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Studies on the antidiabetic effects of methanol extract of *Pentaclethra macrophylla* Benth (Fabaceae) stem bark on alloxan-induced diabetic model

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Abstract
Objective: In this study, theanti-diabetic and associated effects of the methanol extract of the stem bark of *Pentaclethra macrophylla* (*Fabaceae*) on alloxan-induced diabetic rats were evaluated.
Materials and Methods: The anti-diabetic effect of the methanol stem bark extract of *Penta clethra macrophylla* was carried out in the normoglycemic. Alloxan monohydrate was used for induction of diabetic condition.Liver and kidney bio-markers were evaluatedto ascertain the effects of the extracts on the vital organs. The normoglycemic and hyperglycemic rats were administered orally with different doses (200, 400 and 800 mg/kg) of the methanol extract of the stem bark of the plant. 5 mg/kg of Glibenclamide as control with 0.1 m1 of normal saline as negative control. The blood sugar levels (BSL) were measured using the ACCU-check glucometer.
Results: Result obtained showed that the stem bark extract produced a dose-dependent decrease ($P<$ 0.05) in BSLs of both normal and induced rats. At doses of 200 and 400 mg/kg of the extract administered, there was a significant ($P<$ 0.05) reduction in BSL at 14 days with values of 20.6 and 31.1% for the diabetic rats respectively compared to 12.9% of the negative control. The LD_{50} of the crude methanol extract was found to be greater than 5000 mg/kg. Preliminary Phyto-chemical tests carried out on the extract reveals the presence of alkaloids, saponins, triterpenoids, glycosides, flavonoids, tannins and carbohydrate. In diabetic rats, the liver and kidney enzymes levels were significantly elevated which were further reduced after administration of the extract.
Conclusion: From the results of this study, it can be concluded that the stem bark extract of *Pentaclethra macrophylla* have favorable effects in lowering the severity of diabetes together with hepatic protection.

Keywords: *Pentaclethra macrophylla*, antidiabetic effect, stem bark extract, Alloxan induced, diabetic rat

Introduction
Modern medicine has in the beginning depended on herbal remedies for their lead compounds. A good number of plants in Nigeria particularly have been screened for their hypoglycemic effect using diabetic animal models. Some have been found to lower blood sugar in normal but failed in alloxan induced diabetic animal (Iwu, 1980) [10]. Some plants used in Africa by traditional healers for the treatment of diabetes mellitus are: *Bridelia ferugina* (Iwu, 1980) [10], *Persia americana* (Okonta *et al*., 2007) [22], *Lorathus micranthus* (Osadebe *et al*, 2010) [10], *Acanthus montanus* (Odoh *et al*., 2013), *Acalypha wilkesiana* (Odoh *et al*., 2014) [27] to mention but a few.
International Diabetes Foundation (IDF) stated that, globally, people living with type 1 Diabetes have been estimated to be 382 million while type 2 Diabetes is about 90% of this population. It is a chronic on communicable metabolic disorder which results from insulin deficiency or reduced effectiveness of insulin activity (Karu *et al*., 2013, Noor *et al*., 2008) [31]. Nutritionally diabetes is one of the non-communicable diseases that have emerged with industrialization, globalization and adoption of Western dietary patterns (Uchenna *et al*. 2004) [37]. In addition, more than a million lower limb amputations, half a million kidney failures, and 1.5 million cases of blindness occur annually as long-term diabetic complications (IDF, 2013). The increasing number of ageing population, consumption of calories rich diet, obesity and sedentary lifestyle have led to a tremendous increase in number of diabetes worldwide. According to WHO projections, the prevalence of diabetes is likely to increase by 35% yearly (Goodman and Gilman, 2011) [7]. Diabetes constitutes a global burden as its incidence is considered to be on increase coupled with the disease being the fifth course of death in both the developed and underdeveloped countries of the world (Rother, 2007) [37]. Herbal products may contain several active constituents that can act by several modes of action to influence

multiple biological pathways and to alleviate the diabetic symptoms, providing multifaceted benefits. Medicinal plants continue to provide valuable therapeutic agents, both in modern and in traditional systems of medicine (Newairy, 2001) [18]. Medicinal plants also offer good prospect in discovering new drugs particularly against conditions for which modern drugs are inadequate. Usually herbs are more acceptable by patients because it is believed to have less adverse effects. A wide variety of traditional herbal remedies are used by diabetic patients especially in the third world countries (Day, 1998) [5]. Recent available hypoglycemic agents produce some serious side effects like hypoglycemic coma (Larnner, 1985) and hepatorenal disturbances (Amjad *et al*., 2013) [1]. Apart from the side effects, their costs are high for management of diabetic patients and as such alternative are needed for better management of diabetes. Hence, the search for safer and more effective anti-diabetic agents has continued.

