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Antihyperglycaemic and Antihyperlipidaemic Activities of Aqueous Ethanol Root Extract of *Pseudocedrela kotschyi* on Alloxan-Induced Diabetic Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Author GOM designed the experiment and the protocol for the study. He undertook the tissue processing and analysis as well as partook in the write up and final editing of the manuscript. Author AOO conducted the laboratory work as well as managed the literature searches. Author SOO partook in the experimental design and editing of the manuscript and also performed the statistical analysis. Author DAO conducted the biochemical analysis. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To evaluate the antihyperglycaemic and antihyperlipidaemic properties of *Pseudocedrela kotschyi* in alloxan induced diabetic rats.

Materials and Methods: Fasting blood glucose (FBG) was conducted by first inducing diabetes through intraperitoneal administration of alloxan monohydrate (150 mg/kg body weight) (bwt). The diabetic rats, 5 per group received graded extract doses (100, 250 and 500 mg/kg) or glibenclamide (10 mg/kg) or 0.5mL acacia solution (2 %w/v) for 15 days. Blood was collected on days 0, 3, 5, 7, 9, 11, 13, 15 for glucose estimation. In postprandial test, three extract groups (100, 250 and 500 mg/kg) and the control were arranged, each comprised of 5 rats. Each animal was administered orally with glucose at a dose of 2g/kg bwt followed by extract administration 30min later. Blood glucose was monitored at 30, 60 and 120 min intervals. In hypoglycaemic study, the extract was administered at doses of 100, 250 and 500 mg/kg bwt. Lipid profile was analyzed by modified enzymatic procedure and glycated haemoglobin (HbA_{1C}) by standard protocol.

Results: The diabetic rats treated with the extract/glibenclamide showed weight gain. They also experienced dose (250 and 500 mg/kg bwt) dependent decrease in glycaemia with maximum decrease of 259.1±3.0 (24.9%) and 266.1±2.9 (25.3%) respectively while glibenclamide, 227.0±3.8 (36.0%). The postprandial test showed that the extract induced lower blood glucose level after 60 min. The extract also showed to have good hypoglycaemic activity at doses of 250 and 500 mg/kg bwt respectively. The pancreatic tissue analysis from the rats treated with the root extract indicated substantial beta cells survivor. An appreciable decrease in HbA_{1C} level was found in the extract and glibenclamide treated compared to the negative control. In lipid profile study, *Pseudocedrela kotschyi* extract was observed to have ameliorated dyslipidaemia.

Conclusion: The extract showed efficacy in attenuating hyperglycaemia, inducing hypoglycaemia and ameliorating dyslipidaemia.

Keywords: P. kotschyi; antihyperglycaemic; HbA_{1C}; alloxan diabetes; tissue histology.

1. INTRODUCTION

Diabetes mellitus (DM) is a disease that impacts negatively on the quality of life and life expectancy of its victims around the world. It is a disease that has highest rate of prevalence affecting more than 25% of the world's population [1]. Its major characteristic is hyperglyceamia which is as a result of altered metabolism of glucose, protein and lipids. The derangement is caused by defect in insulin secretion, a pancreatic polypeptide hormone-responsible for metabolizing glucose into glycogen [2,3]. Although significant inroad has been made in diabetes management with the introduction of insulin therapy and oral hypoglycaemic agents such as biguanides and sulfonylureas, these drugs however have neither succeeded in stemming the increasing trend of DM nor altered the course of diabetic complications. The major metabolic change caused by sustained hyperglycaemia is glycation of body proteins which more frequently leads to complications affecting blood vessels and nerves [4]. The effect on blood vessels increases the risk of cardiovascular disease which includes atherosclerosis [5]. DM may occur following the generation of free radicals that leads to several chain reactions among them lipid peroxidation which causes derangement in lipid profile [6].

