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Evaluation of the Toxicity Profile and Antidiabetic Potentials of the Methanol Extracts of *Boswellia dalzielii* (Frankincense Tree) In Alloxan-Induced Diabetic Rats

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ABSTRACT

Plants used for the treatment of hypoglycemic and hyperglycemic conditions are of considerable interest to ethno botanical community as they are recognized to contain valuable medicinal properties in different parts of the plant. The present study was aimed at investigating the toxicity and antidiabetic potentials of various parts of *Boswellia dalzielii* in alloxan-induced diabetic rats. Fresh leaf, stem and root barks of *Boswellia dalzielii* were air-dried, pulverized and extracted using cold maceration with 85% methanol and concentrated to dryness. Acute toxicity (LD_{50}) of the plant extracts were evaluated using Lorke's method while their anti-diabetic efficacy was determined on alloxan-induced diabetic rats. All the extracts were considered safe with oral LD_{50} greater than 5000 mg/kg in all the three plant extracts while the leaf was relatively safer with intraperitoneal LD_{50} of 3807.8 mg/kg. The leaf, stem and root extracts significantly ($p < 0.05$) reduced glycaemia by 70.34%, 57.32%, and 57.04%, respectively as against non-treated diabetic rats and a standard drug (glibenclamide) treated rats with -5.92% and 29.02% glycaemia reduction, respectively. Thus, the leaf extract had a more promising antidiabetic activity when compared with the stem and root barks extracts of *Boswellia dalzielii.* The antidiabetic effect of the plant in alloxan-induced diabetic rats is likely due to the presence of phytochemicals of medicinal importance.

Keywords: *Boswellia dalzielii*, diabetes, anti-diabetic, alloxan, toxicity.

Introduction

Nature has been the source of medicine for thousands of years in the maintenance of human health.[1] People have been using plant materials in different forms such as coarse, decoctions or portion and herbal drinks for healing over the past centuries. Ethnobotanical study has led researchers to explore the medicinal plants used by the locals to understand the mechanism of action, improve the preparations used and to find a standard remedy. Diabetes mellitus is a global problem, and successful treatment has not yet been discovered.[2] More than 50% of all the drugs currently in use are of natural product origin.[3] Plants have been the source of medical agents since earliest time and continue to play a dominant role in the healthcare industry.[4] The physiological effect of medicinal plants lies within some of the chemical substances produced by the plants during secondary metabolism. These are called phytochemicals. These secondary metabolites are the compounds in plants responsible for their bioactive properties.[5]

Diabetes mellitus is a group of metabolic disorder characterized by hyperglycaemia resulting from a defect in insulin secretion, its action, or both. It is made up of two types: Types I and II. Type I diabetes often referred to as juvenile diabetes, is insulin dependent and affects only 5% of the diabetic population. The Type II, which is known as non-insulin dependent, usually develops in adults over the age of 40.[6]

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Currently, available therapy for diabetes includes insulin and various oral hypoglycaemic agents such as sulfonylureas, metformin, glucosidase inhibitors, troglitazone, etc. These agents, however, are reported to produce serious adverse effects such as liver problems, lactic acidosis and diarrhea.[7] In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2016, diabetes was the direct cause of 1.6 million deaths and in 2012 high blood glucose was the cause of another 2.2 million deaths.[5] WHO reported that diabetes is currently affecting around 422 million people[5] and the number of those affected is increasing day by day; by 2030 it is predicted to reach 366 million populations worldwide.[8] About 800 plant species have been reported to possess antidiabetic properties.[7] Several plant species have been used for prevention or management of diabetes by the Native Americans, Chinese, South Americans and Asian Indians.[7]

Boswellia dalzielii Hutch is a savannah tree which belongs to the family Burseraceae[9] and it is mostly called the "Frankincense tree".[10] The tree has a characteristic smooth, pale brown bark that peels off in ragged papery patches, which on rapping exudes a whitish fragrant resin. It grows up to 13 m high. The small white flowers, which may appear while the tree is leafless, are fragrant.[10] It is locally abundant in Togo, Cote d'Ivoire, Cameroon, Benin, Ivory Coast, Poland, Ghana, Burkina Faso, Nigeria and the Czech Republic. In Nigeria, the tree is distributed in states such as Kebbi, Kano, Kaduna, and Adamawa.[12]

