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Hypoglycemic and Hypolipidemic Activities of Methanolic Extract of *Sphenocentrum jollyanum* on Streptozotocin-induced Diabetic Wistar Rats

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Authors' contributions

Authors MOA and OSA designed the study. Author OSA supervised all the procedures for the research work. Authors MOA and OMI carried out the procedure for this research. Authors OMI and SAA performed the statistical analyses and author OOA carried out the literature review. All authors took care of the animals and were involved in reading and approval of final manuscript.

Original Research Article

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ABSTRACT

Aims: This study is to provide scientific basis for the folkloric use of *Sphenocentrum jollyannum* roots in the management and/control of *Diabetes mellitus*. The effects of the extract on blood glucose level and serum lipid profile in Streptozotocin-induced diabetic rats was investigated. The efficacy was also compared with that of glibenclamide, a known antidiabetic drug.
Study Design: Experimental Study.
Place and Duration of Study: Department of Anatomy and Cell Biology, Obafemi Awolowo University, Ile-Ife, Nigeria and Department of Chemical Pathology, Ekiti State University Teaching Hospital, Ado Ekiti, Nigeria, between November, 2010 and April, 2012.
Methodology: Twenty four adult Wistar rats were randomly divided into four groups (A, B

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C and D) of six rats each and used for this research. *Diabetes mellitus* was induced in groups B, C and D by a single intraperitoneal injection of streptozotocin (80mg/kg body weight) dissolved in 0.1 M citrate buffer. Group A, the control rats were intraperitoneally injected with an equivalent volume of citrate buffer. Group B diabetic rats were untreated while groups C and D received Methanolic extract of *Sphenocentrum jollyanum* (MESJ) (200mg/kg) and glibenclamide (0.5mg/kg) once daily for two weeks respectively.
Results: The result showed a significant ($P < 0.05$) fall in blood glucose and serum lipid levels with MESJ and glibenclamide administration. A significant ($P < 0.05$) decrease in the raise of lipids in serum and improvement in the lipid levels to an almost normal condition was also observed.
Conclusion: *Sphenocentrum jollyanum* roots possess hypoglycemic and hypolipidemic effects on diabetic rats lending credence to its use in the traditional management and/or control of *Diabetes mellitus.*

Keywords: Diabetes mellitus; sphenocentrum jollyanum; streptozotocin; hypoglycaemic; hypolipidemic.

1. INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from insulin secretion, insulin action or both. Several pathologic processes involved in the development of *Diabetes mellitus* ranges from autoimmune destruction of β –cells of the pancreatic islets of Langerhans and /or diminished tissue response to insulin at one or more points in the complex pathway of hormones action [1]. DM is the most common metabolic disorder with a global prevalence of about 8.5%. It is estimated that by 2030, the prevalence will be 9.9% and the greatest prevalence is expected to occur in Asia and Africa [2]. Insulin and various oral anti- diabetic drugs are used as monotherapy or in combination to achieve better glycemic control; however, each of these drugs elicits a number of serious side effects [3,4]. These drugs are known to manage the hyperglycemia caused by DM leaving the pathogenesis of this disorder i.e. the degeneration of the β-cells of the pancreatic islets of Langerhans. Thus, management of *Diabetes mellitus* without any side effect is still a challenge to the medical system.

Among the most important raw materials researched by pharmaceutical companies are naturally occurring materials obtained from plants [5]. Interest in medicinal plants has been fuelled by the rising costs of prescription drugs in the maintenance of health and by the bio-prospecting of new plant-derived drugs. Also, in spite of the presence of anti diabetic drugs, remedies from medicinal plants are considered to be free from the side effects compared with synthetic ones [6].