The global awareness of the effectiveness of alternative therapy of plant source in the treatment of diseases was a major shift and its popularity in the management of DM has been very remarkable. Its popularity received a boost following the WHO recommendation for research on the beneficial uses of medicinal plants in the treatment of DM [7]. The preferred choice of plant by many may not be unconnected with successes recorded in the use of herbal product in traditional medicine to manage DM [8]. The major advantage however may be as a result of their efficacy, less toxic effect because of their rich natural source and their affordability.

According to a report, over 800 plants are used as traditional remedy for DM but very few have been validated scientifically [9]. Amongst these plants, *Pseudocedrela kotschyi (P. kotschyi)* (Schweinf.) Harms (Meliaceae) is found growing mainly in Savannah Woodland. *P. kotschyi* grows up to 20 meters high with a wide crown, thick bark and fragrant white flowers [10]. The root has bitter taste and is used ethno botanically in the treatment of gastro-intestinal diseases, rheumatism, toothache and internal wounds [11,12,13,14]. It was found to be a potential source of antibacterial agents [15] and was also claimed to be effective in the treatment of DM. The scientific confirmation of the efficacy of *P. kotschyi* roots in DM appears to be lacking. Hence we have evaluated the antihyperglycaemic and antihyperlipidaemic properties in alloxan induced diabetic rats in order to validate the issues previously explained.

2. MATERIALS AND METHODS

2.1 Plant Material

P. kotschyi was collected from a farm land in Kwara State, Nigeria. The plant sample was authenticated in the Forestry Research Institute of Nigeria (FRIN), Ibadan. The voucher specimen has been deposited in the herbarium (FHI/108280).

2.1.1 Preparation of the plant material

The roots of *P. kotschyi* were washed, cut into small pieces and shade-dried at room temperature for 7 days before being subjected to size reduction to a coarse powder with electric grinder. The powder (2100 g) was extracted with 96% aqueous alcohol in three cycles using Soxhlet extractor. The crude extract was filtered with filter paper (Whatman No. 4) and the filtrate was dried by rotary evaporator at 30ºC to obtain 314 g dry residue (15.0% w/w) which was viscouse brownish-coloured extract. It was stored in an air tight bottle kept in a refrigerator at 4ºC till used.

2.2 Animals

Wistar rats (150±10 g) of either sex obtained from the laboratory animal center of the College of Medicine, University of Lagos, Idi Araba, Lagos, Nigeria, were kept under standard environmental condition of 12/12 hrs light/dark cycle. They were housed in polypropylene cages (5 animals per cage), and were maintained on mouse chow (Livestock Feeds Nigeria Ltd), provided with water *ad libitum*. They were allowed to acclimatize for 7 days to the laboratory conditions before the experiment. The use and care of the animals, and the experimental protocol were in strict compliance with the Institute of Laboratory Animals Research (ILAR) guidelines [16].

2.3 Acute Toxicity Study

A group of five mice were fasted for 14 hrs before being administered by gavages a single dose of 5000 mg/kg of *P. kotschyi* root extract dispersed in acacia solution (2 %w/v). They were observed for seven days for mortality and physical/behavioural changes. The animals did not show any mortality at the dose administered hence its $1/10^{th}$ dose (500 mg/kg bwt) was chosen as the highest extract dose. The dose used is consistent with previous investigation on the plant [17].

2.4 Induction of Experimental Diabetes

Rats were fasted for 16 hour and were induced with alloxan monohydrate, 150 mg/kg body weight (bwt), intra-peritoneally (ip) [18]. Hyperglycaemia was confirmed when elevated blood glucose level was greater or equal to 250 mg/dL after 72 hrs of injection [19].

2.5 Fasting Blood Glucose Study

The diabetic rats were initially randomized to the following groups of 5 individuals each: groups I, II and III received graded doses of the extract at 100, 250 and 500 mg/kg bwt respectively by gavages. The extract treated groups were later readjusted to groups I and II following the death of all the animals in 100 mg/kg bwt extract dose before the day 9 of the experiment. Group III received glibenclamide (10 mg/kg bwt) while group IV was diabetic control. Treatment was continued for 15 days. The body weight changes were recorded every five days while blood was collected at days, 0, 3, 5, 7, 9, 11, 13 and 15 and analyzed for glucose by oxidase method [20].