*Pentaclethra macrophylla*trees grow to about 21 m in height and about 60cm girth. Have a characteristic low branching habit and an open crown, which allows substantial light under its canopy. The oil bean seeds contain 4-17% carbohydrate, 44-47% oil which has been found to be rich in oleic acid (Odoemelam, 2005) [19] and linoleic acid (Onwuliri *et al*., 2004) [25]. Onwuliri *et al*., (2004) [25] also found out that the saturated fatty acid, lignoceric acid, occurred in high amounts constituting about 10% of the total fatty acid concentration. Some workers said that the oil content could be as low as 38% (Kar and Okechukwu, 1978) [11]. They also have reported that the oil contains about 75% saturated fatty acids and 25% unsaturated fatty acids. Both saturated and unsaturated fatty acids are found in the seeds. For the saturated fatty acids, lignoceric acid appears to be present in the largest amount constituting about 12% while palmitic acid is the least with 3.4%. Behenic acid is also present with 5.2%. The major unsaturated fatty acid in the seeds is linoleic acid constituting 42.8%. Oleic acid is also present in appreciable amounts (29.0%). Linolenic and gadoleic acids are present in very small amounts (3.2 and 0.28%, respectively). The leaves contribute to soil fertility while the ripe fruits are applied externally to heal wound (Oyeleke *et al*, 2014) [27]. The aim of this study therefore is to evaluate the anti-diabetic effect of the methanol extract of the stem bark of *Pentaclethra macrophylla* (Fabaceae).

Materials and Methods

Plant materials

The stem bark of the plant was collected from Nsukka, Enugu State Nigeria in July. The plant material was identified and authenticated by Mr. Alfred Ozioko of the International Centre for Ethno-medicine and Drug Development (Inter CEDD) Nsukka. The Voucher specimen (PCG/UNN/ 014/507) was assigned to the sample which was deposited in the Herbarium of the Department of Pharmacognosy and Environmental Medicines, University of Nigeria, Nsukka, Nigeria.

Animals

Wister albino rats (73-112 g) and mice (18-28 g) bred in the Animal House of the Department of Zoology, University of Nigeria, Nsukka, were used in the experiments. The animals were housed in white metallic cages and kept under room with access to water and food for 1 week to acclimatize to the laboratory conditions before the commencement of experiments. Permission for the use of the animals was obtained from the Animal use Ethics Committee of the University of Nigeria Nsukka in agreement with International Laboratory animal use Convention U.S.A.

Preparation of extract

A 1 kg of the pulverized stem bark of *Pentaclethra macrophylla* was extracted with 5 litres of 80% methanol using cold maceration technique for 72 hr. The resulting mixture was extracted withmethanol andconcentrated under reduced pressure using a Rotary Evaporator and stored in a refrigerator for further analysis at 4 degrees centigrade.

Acute Toxicity

The LD_{50} of the extract was determined in mice intraperitoneally using Lorke's method (1983). A moderate to high doses were chosen randomly for the study with respect to the LD50 of the whole plant extract and that of the roots and stem barks as reported in literatures (Verma *et al.*, 2010, *Tona et al*., 2001) [34, 35].

Phytochemical Analysis

The phytochemical constituents were investigated using Standard Laboratory Procedure outlined by Harbourne (1984) [8] and Evans (2009) [6].

Antidiabetic Evaluation

Effect of Extract on normoglycemic rats

Twenty five (25) healthy albino Wistar rats were used for the study. The animals were divided into five groups of five animals each. They were fasted overnight for 12 hr. At the end of the fasting period, different doses of the extract was given to the rats orally. Group 1 received 200 mg/kg of the extract, Group 2 received 400 mg/kg of the extract, Group 3 received 800 mg/kg, Group 4 received 5 mg/kg of Glibenclamide as the positive control and Group 5 received water only as negative control. The drugs were administered to the animals daily for a period of 14 days. Blood samples were withdrawn from the tail vein of each animal rats at day 0, 7 and 14 and their blood sugar level determined and recorded using Accu-check glucometer.