Sphenocentrum jollyanum (SJ) is a plant which belongs to the family, Menispermaceae (Linn). It is a deciduous shrub up to 1.5 m tall, with grey bark and spirally arranged leaves which are smooth on both sides [7]. It is distributed from Sierra Leone to Cameroon via Nigeria. *S. jollyanum* has antihypertensive, antioxidant, antinociceptive, antiviral and anti-angiogenic effects in animals [7,8]. The plant is also documented for its use against chronic coughs, worms and other inflammatory conditions as well as tumors [9,10]. It is also believed to be an emetic and purgative, especially when poisoning is suspected; the sap is believed to relieve stomach ache and constipation and to boost appetite and sexual drive [11]. In Cote d' Ivoire, pounded roots are taken against high blood pressure, while the boiled roots are

given against epileptic fits. In Ghana, the pulped root is been applied to treat breast tumors [12]. In Nigeria, a decoction of the root is applied to treat topical ulcer and the edible fruit is taken against fatigue [13]. Traditional health practitioners in the western region claim that the root of *Sphenocentrum jollyanum* is effective for the treatment of *diabetes mellitus*. Also, Mbaka G et al. suggested that the plant may be a potential source of a new anti diabetic agent [14]. Thus, there is need for more information on the scientific basis of the use of this extract.

Streptozotocin (STZ) is an N- nitro derivative of glucosamine. It is a naturally occurring broad spectrum antibiotic and cytotoxic chemical that is particularly toxic to the pancreatic insulin-producing beta cells in mammals. Thus, it is widely used to induce experimental diabetes in various animal models [15,16]. STZ is similar enough to glucose to be transported into the cell by the glucose transport protein GLUT 2 but is not recognized by the other glucose transporters. This explains its relative toxicity to beta cells since these cells have high levels of GLUT 2 [17]. Streptozotocin causes fragmentation of DNA in pancreatic beta cells of rats through the formation of free alkylating radicals leading to a reduction in the cellular levels of nucleotides and related compounds. This causes a rapid necrosis of the β-cell of pancreatic islets [18].

2. MATERIALS AND METHODS

2.1 Animal Care and Management

The study was carried out on healthy male and female Wistar strain albino rats weighing between 150 to 250g. The animals were bred in the Animal Holding of the Department of Anatomy and Cell Biology, Obafemi Awolowo University, Ile-Ife. Animals were housed in clean plastic cages under natural light and dark cycles at room temperature. Animals in all groups were fed normal laboratory chow *ad libitum* and allowed free access to water. The rats of either sex were randomly divided into four groups A, B, C and D of 6 rats each.

2.2 Extraction of *Spenocentrum jollyanum*

The roots of *Sphenocentrum jollyanum* Linn. were collected from a farmland in Ikere Ekiti, Ekiti State in the month of November. The plant was botanically identified by Mr F.O. Omotayo, the Curator of the Department of Plant Science and Forestry, University of Ado Ekiti, Ekiti State. A voucher specimen was placed in the Herbarium of the Department. The roots of *S. jollyanum* were washed with tap water and air dried at room temperature (28ºC) for eight weeks. The air dried roots were pounded using a wooden mortar and pestle and milled into fine powder in an electric blender. 980 g of the powdered root was extracted in a Soxhlet Extractor with methanol (100%) for 24hours. The mixture was filtered and the filtrate evaporated with a Vacuum Rotary Evaporator under reduced pressure at 60ºC. The yellowish brown yield was freeze- dried using a Vacuum Freeze Drier and stored in a desiccator at room temperature (28ºC) throughout the experimental period. An aliquot portion of the crude extract residue was dissolved in distilled water for use on each day of the experiment. According to Mbaka et al. the acute toxicity study for *Sphenocentrum jollyanum* has earlier been confirmed [14].

2.3 Animal Treatment

There was a pre-treatment period of four weeks during which the body weight and blood glucose level was monitored in all the animals. This served as baseline conditions.

Diabetes mellitus was induced in groups B, C and D animals of both sexes by a single intraperitoneal injection of STZ (80 mg/kg body weight) freshly dissolved in 0.1 M citrate buffer [19]. The rats were fasted for 16 hrs before commencement of the experiment. The rats in group A (the control) were given equal volume of the citrate buffer used in dissolving STZ intraperitoneally.

