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Alloxan-induced Diabetes causes liver functions and lipid profile changes in Albino Wistar rats: Role of ethanolic leaf extract of *Guiera senegalensis* (Combretaceae)

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ABSTRACT

In most of African countries, a large number of diseases are treated administering plant infusions to the patients. *Guiera senegalensis* (Gs) has been used many diseases in Northern Nigeria, but its effects on liver function test, blood glucose level and lipid profile in diabetic rats has not been documented. Thirty five male albino rats with average weight of 200g-250g were used for study. They were divided into five groups of seven rats each: Group A (normal control) were not induced with diabetes. Group B (diabetic control) Groups C and D and E were induced with diabetes and treated daily with 100mg/kg, 150 mg/kg and 200 mg/Kg body weight of Gs leaf extract respectively for three (3) weeks. At the end of this experimental procedure, rats were anaesthetized with diethyl-ether vapour. Blood samples were collected through cardiac puncture for measurement of serum metabolites. The result of the present study demonstrated that administration of ethanolic leaf extract of Gs in the alloxan induced diabetes rats has not shown any significant changes in the activities of ALP, AST and ALT when compared with diabetic control. However, a significant increase was recorded in the serum total protein (TP) and albumin (ALB) when all the doses of Gs were compared with diabetic control. Gs administration to the alloxan induced diabetic rats was found to lower the serum glucose level significantly moreover significantly decrease in plasma cholesterol, TG and LDL level, and a significant increase in HDL level. Administration of ethanolic leaf extract of *Guiera senegalensis* to alloxanized diabetic rats at the doses considered possess hypoglycemic activities and the extract is not toxic to the liver.

Key Words: Alloxan, Cholesterol, Diabetes, *Guiera senegalensis* and Liver enzymes

INTRODUCTION

Uncontrolled diabetes leads to several micro-vascular (neuropathy, nephropathy, retinopathy) and macro-vascular (atheroma) complications that affect many organs of the body (Chahinez *et al*., 2012) experimental findings suggest that the liver, similar to other organs, may also be affected by diabetes mellitus (DM) in the long-term (Amanda *et al*., 2013). Liver compromising by diabetes is known by the designation of non-alcoholic fatty liver disease (NAFLD), which, histologically, cannot be distinguished, from ethanol-induced hepatic steatosis (Harrison and Diehl, 2002). The liver helps maintain normal blood glucose concentration in the fasting and postprandial states (Elizabeth and Harris, 2005). Individuals with type 2 diabetes have a higher incidence of liver function test abnormalities than individuals who do not have diabetes. In animal models, chronic hyperinsulinemia is found to predispose the liver to the relative resistance to insulin. This is characterized by a failure of insulin to signal an increase in insulin receptor substrate-2. Upregulation of sterol regulatory element-binding protein 1c (SREBP-1c) also occurs, leading to increased lipogenesis (Shimomura *et al*., 2000). Alloxan diabetes induced biochemical changes in the blood and morphological and ultrastructural lesions in rat liver, ranging from steatosis to steatohepatitis and liver fibrosis, which closely resemble changes in the human liver (Amanda *et al*., 2015). Phytochemical studies carried on Guiera *senegalensis* by (Samboro *et al.,* 2011) showed the presence of seven (7) active principle; Alkaloids, Tannins, Flavonoid, Anthrecenes, Sterol And triterpenes, Cardiotoic heterosides and Saponin.

In most of African countries, a large number of diseases are treated administering plant infusions to the patients. This herbal therapy is used on a traditional basis and bequeathed through generations. Ethnopharmacology is still used up today as a treatment for sickness conditions ranging from abdominal pains, conjunctivitis and diarrhoea, to sexually transmitted infections (Stefano et al., 2014).

