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Evaluation of Antidiabetic, Phytochemical and Acute Toxicity of the Methanol Seed Extract of *Senna occidentalis* Linn

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ABSTRACT

Diabetes mellitus is one of the major chronic medical conditions. Many medicinal plants have demonstrated antidiabetic effect. The study evaluated the phytochemical constituents, acute toxicity and antidiabetic activity of the methanol seed extract of *Senna occidentalis*. Six groups of Wistar rats were used for the antidiabetic study. Group 1 was used as normal control while groups 2 and 3 were used for metformin and insulin as standard controls respectively. Groups 4, 5 and 6 were administered 200, 400 and 800 mg/kg of the methanol seed extract of *S. occidentalis* respectively through oral intubation. The study revealed the presence of carbohydrates, cardenolites, anthraquinones, flavonoids, tannins and triterpenoids. Alkaloids and saponins were not detected. The acute toxicity was greater than 4000 mg/kg body weight with no death during the 10 days observation after oral administration of the extract. The plant extract showed mild hypoglycaemic activity at the dose of 800 mg/kg at 12 hours by 3% and by 21% at 24 hours, slight decrease in blood glucose level was observed at 400 mg/kg by 2% and by 5% at 6 and 24 hours respectively. However, the extract showed no activity at 200 mg/kg throughout the study. The positive control (insulin) reduced the blood glucose level significantly by 65%, 57% and 36% at 3, 6 and 12 hours respectively but hypoglycaemic effect demonstrated by metformin throughout the study. The methanol seed extract of *S. occidentalis* showed mild hypoglycaemic activity. The extract contains phytochemical constituents that might be responsible for its antidiabetic activity.

Keywords: Alloxan monohydrate, Acute toxicity, Diabetes**,** Methanol, *Senna occidentalis.*

Introduction

Increased and renewed interest in the search of herbal drugs for the treatment of different disease including diabetes has been observed in recent times possibly due to undesirable effects, high cost associated with modern conventional drugs. Insulin and synthetic oral hypoglycemic drugs have been used to treat diabetes.[1] Plants have been an important source of drugs in traditional medicine for various diseases including diabetes. The widely use of medicinal plants in the traditional treatment of chronic ailments necessitate investigation of their efficacy and safety to established evidence based knowledge of the therapeutic claims.[2] Medicinal plants with hypoglycemic activities have been used in traditional medicine from ancient time.[3,4] Many medicinal plants have demonstrated varying antidiabetic effect and gain acceptance because of their natural origin, safety and less side effects.[5,4]

Diabetes mellitus presents with episodes of hyperglycemia and glucose intolerance as a result of insulin insufficiency, defective insulin utilization or both, which is often associated with life threatening complications including retinopathy, nephropathy and neuropathy, ketoacidosis, and hyper-osmolar non-ketotic state.[6] Majorly there are two types of diabetes mellitus; type 1 and 2 besides gestational diabetes and other specific types of diabetes.[7]

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Type 1 diabetes is caused by the immune destruction of beta cells of the pancreas while type 2 is caused by insensitivity of tissues to insulin or reduced secretion of insulin.

Diabetes is also associated with macrovascular disorders such as coronary heart disease, cerebrovascular disease, peripheral vascular disease and various organ failure.[8,9,6] There has been a progressive and dramatic increase in the prevalence of diabetes over the last few decades. International Diabetes Federation (IDF) reported that 366 million people in the world had diabetes in year 2011 with a projected increase to 552 million by 2030. The global estimate of prevalence of diabetes for adult between the ages of 20 and 79 in 2015 was 415 million.[10] It was reported that people living with diabetes in Africa increased from 4 million to 25 million between 1980 and 2014.[11] In Nigeria, diabetes is known to affect 3% of adult population[12] with the prevalence rate estimated at 4.7% with rural areas having the lowest rates.[13] Diabetes mellitus is treated with diet modification, physical exercise and pharmacological interventions (oral hypoglycemic drugs and insulin). Treatment with insulin and oral hypoglycemic agents often associated with side effects such as hypoglycemia, gastrointestinal disturbances, skin reactions, hematological disorders and rise in hepatic enzyme level.[14] It is a common practice in many developing countries to use plants in the form of crude extracts, decoction, infusion or tincture to treat common infections and chronic conditions where about 80% of their populace depend on traditional medicines for their primary health care needs.[15]