Twenty four hours after the injection of STZ, *Diabetes mellitus* was confirmed in the animals with blood glucose level greater than 18 mmol/L. After four weeks of STZ induction of diabetes (post-STZ Treatment Period), the rats in group B were left untreated. MESJ was administered orally to the rats in group C for two weeks at 200 mg/kg body weight [14]. Glibenclamide (GB), a standard anti diabetic drug was dissolved in distilled water and administered to group D rats for the same period of time at a dosage of 0.5 mg/kg [20]. The animals were monitored for another four weeks (Post GB/ MESJ Treatment Period).

2.4 Determination of Blood Glucose Level and Serum Lipid Profiles

Blood glucose concentrations were determined with a digital glucometer (Accu-check ® Active, Roche Diagnostic, Germany). After an overnight fast, blood samples were obtained from the tail vein of the rats by cutting the tip of the tail after sterilizing with methylated spirit. A drop of blood was placed on the reagent strip. The strip was inserted into the microprocessor digital glucometer and the reading on the screen noted. For estimation of serum lipid profile, blood samples were collected from overnight fasted rats by cardiac puncture following cervical dislocation. The blood was drained into ice-cold centrifuge tubes and centrifuged in a Denley BS 400 centrifuge (England) at a speed of 3000 rpm for 5 mins. The serum levels of triglyceride (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were measured spectophotometrically using enzymatic colorimetric assay kits (Randox Laboratory, Northern Ireland) with standard methods while low density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C) and antiatherogenic index (AAI) were calculated.

2.5 Statistical Analysis

One-way ANOVA was used to analyze data followed by Student Newman-Keuls test for multiple comparisons. Primer for windows (McGraw-Hill, version 4.0.0.0) was the statistical package used to analyze data. Results were expressed as mean ± standard error of mean. $P<0.05$ was taken as accepted level of significant difference.

3. RESULTS AND DISCUSSION

3.1 Effects on the Fasting Blood Glucose Level

During the pre-experimental period, prior to STZ administration there was no significant difference in the blood glucose level among the four groups of animals(A=4.75±0.06mMol/L, B=4.94±0.06mMol/L, C=4.94±0.08mMol/L, D=4.94±0.07mMol/L) (P=.18). At the end of the Post-STZ treatment period, there was significantly (P=.00) increased blood glucose level in

groups B (23.97±2.72mMol/L), C (22.5±1.77mMol/L) and D (21.28±2.03mMol/L) when compared with the control (4.95±0.04mMol/L) (*P*=0.00). Also, multiple comparisons showed that there was no significant difference among the experimental groups (B, C and D). At the end of week 11, the first week in the Post-GB/SJ treatment period, a fall in blood glucose level was observed in groups C (6.62mMol/L) and D (6.10mMol/L). At the end of week 14, only group B animals had significantly higher blood glucose level (16.3±0.83mMol/L) than the control (5.11±0.12mMol/L) (P=.00). Also, there was no significant difference between groups C and D (*P*=0.14) (Fig. 1).

