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Full Length Research Paper

Effects of aqueous leave extract of *Ficus exasperata* on pathophysiology and histopathogy of alloxan-induced diabetic albino rats

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The effects of treatment with aqeous extract of *Ficus exasperata* on the pathophysiology and histopathology in alloxan-induced diabetic rats was studied. Thirty rats divided into five treatment and one control groups (n = 5 rats each) were used for the study. Rats in the treatment groups were induced by a single intraperitoneal injection of 150 mg/kg alloxan monohydrate. Diabetic groups were thereafter treated with 100, 200 and 300 mg/kg, respectively of acqeous extract of *F. exasperata*, the fourth group was treated with 10 mg/kg glibenclamide, the last group was not treated after induction while the control (non-diabetic) group received distilled water. Hyperglycemia was recorded in all induced rats after alloxan induction, while treatment with the different concentrations of the plant extract reversed hyperglycemia within four days. Values of Packed cell volume (PCV), Haemoglobin concentration (Hb) and Red blood cell count (RBC) were higher in rats treated with the extract than in rats treated with glibenclamide, while ionoregulatory distruptions observed in the diabetic groups reduced significantly ($p < 0.05$) in rats treated with the extract. Lipid profile parameters were higher in rats treated with glibenclamide compared to groups treated with the extract. Treatment with the plant extract ameliorated the various degenerations observed in the pancreas, liver and kidney in contrast to untreated group and group treated with glibenclamide. Results from this study demonstrated the ameliorative effects of acqeous leave extract of *F. exasperata* on the pathophysiological and histopathological complications of diabetes mellitus.

Key words: Diabetes mellitus, *Ficus exasperata,* pathophysiology, hispathology.

INTRODUCTION

Diabetes mellitus has been described as a metabolic disease marked by an elevated blood glucose concentration and the excretion of excess glucose in the urine (Michael, 1999; Peter, 1993; Steiner et al., 1990). The disease occurs either because of lack of insulin or the presence of factors that opposes the actions of insulin (Evans, 1995; Ghosh et al., 2004; Harris, 1995).

The most common method of management of diabetes mellitus is the administration of insulin and other hypoglycaemic agents such as sulphonylureases and biguanides (Evans, 1995 and Ghosh et al., 2004). However, complete cure of the disease has been eluding physician for centuries and the quest for the development of more effective antidiabetic/hypoglycaemic agents is being pursued relentlessly (Geetha et al., 1994; Ghosh and Surywarshi, 2001).

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Many herbal products including several minerals and metals have been described for the cure of diabetes mellitus (Ghosh and Surywarshi, 2001). Herbal formulation alone or in combination with oral hypoglycaemic agents sometimes produces good therapeutic responses in some resistant cases where modern medicines alone have failed (Anturlikar et al., 1995; Ghosh et al., 2004). In many Nigerian communities, various herbal formulations have been recommended for the treatment and management of diabetes mellitus among which is *F. exasperata* (Gidado et al., 2000). Different parts of *F. exasperata* are used for the treatment of various diseases such as ulcers, anaemia, piles, jaundice, haemorrhage of the nose and mouth, diabetes mellitus and various diseases of the blood.

Despite the increasing use of many local herbs in the treatment of various disease conditions, there still exist the problems of standardization for dosage of such herbal products for therapy as well as the effects of the administration of such herbs on the physiology of the treated patients. This study therefore investigated the hypoglycemic potentials of *F. exasperata* leaves extract on alloxan-induced diabetic rats and its effects on the pathophysiology and histopathology in the treated rats.

MATERIALS AND METHODS

Animals

Adult male albino rats *Sprague dawley* weighing between 150 to 180 g were obtained from the animal house of the Department of Biological Sciences, University of Agriculture, Abeokuta for the study. They were kept in rat cages at room temperature (27 ± 2°C) and humidity (55 ± 5%) and a 12 h cycle of light and dark. They were given free access to commercial animal pelleted diet and water. All experiments were performed in accordance with the National Institute of Health guidelines of care and use of laboratory animals.

