ANTIDIABETIC EFFECTS OF HYDROETHANOL EXTRACTS OF *Acanthospermum hispidum* ROOT IN STZ-INDUCED DIABETIC RATS

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Abstract: This study examined the antidiabetic effect of hydroethanol (ethanol: water, 50: 50 v/v) extracts of *Acanthospermum hispidum* root in streptozotocin (STZ) induced diabetic rats. Diabetes was induced in rats by the intraperitoneal injection of 60 mg/kg b.w STZ and treated for 21 days with 150, 300 and 600 mg/kg of *A. hispidum* extract. The fasting blood glucose (FBG) and body weight of animals were taken weekly and the rats were sacrificed at the end of experiment for determination of alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), albumin, total proteins, creatinine, urea, triglyceride (TG), HDL-cholesterol, LDL-cholesterol, total cholesterol (TC), malondialdehyde (MDA), superoxide dismutase (SOD) and catalase (CAT). Treatment with extract of *A. hispidum* at doses of 300 or 600 mg/kg, significantly ($p<0.05$) caused repression of STZ-induced hyperglycemia in diabetic rats, whereby the antihyperglycemic efficiency at the highest dose (600 mg/kg) was comparable with that of glibenclamide (600 µg/kg). Administration of extract significantly ($p< 0.05$) decrease the ALT, AST, ALP, TC, TG, VLDL, LDL and MDA levels as well as caused significant increased ($p<0.05$) in HDL level, SOD and CAT activities in the STZ-induced diabetic rats. Conclusively, the extract of *A. hispidum* roots possesses antidiabetic, hepatoprotective and antihyperlipidemic effects, which may be due to its phytoconstituents.

Keywords: *Acanthospermum hispidum*, fasting blood glucose, antidiabetic, hydroethanol, Streptozotocin

Introduction

Diabetes mellitus (DM) is a chronic disorder of fat, carbohydrate and protein metabolism, usually characterized by insistent hyperglycemia resultant from aberrations in insulin action, insulin secretion or both (Cernea and Dobreanu, 2013). The prevalence of DM has increased precipitously worldwide. Presently, a worldwide population of 425 million people have been diagnosed with DM, and this figure is projected to rise to 629 million by 2045 (Ogurtsova *et al*., 2017). The chief physiological consequence of diabetes mellitus is prolonged hyperglycemia, which leads to microvascular complications that affect the eyes, nerves, kidneys and other diseases like nephropathy, neuropathy, retinopathy and cardiovascular diseases (Skyler *et al.*, 2017). The symptoms of these diseases include hyperglycemia and hyperlipidemia, which lead to variation in lipid and glucose metabolism, also leading to changes in level of liver enzymes (Jayaraman *et al.*, 2018).

There have been numerous insulin and oral hypoglycemic agents including metformin, sulfonylureas, α-glucosidase, DPP-4 inhibitors, SGLT-2inhibitors, glucagon-like peptide-1 (GLP-1) analogs, and many others used for diabetes management (Newman and Cragg, 2016); however, their usage had been linked with several side effects (Kameswararao *et al*., 2003). Consequently, natural substances with better hypoglycemic activities are gradually becoming the appealing therapeutic strategy, owing to the long-term nature of DM treatment (Zhang *et al.*, 2018).

Acanthospermum hispidum DC is a yearly, erect herb, of the Asteraceae family, deriving from tropical America. It is ordinarily known as the Goat's head, Bristly starbur, Starbur and Hispidstarburr (Anup *et al*., 2012). It is known as "ewe onitan meta" and "kashin yawo" in western and Norther Nigeria, respectively. *A. hispidum* is found in an extensive range of habitats, with a characteristic light and somewhat sweet aroma. The plant is normally found in waste areas, cultivated upland crops, roadsides, along railroads, pastures, around corrals and cattle trails. It is mostly modified to textured (light) soils; nevertheless, it also thrives in hefty textured soils (Anup *et al*., 2012; Evani *et al*., 2008).