Senna occidentalis is an annual herb with a pantropical distribution and belong to the family Leguminosae.[16] Its roasted seed of is used as a substitute for coffee, pure or in a mixture with true coffee. In traditional medicine, *S. occidentalis* is considered as panacea, especially in Africa because of its numerous medicinal applications. Different parts of the plant have been reported to have tonic, diuretic, stomachic and febrifuge properties, anti-inflammatory, antihepatotoxic,

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antibacterial, antispasmodic activities and are especially used for dropsy, rheumatism, fevers, diabetes and venereal diseases.[17,18]

Materials and Methods

Collection and identification of plant materials
The seeds of *Senna occidentalis* were collected in November 2018 from Federal Government College along Bama road, Maiduguri Borno State. The plant material was identified by a Taxonomist in the Department of Biological Science and deposited in an herbarium with a voucher number UM/FPH/06b/001/001, University of Maiduguri, Borno State.

Preparation and extraction of the plant materials
The seeds were shed-dried and powdered using grinding machine. Powdered material (1.2 kg) was obtained and stored in an air tight glass container at room temperature. The extraction process was carried out using cold maceration method of extraction. The powdered plant material (1.2 kg) was soaked in 1.4 L of methanol in a closed bottle and kept for 24 hours with occasional agitation. After 24 hours, the extract was filtered through a glass funnel using Whatman's filter paper. The filtrate was allowed to air dry while the marc was used for further extraction. The percentage yield for the plant extract was calculated using the formula below:

$$\text{Percentage yield} = \frac{\textit{Weight of extract}}{\textit{Weight of powdered material}} \times 100$$

Preparation and storage of drug solutions
The stock solutions of the reference drugs and the extract were prepared for the work whenever necessary by taking a weighed amount of the extract/reference drugs and dissolving in a measured volume of distilled water and the unused portion discarded.

Routes of administration
Alloxan and insulin were administered intraperitoneally, while the extract was administered orally.

Experimental animals
Forty-five healthy adult Wistar rats of both sexes weighing (180-229 g) were used. The rats were obtained from the Animal House of the Department of Pharmacology and Toxicology, Faculty of Pharmacy and University of Maiduguri Teaching Hospital and were acclimatized to the laboratory environment before they were used for this study. During the experiment, the rats were housed under controlled environmental condition at room temperature and had free access to feed and water *ad libitum* according to CIOMS and ICLAS, 2012; the guideline for international guiding principles for biomedical research involving animals and, the procedures and protocols as approved by ethics review committee of the University of Maiduguri (UM/11/01/2018).

Preliminary phytochemical screening
The plant extract was screened for the presence of alkaloid, flavonoid, saponins, tannins, glycosides, steroids, terpenes, anthraquinone and reducing sugars using standard procedures.[19,20]

Alloxan induction of diabetes and the antidiabetic effects of S.occidentalis
Thirty rats weighing between (180 and 229) were grouped into six groups each containing five rats where group 1 served as the control and groups 2,3,4,5 and 6 were induced with diabetes using alloxan at the dose of 150 mg/kg. The animals were fasted overnight and their baseline blood glucose level was measured prior to the induction of diabetes. Their blood glucose was taken at 24 and 48 hours of alloxan administration. Blood glucose level of 200 mg/dl and above was considered as diabetic. The animals were regrouped according to the rise in their blood glucose. Group 2 rats were injected with insulin at the dose of 0.5 IU/kg body weight. Group 3 were administered metformin orally at the dose of 50 mg/Kg body weight, whereas group 4, 5 and 6 were administered the plant extract orally at the dose of 200 mg/Kg, 400 mg/Kg and 800 mg/kg respectively. Their blood glucose level was taken subsequently at 3, 6, 12 and 24 hours.