Effect of Extract on hyperglycemic rats.

Twenty five (25) healthy white albino Wistar rats were injected intraperitoneally with 150mh/kg body weight of alloxan monohydrate (Sigma, USA) freshly prepared in normal saline. Animals with fasting blood glucose level of 200mg/kg and above after 3 days of induction were considered diabetic. The animals were grouped into five groups of five animals each. The Albino rats were fasted overnight for 12 h. Group 1 received 200 mg/kg of the extract, Group 2 received 400 mg/kg of the extract, Group 3 received 800 mg/kg of the extract, Group 4 received 5 mg/kg of Glibenclamide as a positive control and Group 5 received feed and water only (negative control). The drugs were administered to the diabetic rats daily for a period of 2 weeks. Blood samples were withdrawn from the tail vein of each animal/ rats at day 0, 7 and 14 and their blood sugar level determined and recorded using Accu-check glucometer.

Determination of Pathological parameters

The assay of alanine aminotransferase, aspartate transferase, alkaline phosphate, creatinine and urea were performed using a Randox commercial enzyme kit which is based on the methods of Reitaman and Frankel (1957) [29] and Schmidt and Schmidt (1963) [30].

Statistical analysis

The results obtained were subjected to statistical analysis using student's t-Test at $p< 0.05$ level of significance (Olaniyi, 2000) [23].

Results and Discussion

The percentage yield of the methanol extract of *Pentaclethra macrophylla* stem bark is 9.3%. The phytochemical tests for the methanol extract showed abundant presence of alkaloids, reducing sugars, glycosides, saponins, fats and oil and steroids as shown in Table 1. The various pharmacological activities of this plant may be attributed to the presence of these major phytoconstituents. Some plants that contain alkaloids have been reported to have hypoglycemic activity (Bever and Zahad, 1979) [2]. The acute toxicity test of the extract in mice showed that it was non-toxic at the dose of 500mg/kg because there was no recorded mortality and therefore is safe for human use at that dose.

The results obtained from the study show that the methanol extract of stem bark of *Pentaclethra macrophylla* has anti-diabetic activity as there was significant ($P< 0.05$) reduction in blood sugar levels of the alloxan-induced diabetic rats at day 0, 7 and 14. The methanol stem bark extract exhibited a significant dose-dependent reduction of bloodsugar level in both normoglycemic and hyperglycemic rats (Table 2 and 3). At the dose of 200mg/kg, the percentage reduction of the blood glucose level was 27% (92.20± 5.48) -66.80± 2.03) of the extract at 14 day of treatment in normoglycemic ratsand the effect was comparable to that of Glibenclamide. At the dose of 800mg of the extract, blood glucose percentage reduction was slightly higher than that of the positive control (Glibenclamide) as shown in Table 2. In alloxan-induced diabetic rats the standard drug exhibited a higher percentage reduction of the blood sugar level than the methanol stem bark extract at the dose of 800mg/kg (Table 3). In the alloxan-induced diabetic rats, maximum reduction of 20.6, 31.1, and 56.4% for the studied doses (200, 400, and 800 mg/kg body weight) of the extract were obtained while the standard drug (glibenclamide) produced a maximum reduction of 64.6%.The positive control, 5 mg/kg glibenclamide (Daonil®) showed a better reduction in blood sugar level than the extract. It has been reported that provided the *B*-cells are fully functional, sulphonylureas, such as Glibenclamide, can cause hypoglycemia since insulin release is initiated even when glucose concentrations are below the normal threshold for glucose-stimulated insulin release (approximately 5 mmol/L or 90 mg/dL) (Krentz and Bailey, 2005) [12]. This suggests that the plant may have similar mode of action to Glibenclamide, an insulin secretagogue, with respect to blood glucose lowering effect.