The customary use of *A. hispidum* for treatment of several ailments (jaundice, hepato-biliary disorders, vomiting, epilepsy, cephalgias, malaria, head-ache, abdominal pain, convulsions, stomachache, constipation, eruptive fever, blennorrhoea, snake bite, diabetes, microbial and infections) has been reported (Lawin *et al.*, 2015; Tijani *et al*., 2013; Anup *et al*., 2012). Also, Kumbhar and Gamit (2018), reported that the root and leaves have antibacterial, and antifungal activities. Similarly, the phytochemical analysis and antidiabetic evaluation of the aqueous leafs extract of the plant, and the antidiabetic activity of its aerial parts have been reported amongst others (Chika *et al.*, 2018; Vasundharamma *et al.*, 2016), but no report about the antihyperglycemic activity of the roots of *A. hispidum* is found in the literature; hence, this study was aimed at assessing the antihyperglycemic activity of hydroethanol (ethanol: water, 50: 50 v/v) extract of its roots.

Materials and Methods

Chemicals

Streptozocin (STZ) was procured from Sigma Chemical Co. (St. Louis, MO, USA). All other chemicals used were of analytical grade and gotten from standard commercial sources.

Plant collection and extraction

The plant was collected from Otukpo in Benue State, Nigeria and identified at the Biological Science Department of Ahmadu Bello University, Zaria. The roots were washed thoroughly under running tap water, air-dried and milled to fine powder by means of mechanical grinder. The dried powder (50 g) was extracted with hydroethanol (ethanol: water, 50: 50 v/v) for 72 h at room temperature with intermittent shaking, and filtered through Whatman no.1 filter paper. Thereafter, the filtrate was evaporated by rotary evaporator and stored at 4°C until use.

Animals and diabetes induction

Male Wistar rats (150 – 180 g) used for this experiment were gotten from the animal house of Anatomy Department, Delta State University, Abraka. The thirty six (36) rats were acclimatized for two weeks before the commencement of the work and were fed on standard diet (Top Feeds Ltd., Sapele, Delta State), and water *ad libitum*. They were kept in line with the institutional Committee guidelines for the Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

To induce diabetes, the rats were fasted overnight and a single dose of freshly prepared STZ (60 mg/kg b.w) dissolved in 0.01M citrate buffer at pH 4.5 was intraperitoneally injected (Gupta *et al.*, 2004). After 72 h of STZ administration, blood

samples were collected from overnight fasted animals to determine their blood glucose levels. Afterwards, rats with fasting blood glucose levels (FBG) above 250 mg/dl were considered permanent DM (Kodikonda and Naik, 2017) and used for the study. Extracts were orally administered to the rats.

Experimental design

To examine the antihyperglycemic effect of *A. hispidum* extract in the STZ-induced diabetic rats; the rats were divided into six groups (6 animals per group), as follows:

Group A: Untreated normal control rats;
Group B: Untreated diabetic control rats;
Group C: Diabetic rats + 150 mg/kg b.w. *A. hispidum* extract;
Group D: Diabetic rats + 300 mg/kg b.w. *A. hispidum* extract;
Group E: Diabetic rats + 600 mg/kg b.w. *A. hispidum* extract;
Group F: Diabetic rats + Glibenclamide (600 µg/kg).

Blood sample collection and determination of biochemical parameters

Blood glucose levels were evaluated using glucose oxidase/peroxidase reactive strips in samples collected from tail vein on weeks 0, 1, 2 and 3. At the end of treatments (day 21), the rats were fasted overnight and sacrificed after which blood samples and organs (liver and kidneys) were collected and processed and used for the various biochemical assays. To obtain the serum, blood sample was centrifuged for 10 min at 3000 rpm. The tissues were then processed for the following assays: Lipid peroxidation (LPO) was evaluated by Buege and Aust (1978) method, catalase (CAT) by the method of Aebi (1974), while SOD was estimated by the McCord and Fridovich (1969) method.

Serum triglycerides, cholesterol, HDL-cholesterol, LDL-cholesterol, alaninine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST) activities and the levels of urea and creatinine were measured using Randox diagnostic kits.

Statistical analysis

Data was analyzed by Graph Pad Prism 6 software, and results were represented as mean ± SD. The One way analyses of variance (ANOVA) was used with Tukey multiple comparisons post hoc test. Values were taken to be statistically significant at $p < 0.05$.

Results and Discussion

Changes in body weight of STZ-induced diabetic rats per week

The body weights of the rats were initially comparable. However, a steady significant ($p< 0.05$) increase in body weight was noted in the normal control rats. Similar trend in weight of body was noticed in the rats treated with either extracts or the standard drug. However, no significant change was observed in body weight of the diabetic control animals for the period of experiment. Thus, the body weights of the normal control animals were considerably higher than that of the diabetic controls (Fig. 1).