Acute toxicity
The acute toxicity (LD_{50}) of the methanol seed extract of *S. occidentalis* was determined using organization for economic cooperation and development (OECD) guideline in rats.[21] The limit dose test, up and down procedure as modified in the study was adopted to evaluate the acute toxicity of the extract of *S. occidentalis* following oral administration in Wistar rats which was determined under the standard conditions and allow free access to feed and water. The animals (n=2 per dose) were fasted for 4 hours prior to the experiment. Animals were administered with single dose of the extract at a dose of 1000 mg/Kg and observed for their mortality and signs of toxicity during the first 4 h, 24 h and 48 h for the short term toxicity outcome and finally monitored the surviving animals for the next 10 days study period for any delayed toxic effects or death. The dose was increased to 2000 mg/kg and were observed up to 10 days then increased up to 4000 mg/kg and observed for the next 10 days. The toxicity observed include increased motor activities, rolling, writhing, depression, behavior pattern, diarrhea, sleep, coma, tremors, convulsions, respiratory frequency etc.

Preparation and staining of the tissues
Approximately 72 hours after induction of experimental diabetes with alloxan monohydrate, the rats were sacrificed humanely and the blood was allowed to drain out. The pancreas of the rats exposed to different doses (200, 400 and 800 mg/kg) of the extract and the controls were identified, trimmed of any adherent tissue, harvested, observed macroscopically and were fixed in 10% buffered neutral formalin in a separate container for each animal. The tissue samples collected were routinely processed for histopathological analysis; the sections were cut in 5-mm thickness, attached to glass slide, smeared and allowed to dry. The slides were stained with hematoxylin and eosin for microscopic examination under different magnification.

Statistical Analysis
Data obtained from this study were analyzed using one-way analysis of variance (ANOVA) to determine the relationship between the variables means using Statistical Package for Social Sciences (SPSS) version 16 and the results were expressed as mean and standard error of the mean (Mean ± SEM). The p-value <0.05 was considered significant.

Results and Discussion

Diabetes mellitus is a metabolic disease associated with impaired glucose utilization which in effect alters intermediary metabolism of lipids and proteins adversely.[18] Alloxan, a diabetogenic agent destroys the pancreatic β-cells of islets of Langerhans which result to decrease or lack of endogenous insulin secretion with subsequent impaired utilization of glucose by body tissues leading to hyperglyceamia and increased levels of cholesterol and triglycerides.[22]

Extractive value and phytochemical constituents of the methanol seed extract of Senna occidsentalis
Extractive value was used to determine the amount in percent of the extract from 1200 g of powdered seed material of *S. occidentalis* which yielded 40 g from cold maceration using 95% methanol and the percentage yield was found to be 3.33%. (Table 1). The methanol seed extract of *Senna occidentalis* was found to contain anthraquinones, carbohydrates, flavonoids, cardenolides, steroids, tannin and terpenes. However, the tests for alkaloids and saponins was negative (Table 2). The finding agreed with the study of Kathirvel and Sujatha [23] which reported the presence of carbohydrates, tannins, flavonoids, steroids, terpenoids, and anthraquinones with the absence of saponins but in contradiction with the absence of alkaloids in this study. In addition to this, Usha *et al.*[24] reported the presence of alkaloids in the aqueous root extract of *S. occidentalis*. Similar studies reported the presence of flavonoids, tannins, phenols, steroids, terpenes, anthraquinones and cardiac glycosides but the absence of alkaloids in the methanol root

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extract of *S. occidentalis*.[25] This inconsistency may occur as result of difference in geographical area of the plant, period and time of collection[26] and solvent system used for extraction.[27] These phytochemical constituents may be responsible for the glucose lowering effect of the extract.[28]

Acute Toxicity of the methanol seed extract of Senna occidentalis

OECD guideline No. 425 was used to determine the acute toxicity (LD_{50}) of the methanol seed extract of *S. occidentalis* via oral route and it showed that the LD_{50} was found to be equal or greater than 4000 mg/kg. There was no death or any sign of toxicity recorded as all the animals were stable for the period of the study (Table 3). This suggest that the extract is relatively non-toxic on acute exposure. This is in agreement with the report of Mirtes *et al* [29] which reported that the extract of the plant is safe up to the dose of 5000 mg/kg.

