

Anti-diabetic and Antidyslipidemic Activities of *Entandrophargma cylindricum* Extract on Streptozotocin-Induced Diabetic Rats

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Abstract: This study aims to validate the anti-diabetic and antidyslipidemic activities of aqueous extract of *Entandrophargma cylindricum* stem on streptozotocin-induced diabetic rats. Thirty healthy male Albino rats (190 ± 10 g) were grouped into 6 groups of 5 each: group A (control) rats were not induced with diabetes; group B (diabetic treated with Metformin 100 mg/kg); group C (diabetic untreated); group D (diabetic treated with *Entandrophargma cylindricum* extract 50 mg/kg); group E (diabetic treated with *Entandrophargma cylindricum* extract 100 mg/kg) and group F (diabetic treated with *Entandrophargma cylindricum* extract 200 mg/kg). Fasting blood glucose concentration and glucose tolerance response increased after 7 days but was reversed near normal on day 14, day 21. Hexokinase activity significantly ($p < 0.05$) increase in the metformin and 200mg/kg bw. However, plasma high-density lipoprotein concentration, plasma insulin concentration, and hepatic glycogen level decreased in the untreated group, 50 and 100 mg/kg bw. Aqueous extract of *E. cylindricum* stem bark possesses significant anti-diabetic and antidyslipidemic activity in diabetic rats.

Keywords: anti-diabetic; *Entandrophargma cylindricum*; diabetes mellitus; glucose tolerance; antidyslipidemic.

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1. Introduction

Diabetes mellitus (DM) is a metabolic derangement characterized by abnormal blood sugar level (hyperglycemia) as a result of deficiencies in the secretion of insulin, insulin action (sensitivity), or both [1]. The hallmark of diabetes is elevated glucose levels and reduced glucose tolerance. Common DM symptoms include frequent urination (polyuria), increased thirst (polydipsia), and increased hunger (polyphagia) [2]. DM is prevalent among patients with hypertension, atherosclerosis, and cardiomyopathy. DM has been reported to have the most comorbid condition in hypertensive patients [3]. Prolonged diabetes is accompanied by organ dysfunction and failure, neuropathy, retinopathy, cataracts, ulcers, loss of body weight, and sexual inadequacies [4]. The synthetic drugs currently available for DM treatment include insulin, thiazolidinediones, sulfonylureas, and biguanides [5]. Although the drugs' inability to effectively control the complications (except insulin under strict glycemic management) that accompany diabetes has brought about the search for new therapeutics.

Therefore, novel hypoglycemic agents with fewer diabetic complications are being explored to solve this health challenge. Several herbs with anti-diabetic activity reported in the literature include *Aloe vera*, *Aloe barbadensis*, *Alium cepa*, *Phyllanthus* species, *Panax* species, *Acacia arabica*, *Momordica charantia* [6,7].

Entandrophragma cylindricum, also called Sapele or sapelli (*Meliaceae*), is a hardwood timber species native to tropical Africa. The tree is about 45 m (rarely 60 m) in height [8]. During the dry season, the leaves are deciduous, pinnate, arranged alternately, with each leaflet about 10 cm long. It is a heliophilous species of the canopy, hermaphrodite, and insect-pollinated. The bark has been exploited as therapy for rheumatism, colds, lung complaints, bronchitis, edema. In Cameroon, it has been used to treat typhoid fever, malaria, diarrhea, stomach-ache, and yellow fever [9-11]. Phytochemical constituents of *Entandrophragma cylindricum* that have been reported include limonoids and highly oxygenated acyclic triterpenes [12]. This study aims to validate the anti-diabetic and antidyslipidemic activities of aqueous extract of *Entandrophragma cylindricum* stem on streptozotocin-induced diabetic rats.