B. dalzielii locally called Hano or Arrarabi in Hausa language (meaning to prevent bad luck), is a popular plant in the Northern part of Nigeria due to its ethno medicinal value. The decocted root bark is used traditionally by the Hausa-Fulanis in Sokoto, Nigeria to treat diabetes.[13] The bark decoction is used as an antiseptic wash for sores in Ivory Coast and is an ingredient of a complicated prescription for leprosy.[12] In the northern part of Nigeria, the stem bark is boiled and taken for the treatment of fever, rheumatism and the fluid is taken internally for gastrointestinal troubles.[12,14] The Fulanis of northern Nigeria use the cold infusion of the stem bark for management of snakebite.[12] The fresh bark of the root is eaten in Adamawa State,

Nigeria, to relief symptoms of giddiness and palpitations as well as an antidote of arrow-poison[12,14] amongst other numerous medicinal uses.
The conventional drugs used for the treatment of diabetes act by improving insulin sensitivity, increasing insulin production and decreasing the amount of glucose in the blood of the patient.[15] The hypoglycaemic effect of pharmacologically active component of plants decrease the effect on α-amylase and various direct and indirect effects of different blood parameters responsible for the development of diabetes.[15] A large number of antidiabetic drugs are available in the pharmaceutical market for the treatment of diabetes, but currently, no effective therapy is available to cure this metabolic disease. However, due to the unwanted side effects of these compounds, there is a demand for new compounds for the treatment of diabetes.[16,17] In the last few years, there has been a growing interest in herbal medicine in the care and management of diabetes both in developing and developed countries, due to their natural origin and less side effects.[18-20]

In spite of the wide use of various parts of *Boswellia dalzielii* in traditional medicine by the local people in Nigeria for the treatment of diabetes, there is no scientific report on bioassay, isolation of active ingredient(s) from the whole plant parts responsible for the antidiabetic activity. More so, as a consequence of negative scientific reports on the adverse effects of most conventional drugs used in the treatment of diabetes as well as drug-resistant incidences, this has necessitated the search for safer and more effective drug(s) for the management of this disease.

Materials and Methods

Sample Collection, Identification and Preparation
Fresh leaves, stem and root barks of *Boswellia dalzielii* were collected from Gulantabar, Song Local Government Area, Adamawa State, Nigeria, in the month of January 2019. The plant material was identified and authenticated by Prof. S.S. Sanusi, a Plant Taxonomist of the Department of Biological Science, University of Maiduguri, Borno State, Nigeria. It was given a voucher specimen of #341 and deposited at the Herbarium of the Postgraduate Research Laboratory of Chemistry Department, University of Maiduguri, Maiduguri, Borno state. The fresh plant samples were cleaned and air-dried under the shade at room temperature for ten (10) days and were rendered free of foreign material through manual picking. The air-dried plant materials were pulverized using a mortar and pestle.

Plant Extraction
The powdered plant material (2 kg each of the leaf, stem and root barks) were macerated using 22.5 L of 85% methanol for 72 hrs with periodic shaking and allowing to stand at room temperature for a proper dissolution of soluble plant chemicals. The liquid mixture of the extract was filtered using a clean muslin followed by filtration using 200 mm diameter of Watmann No. 1 filter paper. The crude extracts were concentrated to dryness at room temperature. The crude methanol extracts were weighed, coded BMLE, DMSE and BMRE - *Boswellia dalzielii* methanol leaf, stem and root bark extracts, respectively. The crude extracts served as the working sample for phytochemical investigation, acute toxicity (LD_{50}) and anti-diabetic studies.

Experimental Animals
All the experiments performed on laboratory animals in this study followed the standard procedure for the treatment of animals. The animals were handled according to the International Guiding Principle for Biomedical Research involving animals.[21]
A total of one hundred and sixty-four (164) albino rats weighing 100-180 g of both sexes were acquired from the Animal House of the Faculty of Pharmacy, University of Maiduguri, Borno State. They were housed in clean plastic; well-ventilated cages with sawdust as beddings under 12 hrs light/12 hrs dark cycle conditions of normal room temperature and humidity in the Veterinary Pharmacology Laboratory, Faculty of Veterinary Medicine, University of Maiduguri, Maiduguri, for the analysis. They were fed with standard feed and allowed access to water *ad libitum.*
Ethical Approval
All experiments were conducted in accordance with the National Institute of Health Guidelines for the Care and use of Laboratory Animals (NIH Publications No.80-23) as revised in 1996. [22]

Extract and Alloxan Preparation
The crude methanol extract and alloxan (2 g each) were dissolved in 10 mL distilled water to give a stock solution of 200 mg/mL.