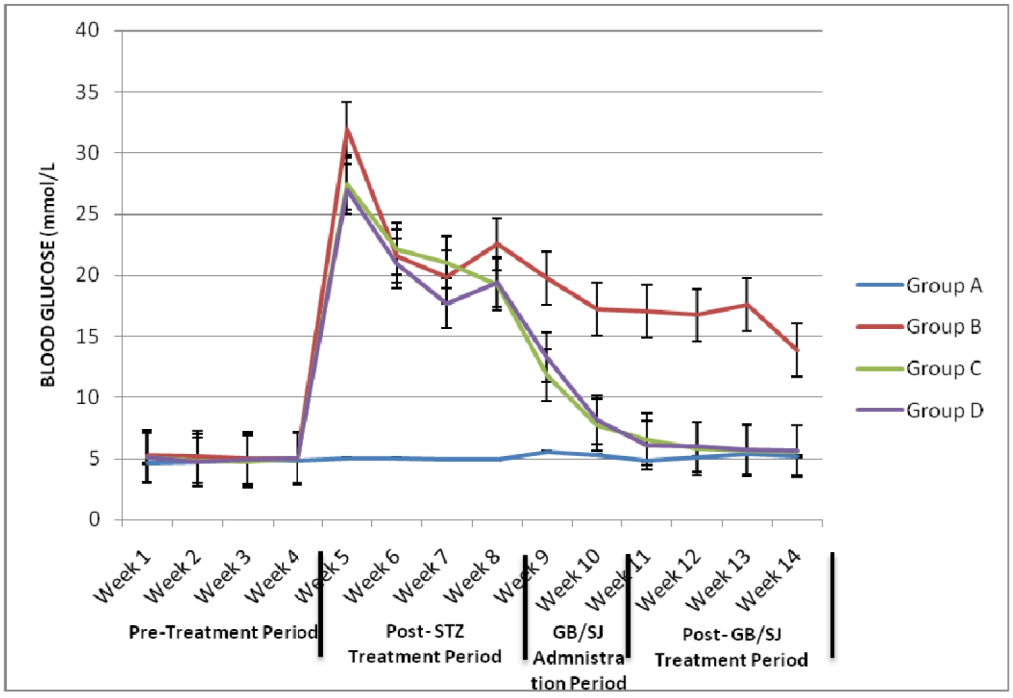

Fig. 1. Weekly changes in blood glucose level of control and experimental animals

3.2 Effects on the Serum Lipid Profiles

As seen in Fig. 2, there was no significant difference in the TC levels when groups C (1.73±0.02mMol/L) and D (1.74±0.03mMol/L) were compared with the control (2.12±0.05 mMol/L) but there was a significant (*P*=.00) difference when group B (2.12±.0.05 mMol/L) was compared with the control (1.66±0.25 mMol/L). Likewise, in Fig. 3, only group B (1.64±0.05 mMol/L) showed a significant difference in TG levels when compared with the control (0.89±0.04 mMol/L). In Fig. 4, Group C (0.77±0.02mMol/L) had significantly (*P*= .02) reduced HDL-C when compared with the control (0.85±0.02 mMol/L) but showed no significant difference (*P*=.12) against group D (0.80±0.02 mMol/L). Also, there was a significant (*P*= 0.02) difference in HDL-C for groups B (0.46±0.02 mMol/L) and C (0.77±0.02 mMol/L) when compared with the control while there was no significant difference between group D and the control (P=.11). In Fig. 5, only group B animals showed a significant (P= 0.01) difference in LDL-C levels (0.91±0.03mMol/L)) when compared with the control (0.41±0.02mMol/L). This was also observed in Fig. 6 where there was a significant (*P*=.00) difference in VLDL-C levels for group B animals (0.75±0.02 mMol/L) when compared with

the control (0.41±0.02 mMol/L). In Fig. 7, groups C (81.37±3.19%) and D (86.78±4.87%) animals were significantly (*P*=.03) reduced in AAI when compared with the control (105.98±8.02%), but there was no significant difference between these two groups (*P*=.00).