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Plants used traditionally as medicines constitute potentially useful resources of new drugs for treatment and control of diseases including diabetes. The plant *Guiera* senegalensis is a shrub found abundantly in the region of West and Central Africa, the shrub can grow to a height of 3m to 5m according to habitat (Samboro *et al*., 2011). The people of the Hausa of Northern Nigeria and Southern Niger called it "Sabara". Although *Gs* leave extract has been used to treat jaundice and many diseases in Northern Nigeria, its leave extract effects on liver function test, blood glucose level and lipid profile in diabetic rats has not been documented.

MATERIALS AND METHODS

Preparation of Ethanolic leaf extract of *Guiera senegalensis*

The plant Gs was collected in the mountain of Barunde, Gombe state in Northern Nigeria. The plant was identified and authenticated in the Department of Biological Sciences, Gombe State University, Nigeria. (Voucher number: 648) The leaf was carefully removed from the plants and dried in shady environment for two weeks. It was then pounded with a mortar and pestle. Extraction of the plant was through maceration using 70% ethanol (Aniagu, 2004). 100 g of Gs was dissolved in 700ml of the mixture of 70% ethanol. It was shocked vigorously for 2 hours and then allowed to settle for 2 days. Decantation and filtration were used to separate soluble from the insoluble portion extract was decanted and filtered by using Muslin cloth followed by Whatman no 1 filter paper finally filtered using vacuum pump (Serial number: R00100188 Stuart U.K.) and subjected to evaporation using hot plate at 40^{o}C to obtain the pure extract from the leaves. 14g of pure extract Gs was obtained from 100g of the raw.

Acute Toxicity Studies

The LD_{50} of Gs was determined according to Lorke's method (Lorke, 1983). In the first stage, three groups of three rats each (n = 3) were given 10, 100 and 500 mgkg^{-1} of Gs, respectively. The animals were then observed for 24 hrs for possible signs of toxicity or mortality. In the second phase, further specific doses of 1000, 1500 and 2000 mgkg^{-1} of Gs were administered to three rats each (n = 1), respectively. Animals were observed for 24 hrs. The LD_{50} was calculated using the formula;

$LD_{50} = \sqrt{\Delta_0 \times \Delta_{100}}$ Where,

Δ_0 is the least dose that resulted in mortality

Δ_{100}= the highest dose that gave no mortality (Lorke, 1983)

Experimental Design

Thirty five male albino rats with average weight of 200g-250g were obtained from the Animal farm unit of the National Veterinary Institute (NVRI) Vom, Plateau State, Nigeria. The rats were kept in metabolic cages which were cleaned of metabolic waste twice a day. They were exposed to 12 hours each of natural daylight and darkness and given rat chow and water *ad libitum* for 2 weeks to acclimatize. They were divided into five groups of seven rats each: Group A (normal control) were not induced with diabetes. Group B (diabetic control) was induced with diabetes, but not treated with Gs. Groups C and D and E (diabetic test groups) were induced with diabetes and treated daily with 100mg/kg, 150 mg/kg and 200 mg/Kg body weight of Gs leaf extract respectively for three (3) weeks. The study was conducted in accordance with internationally-accepted principles for laboratory animal use and care.

At the end of this experimental procedure, rats were anaesthetized with diethyl-ether vapour. Blood samples were collected through cardiac puncture (Ebunlomo *et al.,* 2012). 4 ml of blood was collected in lithium heparin bottles. Blood samples were centrifuged at 3000 x g for 15 minutes. Plasma was collected into bottles using a Pasteur pipette and stored frozen for later analysis.

Induction of Diabetes

Alloxan monohydrate was obtained from Sigma Aldrich (Chemical Co. St. Louis, MO, USA). Five per cent solution of the drug was prepared and used to induce diabetes in rats by intraperitoneal injection at a dose of 150mg/kg body weight to rats fasted for 16 hours. This drug has been reported to act by selectively destroying the beta cells of the pancreas, thereby, reducing insulin secretion (Weaver *et al*., 1978 and Adesokan *et al*., 2009). The blood glucose level was measured 72 hours after alloxan administration using a glucometer. Rats whose blood glucose level greater than 200mg/dL were included in test groups (Stanley and Venogopal, 2001).