2. Materials and Methods

2.1. Collection and identification of plant extract.

Entandrophragma cylindricum bark was obtained from herb sellers in the popular market, "Ojatuntun" in Ilorin, Kwara state Nigeria. It was identified and authenticated at the herbarium, Department of Plant Science, University of Ilorin, Nigeria. The stem bark of *Entandrophragma cylindricum* obtained was chopped into fragments to aid quick drying and oven-dried at 40 °C till a constant weight was obtained. The dried bark was initially grounded using mortar and pestle before using an electric blender to blend into a fine powder. The powdered sample (300 g) was soaked in 3 L of distilled water. The mixture was stirred and allowed to stand for forty-eight hours. The soaked sample was filtered with a muslin cloth, and the filtrate was concentrated with the aid of a vacuum evaporator. The dried extract was then reconstituted into the desired concentrations.

2.2. Chemicals and reagents.

Streptozotocin used was a product of Sigma Aldrich (United Kingdom). All other reagents were of analytical grade.

2.3. Experimental animals and DM induction.

Thirty healthy male Albino rats (190 ± 10 g) were procured from the animal breeding units, Central Research Laboratory, University of Ilorin, Ilorin. Animal handling and treatment were slated by the procedure for laboratory animal care and use and the University of Ilorin Animal Ethics Committee's approval. The research adhered to the protocols for Laboratory Animal Care (NIH publication No.85-23, revised in 2004). The animal house was well-ventilated, clean metabolic cages under a 12 h light-dark cycle at 25 ± 2 °C. For 7 days, the animals were acclimatized and fed a normal diet and water *ad libitum* during this period. Animals were made diabetic by a single intraperitoneal (ip) STZ administration, at 45 mg/kg bw, after fasting overnight. Fasting blood glucose (FBG) test was used to confirm hyperglycemia development in rats after 48 h post-streptozotocin injection.

2.4. Animal grouping and administration.

The animals (30) were grouped into 6 groups of 5 each: group A (control) rats were not induced with diabetes; group B (diabetic treated with Metformin 100 mg/kg); group C (diabetic untreated); group D (diabetic treated with *Entandrophargma cylindricum* extract 50 mg/kg); group E (diabetic treated with *Entandrophargma cylindricum* extract 100 mg/kg) and group F (diabetic treated with *Entandrophargma cylindricum* extract 200 mg/kg). FBG (Fasting blood glucose) and GTT (glucose tolerance test) were recorded at intervals for 21 days. Then, the rats were fasted overnight and sacrificed. The blood and liver were obtained, homogenized, and centrifuged for the biochemical assays.

2.5. Phytochemical screening.

The phytochemical screening was done as determined by Sofowora [13] and Trease and Evans [14].

2.6. Biochemical assays.

Determination of blood sugar was performed using a glucometer, while the determination of plasma insulin was carried out using an insulin ELISA kit. Hexokinase activity was measured using the method of Brandstrup *et al.* [15]. Hepatic glucose was determined using the dinitrosalicylic (DNS) assay [16]. Hepatic glycogen level was measured as glucosyl units following acid hydrolysis [17]. Koide and Oda [18] determined the measurement of glucose-6-phosphatase level. Glucose-6-phosphate dehydrogenase activity was measured by the method of Gancedo and Gancedo [19]. The total cholesterol, HDL-cholesterol, and triglyceride concentrations in the plasma were assayed by the method of Frederickson *et al.* [20], Albers *et al.* [21], and Giacco *et al.* [22], respectively.

2.7. Statistical analysis.

Data were expressed as the means \pm SEM of five determinations. Statistical analysis was done using one-way Analysis of variance (ANOVA) and Duncan Multiple Range Test (DMRT). The data were considered statistically significant at $p < 0.05$.

3. Results and Discussion

Plants have become drug sources for several ailments or sicknesses. *Practitioners of traditional medicine have utilized E. cylindricum for various ailments. The stem bark decoctions of E. cylindricum are used to treat fevers and malaria [7]. The Nigerian herb database has reported E. cylindricum to possess blood glucose-lowering effects in animal models. The phytochemical analysis of the stem bark of E. cylindricum revealed the presence of tannins, glycosides, phenolics, flavonoids, and terpenoids. These secondary metabolites may be responsible for various biological activities, including anti-diabetic. Several investigators have shown that some plants that possess polyphenolic compounds and a host of the other secondary metabolites of the plant possess hypoglycemic activities [23].*

Table 1. Qualitative analysis of *Entandrophargma cylindricum* stems bark extract.