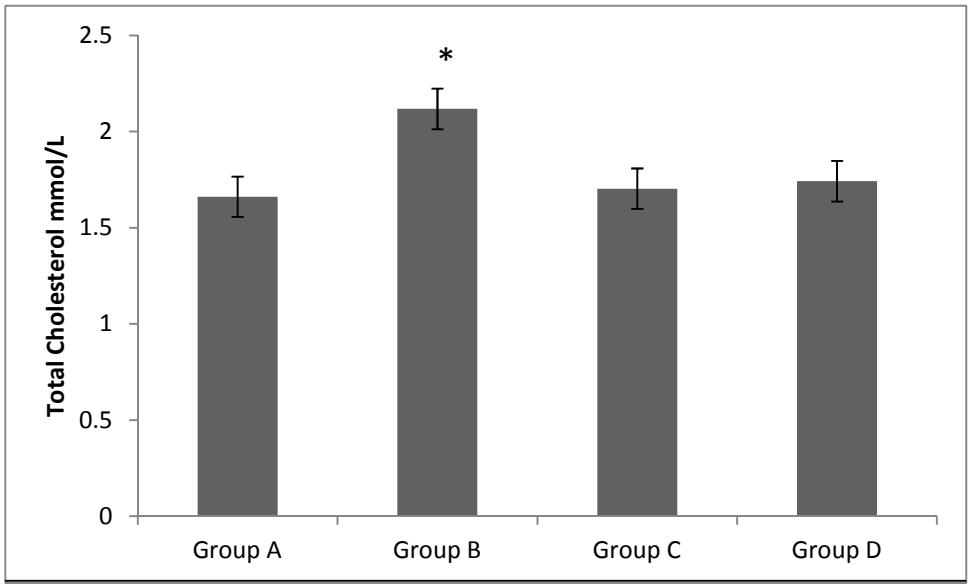

Fig. 2. Total cholesterol (TC) levels of control and experimental animals
*Bars are mean ±SEM. * indicates significant difference (P<0.05) compared to control.*

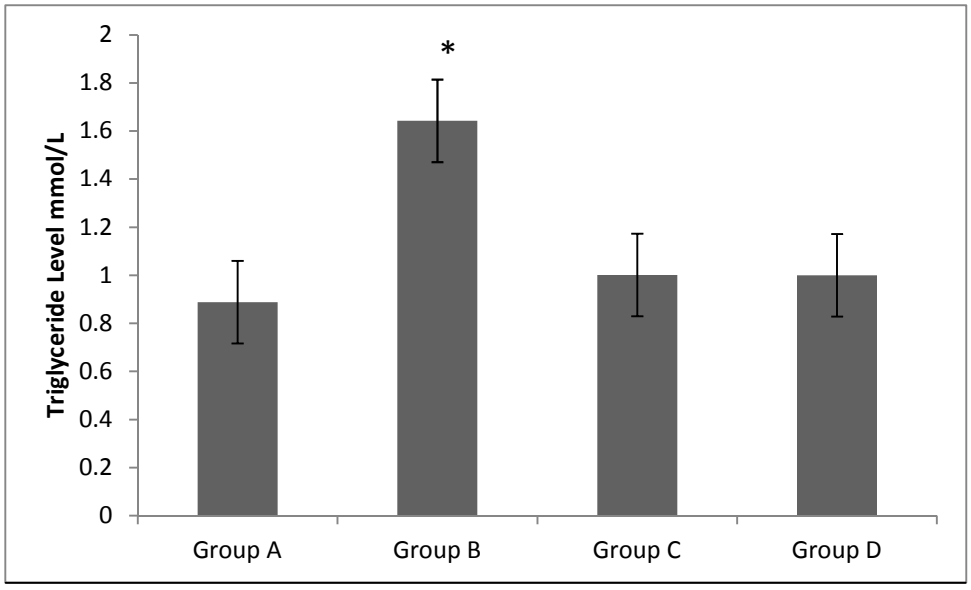

Fig. 3. Triglyceride (TG) levels of control and experimental animals.
*Bars are mean ±SEM. * indicates significant difference (P<0.05) compared to control.*