Enzymes Assay and Measurement of Serum Metabolites

Determination of Serum Alkaline phosphatase, Alanine Aminotransferase and Aspartate Aminotransferase

The measurements of the activities of these liver enzymes were carried out by spectrophotometric determination of their absorbance using analytical grade reagents kits (Randox Laboratories Limited, Crumlin, and County Antrim, United Kingdom). The evaluation was done as described by Friday et al. (2010).

Estimation of Protein Concentration

The protein concentration of various samples was determined using the Biuret method as described by Edem *et al.* (2012). The principle of the test was based on the formation of a coloured complex

between proteins and cupric ions in alkaline solution. The result was expressed in mg/mL.

Determination of serum Albumin

The measurement of serum albumin is based on its quantities binding to indicator 3, 3', 5, 5'-tetrabromo-merosol sulphonephthalein (Bromocresol green). The albumin- Bromocresol green complex absorbed maximally at 578nm. Absorbance was proportional to the concentration of albumin in the sample.

Determination of blood glucose level

The blood glucose level was determined using ne touch glucose meter (Roche, Mannheim Germany. Serial number: GU 03870918 and Art number: 06583202001)

Determination of lipid profile

The cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) assays were carried out by the enzymatic method described by Allain *et al*. (1974)

Statistical analyses

The results were computed for mean values $\pm$ S.E.M. Statistical comparison between variables was carried out using analysis of variance (ANOVA) Tukey's post-hoc method was used to compare the differences between the means. A value of $P < 0.05$ was considered significant.

RESULT

Acute Toxicity Studies: There were no deaths observed in both the first and second phases of the acute toxicity studies. Hence, Gs is considered safe above 2000 mg/kg. Therefore, three doses of 100 mg/kg, 150 mg/kg, and 200 mg/kg were chosen for the experiment.

Tables 1 show the activities of ALP, AST, ALT, TP and ALB respectively in the serum of the experimental animals. There was a significant difference ($P < 0.05$) in the ALP in groups D and E compared to the diabetic control. No significant difference ($P > 0.05$) in the mean value of AST and ALT in the test groups compared to the diabetic control. However, a significant difference was recorded in TP and ALB in the test groups when compared to the diabetic control. Figure 1 shows the hypoglycaemic activity of ethanolic leaf extract of *Guiera senegelensis* in alloxan induced diabetic rats. Administration of alloxan increases the serum glucose level in normal rats. There was a significant ($P < 0.05$) decrease in serum glucose when the treated groups were compared with the diabetic control. The dose of 100mg/Kg, 150mg/Kg and 200mg/Kg of the ethanolic leaf extract of *Guiera senegelensis* decreased significantly ($P < 0.05$) the serum glucose level towards normal levels.

The lipid profiles of normal control and extract treated diabetic rats were depicted in table 2. There was a significant ($P < 0.05$) increase in total cholesterol (CHO), triglycerides (TAG), LDL-cholesterol and a significant ($P < 0.05$) decreased in HDL-cholesterol in the serum of alloxan induced diabetic rats when compared with normal control. Ethanolic leaf extract of *Guiera senegelensis* treated groups in alloxan induced diabetic rats showed a significant ($P < 0.05$) decrease in the mean of CHO, TAG, LDL-cholesterol and significant ($P < 0.05$) increase in the HDL-cholesterol compared to the diabetic control.

Table 1: Activities of alkaline phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Total protein concentration (TP) and Albumin (ALB) in the serum of alloxan-induced diabetic rats treated with ethanolic leaf extract of *Guiera senegalensis*