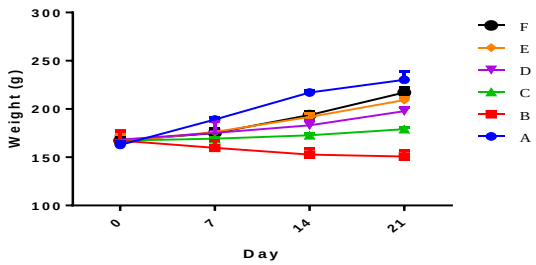

Fig. 1: Effects of *A. hispidum* extracts and glibenclamide on body weight of STZ-induced diabetic rats

*Data are represented as mean ± SD (n=6).
Where, A: Control; B: Diabetic control; C: Diabetic + 150 mg/kg b.w. *A. hispidum*; D: Diabetic + 300 mg/kg b.w.*A. hispidum*; E: Diabetic + 600 mg/kg b.w. *A. hispidum*; F: Diabetic + Glibenclamide (600 µg/kg)

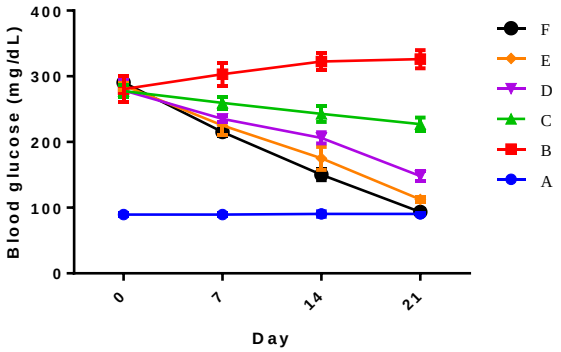

Fig: 2. Effect of *A. hispidum* and glibenclamide on the level of Blood glucose in STZ-induced diabetic rats

*Data are represented as mean ± SD (n=6).
Where, A: Control; B: Diabetic control; C: Diabetic + 150 mg/kg b.w. *A. hispidum*; D: Diabetic + 300 mg/kg b.w.*A. hispidum*; E: Diabetic + 600 mg/kg b.w. *A. hispidum*; F: Diabetic + Glibenclamide (600 µg/kg)

Effects of A. hispidum extracts on blood glucose in STZ-induced diabetic rats

STZ can decrease or terminate the secretion of insulin by causing destruction of the pancreatic β-cell. In this study, the blood glucose level was increasingly raised after the injection of STZ in rats as shown in the diabetic control rats (Fig. 2). Nonetheless, treatment with extract of *A. hispidum* at doses of 300 or 600 mg/kg, significant ($p<0.05$) caused repression of the STZ-induced hyperglycemia in diabetic rats when compared to the untreated diabetic control animals. Thus, repeated administration of *A. hispidum* at the doses of 300 and 600 mg/kg displayed substantial antihyperglycemic effects in the diabetic rats from the first week up to the third week of the experiment. Accordingly, the administration of *A. hispidum* at the 600 mg/kg for one, two and three weeks, reduced the blood glucose concentration to 21.21, 38.81 and 60.60%, respectively; relative to the untreated diabetic control rats. Remarkably, the observed antihyperglycemic efficiency at the highest dose of *A. hispidum* (600 mg/kg) was comparable with that of glibenclamide (600 µg/kg). Therefore, the repeated treatment at all doses (150, 300 and 600 mg/kg) per day for three weeks dose dependently showed the antihyperglycemic effect of the extract in the diabetic rats.

Effects of A. hispidum on the lipid profile of STZ-induced diabetic rats

The effects of repeated treatments with the extracts of *A. hispidum* for three weeks on the lipid profile of STZ-diabetic rats are shown in Table 1. There was significant increase in the level TG in the diabetic control rats when compared to the normal control animals. But, treatment with 600 mg/kg of extract reduced the TG level by 53.57%. Equally, three weeks treatment with *A. hispidum* at the doses of 150 and 300 mg/kg, respectively brought about significant reduction in the TG level by 17.25 and 41.38%, when compared with untreated diabetic control animals.

Similarly, the total cholesterol (TC) and low density lipoprotein (LDL) levels were observed to increase in the diabetic control rats while a decrease in the high density lipoprotein (HDL) level was seen in the untreated STZ-

induced rats when compared with the normal control animals. However, a reversal of these trends was noticed in the treated groups (C-F). Thus, there was concentration dependent significant ($p<0.05$) decrease in TC and LDL with increase in HDL in both extract and drug treated groups of rats as shown in Table 1. Also, a significant ($p < 0.05$) increase in the serum VLDL level was observed in the diabetic control rats when compared with the normal control group. This diabetic induced increased in serum VLDL level was prevented by the oral treatment with either extract or the standard drug.