Plants materials, extracts preparation and treatment

Fresh leaves of *F. exasperata* were collected from the University of Agriculture, Abeokuta campus. The plants were authenticated by expert at the Department of Forestry and Wildlife of the University. Cold water extract of the fresh leaves was prepared by blending 1 kg of the leaves in 100 ml of distilled water and then squeezing out the extract from the plant material. The stock extract was stored at 4°C and diluted to the desired concentration when needed. Diluted extract were administered orally to the rats using oral zoned at 10:00 h daily after an overnight fast for 4 consecutive days. Blood glucose concentration was monitored before and after the administration of treatment.

Experimental set-up

Thirty rats were randomly divided into six groups of five rats each (25 diabetic rats, 5 normal rats) and used for the study. Group 1: Normal control rats, not treated throughout the experiment, but were given free access to standard animal pellet and water; Group 2 to 4 (with code AF1, AF2 and AF3, respectively): Diabetic rats treated with 100, 200 and 300 mg/kg body weight of *F. exasperata* leaves extract daily for four days, respectively; Group 5: Diabetic rats treated with glibenclamide and Group 6: Diabetic rats, non-treated.

Induction of diabetes mellitus

Alloxan induction

The rats were fasted overnight and then subjected to a single intraperitonial injection of 150 mg/kg of alloxan monohydrate dissolved in 0.9% normal saline. Surviving rats after 7 days with blood glucose concentration above 200 mg/dl were considered as diabetic model and used for the experiment as previously recommended (Geetha et al., 1994).

Blood collection and dissection

At the end of the experiment, blood samples were collected from each rat by cardiac puncture into heparinized tubes and the plasma was separated by centrifugation at 1100 × g for 10 min. The rats were sacrificed and dissected. The pancreas, liver and kidney were collected, fixed in 10% formalin and processed routinely for histopathological evaluations.

Blood chemical analysis

Fasting blood glucose was determined using the strip of digital ACCU-CHEK advantage glucose meter (Roche diagnostic, Mannheim Germany). A drop of blood was obtained from tip of conscious rats and placed on the strip. The reading on the meter was noted and recorded as the blood glucose concentration. Concentration of total protein in the blood of each animal was determined by using the biuret method while urea concentration in the blood samples was determined using the Urease -Berthelot (enzymatic) colorimeter method.

Blood chemistry

The flame photometry method was used to determine the concentration of sodium and potassium in the plasma of each rat while colorimeter method was used to determine the concentration of calcium in the blood of the animals. Catalase and peroxidase activities in the plasma were determined using the spectrophotometric method.

Lipid profile

Total cholesterol and triglyceride were determined using the enzymatic (cholesterol oxidase) and (colorimeter) methods, respectively. Low density lipoprotein (LDL) was estimated as the difference between total cholesterol and the content of the supernatant after precipitation of the LDL fraction, while HDL was calculated from the data obtained.

Haematological studies

The PCV was determined by using the microhaematocrit centrifuge. The total haemoglobin concentration (Hb) of the blood samples was estimated using the cyanomethaemoglobin method. The white blood cell count (WBC), Red blood cell count (RBC), Mean cell

Table 1. Heamatology of treated diabetic rats.