Antidiabetic effect of methanol seed extract of Senna occidentalis on blood glucose level

Alloxan was able to induce diabetes in all the test rats within 48 hours of administration. There was a significant decrease in the blood glucose level by insulin (65%) (Standard drug) compare to extract treated groups ($p < 0.05$) but no decrease in blood glucose level of the extract treated groups as well as metformin treated group (standard drug given orally) after 3 hours of the treatment. Similarly, blood glucose level at 6 hours of administration was reduced significantly by insulin as compared to the extract treated groups; equally, no hypoglyceamic effect exhibited by metformin (oral standard drug). Although, insignificant decrease in the blood glucose level by 2% was observed at the dose of 400 mg/kg of methanol seed extract of *Senna occidentalis*. A significant difference of hypoglyceamic effect was noted between insulin and the extract treated groups ($p< 0.05$) after 12 hours of treatment but no difference between metformin and the extract treated groups. On the contrary, the blood glucose level of metformin and the extract treated groups continue to increase except at the dose of 800 mg/kg of the extract where there was also a mild decrease in the blood glucose level by 3% after 12 hours of treatment. After 24 hours of treatment, a significant decrease by 21% in the blood glucose level was observed at the dose of 800 mg/kg of the extract compared to insulin treated group. Likewise, a 5 % reduction in blood glucose level at the dose of 400 mg/kg though not significant compare to insulin and metformin. Insulin has almost lost it hypoglycaemic effect after 24 hours of administration (Table 4). The study revealed that the methanol seed extract of *Senna occidentalis* has mild hypoglycaemic activity with the highest reduction in blood glucose level by 21% at the highest dose (800 mg/kg) followed by 5% decrease at the dose of 400 mg/kg but no hypoglycaemic activity was observed at the lowest dose of the extract (200 mg/kg) within 24 hours of administration. This showed that its activity is dose dependent and this is in concordance with the work of Saurabh *et al* [30] and Emmanuel *et al* [31] which reported that the methanol and aqueous seed extract of *Senna occidentalis* at the dose of 3000 mg/kg exhibited a significant hypoglycaemic activity compared to lower doses. Other studies have shown that the leaf extract of *S. occiedntalis* has better hypoglycaemic activity compared to the seeds.[30] The extract at the dose of 400 mg/kg reduced the blood glucose level by 2% and 5% at 6 and 24 hours of treatment respectively. Likewise, the hypoglycaemic effect of the extract was observed to increase at the dose of 800 mg/kg by 3% and 21% at 12 and 24 hours respectively after its oral administration. Furthermore, the report of Amuri *et al*[32] showed significant glucose lowering effect of the aqueous extract of the plant at 500 mg/kg.

It was also observed that metformin (the standard oral drug) did not reduce the blood glucose within the 24 hours of administration. This is suggestive that the mechanism of glucose lowering effect of the methanol seed extract of *S. occiedntalis* may not be the same with metformin which has a known glucose lowering mechanism neither was it similar with that of insulin because there existed a significant difference in its hypoglycaemic effect as compared to that of the extract. Therefore, the mechanism of hypoglycaemic effect of the extract could be as one of the following; inhibition of α-glucosidase and α-amylase, the effects on glucose uptake and glucose transporters, enhancement of insulin secretion and/or pancreatic *β*-cells proliferation; it may also be due to inhibition of protein tyrosine phosphatase 1B activity and antioxidant activity according to reports of Rios *et al* [33] as the possible mechanisms of action of natural products in diabetes.

