



Anti-diabetic Activity of Aqueous Extract of *Senna fistula* Leaves in Streptozotocin-induced Diabetic Rats

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Abstract: This study aims at evaluating the antidiabetic effect of chronic administration of aqueous extract of *Senna fistula* leaves in streptozotocin-induced diabetic rats. Thirty albino rats (110-140 g) were randomized into 6 groups (A-F). Animals in Group A was the non-diabetic control group, B was the diabetic that received distilled water, C was the diabetic animals treated with 2.5 mg/kg body weight of glibenclamide while animals in groups D, E and F were made diabetic and treated with different doses (28.57, 57.14 and 114.28 mg/kg body weight) of the extract for 28 days. The results showed that the blood glucose level of diabetic rats were significantly and progressively reduced in the extract and glibenclamide treated animals when compared with the diabetic animals that received distilled water. The urine glucose and ketones which were detected in diabetic animals treated with distilled water disappeared in the extract treated animals comparable to the diabetic animals that received the reference drug. Also there was significant reduction in the postprandial blood glucose of diabetic treated animals when compared with diabetic animals that were administered distilled water throughout the exposure period. Furthermore, the level of albumin was normalized by the extract in a manner similar to those treated with glibenclamide. The significant increases in plasma cholesterol, low density lipoprotein and urea in the diabetic animals that received distilled water were reverted back to their respective control values by the extract. The high density lipoprotein was significantly different in all the treated animals. It can therefore be concluded that the oral administration of aqueous extract of *Senna fistula* leaves possess antihyperglycemic activity and it is also effective in controlling some metabolic disturbances associated with diabetes.

KEYWORDS: *Senna fistula*, Leguminosae, Glibenclamide, Streptozotocin

1.0 Introduction

Diabetes mellitus is a group of metabolic disorders that result from relative or absolute deficiency of insulin or peripheral resistant to the action of insulin, usually presented with hyperglycaemia (King *et al* 1998; Wadkar *et al.*, 2008). Globally, the total number of adults aged 20-70 years estimated to have diabetes by the International Diabetes Federation (IDF) in 2011 was 366 million and was the cause of death in 4.6 million people. Almost 80% of these diabetes deaths occur in low and middle income countries (Hu, 2011; Whitting, 2011). In Africa, an estimate of 14.7 million adults has diabetes with a regional prevalence of 4.5% and Nigeria having the highest number with the estimated

burden of about 1.7 million which is expected to increase to 4.8 million by 2030 (IDF, 2011; Chinenye *et al.*, 2012; Oputa and Chinenye, 2012). Diabetes is often associated with complications like erectile dysfunction, renal disease, eye problem, poor obstetric outcome, recurrent infection, skin ulcer and gangrene (Resnikoff *et al.*, 2004; Icks *et al.*, 2009).

Diabetes mellitus is often managed by non-pharmacological means (exercise and diet) and/or pharmacologically by insulin and oral hypoglycaemic drugs/agents like biguanides, sulfonylurea (Khan *et al.*, 2012) most of which are often associated with side effects like gain in weight, worsening of heart problem, abdominal discomfort, bloating, flatulence, diarrhoea and even reduce the blood glucose level below the normal range (70-120 mg/dl) and so on. The management of diabetes with reduced or without

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any side effect, ease of availability of anti-diabetic drug is still a challenge, therefore it is imperative to explore options in medicinal plants.

Senna fistula Linn. (Family leguminosae), is also known as Golden shower, (English) and Aidantoro (Yoruba, Western Nigeria). It is a deciduous and mixed monsoon forest tree that originates from Sri-Lanka and India but now cultivated in tropical countries like South Africa, Nigeria (South West). The tree is about 15 m tall with greenish grey bark, compound leaves that have 3-7 pairs of leaflet and are 5-12 cm long. *Senna fistula* plant has been claimed to be used as a laxative and antibiotic (fruit) (Akanmu *et al.*, 2004). Its hot water extract have been used in the treatment of uterine menstrual disorders and fever (Kaji and Khorara, 1965; Sen and Shukla, 1968). It has also been reported to treat rheumatism and intestinal disorders like ulcer (Biswas *et al.*, 1973; Kirtikar and Basu, 1975). There are reports on its anti bacterial activity against a wide spectrum of bacteria which include *Bacillus subtilis mycides*, *escheichia coli*, *mycobacterium smegmatis*, *pseudomonas aerogenes* and *protein vulgaris* (Perumal *et al.*, 1998). Studies have also suggested its anti-inflammatory, antioxidant (Bhakta *et al.*, 1999; Illavaransan *et al.*, 2005) antitumor (Gupta *et al.*, 2000), antifertility (Yadav and Jain, 1999) effects. Others include antidiabetic and hepatoprotective effects (Nirmala *et al.*, 2008; Bhakta *et al.*, 2001).