2.6 Postprandial Test

Twenty albino rats were randomly assigned to four groups; A, B, C and D with each consisting of five individuals. They were fasted for about 16 hour with access to only water [21]. Glucometer (ACCU-CHEK, Roche Diagnostics) was used to estimate their initial blood sugar level. The extracts suspension was respectively prepared by dispersing 2 g of the extract dissolved in 20 ml acacia (2% w/w), solution. Each animal was administered orally with glucose at a dose of 2g/kg bwt and 30 minutes later were administered the extract as follows:

Group I received *P. kotschyi* (500mg/kg bwt)
Group II received *P. kotschyi* (250mg/kg btw)
Group III received *P. kotschyi* (100mg/kg btw)
Group IV received 0.5ml (2% w/v) acacia solution and served as control.

Blood glucose levels were monitored at 30, 60 and 120 minutes intervals and reported as the average glucose level of each group.

2.7 Evaluation of Hypoglycaemic Activity

Rats fasted for 16 hours were randomly divided into four groups of 5 individuals per group. The first three groups (I, II and III) were administered by gastric gavages (single dose) with the root extract at the concentration of 100, 250 and 500 mg/kg respectively [22] dissolved in

2% acacia solution. The fourth group (IV) (control) received 2% w/v acacia solution. Blood glucose level was determined at 0, 4, 8 and 12 hours later [19].

2.8 HbA_{1C} Assay

Blood collected with EDTA bottle was used to analyze for glycated haemoglobin (HbA_{1C}) using standard protocol [23].

2.9 Lipid Profile

Blood collected with heparinized tube was centrifuged within 5 minutes of collection at 4000 rpm for 10 min to obtain blood plasma which was analyzed for total cholesterol (TC), total triglyceride (TG) and high density lipoprotein-cholesterol (HDL-Chol) levels by modified enzymatic procedures [24]. Low density lipoprotein-cholesterol (LDL-Chol) levels were calculated using Friedwald equation [25].

2.10 Tissue Analysis

The pancreatic tissue from each group was fixed in 10% buffered neutral formalin for seven days before embedding in paraffin wax. This process involved preparing tissues for microtomy. They were further treated with several reagents to process the tissues for routine paraffin wax embedding. Sections of the embedded tissues were made at 5 µm and were stained with Haematoxylin and Eosin (H and E). The stained tissues were examined under PoTop© (Taiwan) light microscope at high power magnification X400 for changes in organ architecture and photomicrographs were taken.

2.11 Statistical Analysis

All values were expressed as mean ± standard error of mean and the statistical significance between treated and control groups were analyzed by means of Student's t-test. $p<0.05$ was considered significant.

3. RESULTS

3.1 Variation of the Body Weight

The body weight changes of the control group, the extract and glibenclamide treatments are summarized in Fig. 1. A progressive weight reduction occurred in the negative control group while the extract and the glibenclamide treated recorded progressive weight gain. The weight gain compared to the initial body weight of the animals was highest in the glibenclamide treated and lowest in the highest extract dose treatment.

3.2 Effect of the Extract on Fasting Blood Glucose

Fig. 2 showed the fasting blood glucose (FBG) study. In the untreated group (negative control) a progressive increase in the blood glucose of the animals from day 0 to the end of the experimental was evident. Treatment with the extract showed significant ($p<0.05$) dose dependent decrease of blood glucose that was continual to the end of the study indicating glycaemic levels (250 and 500 mg/kg bwt) of 259.1±3.0 (24.9%) and 266.1±2.9 (25.3%).

Similarly, the reference drug at the dose treated (10 mg/kg bwt) showed maximum blood glucose decrease of 227.0±3.8 (36.0%) which suggested that the drug possessed higher activity compared to *P. kotschyi* crude extract.