Acute Toxicity Studies (LD_{50})
The LD_{50} of the crude extracts was determined using Lorke's method.[23] The rats were deprived of food for 16-18 hrs prior to administration of the extract. The study was carried out in two phases. Phase 1 consist of three groups of three animals per group. The leaf, stem and root barks of *B. dalzielii* crude methanol extract were administered orally and intraperitoneally in geometrical doses (10 mg/kg, 100 mg/kg and 1000 mg/kg). The treated animals were observed for four hours post-administration for signs of toxicity. Phase 2 was initiated after no death was recorded. In phase 2, three groups of one animal each were given the extracts orally (1600 mg/kg, 2900 mg/kg and 5000 mg/kg), respectively. The animals were observed for signs of toxicity for the first 4 hours and mortality for 24 hrs. The arithmetic mean of the lowest dose that kills an animal and the highest dose that does not kill any animal will be taken as the median lethal dose (LD_{50}) of the extract. i.e:

$$LD_{50} = \sqrt{ab}$$

Where - a = lowest dose that kills an animal
b = highest dose that did not kill an animal

Test for Hypoglycaemic Activity
The animals were fasted for 12 hrs but were allowed free access to water before and throughout the duration of the experiment. At the end of the fasting period, taken as zero time (0 h), blood was withdrawn from the lateral tail vein of each rat under mild anesthesia and the fasting blood glucose (FBG) was estimated with a glucometer (Accu-Check, Roche, Germany).

Evaluation of Extracts Activity in Alloxan-induced hyperglycaemic Rats
The method described by Uzor *et al.*[24] and Ezeigbo[25] were adopted in this study, with little modification. The animals were fasted for 12 hrs with water *ad libitum* and injected intraperitoneally with freshly prepared alloxan monohydrate (150 mg/kg) in ice-cold 0.9% saline. They were given 5 mL of 10% dextrose solution to overcome the drug-induced hypoglycaemia and were provided with standard laboratory diet *ad libitum* after one hour. The FBG was checked before and 72 hrs after alloxan injection by withdrawing blood from the tip of the tail of each rat. The FBG was measured as described above. The animals were considered diabetic when the FBG is greater than 200 mg/dL. They were segregated into six (6) groups of four animals in each. Group I served as the normal i.e, animals fasted and water was given *ad libitum*. Group II-VI were all alloxan-diabetic rats. Group II served as the negative control, received vehicle (normal saline, 2 mL/kg, p.o.), Groups III, IV and V (i.e alloxan-induced diabetic rats), were administered 500 mg/kg each of BMLE, DMSE and BMRE, respectively. Group VI was administered glibenclamide (2 mg/kg, p.o.). Blood glucose concentration was measured after 0, 30 min, 1 hr, 3 hr, 6 hr, 9 hr, and 12 hr after administration of a single dose of each of the regimen.

Statistical Analysis
Results of pharmacological studies were analysed using GraphPad Prism. 2016 Model, Version 7.0 for windows. One-way Analysis of Variance (ANOVA) test followed by Dunnet's Multiple Comparison test was used to analyse and compare the results at a 95% confidence level. Results were expressed as mean ± standard error of mean (SEM).

Results and Discussion

Extraction Profile of Air-dried Powdered Leaf, Stem and Root Barks of B. dalzielii

The methanol extraction of the leaf, stem and root barks of *B. dalzielii* produced extracts with gummy brownish green, gummy brownish and powdery brownish substances, respectively. The leaf extract had the highest yield of 18.00% while the stem and root barks had 16.20% and 12.51% yields, respectively. The result of the extraction profile is shown on Table 1

Acute Toxicity Effect of Methanol Leaf, Stem and Root Bark Extract of Boswellia dalzielii

Table 2 present the result of acute toxicity of methanol leaf, stem and root bark extracts of *B. dalzielii* on rats. No death was recorded on administration of 10, 100 and 1000 mg/kg dose of the leaf, stem and root bark methanol extracts via both the oral and intraperitoneal routes in the phase I. But death was recorded in phase two, when extract dose of 5000 mg/kg of the stem and root extracts were administered intraperitoneally. Though behavioural signs of toxicity were observed in the rat when 5000 mg/kg of the extracts were administered via orally route which included; paw licking, stretching and reduced activity but revived 5hrs afterwards. Thus LD_{50} of the leaf, stem and root bark extracts in rats administered via oral route were ≥5000 mg/kg while intraperitoneal route was calculated as 3807.8, 2154.06, and 2154.06 mg/kg, respectively.

