EFFECTS OF METHANOLIC STEM BARK EXTRACT OF *Cassia sieberiana* DC ON FASTING BLOOD GLUCOSE AND SERUM LIPID PROFILE OF ALLOXAN INDUCED DIABETIC RATS

[1]IHEDIOHA, Thelma Ebele, [1]OMOJA, Valentine Uneojo and [1,2]ASUZU, Isaac Uzoma

[1]Department of Veterinary Physiology and Pharmacology, Faculty of Veterinary Medicine, University of Nigeria, Nsukka, Enugu State, Nigeria.

[2]Office of the Vice Chancellor, Federal University Oye-Ekiti, Ekiti State, Nigeria.

Corresponding Author: Ihedioha, T. E., Department of Veterinary Physiology and Pharmacology, Faculty of Veterinary Medicine, University of Nigeria, Nsukka, Enugu State, Nigeria. Email: thelma.ihedioha@unn.edu.ng Phone: +234 8036868258

ABSTRACT

This study evaluated the effects of methanolic stem bark extract of Cassia sieberiana (MSBECS) on fasting blood glucose (FBG) and serum lipid profile (SLP) of alloxan-induced diabetic albino rats. The extract was prepared by cold maceration and administered orally at the dose of 12.5, 25, 50, 100 and 200 mg/kg body weight to evaluate the effects on fasting blood glucose (FBG) of the diabetic rats, and at 50, 100 and 200 mg/kg body weight (bw) for the serum lipid profile (SLP) assay. A total of 78 male albino rats (Rattus norvegicus) of 12 weeks of age were used for the study; 42 were used to evaluate the effects of the extract on FBG, while 36 were used for the SLP assay. Data from the study showed that the optimum anti-hyperglycemic activity of the C. sieberiana extract on the diabetic rats was recorded in the rat group given 50 mg/kg bw of MSBECS, and this did not differ significantly (p>0.05) from that of glibenclamide-treated rats. Treatment of the diabetic rats with the extract at the doses of 100 and 200 mg/kg bw produced a significant (p<0.05) increase/improvement in the serum **high density lipoprotein cholesterol** ***(HDLC), while rat groups given 50, 100 and 200 mg/kg bw of the extract had a significantly (p<0.05) lower serum triglyceride and very low density lipoprotein cholesterol (VLDLC). It was concluded the administration of MSBECS at 50 mg/kg bw led to significant reduction in FBG of diabetic rats comparable to that obtained in the control group treated with a standard anti-hyperglycaemic drug (glibenclamide), while treatment at doses of 50, 100, and 200 mg/kg bw led to favorable effects on the lipid profile of the diabetic rats. These findings validate the traditional use of the stem bark of C. sieberiana in the management of diabetes mellitus and its dyslipidaemia complications.***

Keywords: *Cassia sieberiana*, Diabetes mellitus, Dyslipidaemia, Blood glucose, Serum lipid profile, Albino rats

INTRODUCTION

The use of herbs or parts of plants to treat diseases is accepted worldwide (Fabricant and Farnsworth, 2001; DaSilva *et al*., 2002). Roots, leaves and the bark of plants were principal sources of drugs for the primitive man in the treatment of diseases (Fabricant and Farnsworth, 2001). The study of traditional use of medicinal plants is recognized as a way to learn about their potential future use as medicines, and many of the pharmaceuticals

currently available to physicians have a long history of use as herbal remedies (Fabricant and Farnsworth, 2001; DaSilva *et al*., 2002). Herbal remedies are believed to be safer and less damaging to the human body than synthetic drugs; they are easier to produce, affordable and more readily available (Abdu *et al*., 2000; Pamploner-Roger, 2004). Although many traditional or herbal treatments for diabetes mellitus are used throughout the world, only a small percentage has been scientifically validated.

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion and/or insulin action, and characterized by symptoms such as polydipsia, polyuria, polyphagia, blurring of vision and weight loss (WHO, 1999; Rother, 2007). The disease is associated with complications such as diabetic ketoacidosis, coma, dyslipidaemia and damage to blood vessels that may accelerate atherogenesis and atherosclerosis (WHO, 1999; Durrington, 2003; Schoen, 2004).