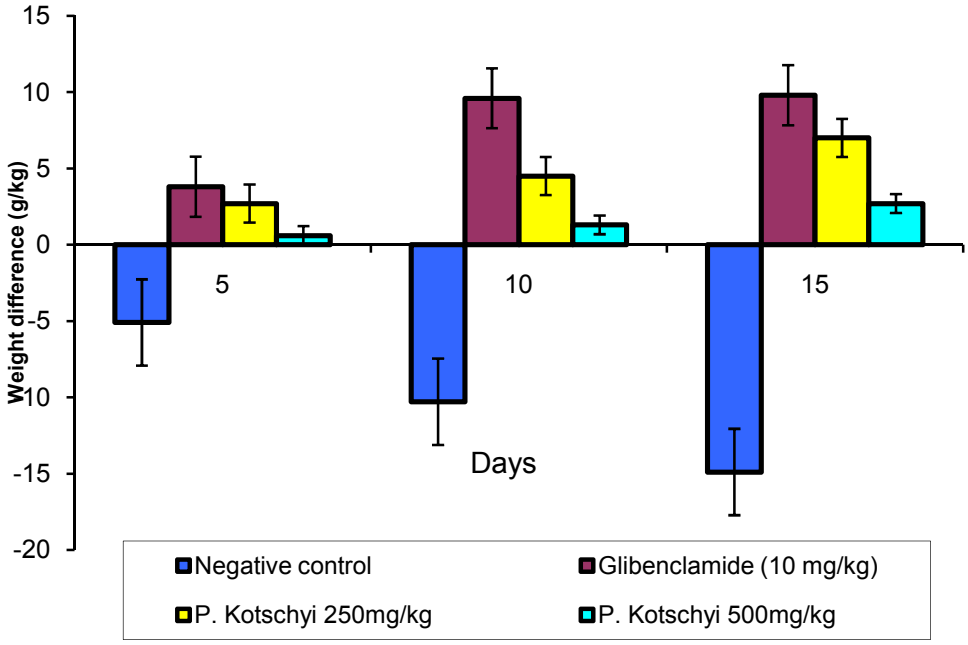

Fig. 1. Weight difference in control and treated rats

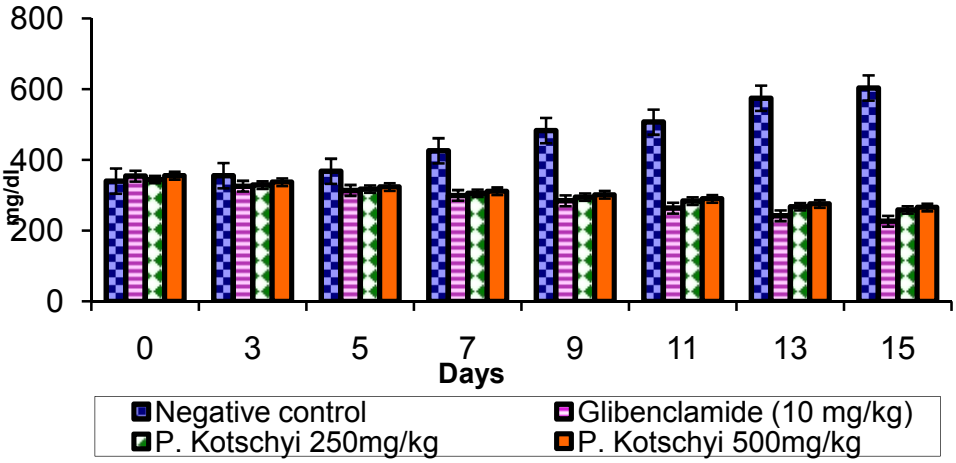

Fig. 2. Plasma glucose level of rats treated with *P. kotschyi* root extract

3.3 Postprandial Study

Glucose tolerance was evaluated by postprandial test (Fig. 3) in which there was significant (p <0.05) decrease in blood glucose level after 60 min of blood glucose load compared to the control. The decrease caused by the extract doses (100, 250 and 500 mg/kg bwt) showed minimal variations. However the highest extract dose was most effective.