Although, Nirmala *et al.*, (2008) reported the hypoglycaemic effects of the n-hexane extract of the stem bark of *Senna fistula* at the doses of 150, 300 and 450 mg/kg body weight once daily in normal and streptozotocin-induced diabetic rats, there is no information on studies that evaluated the effect of aqueous extract of *Senna fistula* leaves at doses of 28.57, 57.14 and 114.28 mg/kg body weight thrice daily for 28 days (as claimed to be used in folk medicine of Nigeria) in diabetic albino rats and some metabolic disorders associated with diabetes.

Therefore, the present study was aimed at investigating the effect of aqueous extract of *Senna fistula* leaves on blood glucose level and some metabolic disorders associated with diabetes mellitus in streptozotocin-induced diabetic rats.

2.0 Materials and Methods

2.1 Plant Material and Authentication

The plant material was obtained from the herb seller at a market (Oja tuntun) Ilorin, Nigeria and was authenticated at the plant Biology Department of University of Ilorin. It was accorded a voucher number of UIH 1020 and a specimen was deposited in the herbarium unit of Plant Biology Department.

2.2 Glucometer and Assay Kit

One touch ultra-blood glucose meter kit was a product of lifeScan, Inc, Milpitas, USA. Assay kits for urea, albumin, cholesterol were product of Randox laboratories, Co-Antrim, UK, ketones urinalysis strips was a product of DIRUI Industrial Co., Ltd China.

2.3 Drugs and Chemicals

Glibenclamide was a product of HOVID Bhd, Ipoh, Malaysia. While streptozotocin and all other chemicals were products of sigma-Aldrich CHEME GmbH, Steinheim, Germany.

Laboratory animals

2.4 Animals

Male and female albino rats (*Rattus norvegicus*) of Wistar strain, weighing 120.83 ± 6.72 were obtained from the animal holding unit of the Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. The animals were fed on rat pellets (Premier Feeds Ltd Ilorin, Nigeria) and water *ad libitum*. The animals were maintained under standard laboratory conditions (photoperiod of 12h lights; dark cycle; temperature: $28-31^{\circ}\text{C}$; humidity: 50-55%).

2.5 Preparation of Extract

Fresh leaves of *Senna fistula* were air dried at room temperature for about two weeks. The dried material was pulverized using an electric blender (Philips comfort blender, model Hr 1727, Holland). A known weight of the powder (142.70 g) was extracted in 2 litres of distilled water for 24 hours. The filtrate was evaporated to dryness using water bath which yielded 38.30 g. calculated amount of the extract was

reconstituted in distilled water to give the required doses of 28.57, 57.14 and 114.28 mg/kg body weight (b.w). The doses used in this study were as obtained from the ethno-pharmacology survey carried out on the plant.

2.6 Determination of Secondary Metabolite and Mineral Constituents of *S. fistula* Leaf Extract

Chemical tests (alkaloids, tannins, flavonoids, saponins) were carried out on the extract using the procedures described by Sofowora, (1993), Trease and Evans (1989) and Harbone (1973) to determine the constituents. The mineral content of the sample was determined by atomic absorption spectrophotometer after dry ashing of the sample.

2.7 Determination of Vitamin C Content of *S. fistula* Leaf Extract

Vitamin C content of *S. fistula* leaves extract was determined using the procedure described by Benderitter *et al* (1998).

2.8 Induction of Chemical Diabetes and Determination of Blood Glucose

The animals were fasted for 18 hours prior to induction of diabetes, and diabetes mellitus was induced by single intraperitoneal injection of freshly prepared STZ (50 mg/kg b.w) in 0.1M citrate buffer (PH 4.5) (Eliza *et al.*, 2009). An hour after STZ injection the animals were given their food (pellet) and 5% dextrose saline to overcome initial hypoglycaemic phase (Sikarwar and Patil, 2010).

Five days after STZ injection, blood was collected from the tail vein of each animal and diabetes was confirmed by glucose oxidase method using One Touch Ultra glucometer. Rats with blood glucose level higher or equal to 12.00 mmol/L were used for the study (Yakubu *et al.*, 2010).

2.9 Animal Grouping and Treatments

Thirty male and female albino rats were randomly assigned into 6 groups of 5 rats each:

Group A - (control) non-diabetic, received 0.5ml of distilled water orally.

Group B - streptozotocin-induced diabetic rats, received 0.5ml of distilled water orally.

Group C - diabetic and treated with 2.5 mg/kg b.w. of glibenclamide (Yakubu *et al.*, 2010).