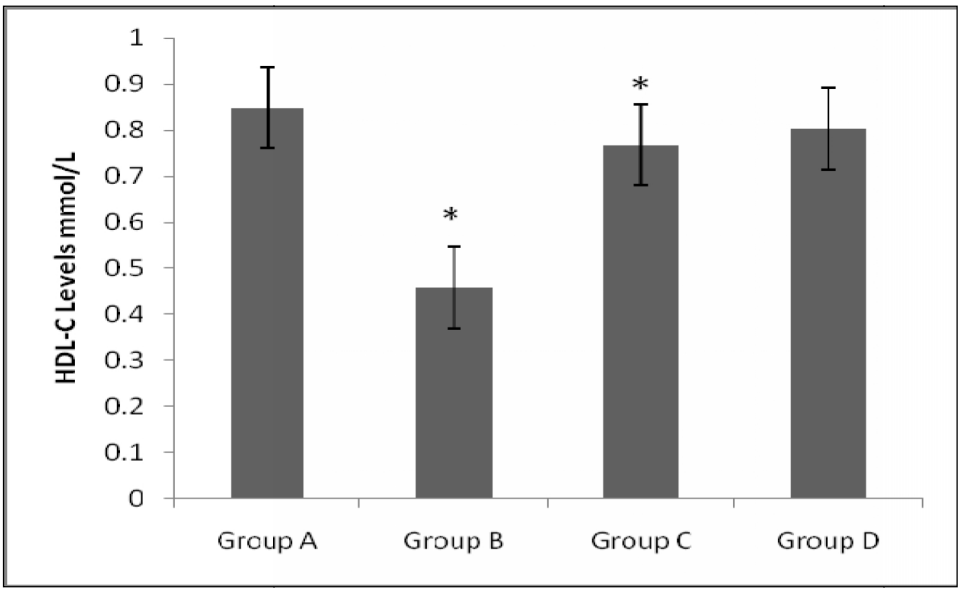

Fig. 4. High density lipoprotein cholesterol (HDL-C) levels of control and experimental animals

*Bars are mean ±SEM. * indicates significant difference (P<0.05) compared to control.*

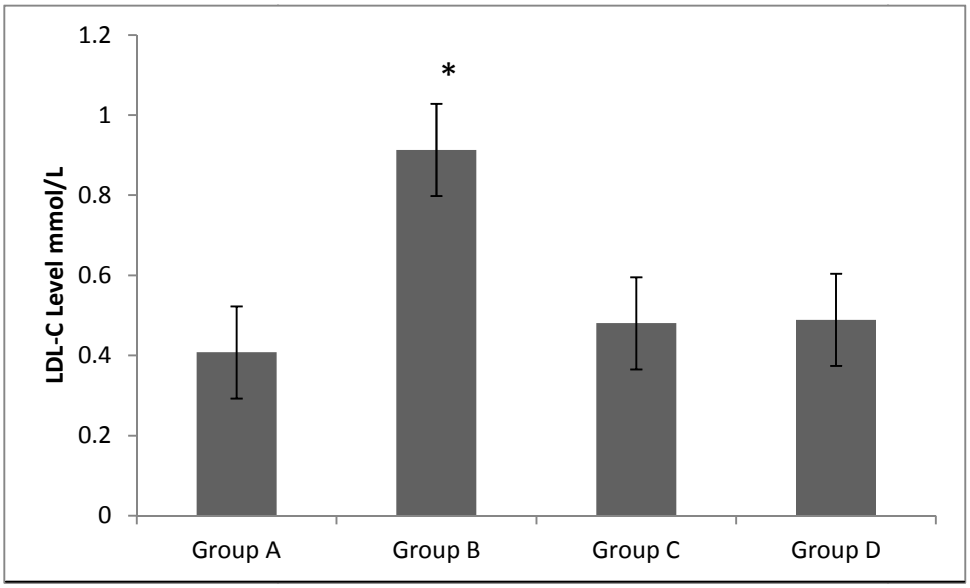

Fig. 5. Low density lipoprotein cholesterol (LDL-C) levels of control and experimental animals

*Bars are mean ±SEM. * indicates significant difference (P<0.05) compared to control.*