GROUP	ALP (IU/L)	AST (IU/L)	ALT (IU/L)	TP (IU/L)	ALB (IU/L)
A	65.75 ± 5.55^{c}	70.15 ± 1.55^{a}	10.75 ± 1.75^{a}	74.00 ± 1.41^{c}	33.20 ± 2.17^{c}
B	101.40 ± 0.55^{b}	76.20 ± 1.62^{b}	34.20 ± 3.79^{b}	70.23 ± 1.80^{b}	29.35 ± 0.75^{b}
C	100.75 ± 8.10^{b}	77.40 ± 5.98^{b}	32.00 ± 2.65^{b}	73.80 ± 1.09^{c}	32.40 ± 0.89^{c}
D	98.65 ± 8.00^{a}	77.00 ± 1.72^{b}	31.50 ± 3.85^{b}	75.20 ± 2.49^{c}	33.10 ± 1.78^{c}
E	97.90 ± 7.80^{a}	76.80 ± 1.73^{b}	31.35 ± 2.75^{b}	76.60 ± 2.30^{c}	33.00 ± 0.25^{c}

Values are Mean ± SEM, n=7. Values with different superscript letters are statistically significant at $P < 0.05$ compared to B
A = (normal control) were not induced with diabetes. B = (diabetic control) were induced with diabetes, but not treated with Gs leaf extract
C = (diabetic test group) 100mg/kg body weight of Gs leaf extract. D = (diabetic test group) 150 mg/kg body weight of Gs leaf extract
E = (diabetic test group) 200 mg/Kg body weight of Gs leaf

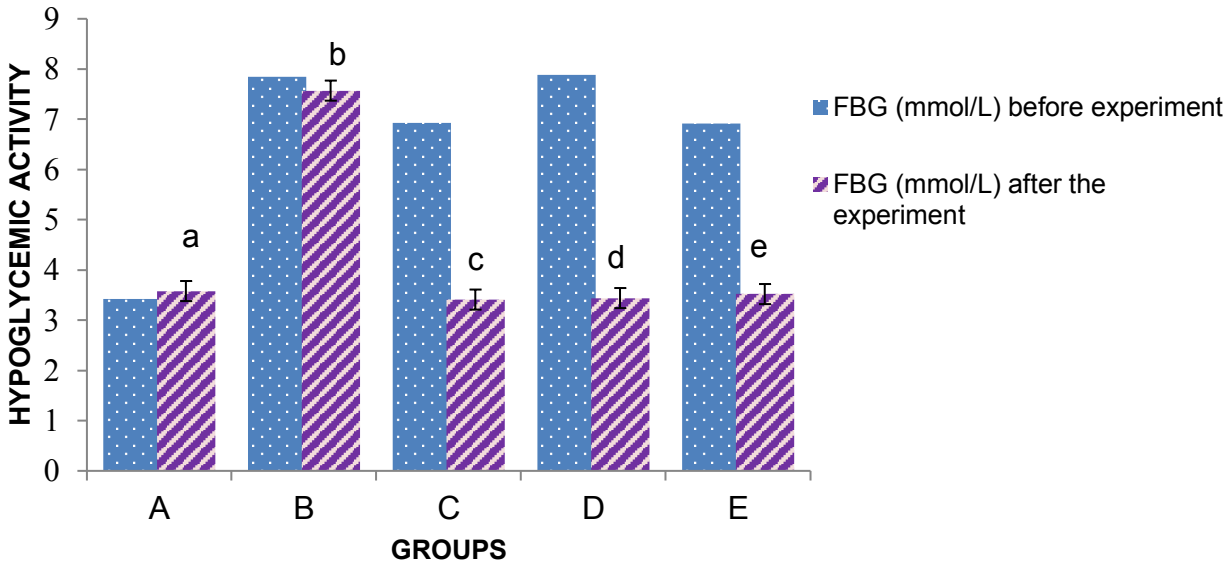

Figure 1: Hypoglycemic activity of ethanolic leaf extract of *Guiera senegelensis* in alloxan induced diabetics' rats

Values are Mean ± SEM, n=7. Values with different superscript letters are statistically significant at $P < 0.05$ compared to B. A = (normal control) were not induced with diabetes. B = (diabetic control) were induced with diabetes, but not treated with Gs leaf extract. C = (diabetic test group) 100mg/kg body weight of Gs leaf extract D = (diabetic test group) 150 mg/kg body weight of Gs leaf extract. E = (diabetic test group) 200 mg/Kg body weight of Gs leaf extract