Group D - diabetic and treated with 28.57 mg/kg b.w. of aqueous extract of *S. fistula*.

Group E - diabetic and treated with 57.14 mg/kg b.w. of aqueous extract of *S. fistula*.

Group F - diabetic and treated with 114.28 mg/kg b.w. of aqueous extract of *S. fistula*.

The extract was suspended in vehicle (distilled water) solution; it was administered orally using oral canula three times per day (morning 8 am, afternoon 2 pm and evening 8 pm) for a period of 28 days (Malhotra *et al.*, 1981).

2.10 Determination of Urine Ketones and Glucose

Rats were fasted overnight prior to the test. Each rat was put in a metabolic cage on designated days (day 0, after induction of diabetes, day 14 (two weeks following treatment and 28th day (last day of the treatment period). Fresh urine was then collected and glucose and ketones in the urine were determined according to the procedures outlined in the urinalysis reagent strips users guide (H₁₀ reagent strip urinalysis Dirui Industrial Co Ltd, China).

2.11 Oral Glucose Tolerance Test (OGTT)

All the animals (rats) were fasted overnight (12-14 hours) prior to OGTT. Initial blood glucose levels of the rats were determined (0 minutes). Forty-five minutes following various treatment schedules, each rats was administered an oral glucose load (3 g/kg b.w) and the blood glucose levels of the animals were determined at 30, 45, 60 and 120 minutes after glucose load.

2.12 Determination of Biochemical Parameters

The biochemical parameters were determined in the blood sample as described for total cholesterol (Friedwald *et al.*, 1972), high density

lipoprotein (HDL-C) (Richmond, 1973), low density lipoprotein (LDL-C) (Friedwald *et al.*, 1972), albumin (Dumas *et al.*, 1971) and Urea (Veniamin and Varkirtzi, 1970)

2.13 Statistical Analysis

All data in this study are expressed as the mean $\pm$ Standard error of mean (SEM), the test for significance was done using ANOVA and Duncan new multiple range test (DMRT). Differences were considered statistically significant at $P < 0.05$.

3.0 Results

The result of the secondary metabolite screening conducted on the extract is shown in Table 1. The screening revealed that *S. fistula* leaf contains alkaloids, flavonoids, tannins, saponins, steroids and terpenoids. The mineral content of the plant revealed the presence of potassium, calcium, magnesium, phosphorus but low amount of zinc (Table 2). The plant contain high amount of Vitamin C.

Table 3 shows the result of fasting blood glucose (FBG) of the animals during the experiment. There was a significant increase in the fasting blood glucose level of diabetic untreated rats throughout the period of the experiment rising from 19.04mmol/L on day 0 to 24.55mmol/L on 28th day. The FBG of all the groups on day 0 were significantly different from the control ($p < 0.05$), however, animals treated with different doses of the extract and glibenclamide had reducing blood glucose level and are significantly different from the diabetic untreated group ($p < 0.05$). By the end of the treatment period the extract at the doses of 28.57, 57.14 and 114.28mg/kg b.w. had reduced the fasting blood glucose of the animals by 78.8%, 83.3% and 78.7% respectively which were comparable to glibenclamide treated group.

In Table 4, Glucose was detected in the urine of diabetic rats, this was sustained throughout the experimental period. However, urine glucose which was detected in other treatment groups

decreased initially but eventually disappeared towards the end of the experimental period in the group treated with different doses of the extract.

Table 5, ketones was detected in the urine of diabetic rats and this was sustained throughout the period of the experiment, whereas the same urine ketones which were detected earlier in diabetic groups disappeared upon administration of the extract and this is similar to that of glibenclamide treated group.

The result of the oral glucose tolerance test is shown in Figure 1. The blood glucose reached peak level in all the animals 30 minutes after oral glucose load, the diabetic rats treated with 28.57, 57.14 mg/kg b.w. and glibenclamide treated group showed a significant ($p < 0.05$) reduction at all periods tested when compared with diabetic untreated animals, while the blood glucose level of the group that was given 114.28 mg/kg b.w. of the extract was not significantly different from the diabetic rats at early stage but exhibited some level of significance ($p < 0.05$) by the end of 2 hours of the experiment.

In Figure 2, serum albumin was found to decrease significantly in STZ-induced diabetic animals when compared with the control and extract treated groups. However, there is no significant difference between the groups treated with glibenclamide, 57.28 and 114.57 mg/kg b.w. of extract treated animals. While the group treated with 28.14 mg/kg b.w. of the extract compared favourably with the control.

In Figure 3, There was a significant ($p < 0.05$) increase in the level of urea in diabetic rats. Administration of the extract cause a significant reduction in the elevated level of urea in diabetic rats. The rats treated with 114.28 mg/kg b.w. of the extract was not significantly different from the control rats ($p < 0.05$).