Dyslipidaemia is an abnormality in the amount of the various lipids in the blood (Durrington, 2003). The lipids commonly assayed for in the blood/serum of humans and animals are cholesterol and triglycerides because of their clinical significance (Oslon, 1998; Brunzell *et al*., 2008). Cholesterol is transported in the blood stream in association with lipoproteins which are named according to their densities; thus, in serum assays, apart from total cholesterol (TC), high density lipoprotein-cholesterol (HDLC), low density lipoprotein-cholesterol (LDLC) and very low density lipoprotein-cholesterol (VLDLC) are usually routinely determined (Oslon, 1998; Brunzell *et al*, 2008; Ihedioha *et al*., 2013a). Although serum lipids are physiologically important in the body, dyslipidaemia had been found to be a major risk factor for the development of atherosclerosis and its consequences which include myocardial infarction, cerebral infarction and peripheral vascular disease often seen in diabetic patients (Oslon, 1998; Durrington, 2003; Schoen, 2004; Brunzell *et al*., 2008; NIH 2008).

Cassia sieberiana is a savanna plant of the family Acacia (Caesalpiniaceae). It is commonly known as African laburnum or drumstick tree. It is found in dry areas of forests and thickets (Vander-Maesen, 2008). In Nigeria, extracts of the roots, stem bark and fruit pulp of *C. sieberiana* are used traditionally for the treatment of inflammatory conditions, fever, joint pains, malaria, diarrhea, leprosy, bilharzias, stomach pains, diabetes mellitus and its complications and other illnesses (Madusolumuo *et al*., 1999; Tamboura *et al*., 2005). In Senegal, Uganda and Cote d'Ivoire, decoctions of the root or infusions of the whole plant are used as purgative and diuretic, and recommended for the treatment of hemorrhoids, bilharzias, leprosy, dropsy, intestinal worm infestations, diabetes mellitus and numerous childhood illnesses (ASICUMPON, 2005; Vander-Maesen, 2008). It had also been shown that *C. sieberiana* extracts has anti-microbial activity against *Neisseria gonorrhoeae*, *Herpes simplex* virus type I and African swine fever virus (Silva *et al*., 1997). Studies in our laboratory had shown that the major phytochemical constituents of methanolic stem bark extract of *C. sieberiana* were tannins, flavonoids, alkaloids, saponins, carbohydrates and reducing sugars, and that the extract possesses anti-oxidant activity, with an LD_{50} of 3,379.33mg/kg bw in albino rats (Ihedioha *et al*., 2013b).

There is paucity of information in available literature on the effects of extracts of *Cassia sieberiana* on fasting blood glucose and serum lipid profile, hence this study which was designed to investigate the effects of varied doses of the crude methanolic stem bark extract of *C. sieberiana* on fasting blood glucose and serum lipid profile of alloxan-induced diabetic rats.

MATERIALS AND METHODS

Plant Extract: Fresh samples of the stem bark of *C. sieberiana* were collected from Adoka in Benue State, Nigeria in April 2010. The plant was identified and authenticated by a plant taxonomist at the Department of Botany, University of Nigeria, Nsukka. One thousand

grammes of dried and powdered *Cassia sieberiana* stem bark were extracted with 80% methanol using the cold maceration method. The extract was filtered with Whatman Filter Paper Number 1, and dried with a rotary evaporator. The residual extract was dissolved in distilled water and used for the study.

Animal: A total of 78 male albino rats (*Rattus norvegicus*) of 12 weeks of age, obtained from the Animal House of the Department of Veterinary Physiology and Pharmacology, University of Nigeria, Nsukka, were used for the study. They were housed in steel cages at room temperature and fed standard rat chow (Vital Feeds Limited, Jos, Nigeria). Forty two (42) rats were used for the dose-response test, while 36 rats were used to evaluate the serum lipid profile (SLP). The rats had free access to food and water. Guidelines for the humane handling of animals were followed all through the study (NRC, 1996).

Induction of experimental diabetes: The rats were fasted for 12 hours and weighed. Alloxan monohydrate (150 mg/kg bw) was weighed for each rat, freshly mixed with distilled water and administered immediately intra-peritoneally (Venugopal *et al*., 1998). After 10 days of alloxan administration, the fasting blood glucose level (FBGL) of the rats was determined using an Accu-chek glucometer based on the glucose oxidase method (ADA, 2003). Rats with FBGL of 6.4 mmol/l and above were considered diabetic and selected for the study.