Groups	PCV (%)	Hb (g/dl)	WBC (cm^{-3})	RBC ($\times10^{12}$/l)	MCV ($\times10^{-15}$)	MCH ($\times10^{-12}$/g)	MCHC (g/dl)
Control	45.2 ± 2.1^{bc}	16.1 ± 1.9^{bc}	$16,000\pm2.1^{a}$	4.53 ± 2.9^{d}	9.93 ± 1.1^{abc}	35.54 ± 3.9^{b}	0.33 ± 2.9^{ab}
A_1	53.4 ± 1.3^{e}	18.8 ± 2.6^{d}	$16,150\pm1.4^{a}$	4.16 ± 2.5^{c}	12.74 ± 3.4^{cd}	45.19 ± 2.2^{d}	0.34 ± 2.9^{abc}
A_2	45.3 ± 1.9^{bc}	15.3 ± 2.7^{bc}	$16,350\pm3.9^{ab}$	4.85 ± 1.1^{de}	9.28 ± 3.5^{ab}	31.55 ± 2.5^{ab}	0.32 ± 2.9^{a}
A_3	51.3 ± 1.4^{d}	17.2 ± 3.5^{c}	$16,600\pm4.0^{abc}$	4.28 ± 3.4^{cd}	11.92 ± 4.2^{c}	40.19 ± 1.6^{bc}	0.32 ± 2.9^{a}
G	41.2 ± 2.6^{b}	14.2 ± 4.0^{b}	$21,300\pm1.2^{d}$	3.47 ± 2.0^{ab}	11.82 ± 3.1^{bc}	40.92 ± 3.4^{c}	0.34 ± 2.9^{abc}
U	31.8 ± 1.9^{a}	10.2 ± 2.3^{a}	$27,250\pm3.2^{e}$	3.30 ± 3.2^{a}	9.39 ± 1.4^{ab}	30.91 ± 1.9^{a}	0.33 ± 2.9^{ab}

Values are mean ± SE. Values within a column having different superscripts are significantly different at $p < 0.05$.

haemoglobin (MCH), mean cell volume (MCV), and the mean cell haemoglobin concentration (MCHC) were also determined.

Statistical analysis

Data obtained were expressed as mean ± SE significant difference between test and control groups and tested using ANOVA of the SPSS computer software, version 16.0 at 95% confidence interval (CI).

RESULTS

Blood glucose

The blood glucose concentrations prior to induction ranged between 80.83 and 82.85 mg/dl (Figure 1). Marked increase in blood glucose concentrations (ranging from 334.80 to 387.35 mg/dl) were however recorded after alloxan injection. Treatment of diabetic rats with the plant extract and glibenclamide caused marked reduction in glucose concentration after each day of treatment. Rats treated with various concentrations of *F. exasperata* had significantly lower blood glucose levels ($p < 0.05$) after each treatment compared to rats treated with glibenclamide. Hyperglycemia was reversed in all treated rats by the 4th day of treatment. Significantly lower glucose levels ($p < 0.05$) was however recorded in rats treated with various concentrations of the plant extract than those treated with glibenclamide. Blood glucose levels in rats treated with various concentrations of the plant extract were observed to reduce with increasing concentration of the extract.

Haematology

The values PCV, Hb and RBC were significantly lower ($p < 0.05$) in untreated diabetic rats than in treated rats (Table 1). Treatment of diabetic rats with various concentrations of the plant extract increased ($p < 0.05$) the values of PCV, Hb and RBC compared to rats treated with glibenclamide. WBC count was highest in the untreated diabetic rats, while groups treated with the plant extract had lower WBC count than rats treated with glibenclamide.

Blood chemistry

Hypernatremia, hyperkalemia and hypercalcemia were recorded in untreated diabetic rats compared to the normal and treated groups. Rats treated with various concentartions of the plants extract showed improvement in ionoregulatory distruptions compared to rats treated with glibenclamide (Table 2). Concentrations of total protein and urea were significantly lower ($p < 0.05$) in the blood of treated and untreated rats than the normal rats. Rats treated with the plant extract however had significantly higher ($p < 0.05$) total protein and urea concentration than rats treated with glibenclamide. Catalase and peroxidase unit activity were highest in the diabetic control groups than in the treated groups. Rats treated with various concentrations of the plant extract recorded lower antioxidant enzyme activities ($p < 0.05$) than those treated with glibenclamide.

Plasma lipid profile

The concentrations of total cholesterol, triglyceride, Low Density Lipoprotein, LDL/HDL ratio and Coronary Risk Index were highest in untreated diabetic rats, whereas the values reduced significantly ($p < 0.05$) in the treated groups (Table 3). Groups treated with the plant extract however had lower total cholesterol, triglyceride, Low Density Lipoprotein, LDL/HDL ratio and Coronary Risk Index values than rats treated with glibenclamide. HDL concentration was lowest in the untreated diabetic group.