Table 1: Lipid profile of STZ-induced diabetic rats treated with *A. hispidum* extracts

Gr	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)
A	83.41±0.80^{a}	67.57±0.68^{a}	34.09±0.94^{b}	35.81±1.81^{a}	13.51±0.14^{a}
B	157.17±2.54^{e}	172.83±6.75^{e}	16.46±0.69^{a}	106.15±2.99^{e}	34.56±1.35^{b}
C	131.46±9.13^{d}	143.02±1.99^{d}	20.06±0.96^{acd}	82.80±10.48^{d}	28.60±0.40^{b}
D	115.07±2.94^{c}	101.32±2.37^{c}	23.59±0.22^{ac}	71.21±2.28^{c}	20.26±0.47^{a}
E	94.21±0.80^{b}	80.25±0.74^{b}	27.44±0.52^{bd}	50.72±0.34^{b}	16.05±0.15^{a}
F	85.09±0.91^{a}	71.82±0.59^{a}	31.40±0.53^{b}	39.32±0.42^{a}	14.36±0.12^{a}

*Data represented as mean ± SD (n=6). **Values with different superscripts down a column differs statistically (P<0.05); Gr. = Group
Where, A: Control; B: Diabetic control; C: Diabetic + 150 mg/kg b.w. *A. hispidum*; D: Diabetic + 300 mg/kg b.w.*A. hispidum*; E: Diabetic + 600 mg/kg b.w. *A. hispidum*; F: Diabetic + Glibenclamide (600 µg/kg).

Effects of A. hispidum on liver and kidney parameters in STZ-induced diabetic rats

Shown in Table 2 are results of the effects of extract/drug treatment on the markers of renal and hepatic function in all groups. A significant ($p<0.05$) increase in the activities of ALT, AST and ALP (liver), and levels of creatinine and urea (kidney) were observed in the diabetic control rats, relative to the normal control animals. However, treatment with *A. hispidum* extracts (300 mg/kg) for 21 days prevented the diabetic induced increase in the renal and hepatic function markers in the treated groups of rats. Thus, there was significant reversal in the levels of ALT, AST and ALP by 43.51 and 43.51 and 46%, respectively when compare with the control (diabetic) group. At 600 mg/kg, *A. hispidum* extract exhibited higher inhibitory effect by reducing the ALT, AST and ALP levels, respectively to 62.77, 50.32 and 57.15%. Thus, the hepatoprotective effect of the extract at 600 mg/kg was also comparable to that of the standard drug. Also, no significant difference was seen in the levels of creatinine and urea and total protein.

Table 2: Changes in the liver and kidney parameters in STZ-induced diabetic rats treated with *A. hispidum* extracts

Parameter	A	B	C	D	E	F
ALP(UI/L)	85.22±0.90^{a}	224.32±7.20^{f}	154.85±2.27^{e}	121.12±2.89^{d}	96.12±1.89^{c}	90.25±1.79^{b}
AST(UI/L)	51.16±0.88^{a}	115.43±1.46^{e}	83.29±1.74^{d}	65.21±1.48^{c}	57.35±2.63^{bf}	53.38±1.41^{af}
ALT(UI/L)	30.14±0.89^{a}	108.24±1.78^{f}	77.56±3.29^{e}	61.14±1.85^{d}	40.30±2.66^{c}	35.56±1.86^{b}
Total Protein (mg/dL)	7.24±0.08^{a}	7.16±0.07^{a}	6.95±0.06^{a}	7.28±0.06^{a}	7.26±0.10^{a}	7.25±0.07^{a}
Albumin (mg/dL)	5.75±0.07^{a}	4.38±0.14^{a}	4.59±0.13^{a}	5.14±0.07^{a}	5.59±0.13^{a}	5.32±0.09^{a}
Creatinine (mg/dL)	0.65±0.01^{a}	0.93±0.02^{a}	0.82±0.01^{a}	0.74±0.02^{a}	0.72±0.01^{a}	0.68±0.01^{a}
Urea(mg/dL)	2.84±0.07^{ac}	7.86±0.08^{b}	5.87±0.07^{bc}	4.03±0.02^{bc}	3.56±0.02^{a}	3.03±0.02^{a}