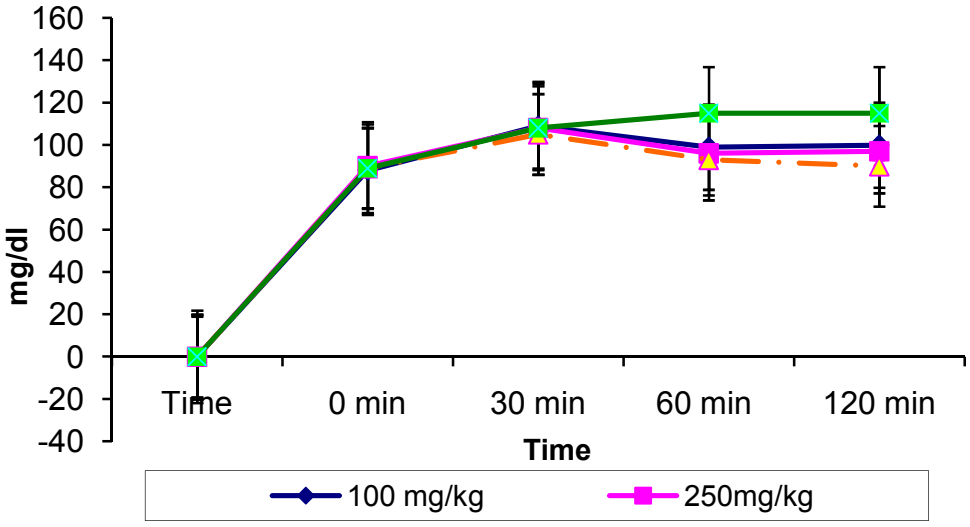

Fig. 3. Evaluation of *P. kotschyi* root extract and control effect on postprandial glucose level in rats

3.4 Effect of the Extract on Normoglycaemic Rats

The hypoglycaemic activity of the extract is shown in Fig. 4 which was evaluated at 4 hours interval. The extract at 100 mg/kg bwt showed no remarkable decrease of blood glucose level (16.1%) after 12 hours of observation. At the extract doses of 250 and 500 mg/kg bwt respectively, significant (p <0.05) decrease (28.65 and 29.45%) occurred after 8hrs interval. The maximum glycaemic decrease was observed after 12 hours interval which showed blood glucose levels of 52.5±3.8 (37.5%) and 54.0±3.8 (32.5%) respectively. The 250 mg/kg extract dose exhibited most effective hypoglycaemic activity.

3.5 Effect of the Extract on Blood HbA_{1C} Level

In the diabetic control, there was significant increase (p <0.05) in glycated haemoglobin level compared to normal, whereas, in the extract/glibenclamide treated, marked decrease occurred compared to the diabetic control. The extract treated exhibited dose effect (Fig. 5).