The present study revealed that there was no mortality at all dose levels of the leaf, stem and root barks of *B. dalzielii* when administered to the laboratory rats orally. But, there was mortality at 5000 mg/kg of the leaf and both 5000 and 2900 mg/kg doses for the stem and root bark methanol extracts when administered intraperitoneally. Opinion of Clarke and Clarke[26] states that, compounds with LD_{50} of 1500 mg/kg and above is considered of low toxicity. The extract is therefore likely to be safe and this could explain the safe use of the plant by the local people who have been using it in the traditional management of several illnesses in North-Eastern Nigeria.[27]

Effect of Leaf, Stem and Root Barks of Methanol Extracts of B. dalzielii on Alloxan-Induced Wistar Rats

The antidiabetic effect of methanol extracts of the leaf, stem and root barks of *B. dalzielii* is shown in Table 3. A single dose of 500 mg/kg was administered to the alloxan-induced diabetic Wistar rats in order to compare the antidiabetic effect of the extracts for further studies. The leaf extract had the highest percentage (%) inhibition of glycaemia with a percentage reduction of fasting blood glucose level of 70.34% compared to the stem and root bark with 57.32 and 57.04% reduction, respectively. Although the extracts all had a more significant effect greater than the conventional standard drug (glibenclamide, 2.0 mg/kg) used for this study (29.02%). Interestingly, the antidiabetic activities of the plant parts are in agreement with the folkloric usage of the plant root and stem in the management of diabetes.

Diabetes mellitus is one of the rapidly growing endocrine disorders with major complications affecting the global population.[28] The pathophysiological mechanisms are being scrutinized and the knowledge on heterogeneity and complexity of this disease is being advanced. Currently, the search for more appropriate therapy is also being underway. In line with that, traditional medicines are used substantially by diabetic patients across the globe[29] and medicinal plants have been identified to be a target for scientists to come up with newer and better therapeutic options in the future.

Herbal treatments for diabetes have been used in patients with insulin-dependent and non-insulin-dependent diabetes, diabetic retinopathy, diabetic peripheral neuropathy. However, many herbal remedies used today have not undergone careful scientific evaluation and some have the potential to cause serious toxic effects and major drug-drug interaction. Compounds with different structure but with the same therapeutic activity isolated from different plant species act as active moieties for the treatment of various diseases. The use of these plants and phytoconstituents may delay the development of diabetic complications and may regulate the metabolic abnormalities through a variety of mechanisms.[30] The observed hypoglycaemic activity could be associated with the reported phytochemicals and phytonutrients present in the plant. These compounds are also known to exert pharmacological and antagonistic effects, while some are capable of protecting the active ingredient in herbs from decomposing either chemically or physiologically.[31]

The possible mechanisms underlying the hypoglycaemic activity exhibited by *B. dalzielii* include inhibition of intestinal absorption of glucose, facilitation of glucose-induced insulin release, enhancement of peripheral glucose uptake, promotion of the regeneration of β-cell of islets of Langerhans and amelioration of oxidative stress[32] attributed to the presence of a variety of phytoconstituents present in this plant.[33]

The hypoglyceamic effect of the stem bark agrees with the findings of Balogun *et al*.[34] who reported the significant lowering of blood glucose concentration in both normal and alloxan-induced hyperglycemic rats at doses of 153 mg/kg and 297 mg/kg.

Alloxan and its reduction product, dialuric acid, establish a redox cycle with the formation of superoxide radicals which undergo dismutation to hydrogen peroxide. This leads to the formation of highly reactive hydroxyl radicals by Fenton reaction. The action of reactive oxygen species with a simultaneous massive increase in cytosolic calcium concentration causes rapid destruction of β-cells.[35] Thus, alloxan can possibly produce different grades of severity of the disease by varying the dose of alloxan used. These may be classified by measuring FBG levels such as FBG level of 180-250 mg/dL which is considered moderately diabetic level in rabbits and severe diabetes as an FBG level of above 250 mg/dL.[36] Thus the diabetes induced in the present study could be regarded as severe as the FBG of the animals were generally greater than 250 mg/dL.