The effects of oral administration of aqueous extract of *Senna fistula* leaves on lipid profile of diabetic rats is shown in Figures 4-6. The total cholesterol and LDL-C were significantly increased ($p < 0.05$) in diabetic group. Administration of the extract significantly reduction the total cholesterol and LDL-cholesterol in diabetic rats. However, the extract treated groups (28.57 mg/kg b.w.

57.14mg/kg b.w. and 114.28mg/kg b.w) were found to compare favourably with the control and glibenclamide treated groups. There was no significant difference in HDL-C level of all the

groups except the group given high dose of the extract (114.28 mg/kg b.w) which is significantly different from other groups ($p<0.05$).

Table 1: Secondary metabolite constituents of aqueous extract of *Senna fistula* leaves

Compounds	Inference
Alkaloids	Present
Flavonoids	Present
Tannins	Present
Saponins	Present
Sterol	Present
Terpenoids	Present
Cardiac glycosides	Present
Cyanogenic glycosides	Absent

Table 2: Some mineral and Vitamin C content of aqueous extract of *Senna fistula* leaves

Minerals/Vitamins	Concentration (%)
Potassium	0.84 ± 0.01
Calcium	0.47 ± 0.01
Magnesium	0.49 ± 0.02
Iron	0.10 ± 0.00
Zinc	0.003 ± 0.00
Manganese	0.04 ± 0.00
Phosphorus	0.23 ± 0.02
Vitamin C	13.67 ± 0.05 mg/100g

Values are means $\pm$ SEM of three replicates

Table 3: Effect of administration of aqueous extract of *Senna fistula* leaves on fasting blood glucose of streptozotocin-induced diabetic rats

Treatment Group	Blood Glucose		
	Day 0	Day 14	Day 28
Control	5.60 ± 0.46^a	3.40 ± 0.29^a	3.30 ± 0.23^a
Diabetic + Distilled Water	19.04 ± 2.75^{bc}	22.28 ± 3.62^c	24.44 ± 4.86^b
Diabetic + Glibenclamide	12.34 ± 2.00^b	4.50 ± 0.26^a	2.30 ± 0.36^a
Diabetic + 28.57 mg/kg b.w.	15.10 ± 2.92^{bc}	3.70 ± 0.12^a	3.20 ± 0.16^a
Diabetic + 57.14 mg/kg b.w.	23.97 ± 4.51^c	5.00 ± 0.57^{ab}	4.00 ± 0.28^a
Diabetic + 114.28 mg/kg b.w.	21.93 ± 4.26^c	10.98 ± 3.19^b	4.68 ± 0.47^a

Values are mean $\pm$ SEM of 5 replicates; Test values for each day with superscripts different from those of the control, a, are significantly different ($P<0.05$).

Table 4: Effect of oral administration of aqueous extract of *Senna fistula* leaves on urine glucose of streptozotocin-induced diabetic rats

Treatment Group	Urine Glucose (mmol/l)		
	Day 0	Day 14	Day 28
Control	ND	ND	ND
Diabetic + Distilled Water	+++	+++	+++
Diabetic + Glibenclamide	+++	ND	ND
Diabetic + 28.57 mg/kg b.w.	+++	ND	ND
Diabetic + 57.14 mg/kg b.w.	+++	ND	ND
Diabetic + 114.28 mg/kg b.w.	+++	+	ND

ND = Not detected, (+) = 0.25% or 5.5mmol/l sugar, (+++) = more than 2% or 55mmol/l sugar

Table 5: Effect of oral administration of aqueous extract of *Senna fistula* leaves on urine ketones of streptozotocin-induced diabetic rats

Treatment Group	Urine Ketones (mmol/l)		
	Day 0	Day 14	Day 28
Control	ND	ND	ND
Diabetic + Distilled Water	+	+	+
Diabetic + Glibenclamide	+	ND	ND
Diabetic + 28.57 mg/kg b.w.	+	ND	ND
Diabetic + 57.14 mg/kg b.w.	+	ND	ND
Diabetic + 114.28 mg/kg b.w.	+	+	ND