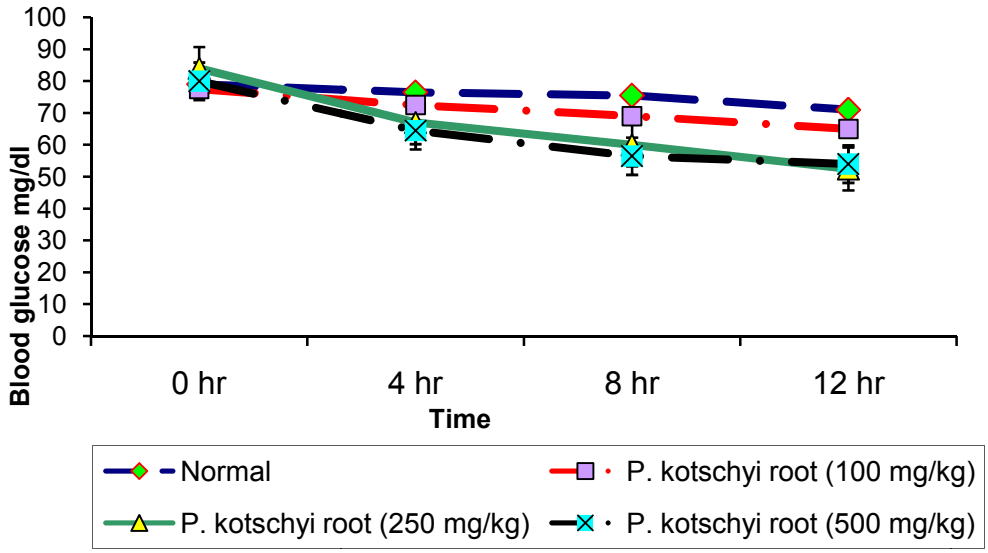

Fig. 4. Hypoglycaemic assessment of *P. kotchi* root extract
Each bar represent Mean ± SEM (n=5)

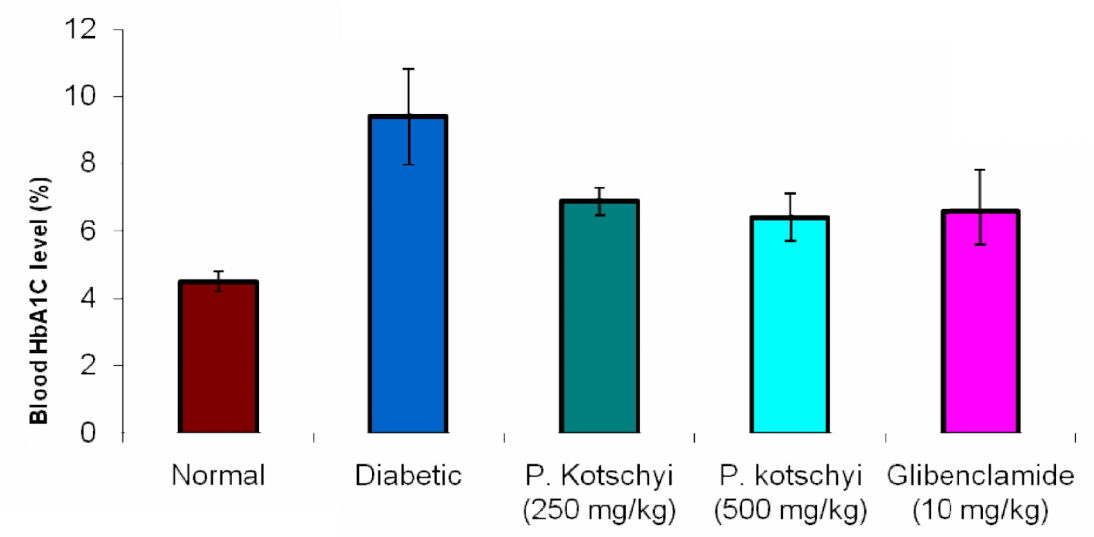

Fig. 5. Plasma HbA1C level post treatment
Values represent mean ± n=5

3.6 Effect of the Extract on Lipid Profile

In the diabetic rats treated with different concentrations of *P. kotschyi* extract (250 and 500 mg/kg bwt) and glibenclamide (10 mg/kg bwt), significant decrease (p <0.05) occurred in

plasma levels of TC, TG, LDL-Chol while marked recovery of HDL-Chol level was observed in the two extract doses and glibenclamide treatment which indicated 22.4±0.4 (31.8%), 27.5±0.2 (62.3%), 23.1±0.7 (35.3%) respectively (Table 1).

3.7 Histopathology of the Pancreatic Tissue

The photomicrograph of normal pancreatic tissue (Fig. 6a) showed the formation of Islet cells with normal cellular population. The diabetic untreated animals (Fig. 6b) showed necrotic changes with severe depletion of beta cells population. In contrast, the diabetic animals treated with the extract (Fig. 6c) showed a considerable number of beta cells population. This last finding could be compared to the diabetic animals treated with the reference drug (Fig. 6d) which showed more cellular density of the Islet cells.