Pancreatic histology of normal and diabetic rats after 48 hours of alloxan administration

The pancreatic histology of the tissues showed numerous exocrine acini and islets of Langerhans. The pancreatic tissues of the normal control showed a distinctive islet of Langerhans containing numerous nuclei (plate A). At the dose of 200mg/kg and 400 mg/kg the islets of Langerhans contain fewer nuclei compare to normal control (plate B and C). There was hyperplasia of islet cells at the dose of 800 mg/kg (plate D). In the insulin treated group the pancreatic histology showed an atrophied islet of Langerhans which contain fewer nuclei (plate E). The islet of Langerhans in the metformin treated group contains few nuclei (plate F).

Table 1: The extractive value of methanol seed extract

Weight of powdered plant material (g)	Weight of extracts (g)	Percentage yield (%)
1200	40	3.33

Table 2: Preliminary Qualitative Phytochemical Screening of Methanol Seed Extract of *Senna occidentalis*

Phytochemical constituents	Results
Alkaloid	-
Anthraquinones	+
Carbohydrates	+
Cardenolides	+
Flavonoids	+
Saponins	-
Steroids	+
Tannins	+
Terpenoids	+

+ = present - = absent

Table 3: Acute toxicity study of methanol seed extract of *Senna occidentalis*

Doses of extract	Animals per group	Route of administration	Observation of death
1000 mg/kg	2	Oral	0/2
2000 mg/kg	2	Oral	0/2
4000 mg/kg	2	Oral	0/2

$LD_{50} \geq 4000$ mg/kg, 0/2 = Zero death out of the 2 animals used.

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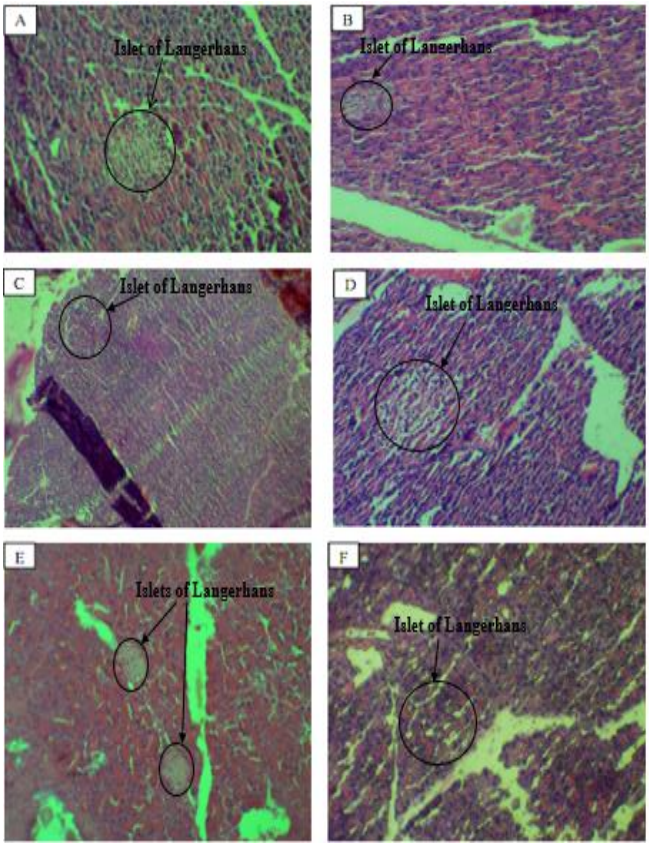
Table 4: Effect of methanol seed extract of *Senna occidentalis* on blood glucose levels in alloxan-induced diabetic rats