Phytochemicals	Result
Flavonoids	++
Tannin	++

Phytochemicals	Result
Phenol	++
Alkaloids	-
Terpenoids	++
Steroids	++
Glycosides	++
Reducing sugar	+
Saponin	-
Anthraquinone	++
Oil	-

Note: + = Trace, ++ =Present, - =Absent.

Table 2.Fasting blood glucose concentration of animals administered with aqueous extract of *E. cylindricum* stem.

Group	Day 0	Day 7	Day 14	Day 21
Control	94±5.45 ^a	105±4.55 ^a	120±7.35 ^a	115±8.55 ^a
Metformin	102±3.45 ^a	235±5.25 ^b	155±4.65 ^a	136±3.75 ^a
Diabetic untreated	116±4.02 ^a	320±8.55 ^b	375±7.65 ^c	290±3.46 ^b
Diabetic + 50 mg/kg bw extract	98±4.84 ^a	285±3.50 ^b	209±2.15 ^b	184±2.45 ^a
Diabetic + 100 mg/kg bw extract	122±3.25 ^a	244±3.50 ^b	173±3.43 ^a	128±3.25 ^a
Diabetic + 200 mg/kg bw extract	125±3.15 ^a	246±5.23 ^b	163±3.45 ^a	106±4.55 ^a

Values are presented as means (n=5) ± S.E.M. Values with different superscript are significant at $p < 0.05$ versus control.

Pancreatic β -cells are responsible for insulin production. STZ induces diabetes in animals by destroying pancreatic- β -cells. Deficiency or massive reduction in insulin may cause hyperglycemia, which insulin only can reverse [24]. Fasting blood glucose concentrations after administration with aqueous extract of *E. cylindricum* stem bark at day 0, day 7, day 14, day 21 in animals are shown in Table 2. The high glucose values in diabetic rats were reduced on day 7, but it was reversed near normal compared with the non-diabetic group on day 14, day 21. The results indicated that *E. cylindricum* stem bark significantly reduced the blood glucose level of diabetic rats. Other plant studies have also been reported to reduce the fasting blood glucose level of diabetic rats [25-27]. The observed reduction in the fasting blood glucose level may be attributed to high phenolics, a secondary metabolite found in the extract [26]. The results also showed that postprandial glucose reduction in the animals might have been associated with reduced glucogenic activity with decreased excretion of urea or glycogenolysis inhibition as suggested by liver glycogen increase [28].

Glucose tolerance response in streptozotocin-induced diabetic albino male rats administered with aqueous extract of *E. cylindricum* stem at 0 min, 15 min, 30 min, 60 min, and 90 min after 7 days, 14 days, and 21 days was shown in figure 1.

The treated groups of *Entandrophargma cylindricum* extract have a high blood glucose level (mg/dl) compared to the non-diabetic group (untreated) after 7 days. However, the treated groups have their blood glucose level (mg/dl) normal compared to the non-diabetic group (untreated) on the 14th day and 21st day.

Hexokinase activity of animals administered with aqueous extract of *E. cylindricum* stem bark showed a significant ($p < 0.05$) increase in the metformin and 200mg/kg bw compared with the control group, as shown in Figure 2a. Significant increase in hexokinase activity in the group administered with 200 mg/kg bw *E. cylindricum*. This enzyme is located

in the glycolytic pathway. It converts glucose to glucose 6 phosphate with the use of ATP. This enzyme was boosted in diabetic rats following *E. cylindricum* stem bark administration.

Plasma insulin concentration of animals administered with aqueous extract of *E. cylindricum* stem showed a significant ($p > 0.05$) decrease in the untreated group 50 and 100 mg/kg bw of the extract as shown in figure 2b. Plasma insulin concentration significantly decreases in the untreated group and 50 mg/kg bw and 100 mg/kg bw *E. cylindricum*. Serum insulin concentration is responsible for the conversion of excess glucose to glycogen. The reduction in insulin concentration reduces glycogen conversion, thereby making the glucose more available to the cell.