Evaluation of the effects of the extract on fasting blood glucose of the diabetic rats: Forty two diabetic rats, randomly assigned into seven groups (Groups 1 – 7) of six rats each were used for this experiment. Rats in groups 1, 2, 3, 4 and 5 were treated *per os* with the methanolic stem bark extract of *C. sieberiana* (MSBECS) at the doses of 12.5, 25, 50, 100 and 200 mg/kg bw, respectively. Group 6 rats were treated *per os* with glibenclamide (a standard anti-hyperglyceamic drug) at the dose of 2 mg/kg bw (positive control), while group 7 rats were treated *per os* with distilled water at the dose of 10 ml/kg bw (negative control). The FBGL of the rats was measured before treatment (0 hour) and at hours 1, 3, 6 and 8 post-treatment, using Accu-chek glucometer based on the glucose oxidase method of blood glucose assay (ADA, 2003). The percentage reduction in FBGL was calculated for each of the specified test time.

Evaluation of the effects of the extract on serum lipid profile (SLP) of the diabetic rats: Thirty diabetic rats and six non-diabetic rats were used for this experiment. The 30 diabetic rats were randomly assigned to five groups (Groups A - E) of six rats each. Rats in groups A, B and C were treated *per os* with 200 mg/kg bw, 100 mg/kg bw, and 50 mg/kg bw of the MSBECS daily, respectively. Group D rats were treated *per os* with 2 mg/kg bw of Simvastatin (a standard anti-hypercholesterolaemic drug) daily (positive control), while group E rats were treated *per os* with 10 ml/kg bw of distilled water daily (negative control). Group F rats were the non-diabetic control; they were treated *per os* with 10ml/kg bw of distilled water daily. Treatment was carried out for fourteen days. Blood samples were collected before inducing diabetes mellitus, ten days after diabetes induction, and after fourteen days of treatment, to assay the SLP following standard biochemical procedures after a 12-hour overnight fast, using Quimica Clinica Aplicada (QCA) test kits (QCA, Spain). The serum TC was determined by the enzymatic colorimetric method (Allain *et al*., 1974), while the serum HDLC was determined by the dextran sulphate-magnesium (II) precipitation method (Albers *et al*., 1978). The serum triglyceride was determined by the glycerol phosphate oxidase method (Bucolo and David, 1973). The serum VLDLC was calculated as 1/5 of the serum triglyceride (Rifai *et al*., 2008), while the serum LDLC was calculated using the Friedewald formula (Friedewald *et al*., 1972; Warnick *et al*., 1990).

Statistical Analysis: Data obtained from the study were subjected to a one way analysis of variance (ANOVA), and variant means were separated post-hoc using the least significant difference (LSD) method. Significance was

accepted at $p<0.05$. Results in means and standard deviations were presented in tables.

RESULTS

Treatment with varied doses of the MSBECS led to significantly ($p<0.05$) higher reduction in FBGL of all the rat groups treated with the extract and the group treated with glibenclamide at all specified test times (1, 3, 6 and 8 hours post-treatment), when compared to the negative control treated only with distilled water (Table 1). On the first and third hours post-treatment with the MSBECS, the mean percentage reduction in FBGL of the groups treated with 12.5, 25.0, 50.0 and 100.0 mg/kg bw compared favorably ($p>0.05$) with that of the group treated with glibenclamide, with the percentage reduction achieved by treatment with 200.0 mg/kg bw being significantly ($p<0.05$) lower than that of others (Table 1). However, on the 6^{th} hour post-treatment, the mean percentage reductions in FBGL of the group treated with glibenclamide was significantly higher ($p<0.05$) than that of the other rat groups treated with the varied doses of the MSBECS (Table 1). On the eight hour post-treatment, the mean percentage reduction achieved by treatment with glibenclamide was significantly higher ($p<0.05$) than only that of the group treated with 25.0 mg/kg bw MSBECS (Table 1). When the overall mean percentage reduction across the eight hours post-treatment was compared, the FBGL of the rat groups treated with the varied doses of the MSBECS and the group treated with glibenclamide were significantly higher ($p<0.05$) than that of the group treated with distilled water (negative control), and there were no significant variations ($p>0.05$) between the FBGL of the rats treated with the varied doses of MSBECS and the rat group treated with glibenclamide (Table 1). Amongst the rat groups treated with the varied doses of MSBECS, the group treated with 50 mg/kg bw achieved the highest percentage reduction of blood glucose of the diabetic rats (Table 1).