	Mean ± SEM (mg/dL)					
Groups	**A (mg/dL)**	**B (mg/dL)**	**3 h**	**6 h**	**12 h**	**24 h**
NC (2 mL/kg)	76.20 ± 4.27	95.80 ± 4.62	112.40 ± 3.37 (17%)$^{\uparrow}$	109.20 ± 3.18 (14%) $^{\uparrow}$	118.40 ± 2.16 (24%)$^{\uparrow}$	118.00 ± 3.65 (23%)$^{\uparrow}$
IS (0.5IU/Kg)	79.60 ± 4.68	595.40 ± 2.86	204.60 ± 101.71 (65%)	257.40 ± 110.93 (57%)	381.60 ± 134.06 (36%)	564.20 ± 35.80 (5%)
MT (50 mg/Kg)	80.00 ± 2.81	551.60 ± 19.91	583.20 ± 13.78 (6%)$^{\uparrow *}$	574.00 ± 16.03 (4%)$^{\uparrow *}$	592.80 ± 4.21 (7%)$^{\uparrow}$	597.40 ± 2.14 (8%)$^{\uparrow}$
SO (200 mg/Kg)	76.40 ± 6.50	500.80 ± 30.48	516.00 ± 47.41 (3%)$^{\uparrow *}$	546.20 ± 53.80 (9%)$^{\uparrow *}$	597.00 ± 2.32 (19%)$^{\uparrow}$	593.80 ± 3.83 (19%)$^{\uparrow}$
SO (400 mg/Kg)	64.00 ± 5.30	513.00 ± 61.23	530.00 ± 40.92 (3%)$^{\uparrow *}$	502.60 ± 44.71 (2%)	558.00 ± 25.79 (9%)$^{\uparrow}$	485.00 ± 52.15 (5%)
SO (800 mg/Kg)	90.60 ± 3.54	456.00 ± 94.91	548.60 ± 46.10 (20%)$^{\uparrow *}$	531.80 ± 67.20 (17%)$^{\uparrow *}$	440.60 ± 91.39 (3%)	361.00 ± 85. (21%)*
P-values	0.019	0.000	0.000	0.000	0.000	0.000

Values were presented as mean ± SEM, (n = 5); assessed by one-way ANOVA. Values marked with * are significantly different at $p < 0.05$ compared with the control. A (mg/dL) = blood glucose level before induction of diabetes with alloxan, B (mg/dL) = blood glucose level after 48 hours of alloxan administration (150 mg/kg), NC = normal control, IS = Insulin (standard drug control), MT = Metformin (standard drug control), SO = *Senna occidentalis*, p-value < 0.05 = significant



Plates A-F: A cross sectional view of pancreatic tissue slices from alloxan induced diabetic rats treated with methanol seed extract of *S. occidentalis* at doses of (B) 200 mg/kg, (C) 400 mg/kg, (D) 800 mg/kg (E) Insulin 0.5 IU/kg and Metformin 50 mg/kg body weight compared with the normal control (A) treated with distilled water (Magnification, x 1 00).
In plates;
A- Showed islets of Langerhans containing numerous nuclei and numerous exocrine acini
B- C: Showed islets of Langerhans with less nuclei, numerous exocrine acini, vascular and connective
D- Showed islets of Langerhans and hyperplasia of islet cells
E- Showed islets of Langerhans containing few nuclei, numerous exocrine acini and collagen fibres
F- Showed hyperplasia of islet cells, numerous exocrine acini and collagen fibre

The normal control group has distinctive islet of Langerhans with normal histological architecture as compared to the alloxan induced diabetic groups which contain less nuclei compare to the normal control. This showed that alloxan was able to destroy the beta cells of the pancreas after 48 hours of administration. Also there was an atrophy of islet of Langerhans in the insulin treated group in plate E. This may suggest that the extract might have repairing or regenerative effect on the islet of Langerhans since they contain more nuclei as compared to the insulin and metformin treated groups. This may corroborate the claim of Laxmi *et al* [34] which reported that the plant extract has regenerative effect on the islet of Langerhans.

Conclusion

The study revealed that the methanol seed extract of *Senna occidentalis* contained many phytochemical constituents such as carbohydrates, cardenolites, flavonoids, glycosides, tannins and terpenoids which could be responsible for its hypoglycaemic effect. The extract showed glucose lowering effects in rats, with the highest effect at the dose of 800mg/kg. Furthermore, the extract is relatively non-toxic on acute exposure with the lethal dose greater than 4000 mg/kg body weight. The pancreatic histology showed that alloxan destroyed the islets of Langerhans in the diabetic groups.

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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