*Data represented as mean ± SD (n=6). **Values with different superscripts across a row differs statistically (P<0.05).
Where, A: Control; B: Diabetic control; C: Diabetic + 150 mg/kg b.w. *A. hispidum*; D: Diabetic + 300 mg/kg b.w.*A. hispidum*; E: Diabetic + 600 mg/kg b.w. *A. hispidum*; F: Diabetic + Glibenclamide (600 µg/kg)

Table 3: Changes in oxidative stress markers of liver and kidney in STZ-induced diabetic rats treated with *A. hispidum* extracts

Group	A	B	C	D	E	F
			LPO (µ moles of malondialdehyde (MDA) formed/mg protein)			
Liver	9.18±0.38^{a}	20.66±0.35^{c}	14.43±0.54^{b}	11.27±0.45^{a}	10.41±0.75^{a}	10.27±0.74^{a}
Kidney	8.32±0.62^{a}	18.53±0.45^{c}	11.78±0.32^{b}	9.56±0.22^{ac}	9.05±0.05^{a}	9.06±0.04^{a}
			SOD (units/mg protein)			
Liver	35.25±0.77^{e}	16.52±0.51^{a}	21.41±0.56^{b}	26.44±0.74^{c}	30.83±1.96^{d}	32.61±0.71^{d}
Kidney	33.82±0.22^{e}	14.01±0.18^{a}	18.38±0.65^{b}	23.04±0.28^{c}	28.22±0.34^{d}	29.54±0.64^{d}
			CAT (µ moles of hydrogen peroxide consumed/min/mg protein)			
Liver	57.02±1.12^{e}	19.45±0.85^{a}	27.93±0.22^{b}	46.26±2.22^{c}	54.07±1.10^{df}	55.09±1.92^{ef}
Kidney	48.03±1.04^{d}	17.20±0.39^{a}	23.23±0.83^{b}	40.21±2.06^{c}	47.33±1.66^{d}	46.68±2.40^{d}

*Data represented as mean ± SD (n=6). **Values with different superscripts across a row differs statistically (P<0.05).
Where, A: Control; B: Diabetic control; C: Diabetic + 150 mg/kg b.w. *A. hispidum*; D: Diabetic + 300 mg/kg b.w.*A. hispidum*; E: Diabetic + 600 mg/kg b.w. *A. hispidum*; F: Diabetic + Glibenclamide (600 µg/kg).

Effect of A. hispidum on markers of oxidative stress in liver and kidney

The results for the effects of *A. hispidum* extract/glibenclamide treatment on markers of oxidative stress in both kidney and liver of STZ-induced rats are shown in Table 3. A significant increase in MDA level and decrease in the SOD and CAT activities were observed in the diabetic control group when compared with the normal control rats. But treatment of STZ-induced rats with the extracts for 21 days, dose dependently normalized the diabetic induced oxidative stress in the animals with the highest dose (600 mg/kg) normalizing the activities of these enzymes to comparable level with that of the standard drug (glibenclamide) used. Thus, the results showed that oral treatment with *A. hispidum* could enhance the antioxidant defense mechanism of the animals, so protecting their tissue from diabetes induced damage.

Diabetes mellitus is a disease that can also result from life style and currently has no adequate and active therapy or medication for its treatment (Ali *et al*., 2006). Thus, the search

for potential plant-based antidiabetic compounds with multiple disease-related effects and proven lasting safety for DM treatment continues (Nicolle *et al.,* 2011). Several bioactive compounds from different medicinal plant sources, such as saponins, glycosides, flavonoids, alkaloids, tannins, carotenoids, anthocyanins and terpenoids, are stated to have effective antidiabetic activity (Sayem *et al.,* 2018; Upadhyay and Dixit, 2015). The presence of these phytochemicals have also been reported in *A. hispidum* (Chika *et al.,* 2018; Roy, 2013). This study evaluated the antihyperglycemic activity of hydroethanol extract of *A. hispidum* roots.