Histological studies

The pancreas

Pancreas of the control rats showed normal appearance of the islets of Langerhans scattered throughout the tissue (Figure 2A). Marked vacoulations of the focal

Table 2. Blood chemistry of treated diabetic rats.

Groups	Na^+ (mmol/L)	K^+ (mmol/L)	Ca^{2+} (mmol/L)	Total protein (g/L)	Urea (mg/dl)	Peroxidase activity (U/L)	Catalase activity (U/L)
Control	98.2±1.5^{a}	7.8±3.3^{abc}	2.4±2.5^{ab}	93.9±1.5^{f}	65.4±3.8^{e}	1.052±2.7^{ab}	0.631±2.3^{a}
A_1	102.3±1.4^{bc}	7.2±2.4^{ab}	2.2±1.9^{a}	78.3±2.7^{bc}	57.8±3.3^{cd}	1.102±3.3^{bc}	0.986±1.5^{bc}
A_2	106.8±2.9^{c}	7.0±1.7^{a}	2.6±4.4^{abc}	80.1±2.5^{c}	54.6±1.2^{c}	1.003±2.8^{a}	0.686±3.9^{a}
A_3	100.5±1.6^{b}	7.9±2.7^{abc}	2.5±3.6^{ab}	83.5±3.6^{de}	58.5±2.5^{d}	1.103±2.5^{bc}	0.860±2.2^{b}
G	122.3±3.5^{e}	10.0±1.9^{d}	2.8±3.8^{bc}	73.1±4.8^{a}	46.8±1.3^{a}	1.902±4.8^{e}	1.158±2.4^{d}
U	117.8±2.6^{d}	19.8±2.4^{e}	3.7±2.3^{d}	75.7±2.9^{ab}	48.8±1.4^{ab}	1.853±1.5^{d}	1.516±4.0^{e}

Values are mean ± SE. Values within a column having different superscripts are significantly different at $p < 0.05$.

Table 3. Plasma lipids of treated diabetic rats.

Group	Total cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	LDL/HDL	CRI
Control	84.6±3.4^{a}	69.2±2.9^{a}	59.84±2.4^{bc}	38.6±3.9^{a}	0.65±3.9^{a}	1.41±1.5^{a}
A_1	108.5±3.6^{bc}	73.2±3.4^{bc}	66.94±4.6^{de}	56.2±2.5^{b}	0.84±2.5^{b}	1.62±2.3^{b}
A_2	100.4±2.4^{b}	74.5±3.8^{c}	52.34±1.0^{b}	63.0±4.7^{c}	1.20±4.4^{d}	1.92±2.5^{d}
A_3	106.7±2.3^{b}	75.8±4.5^{cd}	62.06±3.9^{c}	59.8±1.4^{b}	0.96±5.3^{c}	1.72±3.8^{c}
G	115.4±4.9^{d}	86.3±2.4^{e}	66.66±3.4^{d}	66.0±3.5^{cd}	0.99±2.4^{c}	1.73±3.9^{c}
U	123.1±2.6^{e}	94.5±2.5^{f}	46.60±4.5^{a}	95.4±1.4^{e}	2.05±3.5^{e}	2.64±2.4^{e}

Values are mean ± SE. Values within a column having different superscripts are significantly different at $p < 0.05$.