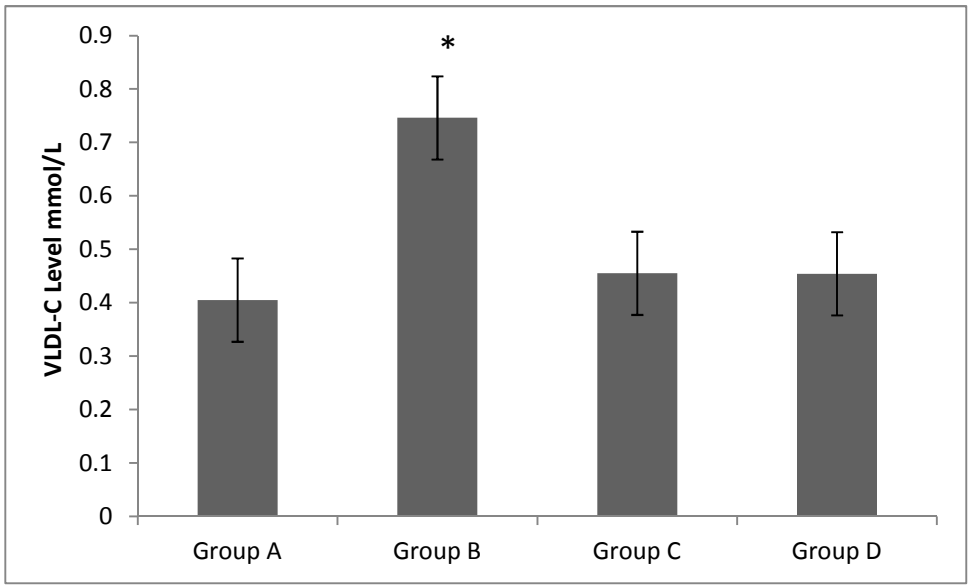

Fig. 6. Very low density lipoprotein cholesterol (VLDL-C) levels of control and experimental animals

*Bars are mean ±SEM. * indicates significant difference (P<0.05) compared to control.*

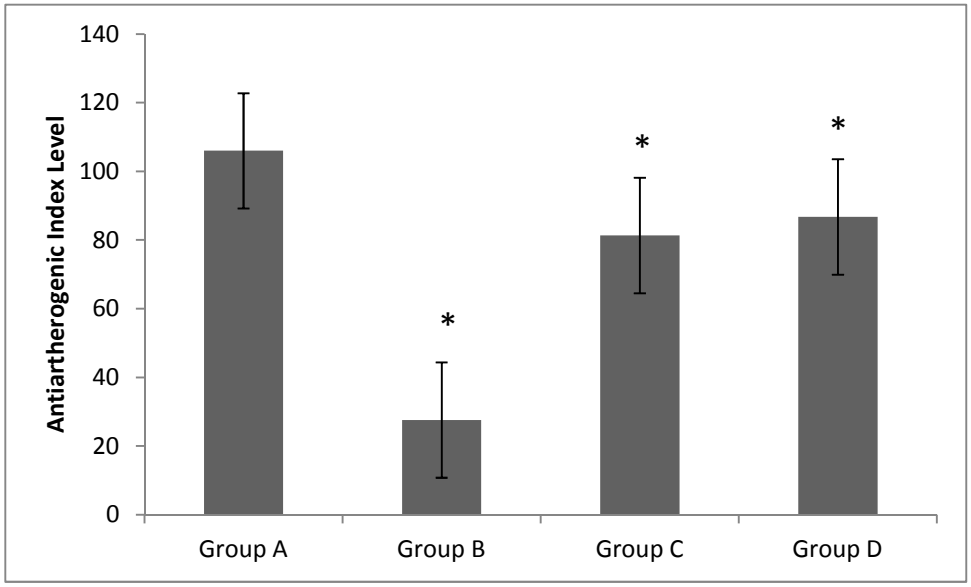

Fig. 7. Antiartherogenic (AAI) index of control and experimental animals

*Bars are mean ±SEM. * indicates significant difference (P<0.05) compared to control.*

3.3 Discussion

Streptozotocin has been used as an animal model of insulin-dependent *Diabetes mellitus* for ages [21]. STZ selectively destroys the pancreatic insulin secreting β-cells, leaving less active pancreatic cells and resulting in *Diabetes mellitus* [22]. This well-established model is characterized by insulin deficiency associated with insulin resistance [23]. Consequently, there is reduced secretion of insulin leading to clinical conditions such as hyperglycemia, polyphagia, polydipsia, polyuria and weight loss [24]. In this study, all these conditions were observed in the STZ treated rats.