Table 2: Effects of ethanolic leaf extract of *Guiera senegelensis* on lipid profiles in alloxan induced diabetic rats

GROUPS	CHO mmol/L	TAG mmol/L	HDL mmol/L	LDL mmol/L
A	1.22 ± 0.16	1.44 ± 0,05	0.88 ±0.13	0.41 ± 0.03
B	2.16± 0.04^{b}	3.36± 2.27^{b}	0.68±1.28^{b}	1.40± 0.12^{b}
C	1.29± 0.19^{a}	2.00± 0.17^{a}	0.78± 0.11^{a}	0.44± 0.02^{a}
D	1.21± 0.16^{c}	1.83± 0.13^{c}	0.89± 0.13^{c}	0.44± 0.02^{c}
E	1.18± 0.16^{d}	1.43± 0.22^{d}	0.97± 0.22^{d}	0.41± 0.03^{d}

Values are Mean ± SEM, n=7. Values with different superscript letters are statistically significant at $P < 0.05$ compared to B. A = (normal control) were not induced with diabetes. B = (diabetic control) were induced with diabetes, but not treated with Gs leaf extract. C = (diabetic test group) 100mg/kg body weight of Gs leaf extract. D = (diabetic test group) 150 mg/kg body weight of Gs leaf extract. E = (diabetic test group) 200 mg/Kg body weight of Gs leaf extract. CHO = Total cholesterol. TAG =Triglycerides. LDL = Low density lipoprotein. HDL = High density lipoprotein

DISCUSSION

The result of the present study demonstrated that administration of the ethanolic leaf extract of *Guiera senegalensis* (Gs) at a dose of 100mg/Kg in the alloxan induced diabetes has not shown any significant changes in the activities of ALP, AST and ALT when compared with diabetic control, However a significant increase was recorded in the serum total protein (TP) and albumin (ALB) when all the doses of Gs leaf extract were compared with diabetes control. But a significant decrease in the activity of ALP was observed and there were no significant changes in the activities of AST and ALT in the Gs treated group in the 150mg/Kg and 200mg/Kg doses when compared to the diabetic control rats as shown in table 1. The increase activities of ALP, AST and ALT in diabetic control might be due to histopathological changes in the liver, including dilated sinusoids and hepatocytic necrosis (Azza *et al*., 2011). ALP is a membrane bound enzyme while ALT and AST are cytosolic enzymes. These enzymes are highly concentrated in the liver and are only found in the serum in significant quantities when the cell membrane

becomes leaky and even completely ruptured (Adesokan *et al*., 2009). The present result indicates that the administered extract of Gs has no significant mitigating effect on the cytosolic liver enzymes. However, the result of the study demonstrated that administration of Gs extract increased total protein (TP) and albumin (ALB) concentration when compared with diabetic control which was not significantly different from that of the normal control. The Gs extract may have ameliorated the protein oxidation due stress induced by the chemical alloxan.

Ethanolic leaf extract of *Guiera senegalensis* (Gs) administration to the alloxan induced diabetic rats was found to lower the serum glucose level significantly when compared with the diabetic control group in the present study (figure 1). The result demonstrated the Gs extract has a hypoglycaemic effect at all doses used in this study. The result was in agreement with findings of Hii and Howell (1985), that plant with hypoglycaemic effects usually contains alkaloid, flavonoid, terpenoids. Marles and Famsworth, 1995, suggested that flavonoids cause stimulation of insulin secretion from pancreatic β-cells or by insulin like effect. The present study was in accord with suggestions of Fang *et al.* (2008) that the antihyperglycemic activity of *Guiera senegalensis,* may result from enhancing the insulin signalling pathway or through other mechanism like reducing the rate of carbohydrate absorption into the hepatic portal circulation, decreasing the release of glucose from the liver or increasing glucose uptake by muscle and fat cells or by increasing glycogen synthesis (Fang *et al.,* 2008).