ND = Not detected, (+) = 1.5mmol/l of urine ketones

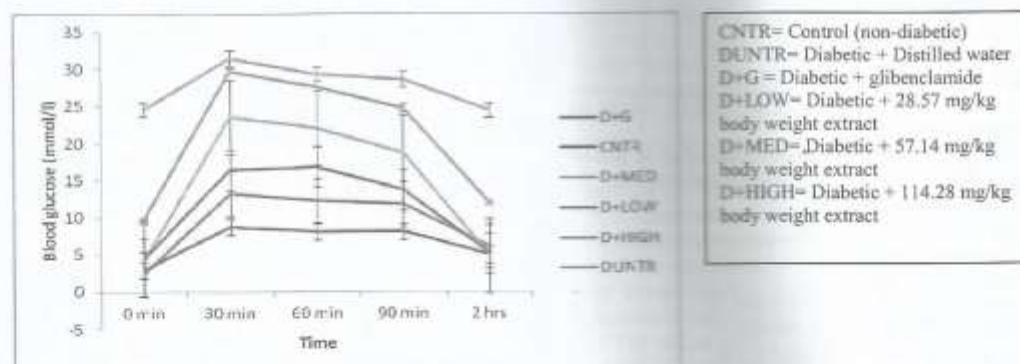


Figure 1: Effect of *S. fistula* leaf extract on oral glucose tolerance test (OGTT) in STZ-induced diabetic rats

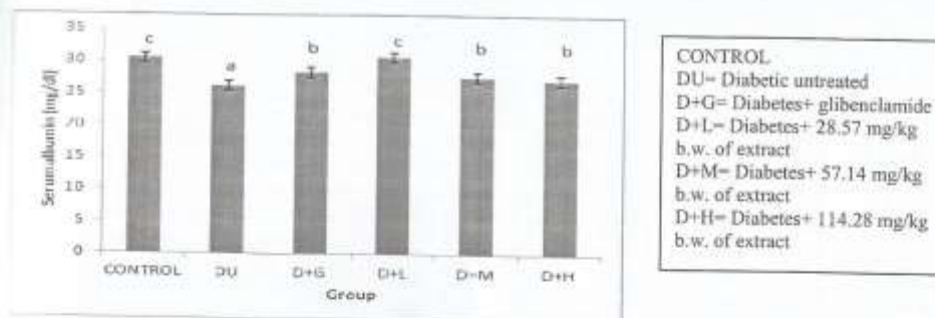


Figure 2: Effect of administration of aqueous extract of *Senna fistula* leaves on serum albumin of streptozotocin-induced diabetic rats

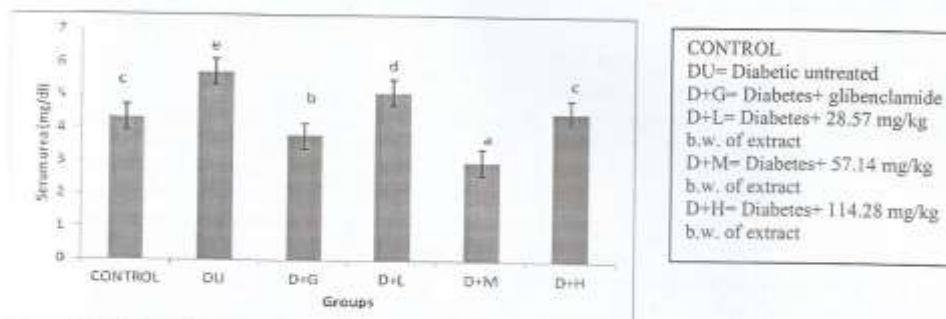


Figure 3: Effect of *S. fistula* leaf extract on serum urea level of STZ-induced diabetic rats

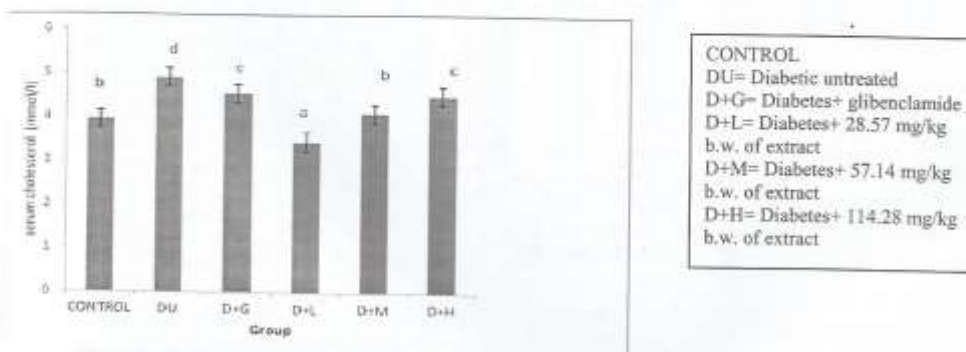


Figure 4: Effect of *S. fistula* leaf extract on serum cholesterol level of STZ-induced diabetic rats