The sulphonylureas have been used in the management of type 2 Diabetes. The mechanism of action involves a direct secretory effect on the pancreatic islet beta-cells. Adenosine triphosphate (ATP)-sensitive potassium channels (K+ ATP) of the beta-cells play an essential role in the release of insulin and consist of two components: a pore and a regulatory subunit (SUR-1). The sulphonylureas act to enhance the sensitivity of the beta-cell to glucose and, when bound to the transmembrane sulphonylurea receptor (SUR-1), mediate the closing of the potassium –sensitive ATP channels on the cell membrane. Cellular efflux of potassium is reduced and membrane depolarization takes place. Calcium influx is mediated by the opening of voltage-dependentCa2+-channels that promote the release of pre-formed insulin granules which lie just adjacent to the plasma membrane. Hypoglycaemia can occur because these drugs potentiate the release of insulin even when glucose concentrations are below the normal threshold for glucose-stimulated insulin release (< 5 mmol/l) (Bosenberg and Van Zyl, 2008) [3]. The effect of *P. macrophylla* could be related to a stimulation of remaining β cells or regeneration of β – cells. It had been reported that β-cells regeneration occurred through both increasing the replication of pre-existing β- cells and neogenesis from the precursor cells located in or by the pancreatic duct (Lei *et al.*, 2004).

Results obtained from the pathological studies showed that at day 0, the values of pathological parameters of blood urea nitrogen (BUN), creatinine, ALT, AST and ALP are within the normal range (Table 4). The liver, an insulin dependent tissue that plays a vital role in glucose and lipid homeostasis, is severely affected during diabetes. The liver and kidney participate in the uptake, oxidation and metabolic conversion of free fatty acids, synthesis of cholesterol, phospholipids and triglycerides (Neeleshi *et al*, 2010). On induction of diabetes using alloxan, these parameters (ALT, AST, ALP and BUN) increased showing the toxicity effect of alloxan (Table 5). This is as a result of the fact that raised plasma trans- aminase concentrations are indicative of hepatocyte damage which may be drug/toxin-induced (Crook, 2006). Diabetes mellitus is associated with dyslipidemia (marked alterations in the level of serum lipid, triglycerides and lipoprotein levels) Maghrani *et al.*, 2004).This abnormality in the elevation of serum lipid concentration in diabetes is mainly due to the increase in the mobilization of free fatty acids from the peripheral depot (adipose tissue) to the blood (Shukla *et al*., 2003), since insulin is known to inhibit the hormone sensitive lipase (Daisy and Feril., 2013). In this present evaluation, Alloxan induced diabetic rats had an increase in serum lipids and this is in agreement with earlier reports in experimentally induced diabetes mellitus (Dolui *et al*., 2012, Akah *et al*., 2009) [36]. When the diabetic animals were treated with the extract, there was significant reduction in the liver biomarker ALT, AST and ALP with increased dose. The kidney biomarkers; Urea and Creatinine were within normal range. At day 14, the values of the pathological parameters of diabetic rats (ALT, AST, ALP, BUN and creatinine) decreased suggesting that the extract do possess hepato-protective property (Table 6). Reduction in the liver biomarkers shows that the extract helped in the recovery of the animals by protecting the liver. The stem bark of *Pentaclethra macrophylla* contains some bio-active principles responsible for its hypoglycemic activities in normal and alloxan-induced diabetic rats. The claim of the use of this plant in traditional medicine is justifiable. From this study it could be recommended that further anti-diabetic study on this plant could be done with other parts of the plant to compare the potencies of the different plant part(s).

Table 1: Phytoconstituents of methanol stem bark extract of *Pentaclethra macrophylla*

Phytoconstituents	Inference
Alkaloids	+
Carbohydrates	+
Reducing sugars	+

Glycosides	+
Saponins	+
Tannins	+
Flavonoids	+
Resins	+
Fats and oil	+
Steroids	+
Terpenoids	+
Acidic compounds	-
Proteins	+

Key: + Present, - Absent

Table 2: Results of the anti-diabetic effect of the methanol extract of the stem bark of *Pentaclethra Macrophylla* on the FBG levels of the normoglycemic rats

Treatment Groups	Dose(s) (mg/kg)	Mean Blood Glucose Concentration (mg/dl)			Percentage Maximum reduction (%)
		Day 0	Day 7	Day 14	
Extract	200	92.20 ± 5.48	80.40± 1.44*	66.80±2.03*	27.5
	400	87.60 ± 1.86	73.60 ± 2.25*	57.80 ± 3.31*	34.0
	800	119.20 ± 5.19	87.80 ± 1.50*	60.20 ± 4.97*	49.5
Glibenclamide (positive control)	5	102.20 ± 8.62	68.00 ± 3.85*	53.40 ± 4.45*	47.7
Normal saline (negative control) 0.1ml/kg	-	91.40 ± 2.04	86.20 ± 0.97	84.20 ± 0.86	7.9