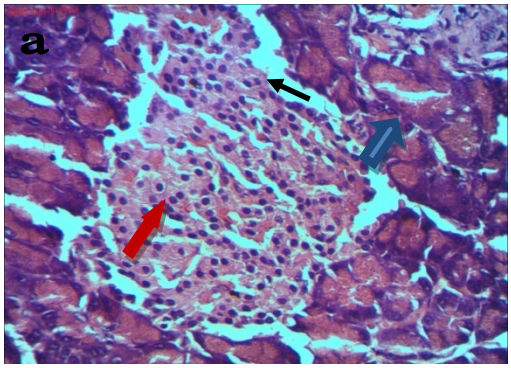

Fig. 6a. Normal Islet cells, red arrow point to beta cell, blue to pancreatic acni and black to the islet capsule (X 400)

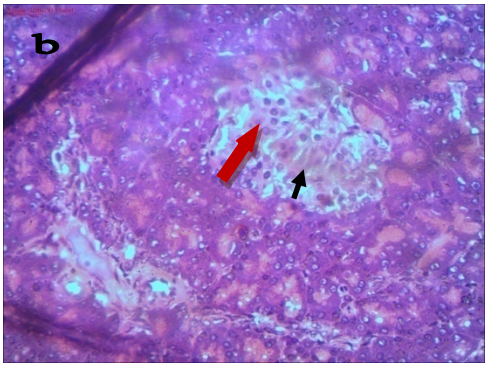

Fig. 6b. Diabetic control, red arrow point to few survivor beta cells, black to necrotic area (X 400)

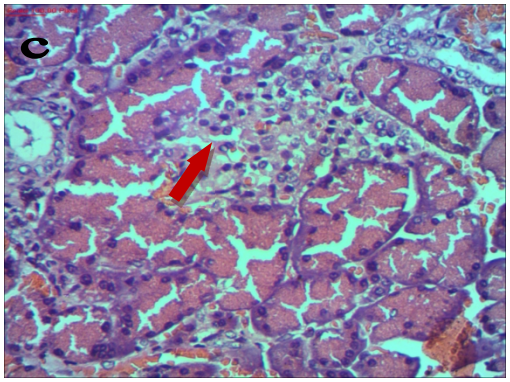

Fig. 6c. Pancreatic tissue post treatment with the extract at 500mg/kg indicating (red arrowed) survivor beta cells (X 400)

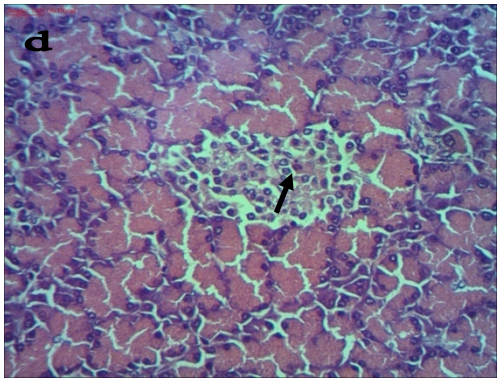

Fig. 6d. Pancreatic tissue post treatment with glibenclamide indicating survivor beta cells arrowed with black (X 400)

Table 1. The biochemical analysis showing the lipid profile

	Dose mg/kg	Total CHOL mg/100ml	HDL mg/100ml	LDL mg/100ml	TG mg/100ml
Normal		95.1±1.1	34.7±1.0	53.7±0.5	95.1±2.1
Diabetic		338.4±4.2	15.3±0.4	202.1±6.1	398.7±6.7
Glibenclamide	10	98.2±1.4*	23.1±0.7*	55.4±0.8*	119.8±3.9*
P. kotschyi	250	101.3±1.2*	22.4±0.4*	73.1±1.2*	231.1±3.1*
P. kotschyi	500	96.3.8±1.1*	27.5±0.2*	57.4±1.7*	179.7±1.4*