Glucose concentration in the liver of animals administered with aqueous extract of *E. cylindricum* stem bark showed a significant ($p < 0.05$) decrease in the untreated group, while a significant increase was observed in the metformin group (Figure 3a). Hepatic glycogen levels significantly ($p < 0.05$) decrease at 50 and 100 mg bw of the extract-treated group (Figure 3b).

Plasma glucose-6-phosphatase concentration of animals administered with aqueous extract of *E. cylindricum* stem showed no significant changes across all groups compared with the control (Figure 4a). Hepatic glucose 6 phosphate dehydrogenase activity in the animals administered with aqueous extract of *E. cylindricum* stem showed a significant ($p < 0.05$) increase in the group treated with metformin. The untreated group had a significant decrease compared with the control group, as shown in Figure 4b. The observed increase in glucose-6-phosphatase activity in the group treated with metformin and 50 mg/kg bw *E. cylindricum* compared with the non-diabetic group was noted. This enzyme is located in the gluconeogenesis pathway, a metabolic pathway that produces glucose from non-glucose metabolites. It converts glucose-6-phosphate back to glucose [29]. This enzyme was significantly increased, hence increasing its activities.

Several studies have reported that a rise in serum lipids such as TC and triacylglycerols could suggest the induction of diabetes due to changes in lipid metabolism [30]. The aberrations in cellular cholesterol metabolism could alter the serum cholesterol levels in diabetic patients and oxidative stress, associated with increased lipid accumulation in the cells [31]. The anomalies in the metabolism of lipids in diabetic conditions lead to variations in serum lipids and lipoproteins, which in turn causes severe atherosclerosis that affects diabetic patients [32]. Measurements of these parameters are essential to avert cardiac complications in diabetic conditions [32]. The major distinctive features of diabetic dyslipidemia are high serum triacylglycerol concentration and low-density lipoprotein cholesterol with corresponding low high-density lipoprotein cholesterol [33]. There is a need for therapeutic agents with both anti-diabetic and anti-obese effects of immense potential benefit. The aqueous extract of *E. cylindricum* stem bark may serve these benefits. Cholesterol concentration in the plasma of animals administered with aqueous extract of *E. cylindricum* stem showed a significant ($p < 0.05$) increase in the untreated group compared with the control group, as shown in Figure 5a. Plasma high-density lipoprotein concentration in the animals administered with aqueous extract of *E. cylindricum* stem significantly ($p < 0.05$) decreased in the untreated group, 50 and 100 mg/kg bw of the extract as shown in Figure 5b. Triglycerides concentration in the plasma of animals administered with aqueous extract of *E. cylindricum* stem bark showed no significant changes (Figure 5c). The metformin administration and the aqueous extract *E. cylindricum* stem bark led to a drop in total cholesterol and triacylglycerol with a corresponding increase in High-density lipoprotein. Therefore, the aqueous *E. cylindricum* stem bark extract

shows that it may control lipid metabolism and avert the upsurge of coronary artery disease and atherosclerosis.