Alloxan injection had no significant ($p>0.05$) effect on the mean serum TC of the groups given alloxan (groups A to E) and treatment with the MSBECS for 14 days also did not lead to any significant ($p>0.05$) change in the serum TC of the extract-treated rat groups, rather the group D treated with Simvastatin had a significantly lower ($p<0.05$) mean serum total cholesterol (Table 2). After alloxan injection, there was a significant ($p<0.05$) reduction in the mean serum HDLC in all the rat groups injected with alloxan (Table 3). Treatment with the MSBECS for 14 days at 100 and 200 mg/kg bw led to significant ($p<0.05$) increase in the serum HDLC of the alloxan-injected rats from its low post-alloxan injection levels, with the group given 200 mg/kg bw extract comparing favorably ($p>0.05$) with the non-diabetic control (Table 3). Ten days after injection of alloxan, there was a significant ($p<0.05$) increase (more than double) in the values of the mean serum triglyceride of rats in groups A to E (Table 4). Treatment of the alloxan-injected rats with the MSBECS at all doses and Simvastatin led to a significant ($p<0.05$) reduction in the serum triglyceride levels from their very high post-alloxan injection levels, when compared to the untreated diabetic control (Table 4). The serum VLDLC followed the same pattern as the serum triglyceride with a significant increase ($p < 0.05$) post-alloxan injection, and significant ($p<0.05$) reduction after treatment for 14 days with the MSBECS and Simvastatin (Table 5). Alloxan injection led to an elevation of the serum LDLC of all the alloxan-injected groups though this was not found to be statistically significant ($p>0.05$) (Table 6). Treatment with both the MSBECS and Simvastatin did not produce any significant ($p>0.05$) effect on the post-alloxan injection elevated serum LDLC (Table 6).

DISCUSSION

The increased FBGL in alloxan injected rats 10 days post-injection indicated that diabetes was successfully induced. The finding in this present study that MSBECS showed anti-hyperglycemic activity in diabetic rats is in agreement with the reports of significant decreases in blood sugar of experimentally induced diabetic rats treated with aqueous extract of *Cassia auriculata* flower (Pari and Latha, 2002).

Table 1: Percentage reduction of blood glucose in diabetic rats treated with varying doses of methanolic stem bark extract of *Cassia sieberiana*

Treatment groups	Reduction of blood glucose (%)				
	1st hour	3rd hour	6th hour	8th hour	Overall mean
A: 12.5 mg extract /kg bw	19.42 ± 3.64[a]	37.46 ± 3.97[a]	44.53 ± 3.37[a]	55.74±1.31[a b]	39.29±7.62[a]
B: 25.0 mg extract /kg bw	19.32 ± 2.58[a]	31.91 ± 4.23[b]	41.38±5.34[a]	52.61±0.70[a]	36.31±7.07[a]
C: 50 mg extract /kg bw	20.14 ± 8.12[a]	30.88 ± 5.65[b]	43.23±4.95[a]	63.62±7.96[b]	39.47±9.33[a]
D: 100 mg extract /kg bw	15.19 ± 6.76[a]	29.88 ± 9.77[b]	40.27±8.97[a]	59.28± 6.26[a b]	36.16±9.27[a]
E: 200 mg extract /kg bw	12.67 ± 4.27[b]	25.80 ± 2.97[c]	41.00±8.08[a]	59.26±5.71[a b]	34.68±10.03[a]
F: 2 mg Glibenclamide /kg bw	23.52 ± 2.17[a]	33.96 ± 3.42[a b]	56.96±8.78[b]	69.55±6.03[b]	46.00±10.51[a]
G: 10 ml distilled water /kg bw	0.76 ± 3.25[c]	1.83 ± 4.57[d]	- 1.05±4.90[c]	0.69±5.54[c]	0.56±0.60[b]

[a b c] Different superscripts in a column indicate significant difference between the means (p<0.05)

Table 2: Serum total cholesterol of alloxan induced diabetic rats treated with methanolic stem bark extract of *Cassia sieberiana*

Treatment groups	Serum total cholesterol (mg/dl)		
	Before alloxan injection	10 days after alloxan injection	After 14 days of treatment with extract
A: 200 mg extract /kg bw	89.48 ± 3.14	93.14 ± 6.01	103.69 ± 17.88[a]
B: 100 mg extract /kg bw	90.89 ± 10.40	89.79 ± 5.72	85.58 ± 4.52[a]
C: 50 mg extract /kg bw	95.44 ± 10.08	92.49 ± 10.08	86.86 ± 3.05[a]
D: 2 mg simvastatin /kg bw	88.34 ± 10.30	87.89 ± 4.64	74.10 ± 3.92[b]
E: untreated diabetic control	89.85 ± 16.87	90.17 ± 12.12	95.89 ± 14.04[a]
F: non-diabetic control	92.24 ± 10.03	94.39 ± 7.17	93.40 ± 6.69[a]

[a b] Different superscripts in a column indicate significant difference between the means (p<0.05).