*Values are Mean ± SEM; n=5, *p<0.05 compared to control (Student's t-test)*

4. DISCUSSION

Normal rats administered with alloxan intraperitonially became diabetic which also showed body weight loss. Body weight loss is usually precipitated by diabetic condition and characterized by muscle wasting and loss of tissue protein [26,27]. After treatment with the extract/ the reference drug, the animals had progressive weight gain. It was obvious that the two treatment regimens improved the activity of beta cells challenged with alloxan to enhance insulin secretion. In FBG study, the extract was a potent blood sugar lowering agent by effecting significant decrease in blood glucose after 15 days of oral administration. This was corroborated with quantitative change observed in the pancreatic tissue photomicrograph in which more survivor beta cells in the extract treated were seen compared to the negative control. Although the mode of action was not examined, the extract may have initiated proliferation and differentiation of beta cells after oxidative damage by the diabetogenic agent. There are reports that plants do have the potential to cause beta cells differentiation [28,29,30]. The fact that maximum blood glucose decrease after treatment was only 25.3% suggests otherwise. It is probable that the mode of action was by the potentiation of the survivor beta cells to enhance insulin secretion. The reference drug compared to the extract showed 36% decrease of blood glucose. Its tissue histology also indicated comparably higher density of survivor beta cells compared to the extract treated. Appreciable decrease in plasma HbA_{1C} level in the extract and glibenclamide treatment equally occurred compared to the negative control which implied that both treatments effectively lowered the plasma glucose level leading to haemoglobin recovery. Haemoglobin becomes glycosylated in the presence of hyperglycaemia leading to reduced affinity of oxygen binding to it [31]. The rate of formation of HbA_{1C} has been observed to be directly proportional to blood glucose level [32]. The assessment of HbA_{1C} is therefore considered a reliable index of diabetic control [33,34].

The maintenance of blood glucose homeostasis is crucial to decreasing the risk of macro vascular complications [35]. The extract exhibited anti-hyperglycaemic activity by clearing excess blood glucose which was remarkable after 60 min of oral glucose load compared to the control. The decrease of blood glucose which occurred in dose manner after oral glucose challenge did not show appreciable difference.

The root extract of *P. kotschyi* exerted significant hypoglycaemia at 250 and 500 mg/kg bwt respectively after 4 hours of oral dose. The maximum hypoglycaemic decrease was observed after 12 hours which was comparable to other plants considered effective hypoglycaemic agents [30]. Therefore, the extract could be regarded as a good hypoglycaemic agent. The factor responsible for its hypoglycaemic activity was not clear but its phytochemical screening earlier conducted [36] revealed the presence of saponin and glycosides compound which are classified as hypoglycaemic agents [37]. The significant

hypoglycaemic activity noticed in the root extract of *P. kotschyi* also corroborated with the earlier investigation on the leave of the plant which showed similar activity [38].

Insulin deficiency precipitates various metabolic disorders. Hyperlipidaemia could be included as a metabolic disorder due to the lack of insulin which elevates counter-regulatory hormone lipase, releasing free fatty acid from the adipose tissue [39]. Compounds such as metformin that can modulate blood plasma lipid levels usually minimize the risk of exposure to cardiovascular disease [40]. This study demonstrated the efficacy of *P. kotschyi* root extract in the modulation of hyperlipidaemia. After treatment with the extract, there was significant decrease in TC, TG and LDL-Chol levels while appreciable increase was observed in HDL-Chol. It was obvious the extract inhibited the hormone sensitive lipase from mobilizing free fatty acid from the peripheral fat deposit to the blood vessels. It was also certain that the insulin produced may have activated lipoprotein lipase to hydrolyze excess TG and LDL from the blood stream hence minimizing the progression of cardiovascular disease. Studies have demonstrated the effectiveness of plant extract in modulating diabetic hyperlipidaemia [41,30].

5. CONCLUSION

P. kotschyi root extract showed to be a potent sugar lowering agent which improved the condition of the diabetic rats leading to appreciable weight gain. The extract lowered HbA_{1C} level leading to haemoglobin recovery and ameliorated dyslipidaemia. Altogether this experiment has confirmed the usefulness of *P. kotschyi* root in ethno medical practice for diabetes treatment.

CONSENT

This was not applicable since the study was on animals and not on humans.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee of our Institution".

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki".

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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