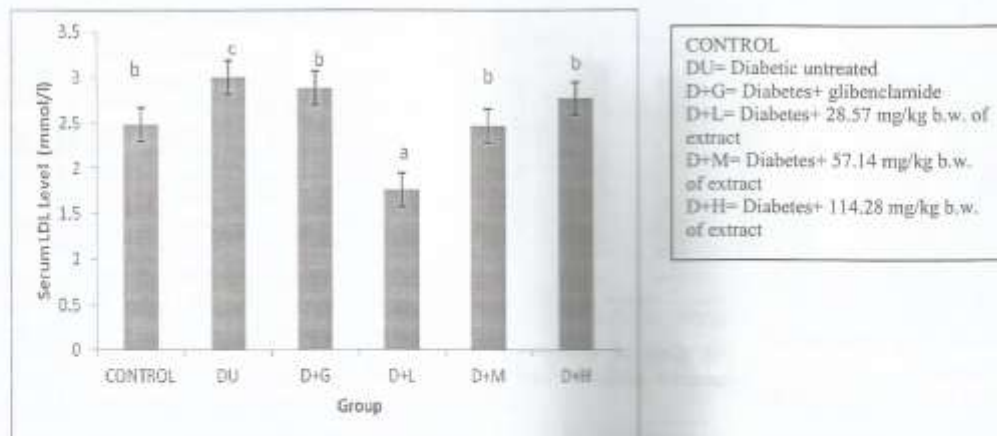


Figure 5: Effect of *S. fistula* leaf extract on serum low density lipoprotein level of STZ-induced diabetic rats

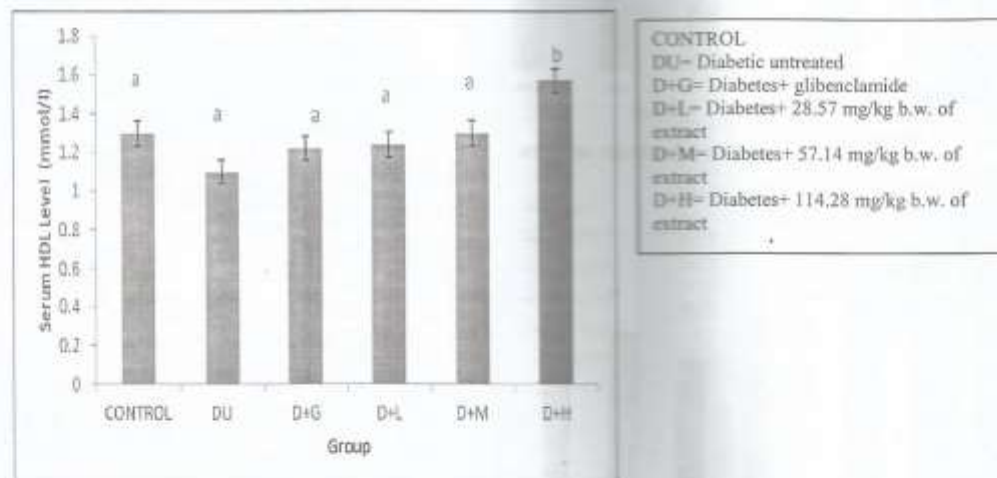


Figure 6: Effect of *S. fistula* leaf extract on serum high density lipoprotein level of STZ-induced diabetic rats

4.0 Discussion

Medicinal plants have been used in virtually all cultures as a source of medicine and ethnopharmacological investigations have identified more than 1200 plants that are used in traditional medicine for their assumed hypoglycemic activity (Kesari *et al.*, 2007). Several drug-induced hyperglycaemic models have been used to investigate antihyperglycaemic effects of medicinal plants that have antidiabetic potentials; the models include alloxan, Streptozotocin, diazoxide (Adeneye and Agbaje, 2008). Streptozotocin model used in this study has been reported to selectively destroy β cells of the pancreas; leading to a decreased synthesis and secretion of endogenous insulin which is characteristically similar to type I diabetes in human (Szkulski, 2001).

Furthermore, glibenclamide was used in the present study as a reference drug mimicking insulin action using several mechanisms such as decreasing K^+ permeability of β cells, thereby blocking potassium Adenosine Triphosphatase (K_{ATP}) channels leading to depolarization which results in reduction of blood glucose, other mechanisms include increasing glucose uptake in insulin sensitive tissues, decrease hepatic glucose output (Luzi and Pozza, 1997).