The present results showed significant ($p < 0.05$) increase in plasma cholesterol, TG, and LDL in the diabetic rats, while HDL level was reduced. Treatment with the ethanolic leaf extract of *Guiera senegalensis* (Gs) resulted in a significant decrease in plasma cholesterol, TG and LDL level and a significant increase in HDL level. The significantly higher ($p<0.05$) Plasma Cholesterol level observed in the alloxan induced diabetic control rats when compared to normal control might be as a result of disturbance in the regulation of the activity of the hormone-sensitive enzyme, lipase, by insulin due to its deficiency or absence, caused by the alloxan induced destruction of beta islet cells (Khan *et al*., 2003). There was also a significant increase in Triglyceride concentration in diabetic rats and treatment with the ethanolic leaf extract of *Guiera senegalensis* (Gs) results in a significant decrease in the triglyceride concentration as shown in table 2. Lipase is known to convert triglycerides to free fatty acids and glycerol. Insulin inhibits the hormone-sensitive lipase in adipose tissue and in the absence of insulin, the plasma level of free fatty acids increases. The abnormally high concentration of triglycerides in the diabetic control rats may also be due to increase in the mobilization of free fatty acids from the peripheral fat depots by glucagons in the absence of insulin (Pari and Latha, 2005). Excess of fatty acids in plasma produced by the alloxan-induced diabetes promotes the liver conversion of some fatty acids into triacylglycerol, phospholipids and cholesterol which may be discharged into the blood as lipoproteins (Bopanna *et al.,* 1997). HDL concentration significantly decreases in the diabetic rats and treatment with the ethanolic leaf extract of *Guiera senegalensis* resulted in a significant increase of the HDL concentration. It was observed that decrease in plasma cholesterol levels in the treated groups was accompanied by a significant increase in HDL level when compared to that of the control group. High levels of HDL have been reported to be inversely related to the incidence of coronary heart disease (Khan *et al.*, 2003). HDL may foster the removal of cholesterol from peripheral tissue to the liver for catabolism and excretion. Also, high levels of HDL may compete with LDL receptor sites on arterial smooth muscle (Bopanna *et al.,* 1997). The increase in LDL concentration in diabetic rats and treatment with the ethanolic leaf extract of *Guiera senegalensis* (Gs) results in a significant decrease in the triglyceride concentration. The plasma concentration of LDL will reduce since there is no elevated level of fatty acids (from lipolysis and from the breakdown of triacylglycerol by the hormone- sensitive lipase) that will be converted to acetyl CoA in the liver.

The significant ($p<0.05$) hypolipidemic activities shown by the extract administered orally in different doses when compared to control might be due to ability of the extract of *Guiera senegelesis* to cause regeneration of the β-cells of the pancreas and potentiation of insulin secretion from surviving β-cells (Bopanna *et al.,* 1997). The increase in insulin secretion and the consequent decrease in blood glucose level may lead to stimulation of fatty acid biosynthesis (Insulin stimulates lipid synthesizing enzymes (fatty acid synthase, acetyl-CoA carboxylase) and also the incorporation of fatty acids into triglycerides in the liver and adipose tissue). In the presence of insulin, the hormone-sensitive lipase will be inhibited in the adipose tissue, and mobilization of fatty acid from adipose tissue by glucagons will also be inhibited and therefore leading to the observed decrease plasma level of free fatty acids (Best and Taylor, 1989).

CONCLUSION

This study indicated that administration of ethanolic leaf extract of Guiera *senegalensis* to alloxanized diabetic rats at the doses considered possess

hypoglycemic activities by lowering the blood glucose level of alloxan induced diabetic rats and the extract is not toxic to the liver moreover it has hepatoprotective ability and may reduce liver damage induced by alloxan in addition *Guiera senegelensis* ethanolic leaf extract have potential of improving hypolipidaemia and to reduce the complications associated with experimental diabetes. This study also supports the folklore usefulness of this plant in the treatment of diabetes. It can be concluded that the leaves of this plant could be further investigated for antidiabetic bioactive principles.

Conflict of interests
No conflict of interests asserted by the authors

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