* significantly increase the red blood cell count, packed cell volume, hemoglobin, monocytes and granulocytes concentration when compared with the control groups. However, the platelet count in the treated groups display no significant increase when compared with the untreated control. While the lymphocyte percentage had a significantly reduction when compared to the control groups. This concurred with the findings of Vlagopoulos *et al.* (2005) that evaluates anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes, which is the impact of chronic kidney diseases.

The results obtained from this present study showed that the graded doses (200 and 400 mg/kg) of *A. caillei* leaf aqueous and methanol extracts exhibited a significant increase in high density lipoprotein (HDL), low density lipoprotein (LDL), serum cholesterol and triglyceride except at 400 mg/kg of the aqueous extract and 200 mg/kg of methanol extract that have a significant reduction when compared with the untreated control. This is in line with the work of Akindele et al. (2012) reported on the abnormal high serum cholesterol and triglyceride levels common to obese diabetic patients, increasing the risk of atherosclerosis. Hence, this study indicated that diabetes state required high HDL for the removal of bad fat responsible in triggering

diabetes associated atherogenic risk, which was what the extracts displayed.

The total and direct bilirubin concentrations of the graded doses (200 and 400 mg/kg) of *A. caillei* aqueous and methanol leaf extracts elicited a sight significant increase when compared with the control groups. A slight significant increase in total protein across the graded doses of the treatment groups when compared with the untreated control, this could be attributed to the non-enzymatic glycation of proteins associated with diabetes of long term complications. This concurred with the report of Hull and Agarwal (2014) that investigated the potential biomarker and therapeutic target for diabetic nephropathy. The results of the enzymatic liver function test across graded doses of the treatment groups showed no significant difference in the levels of Aspartate aminotransferase (AST); Alanine aminotransferase (AT); Alkaline phosphate ALP specifically at 200 and 400 mg/kg of methanol extract when compared with the untreated control. This is in line with the study of Vitek (2012) that worked on the role of bilirubin and liver enzymes in diabetes, metabolic syndrome and cardiovascular diseases.

The results obtained from the body weight revealed that the aqueous and methanol extracts triggered a slight significant increase in graded doses (200 and 400 mg/kg) of the treatment in weeks 1, 2, 3 and 4 when compared with untreated control that showed a significant weight loss possibly due to tissue wasting during the occurrence of diabetes. This is in agreement with the findings of Zafar and Naqvi (2010) that worked on the effects of STZ-induced diabetes on the relative weights of kidney, liver and pancreas in albino rats. The weight of the understudied organs (heart, kidney, liver, lungs, gonads and pancreas) at graded doses of the extracts had no significant different when compared with the control groups. The values gotten from the heart organ weight across the graded treatment elicited no significant increase when compared with the control groups. However, a slight significant increase in the weights of the liver and kidney in proportion to the body weights when compared with the untreated control. . This could be responsible for the several alteration in the body and organ weight and other dysfunction of body. This is termed of hypertrophy growth in the organs, concurred with the findings of Zafar and Naqvi (2010) that worked on the injurious effects of STZ on selected organs. The weight of the lung and pancreas displayed a sight significant increase in graded doses of the treatment groups when compared with the untreated control. This cud be as a result of the destruction done to beta cells by STZ that altered the relative weights of the pancreas.

The result of the histopathological study showed that graded doses (200 and 400 mg/kg) of the aqueous and methanol leaf extracts of *A. caillei* extracts elicited a lymphocytes associated with inflamed cells and the activation of immune system of liver cells when compared with the untreated control. It also triggered the activation of kupffer cells that activated the immune boosting properties of the plant extracts when compared with the controls. This findings concurred with the work of Amin (2011) that evaluated the hypoglycemic effects in response to *Abelmoschus esculentus* treatment in STZ-induced diabetic rats. The cardiac cells treated with graded doses of the aqueous and methanol leaf extracts of *A. caillei* extracts of the rat heart showed bundles of myocardia fibers, with absent vasculopathy, asymmetric medial hypertrophy and the repaired blood vessel when compared with the untreated control. Similarly, the kidney cells in graded doses of the extracts revealed normal functioning of the glomerulus with a mild vascular congestion when compared with the control

groups. The results obtained from the rat lungs across graded doses of the treatment groups elicited no vascular hypertrophy with ameliorative congestion void of no lymphoid aggregate when compared with the untreated control. The report of Fadillioglu *et al*. (2008) Melatonin treatment against remote open injury induced by renal ischemia reperfusion injury in diabetes mellitus. The results from the frame work of the pancreas histopathological at graded doses (200 and 400 mg/kg) of *A. caillei* aqueous and methanol leaf extracts exhibited a fairly resurgent islets of Langerhans when compared with the untreated control that showed a moderate proteinaceous luminal cast in the duct due to the destruction of beta cells in diabetic with patchy vascular intimal erosion and islets completely absent. This present study is similar and agreed with the reports of Zalzman *et al.* (2003) whose work had a reversal of hyperglycemia in mice by using human expandable insulin-producing cells differentiated from fetal liver progenitor cells.

Conclusion

This study has revealed for the first time that *Abelmoschus caillei* fruit extracts possess remarkable hypoglycemic properties. From the above results, it may be concluded that the extracts did not cause any significant increase in the body weights of the experimental animals. The hematological parameters analyzed were not significantly altered in all groups when compared to normal values. While the activation of immune modulatory activities of bilirubin was promoted by the plant extracts, other biochemical parameters were in their normal value ranges. In addition to the hypoglycemic property of this plant, it also produced a level of ameliorative effect on the vascular injuries caused by STZ and caused the activation of the cells of the immune system. However, further research should be carried out on this plant to identify and isolate the phytochemicals present and to ascertain the mechanism of actions through which this plant exerts its ameliorative effect.

Statement & Declarations

We did intend to submit our manuscript to your reliable journal and a copy of this manuscript has not in any way been under consideration or published elsewhere. No issue concerning the Journal policy, no potential competing interest. All authors have agreed for the publication of this manuscript. All procedures using animals obtained the approval of Life Sciences Institutional Animal Ethical Committee, University of Benin with LS17462 ethical number.

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Competing interests

No competing interest

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