A number of plants have been used traditionally to treat diabetes and some have been proven to have hypoglycemic effects. Studies have identified compounds like terpenes and tannins [25], alkaloids [26] and flavonoids [27] to be responsible for the hypoglycemic properties. The chemical analyses of *S. jollyanum* showed the prescence of terpenes, tannins, alkaloids and flavonoids among others [28]. Although the mode of action of this extract has not been documented, the observed hypoglycemic effects could be due to the combined activity of these compounds.

Glibenclamide, like the plant extract also shows significant hypoglycemic activity in the diabetic group of animals. The present findings appear to be in consonance with earlier suggestion of Jackson and Bressler (1981) that sulphonylureas such as glibenclamide have extrapancreatic hypoglycemic mechanism of action secondary to their causing insulin secretion and the attendant glucose uptake into and utilization by the tissues [29].

The comparable pattern of the hypoglycemic activity of the extract under study with that of the reference drug, glibenclamide, demonstrated a possible similarity in their mechanism of action to insulin secretion.

Serum lipid and lipoprotein profiles are usually altered in diabetes and these present a risk for the incidence of coronary heart disease [30]. Results from this study showed an increase in serum triglycerides and cholesterol in diabetic rats. The treatment with *S. jollyanum* decreased the raise of lipids in serum and improved the lipid level to a normal condition which may be attributed to its potent antidiabetic activity. This effect was also observed in the reference drug, glibenclamide.

Altered carbohydrate metabolism during diabetes is also accompanied by a disorder in fat and protein metabolism [31]. The characteristic features of diabetic dyslipidemia are a high plasma triglyceride concentration, low HDL-cholesterol concentration and increased concentration of small dense LDL-cholesterol particles [32]. Faulty glucose utilization causes hyperglycemia and mobilization of fatty acids from adipose tissue for energy purpose [33]. The lipid changes associated with diabetes mellitus are attributed to increased influx of free fatty acids into the liver secondary to insulin deficiency/resistance [34,35]. This results in excess fatty acid accumulation in the liver, which is converted to triglycerides [32,33]. The impaired ability of insulin to inhibit free fatty-acid release leads to elevated hepatic VLDL-cholesterol production [36]. The increased VLDL-cholesterol and triglyceride levels decrease the level of HDL-cholesterol and increase the concentration of small dense LDL-cholesterol particles by activation of lipoprotein lipase and lecithin acyl-cholesterol transferase [37]. In the present study, elevated levels of serum TC, TG, LDL and VLDL-cholesterol and decreased HDL-cholesterol concentration observed in STZ-induced diabetic rats are in accordance with previous research findings [38]. However, treatment with MESJ normalized

all the lipid profile parameters. This may be attributed to the potent anti-hyperglycemic activity.

The result of this study indicated that there was no significant difference between the effects of the extract and the reference drug, glibenclamide. MESJ was also observed to significantly decrease atherogenicity without any significant difference to glibenclamide.

4. CONCLUSION

The findings from this study revealed the beneficial effects of the MESJ roots on blood glucose level and serum lipid profiles in STZ induced diabetic rats. Hence, apart from controlling hyperglycemia, it would also be beneficial in the alleviation of associated diabetic complications such as dyslipidaemia, a risk factor for the development of atherosclerosis and other coronary artery diseases. However, further studies are needed to investigate and elucidate the possible mechanism of action of the active ingredients and evaluate the potential value of MESJ roots for the management of diabetes and hyperlipidemia in the clinic. This may prove helpful for developing new drugs from this plant for managing diabetes and its associated complications.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that 'Principles of laboratory animal care'(NIH publication No. 85-23, revised 1985) were followed. All experiments have been examined and approved by the appropriate ethics committee.

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COMPETING INTERESTS

Authors hereby declare that there are no competing interests.

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