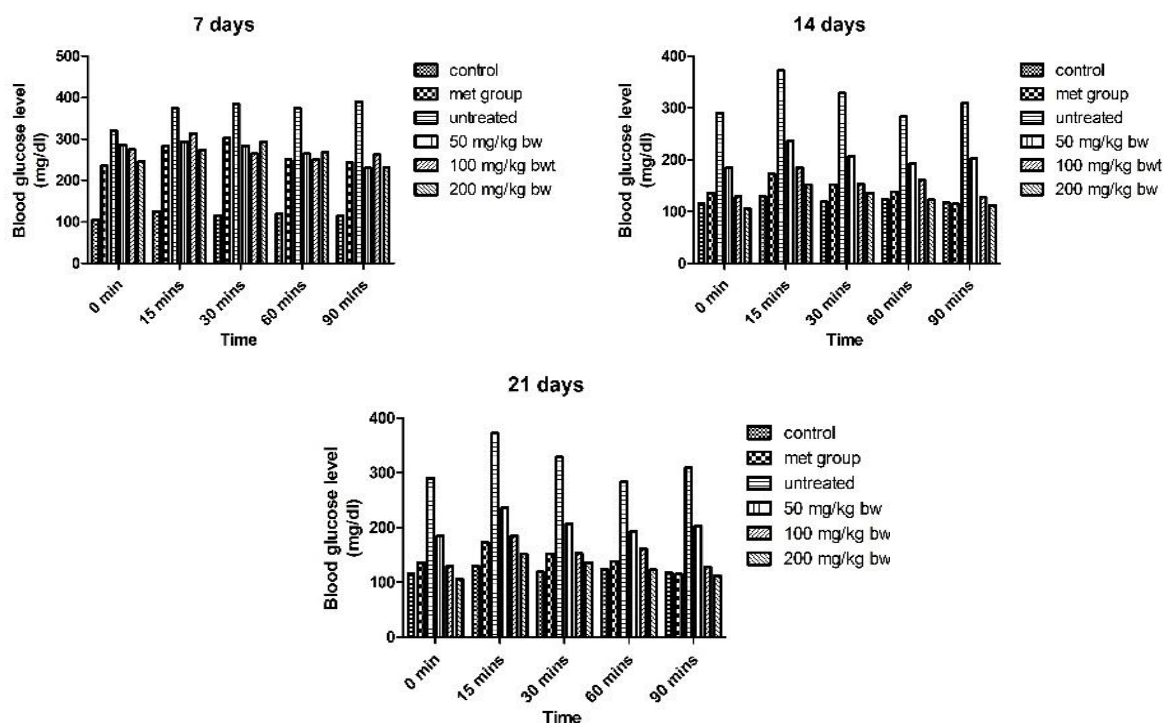


Figure 1. Glucose tolerance response in the blood after administering an aqueous extract of *E. cylindricum* stem after 7 days, 14 days, and 21 days of treatment.

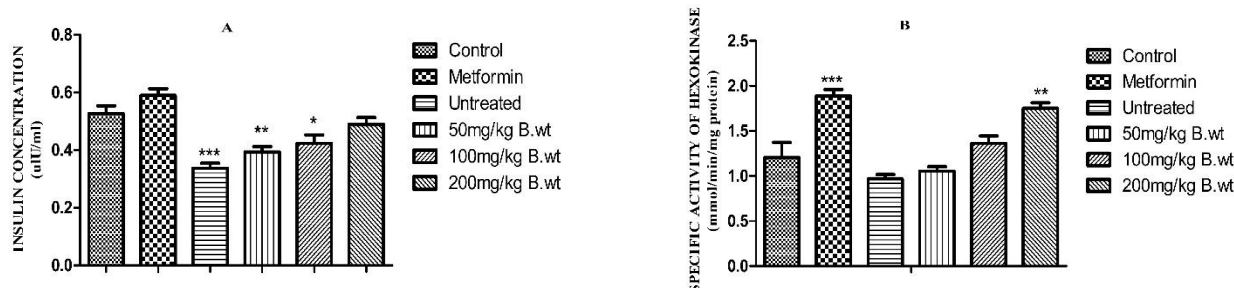


Figure 2. (A) Plasma insulin concentration; (B) hexokinase activity of animals administered with aqueous extract of *E. cylindricum* stem. Values are presented as means ($n=5$) \pm S.E.M. Values with different superscript are significant at $p < 0.05$ versus control.