Preliminary phytochemical screening showed that the leaf extracts of *S. fistula* contain various constituents which can be responsible for its hypoglycemic activities. Some of these compounds include alkaloids, tannins, flavonoids, and saponins. Literature has documented that medicinal plants with antihyperglycaemic and antidiabetic effects often contain high amount of alkaloids, flavonoids (Oladele *et al.*, 1995; Rao and Rao, 2001; Sharma *et al.*, 2008) sterol glycosides (Ivorra *et al.*, 1989; Adallu and Radhika, 2000) and Terpenoid (Shane-McWhorter, 2001). Similarly the mineral composition revealed the presence of some minerals like K, Ca, Zn, Mn, Mg, which are important for the maintenance of good health. Clinical research has suggested that diabetes causes disturbance of mineral trace element in the body (Day, 1998). These micro-minerals play an important role in the production of secondary metabolites which are responsible

for pharmacological actions of medicinal plants. Minerals like K, Ca, Zn, iron, Mn have been reported to be responsible for the secretion of insulin from the beta cells of the pancreas (Chausmer, 1998). Cu, Fe and Zn present in the leaf extract are important for maintaining proper metabolism (Singh and Garg, 1997). Also Mg is a cofactor in various enzyme pathways involved in glucose oxidation and it modulates glucose transport across cell membranes, it may also increase insulin secretion and peripheral glucose uptake. Similarly, its high vitamin C contents could also contribute to glucose control (Eriksson and Kohvakka, 1995) and antioxidant activity (Padayatty *et al.*, 2003).

In the present study aqueous extract of *Senna fistula* leaves significantly reduced both urine and blood glucose level in streptozotocin induced diabetic rats with all the three doses exhibiting profound antidiabetic activity similar to the reference drug (glibenclamide). Therefore, the reduction in both urine and blood glucose levels recorded in diabetic rats treated with the extract suggest that the plant has antihyperglycaemic effects at all the doses used in this study. The result obtained in this study is in agreement with the work of Nirmala *et al.* (2008); although these author used n-hexane fraction of the stem bark of *Senna fistula* and at the doses of 150, 300, 450 mg/kg, while the present study used an aqueous leaf extract (the form which is used locally) and at lower doses of 28.57, 57.14, 114.28 mg/kg (as obtained from ethnopharmacological survey carried out on the plant). The recorded antihyperglycaemic effect of the aqueous extract of *Senna fistula* leaves could be due to the presence of one or combination of the active metabolites/principles contained in the extract; because the result of the phytochemical studies showed that aqueous extract of *Senna fistula* leaves contains alkaloids, flavonoids, saponins, tannins, cardiac glycosides, fibre, vitamins and minerals. It has been documented that medicinal plants with hypoglycaemic property usually contain alkaloids, flavonoids, terpenoids (Marles and Farnsworth, 1995; Ojewole, 2005). Similarly, the presence of these chemical compounds could account for the antihyperglycaemic effect of the extract either alone or in synergy with one another, for example hypoglycaemic action of

flavonoids has been reported to be caused by the stimulation of insulin secretion from pancreatic β -cells or by an insulin-like effect (Marles and Farnsworth, 1995). It has also been shown that alkaloids possess anti-hyperglycaemic activity that is mediated by the inhibition of α -glucosidase (Prashanth *et al.*, 2001), fibre mediates its anti-hyperglycaemic effect by delaying absorption of carbohydrates while saponins, terpenoids possess insulin-like activity by enhancing the release of insulin and slowing down gluconeogenesis (Prabhakar and Doble, 2008). Apart from the above mentioned antihyperglycaemic mechanism; it may be that the aqueous extract of *Senna fistula* leaves could be mediating its antihyperglycaemic activity through enhancing insulin signalling pathway (Giron *et al.*, 2009; Montagut *et al.*, 2010) or through other mechanism like decreased rate of carbohydrate absorption into the portal hepatic circulation, or decreasing the release of glucose from the liver or increasing glucose uptake by muscle and fat cells or by increasing glycogen synthesis (Naik *et al.*, 1991; Cetto *et al.*, 2000; Shane-McWhorter, 2001; Fang *et al.*, 2008).

Oral glucose tolerance test in rats is a simple and appropriate test used as a routine tool for preliminary screening of the antihyperglycaemic properties of many medicinal plants (Prakassam *et al.*, 2003; Somani *et al.*, 2008; Yasodha *et al.*, 2008). In human, it is an important test used in clinical diagnosis of diabetes. 1 to 5% of people with impaired glucose tolerance (IGT) actually develop diabetes each year.

Since impaired oral glucose tolerance is an indicator of diabetic predisposition, agents that are capable of bringing blood glucose concentration within normal limits will help to arrest the progression of impaired glucose tolerance to diabetes (Eseyin *et al.*, 2010). Therefore, the presently observed decrease in postprandial blood glucose level of extract-treated diabetic rats challenged with glucose solution in a manner similar to that of the reference drug (glibenclamide) further suggests that the extract has antidiabetic activity. The decrease in blood glucose level might be due to the extrapancreatic action of extract either by inhibiting glucose absorption in intestine or by increasing glucose tolerance in rats by enhancing the glucose uptake in tissues such as

muscles and liver and thereby stimulating glycolysis and hepatic glycogenesis (Qureshi and Bhatti, 2009). It may also be due to direct stimulation of the secretion of insulin from the surviving β cells (Oguanobi *et al.*, 2012) or a combination of these modes.