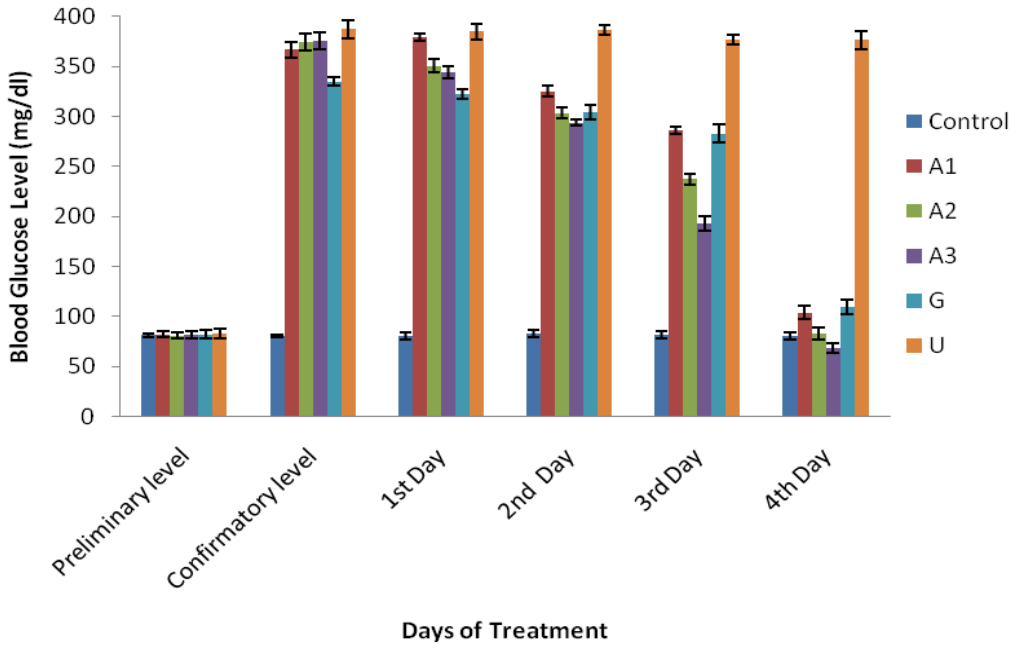

Figure 1. Blood glucose concentration of treated alloxan-induced rats.

areas of the islets of Langerhans was observed in the pancreas of untreated alloxan-induced rats and rats treated with glibenclamide (Figure 2B). However, the degree of vacoulations was observed to reduce in rats treated with various concentrations of the plant extract (Figure 2C).

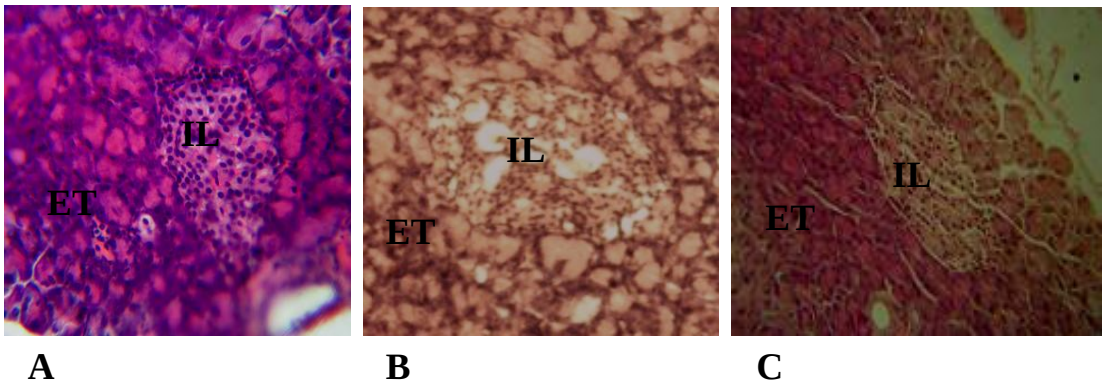

Figure 2. (A) Pancreas of control rat showing normal appearance of the islet of langerhans (IL) located in the exocrine tissue (ET). ×300 H and E; (B) pancreas of untreated alloxan-induced diabetic rat, showing marked degeneration of the Islets of Langerhans (IL). ×300 H and E; (C) pancreas of alloxan-induced diabetic rat treated with 300 mg/kg *F. exasperata* showing mild vacoulation of the islets of langerhans (IL).×300 H and E.