The blood glucose-lowering effect of the plant extracts may be attributed to the presence of total phenols, flavonoids, alkaloids, tannins, terpenoids, and saponins that have been known to confer hypoglycaemic activity.[37] Some plants have been reported to induce pancreatic beta cells regeneration and repair. Chakravarti *et al*.[38] reported the pancreatic *β*-cell regenerative action of plants such as *Pterocarpus marsucipium* in diabetes rats. The leaf extract of *Gymnema sylvestre*s was also shown to exhibit hypoglycaemic effects in non-insulin dependent diabetes mellitus in rats.[39] The activity of the plant can be ascribed to regeneration, revitalization and repair of the pancreatic islets.

Table 1: The extraction profile of air dried powdered leaf, stem and root barks of *B. dalzielii*

Sample	Mass (g)	%Yield	Colour	Texture
Leaf	360.00	18.00	greenish brown	Gummy
Stem bark	324.06	16.20	Brown	Gummy
Root bark	250.20	12.51	Brown	Powdery

Table 2: Acute toxicity of methanol leaf, Stem and Root bark extracts of *Boswellia dalzielii* in rats

Phase	Dose	No. of Rats	Mortality Rat					
			Leaf		Stem		Root	
			Oral	I.P	Oral	I.P	Oral	I.P
I	10	3	0/3	0/3	0/3	0/3	0/3	0/3
	100	3	0/3	0/3	0/3	0/3	0/3	0/3
	1000	3	0/3	0/3	0/3	0/3	0/3	0/3
II	1600	1	0/1	0/1	0/1	0/1	0/1	0/1
	2900	1	0/1	0/1	0/1	**1/1**	0/1	**1/1**
	5000	1	0/1	**1/1**	0/1	**1/1**	0/1	**1/1**

0/1 and 0/3 (no death), 1/1 (death)
Leaf ip LD_{50} = 3807.8 mg/kg: Stem ip LD_{50} = 2154.06 mg/kg; Root ip LD_{50} = 2154.06 mg/kg

Table 3: Effect of methanol leaf, stem and root bark extracts of *Boswellia dalzielii* on alloxan-induced diabetic Wistar rats

Treatment	Fasting Blood Glucose (mg /dL) Time (min) after treatment (Mean ± SEM)							
	0	30	60	180	360	720	900	% Inhibition of glycaemia
normal	73.00 ± 01.93	72.75 ± 2.25	73.10 ± 73.00	72.75 ± 1.70	72.75 ± 1.93	72.5 ± 1.85	73.50 ± 1.92	0.33
-ve control	455.80 ± 46.15	460.80 ± 44.33	464.50 ± 44.95	472.30 ± 44.14	471.30 ± 43.76*	476.30 ± 44.76*	482.80 ± 43.94*	-5.92
leaf (500 mg/kg)	394.50 ± 56.01[a]	336.00 ± 44.10	274.00 ± 74.72	267.80 ± 70.07	231.30 ± 62.85*	178.30 ± 47.40*[a]	117.00 ± 47.60*	70.34
stem (500 mg/kg)	423.00 ± 94.09	397.30 ± 85.51	333.80 ± 69.31	284.30 ± 47.16	255.30 ± 64.74	182.30 ± 52.51*	180.50 ± 70.84*	57.32
root (500 mg/kg)	467.50 ± 26.33[b]	418.50 ± 27.31[c]	400.80 ± 29.16[d]	365.80 ± 21.1[e]	314.00 ± 25.28[b]	244.30 ± 30.64[bcde]	200.80 ± 23.22*[bcde]	57.04
Glibenclamide (2mg/kg)	417.3 ± 61.48	410.3 ± 60.98	400.3 ± 61.77	372.0 ± 63.06	348.8 ± 65.24	315.5 ± 67.52	296.3 ± 68.23	29.02

Results expressed as Mean ± SEM (n = 4). *P < 0.05, as compared with control group (One-way ANOVA followed by Dunnet's t-test, 2 sided). % Inhibition of glycaemia denote percentage reduction of blood glucose from 0 h. Basal FBG = FBG before induction of diabetes; DC = diabetic control; -ve control: alloxan-induced diabetic animals without treatment

Conclusion

In conclusion, the present study revealed that the plant *Boswellia dalzielii* is a relatively safe regimen. The methanol leaf extract of *Boswellia dalzielii* was more effective than the stem and root extracts. Therefore, further antidiabetic study on the leaf of *Boswellia dalzielii* should be carried out in order to ascertain the actual bioactive constituent(s) responsible for this effect.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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