Increased amount of ketone bodies present in the urine constitute ketonuria which is one of the common features in diabetes mellitus (Ganong, 2006). Insulin deficiency causes the body to metabolize triglyceride and glycogen instead of glucose for energy. Serum level of glycerol and free fatty acids (FFAs) rises because of fat catabolism. Glycerol and alanine provide substrate for hepatic gluconeogenesis which is stimulated by the excess of glucagon that usually accompanies insulin deficiency. Glucagon also stimulates mitochondrial conversion of FFAs to ketones. Normally insulin blocks ketogenesis by inhibiting the transport of FFA derivatives into mitochondrial matrix, but ketogenesis proceeds in the absence of insulin. This is evidenced in the present study by the presence of elevated amount of ketones in the urine of diabetic rats. The presence of ketones in the urine of diabetic rats may be attributed to increased lipolysis in adipose tissue and the resultant free fatty acids are substrate for ketogenesis in the liver or utilization of these ketone bodies in the muscle and other tissues may be impaired because of lack of oxaloacetate (Murray *et al.*, 2006; Wadkar *et al.*, 2008). All the doses of aqueous extract of *S. fistula* leaves (ASFL) attenuated the urine ketones in diabetic rats in a manner similar to that of glibenclamide group. This study buttresses the effectiveness of the plant extract as an antidiabetic plant and its effectiveness against some metabolic disorders associated with diabetes.

Hypoproteinaemia has been reported to occur in diabetes, protein like albumin (Ganong, 2006) and this has been further corroborated in the present study by the decrease in the serum albumin in diabetic rats. The level of this molecule in the blood was normalized by the extract back to the control value in a manner similar to that of glibenclamide treated. The result of this study is in agreement with the studies of Wanke and Wong (1991), Shanmugasundaram *et al.* (2011) who reported that diabetes causes decrease in serum albumin.

This decrease could be due several reasons like, decrease synthesis of hepatic albumin, increased rate of amino acid conversion in to glucose (Chu *et al.*, 2002) and decreased amino acid uptake.

In this study, elevated level of total cholesterol and LDL-cholesterol were recorded in diabetic rats. Administration of the extract decreased the values of this parameter in a manner that is comparable to that of glibenclamide treated group. This suggests hypolipidemic effect of the aqueous extract of *S. fistula* leaves (ASFL) which may be related to its compositions such as Alkaloids, flavonoids, tannins, saponins, and terpenoids. All these components have been found to reduce serum lipid level in animals (Abdel Barry 2000; Ezekwe and Obidoa, 2001, Li *et al.*, 2007). The observed hypolipidemic effect may also involve the inhibition of the synthesis of cholesterol via the mevalonate or HMG CoA reductase (HMGCR) pathway (Li *et al.*, 2000) or enhance the conversion of cholesterol into the bile acid, and as a result increase the excretion of cholesterol via the bile (Lin *et al.*, 2008). Also the increase in serum cholesterol and LDL-cholesterol in diabetic rats may be unconnected to the fact that glucose is known to form chemically reversible early glycosylation products with protein. LDL, because of its protein moiety, is therefore, subject to glycosylation. Glycosylated LDL binds poorly to the LDL receptor (Steinbrecher and Witztum, 1984) and this may be one explanation for the increased cellular cholesterol and raised LDL-cholesterol found in diabetic subjects.

Uremia has also been reported to occur in diabetic subject (Sokeng *et al.*, 2005). This occurs as a result of accumulation in the blood of breakdown product of protein metabolism. Administration of aqueous extract of *S. fistula* leaves (ASFL) reduced the elevated blood level of urea in diabetic rats which is similar to that of glibenclamide treated group. This attenuation further indicates that aqueous extract of *Senna fistula* leaves could ameliorate some metabolic disorders associated with diabetes.

In conclusion, this study has shown that oral administration of aqueous extract of *Senna fistula* leaves have significantly reduced the elevated urine and blood glucose level in diabetic rats in a manner similar to that of the

reference drug glibenclamide, with all the three doses exhibiting profound antidiabetic activity. This study also revealed that aqueous extract of *Senna fistula* leaves can effectively control dyslipidemia and some metabolic disorders associated with diabetes. Therefore, this study provides scientific evidence to justify its use in the folk medicine of Nigeria. Work is in progress to identify the exact mechanism of action of the plant in ameliorating diabetes and its associated disorders.

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