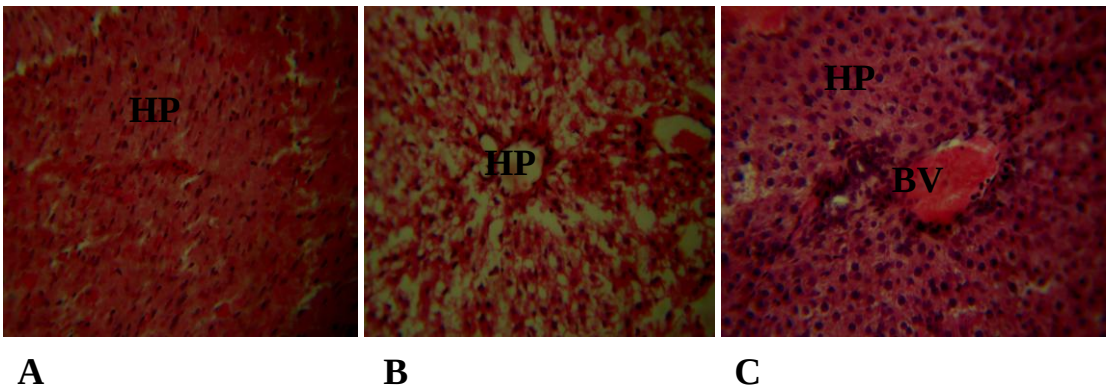

Figure 3. (A) Liver of control rat, showing normal arrangement of the hepatocytes (HP) with no visible lesion. ×300 H and E; (B) liver of untreated alloxan-induced rat showing severe degeneration of the hepatocytes (HP) with numerous vacuolations. ×300 H and E; (C) liver of alloxan-induced diabetic rat treated with 200 mg/kg *F. exasperata* showing congestion of the blood vessels (BV). ×300 H and E.

The liver

Histological examination of the liver of the control rats revealed normal appearance of the hepatocytes (Figure 3A). Liver of untreated diabetic rats revealed severe degenerations and vacoulations of the hepatocytes (Figure 3B), whereas rats treated with various concentrations of *F. exasperata* extract revealed improvement in the observed vacoulations (Figure 3C).

The kidney

Histology of the kidney of control rats showed normal appearance of the organ with no visible lesions (Figure 4A). Kidneys of untreated diabetic rats revealed marked degeneration of the glomeruli with wider glomerular spaces (Figure 4B). However, kidneys of rats treated with 200 mg/kg of the plant extract revealed normal glomeruli but mild vacoulations of the tissue (Figure 4C).

DISCUSSION

Diabetes mellitus is a metabolic disorder that is characterized by abnormally high level of blood glucose (Nimenibo-Uadia, 2003). Marked increase in blood glucose concentrations observed in all rats after the single intraperitoneal injection of alloxan monohydrate confirmed the induction of insulin-dependent diabetes mellitus (IDDM) in the rats. Earlier works by Anturlikar et al. (1995), Gidado et al. (2000) and Ghosh and Surywarshi (2001) all reported multiple increases in blood glucose concentration after a single injection of alloxan monohydrate. This increase is due to the toxic effect of alloxan on the beta cells of the pancreas (Bansal and Kiduai, 1980; Bansal, 2001).

All treated rats responded positively to treatment with

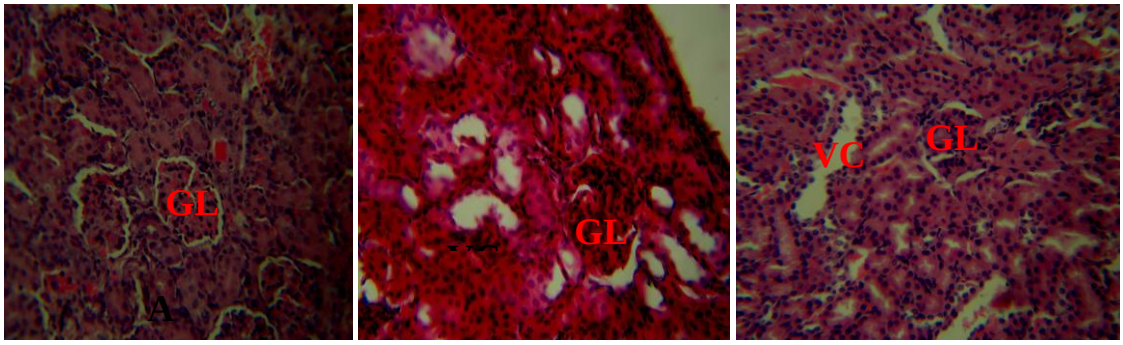

Figure 4. (A) Kidney of normal rat showing normal appearance of the glomeruli (GL). ×300 H and E; (B) kidney of untreated alloxan-induced diabetic rat showing vacoulation of the kidney (VC). ×300 H and E; (C) kidney of alloxan-induced rats treated with 200 mg/kg *F. exasperata* showing normal glomerulus with mild vacoulations of the tissue. ×300 H and E.