In this study, the blood glucose level was increasingly raised after the injection of STZ in rats, as shown in the diabetic control rats. STZ is a diabetogenic agent generally used to induce diabetes in experimental animals because of its lethal influence on pancreatic β-cells, leading to a loss of insulin secretion (Oltésová *et al.,* 2011). The production of free radicals and nitric oxide which weaken the mitochondrial role of beta cells is the mechanism in which streptozotocin produces its diabetic state (Rakieten *et al.,* 1963). However, the oral administration of *A. hispidum* was noticed in this study to lower the STZ-induced blood glucose level increase. Thus, treatment with extract of the plant at doses of 300 or 600 mg/kg, significantly caused repression of the hyperglycemia in the STZ-induced rats, when compared to the untreated diabetic control animals. Remarkably, the observed antihyperglycemic efficiency at the highest dose (600 mg/kg) was comparable with that of glibenclamide (600 µg/kg). Therefore, the repeated treatment at all doses (150, 300 and 600 mg/kg) per day for three weeks dose dependently showed antihyperglycemic effect of the extract in the diabetic rats. This observation is consistent with previous reports about the antidiabetic activities of the leaves/ aerial parts of the plant (Chika *et al.,* 2018; Vasundharamma *et al.,* 2016).

The body weight of the rats in all groups was initially comparable. However, a steady and significant ($p<0.05$) increase in body weight was observed in the normal control rats during the period of the study. Similar trend in weight of body was also noticed in the rats treated with either extracts or the standard drug. On the other hand, there was no significant ($p>0.05$) change seen in the body weight of diabetic control animals for the period of experiment. Thus, the body weight of the normal control animals was considerably higher than that of the diabetic control group. Earlier studies established that several plant extracts prevented loss of body weight in diabetic animals. The body weight loss seen in the STZ-induced diabetic rats may be due to increase in protein catabolism, occasioned by insulin deficiency (Stirban *et al.,* 2014; Eleazu *et al.,* 2013). The enhancement in body weight seen in the extract treated groups may suggest that *A. hispidum* extract have protecting effects against catabolism of protein and the muscle wasting, which possibly may be due to improvement of insulin action or/and secretion.

The kidney and liver are two critical organs of the body concerned with most biochemical pathways. In this experiment, a significant ($p<0.05$) increase in the activities of ALT, AST and ALP (liver), and creatinine and urea (kidney) were observed in the diabetic control rats, relative to the normal control animals. This may be interrelated with hepatic dysfunction, like cell necrosis of tissues, and may result from leakage of the hepatic enzymes and failure of cell membrane functional integrity in the liver (Swamy *et al.,* 2018). However, treatment with *A. hispidum* extracts for 21 days prevented the diabetic induced increase in the renal and hepatic function markers in the treated groups of rats. Thus, there was significant ($p<0.05$) reversal in the levels of ALT, AST and ALP when compare with the control (diabetic) group, and this is in agreement with previous findings (Khattab *et al.,* 2013). At the highest dose of extract, hepatoprotective effect of the extract was comparable to that of the standard drug. Diabetes mellitus is reported to induce hepatic injury, leading to elevation in the levels of ALT, ALP and AST (Zhu *et al.,* 2016). The hepatocytes of STZ-induced diabetic rats may have been damaged, thereby resulting to increase in the release of ALT and AST, which is linked with glycometabolism disturbance (Jayaraman *et al.,* 2018). Earlier studies reported that reduction of apoptosis, advancement of hepatocyte proliferation and hypertrophy, accounts for observed hepatomegaly in STZ-induced diabetic animals (Herrman *et al.,* 1999). Thus, the anti-hyperglycemic potential exhibited by the extract against the STZ induced hyperglycemia may be, by safeguarding of the liver by liver index restoration and reducing of ALT, AST and ALP levels.

Diabetes related dyslipidemia has been reported (Mooradian, 2009). In this experiment, a significant increase was seen in the level TG in the diabetic control rats when compared to the normal control animals. Similarly, TC, VLDL and LDL levels were observed to increase in the diabetic control rats while a decrease in the high density lipoprotein (HDL) level was seen in the untreated STZ-induced rats when compared with the normal control animals. This observation agrees with previous reports, that increase in TG, TC, LDL and VLDL levels, and decrease level of HDL are seen during diabetes (El-Baz *et al.,* 2016). This observed reduction in HDL levels of the diabetic control group, may be due to inadequacy in metabolism of fatty acid, augmented gluconeogenesis and elevated ketone bodies production in the diabetic state, leading to a rise in hypertriglyceridemia and hypercholesterolemia, which are the usually associated abnormalities of lipid metabolism in diabetes (Shepherd, 2005).