Values are the mean ± SEM (n =5), * *P*< 0.05 Vs negative control

Table 3: Results of the anti-diabetic effect of the Methanol extract of the Stem bark of *Pentaclethra macrophylla* on the FBG levels of the alloxan-induced diabetic rats

Treatment Group	Dose(s) (mg/kg)	Mean Blood Glucose Concentration (mg/dl)			Percentage Maximum reduction (%)
		Day 0	Day 7	Day 14	
Extract	200	285.80±10.10	255.80±15.62*	227.00±15.02*	20.6
	400	282.80±7.32	229.00±11.03*	194.80±10.13*	31.1
	800	304.2±14.59	228.20±15.46*	132.60± 8.67*	56.4
Glibenclamide (positive control)	5mg	302.20±10.12	198.20±5.12*	107.00± 5.39*	64.6
Normal saline (negative control) 0.1mg/kg	___	245.80±2.71	-	-	-

Values are the mean ± SEM (n =5), * *P*< 0.05 Vs Negative control (Normal saline)

Table 4: Mean values of Pathological Parameters of normoglycemic rats at Day 0

Treatment groups	Dose(s) (mg/kg)	Liver bio- markers			Kidney bio- markers	
		ALT(U/L)	AST(U/L)	ALP(U/L)	Urea (mmol/L)	Creatinine (mmol/L)
Extract	200	12.332.±333	8.00±1.154	43.33±2.906	1.25±0.013	0.35±0.037
	400	12.67±1.453	17.33±3.331	40.00±0.577	1.56±0.031	0.72±0.014
	800	13.33±2.333	16.33±2.185	46.33±2.906	1.19±0.017	0.87±0.017
Glibenclamide (positive control)	5mg	12.33±1.333	11.67±1.763	37.67±2.962	1.15±0.066	0.64±0.023
Normal saline (negative control) 0.1mg/kg	___	12.67±1.76c3	14.00±1.732	39.12 ± 0.23	1.47± 0.11	0.47±0.035

Values are the mean ± SEM (n = 5)

Table 5: Results of the effect of methanol stem bark extract of *Pentaclethra macrophylla Bent!h*on Pathological parameters of alloxan-induced diabetic rats at day 0

Treatment groups	Dose(s) (mg/kg)	Liver bio- markers			Kidney bio- markers	
		ALT(U/L)	AST(U/L)	ALP(U/L)	Urea (mmol/L)	Creatinine (mmol/L)
Extract	200	54.67±2.40*	23.33±1.26*	86.67±7.35*	4.47±0.26	0.61±0.05
	400	75.00±1.15*	18.33±3.53	80.67±3.52*	5.10±0.18	0.64±0.04
	800	95.00±2.65*	26.33±6.64*	84.00±1.82*	5.67±0.50	0.42±0.32
Glibenclamide (positive control)	5mg	53.67±4.33*	27.67±2.33*	89.33±8.74*	5. 70±0.56	0.49±0.48
Normal saline (negative control) 0.1mg/kg	___	71.33±4.67*	28.00±1.25*	93.33±4.05*	5.53±0.11	0.84±0.12

Values are the mean ± SEM (n =3), * *P*< 0.05 Vs Negative control (Normal saline)

Table 6: Mean values of the pathological parameters of the methanol stem bark extract of *Pentaclethra macrophylla* Benth on alloxan-induced diabetic rats at day 14

Treatment groups	Dose(s) (mg/kg)	Liver bio- markers			Kidney bio- markers	
		ALT(U/L)	AST(U/L)	ALP(U/L)	Urea (mmol/L)	Creatinine (mmol/L)
Extract	200	33.67±2.03*	13.33±1.76*	45.33±1.42*	3,.50± 0.30*	0.53±0.094
	400	52.00±2.31*	15.67±1.24*	53.67±2.02*	3.22 ±0.55*	0.47±0.010
	800	81.67±3.18*	14.33±0.48*	61.33±7.51*	2.45 ± 0.80*	0.36±0.018
Gljbenclamide (positive control)	5mg	45.67±3.28*	21.67±1.50*	13.67±1.45*	2.29 ± 0.98*	0.42±0.026
Normal saline(negative control) 0.1mg/kg	-	-	-	-	-	-

Values are the mean ± SEM (n =3), **P*< 0.05 vs Negative control

Competing Interest

The authors declare that they have no competing interest.

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