the plant extract and the standard antidiabetic drug. This therefore confirmed the hypoglycaemic potential of extract of *F. exasperata* for the treatment of diabetes. Various concentrations of the plant extract exhibited better hypoglycemic effects than glibenclamide as rats treated with the exctract recorded higher reduction in blood glucose concentration than the standard anti-diabetic drug. Earlier study by Ghosh et al. (2004) also reported that ethanolic extract of the bark of *F. hispida* caused better hypoglycemic effect than gliben-clamide 2 h after administration.

Results obtained from this study demonstrated the induction of acute anemia in the diabetic rats. However, treatment with the extract increased the values of PCV, Hb and RBC compared to the untreated rats and rats treated with glibenclamide. This result therefore demonstrated the haemopoetic ability of *F. exasperata* (Ogwumike, 2002).

Hypernatremia is a physiological state which is common in conditions of water loss in excess of ion loss, while increased potassium concentration is seen in excess destruction of cells with redistribution of k^+ from the intra to the extracellular compartment (Uthman, 1994). These physiological conditions could have accounted for the hypernatremia and hyperkalemia recorded in treated and untreated diabetic rats in this study. These conditions were however observed to improve in rats treated with the extract compared to those treated with glibeclamide.

Concentrations of total cholesterol, triglyceride, HDL/LDL ratio and CRI are indicators of susceptibility to cardiovascular diseases (CVDs) (Appleton, 2002; Halim and Ali, 2002; Uthman, 1994). The marked reduction of these parameters in diabetic groups treated with the extract compared to those treated with glibenclamide demonstrates the potential of *F. exasperata* to reduce the risk of CVDs. Treatment of diabetes mellitus with the extract could therefore prevent and/or reduce the risk of cardiovascular complications of diabetes. Report by Nimenibo-Uadia (2003) also stated significant decrease in plasma cholesterol in blood of diabetic rats treated with aqueous extract of *Canavalia ensiformis.*

Marked vacoulations of the islets of Langerhans observed in the pancreas of untreated diabetic rats is due to toxic action on the alloxan. Alloxan monohydrate has been described as a toxic glucose analogue which selectively destroys the insulin-producing beta cells of the pancreas (Bansal and Kiduai, 1980; Bansal, 2001). Mild vacoulations of the the islets was however observed in pancreas of rats treated with the plant extract which is probably indicative of the ability of the extract to restore the degenerations cause by alloxan-induced diabetes mellitus. Complete restoration could however be possible if the extract was administered for longer duration (Thomas, 2002). Severe degeneration of the hepatocytes and glomeruli of the liver and kidney, respectively was observed in the untreated diabetic rats. Report by Malmberg (1995) stated that diabetic nephropathy is an important cause of mortality and morbidity and among the most common causes of end-stage renal failure. The potentials of the extract to ameliorate the pathological effects of diabetes mellitus was also demonstrated as rats treated with the extract showed mild degeneration compared to rats treated with glibenclamide.

Results of this study have confirmed the hypoglycemic potential of acqeous extract of *F. exasperata* and have also demonstrated its potential as an effective herb in the treatment and management of the disease. It is also worthy to note that different doses of the plant extract used in this study demonstrated the haemopoetic, hypolipidemic and antioxidant abilities of the plant. Results obtained from this study have therefore demonstrated the ability of *F. exasperata* to ameliorate the pathophysiological and histopathological complications caused by diabetes mellitus. Further studies is therefore neccessary to isolate and characterise the active ingredents of the

plant extract.

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