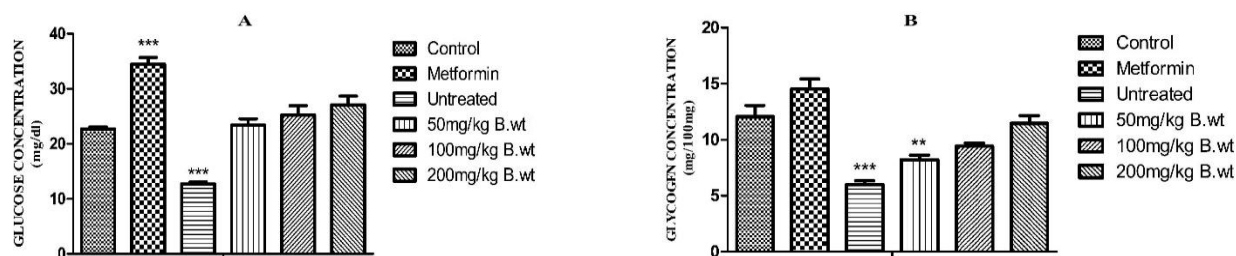


Figure 3. (A) Glucose concentration; (B) glycogen concentration in the liver of animals administered with aqueous extract of *E. cylindricum* stem. Values are presented as means ($n=5$) \pm S.E.M. Values with different superscript are significant at $p < 0.05$ versus control.

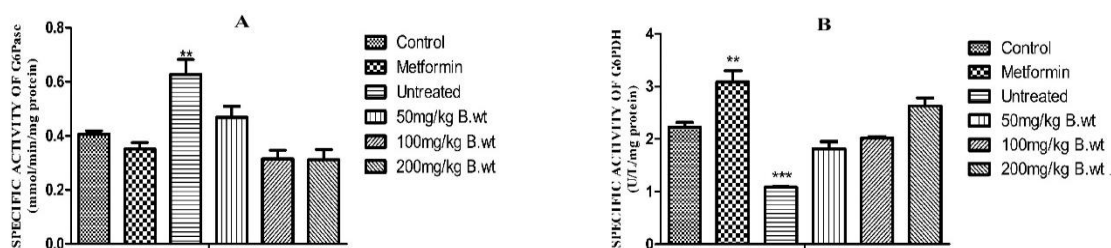


Figure 4. (A) Plasma glucose-6-phosphatase concentration; (B) Glucose 6 phosphate dehydrogenase activity in the liver of animals administered with aqueous extract of *E. cylindricum* stem. Values are presented as means (n=5) \pm S.E.M. Values with different superscript are significant at $p < 0.05$ versus control.

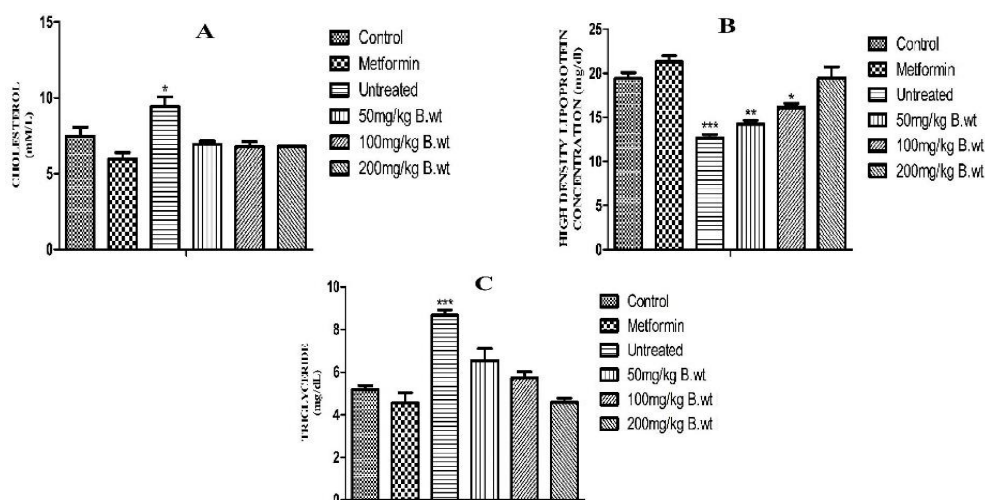


Figure 5. (A) Cholesterol concentration; (B) high-density lipoprotein concentration; (C) triglycerides concentration in the plasma of animals administered with aqueous extract of *E. cylindricum* stem. Values are presented as means (n=5) \pm S.E.M. Values with different superscript are significant at $p < 0.05$ versus control.

4. Conclusions

Overall, we can suggest that the aqueous extract of *E. cylindricum* stem bark possesses significant anti-diabetic and antidyslipidemic activity in diabetic rats as it regulates lipid metabolism

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Conflicts of Interest

The authors declare no conflict of interest.

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