Higher levels of serum lipids as seen in the diabetic control animals, may be due to disorder of hormone sensitive enzyme (lipase), because insulin deficiency is known to cause an increase in concentration of lipase, which allows free fatty acid mobilization from peripheral fat depot (Schofield *et al.,* 2016). The STZ induced insulin deficiency, usually arises from β-cell damage, leading to elevated levels of serum lipids (Shankarprasad *et al.,* 2017). However, treatment of the STZ induced rats for 21 day with various doses of the plant extract led to a concentration dependent significant decrease in TC, TG, VLDL and LDL levels, with increase in HDL level.

The observed increased in lipid the profile parameters and liver marker enzymes (AST, ALP and ALT) in the negative control animals may also be, as a result of hepatocytic degeneration and fatty changes (cytoplasmic vacuolation) in the liver, which may be due to STZ conversion of liver metabolites, thereby causing catalytic phospholipid peroxidation of membrane, resulting in the breakdown of endoplasmic reticulum, eventually causing a reduction of liver cells lipid export and so causing a buildup of hepatocytes lipids (Hashemnia *et al.,* 2012).

Diabetes is usually linked with increased free radicals formation, thereby tilting the antioxidant defense system balance, resulting in oxidative stress (Nazirogilu and Butterworth, 2005). The results of this study also revealed a significant increase in MDA level and decrease in the SOD and CAT activities in the diabetic control group when compared with the normal control rats, which agrees with previous works (Sarkhail *et al*., 2007). But treatment of the STZ-induced rats with *A. hispidum* extracts for 21 days, dose dependently normalized the diabetic induced oxidative stress in the animals with the highest dose of extract bringing the activities of these enzymes to comparable level with that of the standard drug (glibenclamide) used. Thus, the results showed that oral treatment with *A. hispidum* could enhance the antioxidant defense mechanism of animals, so protecting their tissue from diabetes induced damage. Consequently, the exhibited antidiabetic potential by the extract may be as a

result of reduction of ROS production by inhibition of glucose autooxidation, thereby eliciting *in-vivo* antioxidant potential (Sarkhail *et al*., 2007).

The SOD is an important antioxidant enzyme in the body, which precludes oxidative damage to our body. Superoxide radical reduction into hydrogen peroxide is achieved by SOD enzymes. Formed hydrogen peroxide is then converted to water molecule (Matcovis *et al.,* 1982). MDA is a known breakdown product resulting from polyunsaturated fatty acid oxidation in the cells. High serum MDA concentration usually signals higher concentration of lipid peroxidation, producing high oxidative stress and diabetes development (Ceriello, 2000).

Albumin accounts for around 50% of the total concentration of serum protein and it is a key carrier protein, which circulates in bloodstream. Thus, a want of serum albumin implies chronic liver impairment, which may be due to infection (Mahmoodzadah *et al.,* 2017). In this study, a slightly higher level of albumin was noticed for the hydroethanol extract treated groups (300 and 600 mg/kg), compared to the diabetes control rats and this may be as a result of efficacy of the plant extract, to boost glucose concentration, which occurs due to failure of the usual feedback inhibition in the liver, of gluconeogenesis followed by an enlarged breakdown of proteins and fats, and the possible conversion of the glucogenic amino acids, to glucose (Qaid and Abdelrahman, 2016). However, no significant difference was seen in the levels of total protein and albumin in the treated groups when compared with the diabetic control animals.

Urea and creatinine are two end products (nitrogenous) of metabolism which suggest glomerular filtration rate. Creatinine is formed from the cleavage of phosphocreatine to generate energy for muscle activity (Stryer *et al.*, 1997). Urea is formed from amino acids deamination, thereby generating ammonia which is conveyed to the liver and used for urea formation by the urea cycle. In this experiment, higher levels of urea and creatinine was observed in the diabetic control rats relative to the normal control ones, which signals renal dysfuntion and metabolic disorder caused by diabetes (Helal *et al*., 2014).

Conclusion

Treatment with extract of *A. hispidum* significantly caused repression of STZ-induced hyperglycemia in diabetic rats, whereby the antihyperglycemic efficiency at the highest dose of extract was comparable with that of glibenclamide. Administration of extract for 21 days at different doses displayed hepatoprotective and antihyperlipidemic effects in the STZ-induced diabetic rats. Thus, the extract of *A. hispidum* roots possesses antidiabetic effect, which may be due to its phytoconstituents.

Conflict of Interest

Author declares that there is no conflict of interest in this study.

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