Table 3: Serum high density lipoprotein (HDL) cholesterol of alloxan induced diabetic rats treated with methanolic stem bark extract of *Cassia sieberiana*

Treatment groups	Serum HDL cholesterol (mg/dl)		
	Before alloxan injection	10 days after alloxan injection	After 14 days of treatment with extract
A: 200 mg extract /kg bw	51.72 ± 7.57	31.39 ± 7.19 [a]	46.21 ± 8.77 [ab]
B: 100 mg extract /kg bw	53.47 ± 4.31	32.48 ± 3.15 [a]	38.54 ± 6.03 [b]
C: 50 mg extract /kg bw	52.46 ± 5.61	33.49 ± 6.19 [a]	27.94 ± 2.43 [c]
D: 2 mg simvastatin /kg bw	50.77 ± 8.08	30.37 ± 5.64 [a]	20.25 ± 3.96 [d]
E: untreated diabetic control	53.68 ± 7.65	30.86 ± 7.10 [a]	22.86 ± 4.13 [cd]
F: non-diabetic control	51.73 ± 4.41	52.82 ± 2.99 [b]	50.62 ± 6.51 [a]

[a b c d] *Different superscripts in a column indicate significant difference between the means (p<0.05).*

Table 4: Serum triglyceride of alloxan induced diabetic rats treated with methanolic stem bark extract of *Cassia sieberiana*

Treatment groups	***Serum triglyceride (mg/dl)***		
	Before alloxan injection	**10 days after alloxan injection**	**After 14 days of treatment with extract**
A: 200 mg extract /kg bw	17.61 ± 3.13	45.44 ± 11.39 [a]	28.58 ± 4.79 [ab]
B: 100 mg extract /kg bw	19.13 ± 4.51	48.16 ± 5.98 [a]	27.40 ± 3.01 [a]
C: 50 mg extract /kg bw	18.36 ± 6.63	45.47 ± 6.45 [a]	36.65 ± 5.92 [b]
D: 2 mg simvastatin /kg bw	19.37 ± 4.28	46.50 ± 7.54 [a]	25.03 ± 4.42 [ad]
E: untreated diabetic control	18.42 ± 3.87	45.10 ± 11.34 [a]	48.71 ± 11.04 [c]
F: non-diabetic control	18.89 ± 5.59	19.69 ± 7.22 [b]	19.02 ± 6.11 [d]

[a b c d] *Different superscripts in a column indicate significant difference between the means (p<0.05).*

Table 5: Serum very low density lipoprotein (VLDL) cholesterol of alloxan induced diabetic rats treated with methanolic stem bark extract of *Cassia sieberiana*

Treatment groups	Mean serum VLDL cholesterol (mg/dl)		
	Before alloxan injection	10 days after alloxan injection	After 14 days of treatment with extract
A: 200 mg extract /kg bw	3.52 ± 0.63	9.09 ± 2.27 [a]	5.72 ± 0.96 [ab]
B: 100 mg extract /kg bw	3.82 ± 0.90	9.63 ± 1.20 [a]	5.48 ± 0.60 [a]
C: 50 mg extract /kg bw	3.67 ± 1.33	9.09 ± 1.29 [a]	7.33 ± 1.18 [b]
D: 2 mg simvastatin /kg bw	3.87 ± 0.85	9.03 ± 1.51 [a]	5.00 ± 0.88 [ad]
E: untreated diabetic control	3.68 ± 0.76	9.02 ± 2.27 [a]	9.74 ± 2.21 [c]
F: non-diabetic control	3.78 ± 1.12	3.94 ± 1.45 [b]	3.80 ± 1.22 [d]

[a b c d] *Different superscripts in a column indicate significant difference between the means (p<0.05).*

Table 6: Serum low density lipoprotein (LDL) cholesterol of alloxan induced diabetic rats treated with methanolic stem bark extract of *Cassia sieberiana*

Treatment groups	Serum LDL cholesterol (mg/dl)		
	Before alloxan injection	10 days after alloxan injection	After 14 days of treatment with extract
A: 200 mg extract /kg bw	34.24 ± 3.95	52.67 ± 11.69	51.77 ± 13.26 [ab]
B: 100 mg extract /kg bw	33.59 ± 6.81	47.68 ± 8.80	44.56 ± 3.54 [ac]
C: 50 mg extract /kg bw	39.31 ± 13.92	49.91 ± 17.29	51.59 ± 6.11 [a b]
D: 2 mg simvastatin /kg bw	33.70 ± 7.94	48.23 ± 1.12	48.76 ± 7.28 [abc]
E: untreated diabetic control	32.48 ± 11.46	50.29 ± 12.40	63.29 ± 9.95 [b]
F: non-diabetic control	36.73 ± 8.36	37.63 ± 9.42	38.97 ± 6.21 [c]

[a b c d] *Different superscripts in a column indicate significant difference between the means (p<0.05).*

The anti-hyperglycemic activity recorded in this study for MSBECS was time related, with the maximum activity occurring at the 8th hour post-treatment at the dose of 50 mg/kg bw, and comparing favorably with glibenclamide at the dose of 2 mg/kg bw. The comparable mean percentage fasting blood glucose (FBG) reductions in the diabetic rat group given 50 mg/kg bw of MSBECS and glibenclamide at the 8th hour post-treatment suggests that they are of nearly equal potency. The reduction of FBGL by MSBECS may be attributed to the phytochemical constituents of MSBECS which include tannins and flavonoids (Ihedioha *et al*., 2013b). It had been reported that flavonoids constitute the active biological principle of most medicinal plants with hypoglycemic and anti-diabetic properties (Wollenweber *et al*., 1988). The findings in this present study that MSBECS could significantly reduce blood glucose of diabetic rats to a level comparable to that achieved by glibeclamide validates the traditional use of *C. sieberiana* in the treatment of diabetes mellitus.

The decrease in the serum HDLC, increase in serum triglyceride, VLDLC, LDLC, and no effect on serum total cholesterol (TC) seen after alloxan injection to rats in groups A to E is consistent with findings in clinical diabetes mellitus, where impaired insulin action has been reported to significantly affect fat metabolism resulting in increased free fatty acid flux and triglyceride levels and reciprocally low levels of HDLC (Brunzell *et al*., 2008). The dyslipidaemia reported in the diabetic rats in this present study is in agreement with earlier reports in experimentally induced diabetes mellitus (Sharma *et al*., 1996; Pushparaj *et al*., 2000).

The findings of increased mean HDLC in the rat groups treated with 100 and 200 mg/kg of the MSBECS, and decreases in mean triglyceride and mean VLDLC recorded for the groups treated with 50, 100, and 200 mg/kg of MSBECS is in agreement with an earlier report on the effect of aqueous extract of the flower *of C. auriculata* on diabetic rats (Pari and Latha, 2002). The significant increase in HDLC and reductions in triglyceride and VLDLC in the MSBECS-treated rat groups in this present study may be attributed to the anti-oxidant activity of the extract (Ihedioha *et al*., 2013b), as numerous studies had showed that anti-oxidant treatment protects against dyslipidamia-induced atherogenesis and atherosclerosis (Steinberg and Witztum, 1990; Witztum and Steinberg, 1991; Jha, 1995; Steinberg and Witztum, 2002).

Based on the results of this study, it was concluded that treatment of the alloxan-induced diabetic rats with crude methanolic stem bark extract of *C. sieberiana* led to significant reductions in the FBGL of the rats during the 8 hour post-treatment study period comparable to that obtained by treatment with glibenclamide. Furthermore, treatment with MSBECS at 100 and 200 mg/kg bw led to increase/improvement in the already compromised serum HDLC of the alloxan-induced diabetic rats, and treatment with 50, 100, and 200 mg/kg bw MSBECS led to reductions in the elevated serum triglyceride and VLDLC levels of the diabetic rats. The results obtained from this study validate the traditional use of the stem bark of *C. sieberiana* in the treatment of diabetes mellitus, and also strongly suggest that the methanolic stem bark extract of *C. sieberiana* can be effectively used for the treatment of dyslipidaemia and its associated complications usually observed in diabetic patients.

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