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ANTIOXIDANT AND ANTIHYPERGLYCEMIC PROPERTIES OF *STERCULIA SETIGERA* ROOT BARK EXTRACT ON ALLOXAN MONOHYDRATE-INDUCED WISTAR RATS

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Abstract

Diabetes has racked serious havoc on human lives, and efforts to find a cure/remedy have extended to the use of traditional materials, especially from the plant kingdom. Therefore, the present study investigated the antioxidant and antihyperglycemic properties of *S. setigera* root bark. The plant material was obtained from the wild and gave a good yield of extract (25.12%) through cold maceration. Thirty Wistar rats weighing between 70 and 140 g were used in the antihyperglycemic study. The animals were divided into six groups of five rats per group. 25 rats were made diabetic through intraperitoneal (i.p) injection with 120 mg/kg of 150 mg alloxan monohydrate constituted in normal saline. Three groups of diabetic rats were treated oragastically with the extract 300 mg/kg, 750 mg/kg, and 1000 mg/kg). One group was left untreated and served as the diabetic control; the other was treated with the standard drug glibenclimide. The results showed a significant ($p > 0.005$) reduction in blood glucose level compared with the diabetic control. The extract was also active against ABTS and DPPH oxidants and reversed lipid parameters associated with diabetes. This indicated that the extract could be a potent drug source for the management of diabetes mellitus.

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INTRODUCTION

1.1 Background Information

Diabetes is a multifaceted disorder characterized by a rise in fasting blood glucose levels due to relative or absolute insulin deficiency (Sicree *et al.* 2006). This condition impairs metabolic activities and generates active molecules (oxidants); thus, when not properly managed, it could cause complications such as liver, kidney, and pancreatic cell damage, hypertension, stroke, blindness, and death (Piero *et al*. 2014). The common symptoms of diabetes mellitus include: increased thirst, frequent urination, extreme hunger, weight loss, and fatigue (Nisha, 2016).

Plants are a great source of medicine with the notable advantage of no or minimal side effects when consumed as drugs compared with synthetic chemotherapy regimens (Venkata *et al.* 2016). This motivated research in the plant kingdom for new drugs that would be devoid of the inherent disadvantage of chemotherapy regimens.

Sterculia setigera (*S. setigera*) Del is a forest woody tree that belongs to the Malvaceae (formerly Sterculiaceae) family, with more than one thousand species growing under different ecological and soil conditions. The plant is known by different indigenous cultural communities in Nigeria: Hausa (kukuki), Fulani (boboli), Yoruba (Ose-awere), and Tiv (Kumenduul). The seeds have yellow aril, and the tree is found in open Savannahwoodlands, near stony hills (Tor-Anyiin *et al*. 2011). Found in abundance in countries in West and East Africa it is a deciduous tree with solid roots. The leaves have a triangular lobe shape, and the fruits are follicles containing a big seed, which are black with a yellow cap (Atakpama *et al*. 2012).

The S. setigera plant is used in traditional medicine by various indigenous communities. The Yoruba people of Southern Nigeria used a mixture prepared from fruits and seeds as dermatoid and a root bark decoction to treat diabetes (Adjanohoun *et al*. 1991). The Tiv and Igedes tribes (North Central Nigeria) used stem bark to treat diarrhea and dysentery, respectively (Igoli *et al*. 2005). The leaves and stem bark decoction is used to treat malaria, rickets, asthma, bronchitis, wounds, fever, toothache, gingivitis, and sores (Belem *et al*. 2007; Betti *et al*. 2011; Atakpama *et al*. 2012). In Senegal, *S. setigera* gum is used in human nutrition, medicine preparation, cosmetics, and soft drinks (Atakpama *et al*. 2012).

There is no documented drug yet for the cure of diabetes (Kelly, 2023); treatment relies on management styles (Mahmoud*et al*. 2014); hence, the need to continue the search for a cure, especially from the plant kingdom, is important and necessary. Other parts of *the S. setigera* plant have been exploited for their phytochemical, nutritional, antimicrobial, antioxidant, and antidibetic potentials (Tor-Anyiin *et al*. 2011; Tchoubou *et al*. 2023). However, the potency of its root as a remedy for diabetes has not been investigated. Therefore, this study investigated the antidiabetic effect, antioxidant, and lipid profile of the root extract of *S. setigera* on diabetic Wistar rats.

MATERIALS AND METHODS

2.1 Materials

A centrifuge (Denley B5400, England) and a Jenway 6310 UV-visible spectrophotometer were used. A rotary evaporator, Glibenclamide (5 mg/kg), and normal saline were purchased from a pharmacy. Accu-Check Active Glucometer (Roche Diabetes Care GmbH Stand Hofer Strasse 11668305 Mannheim, Germany), Absolute ethanol 99.9% (JBH); 1, 1-diphenyl-2-picrylhydrazyl radical, DPPH, and trichloroacetic acid were obtained from Sigma-Aldrich, and anhydrous ferric chloride, potassium ferricyanide, anhydrous sodium carbonate, potassium persulphate ($K_2S_2O_8$), and ascorbic acid were obtained from BDH Chemical Laboratory, England, UK. All chemicals were of analytical grade.

2.2 Collection of plants

The stem bark of *Sterculia setigera* was obtained from the wild at Mbalumun-Nanev in Kwande local government area, Benue state, Nigeria. The plant was authenticated by Joseph Waya of the Botany Department, Benue State University, Makurdi, Nigeria, and the specimen's Voucher No: 232 was deposited at the Herbarium unit.

2.3 Experimental Animals

Thirty Wistar rats weighing between 70 and 140 g were used in this study. Animals were obtained from the animal holding unit, College of Health Sciences Benue State University Makurdi. The animals were housed in wooden cages and acclimatized for 2 weeks in the animal house department of the chemical sciences University of Mkar. They were maintained under standard conditions (room temperature 28^{o}C±3^{o}C, humidity 35-60%, light and dark period, 12/12 h. All animals had a regular supply of clean drinking water and food.

3.1 Methods

3.1.1 Preparation and extraction of the plant extract

The dried root bark of *S. setigera* was crushed to powder using a mortar and pestle. The crushed plant sample (200 g) was soaked in 96.90% alcohol (1 L) and allowed to stand for 72 h with occasional shaking at different intervals. The extract was decanted and filtered using the Whatman No. 1 filter paper. The extract was then concentrated using a rotaryevaporator at 40^{o}C and evaporated to dryness using a water bath. The crude extract was kept in the refrigerator for experimental studies.

3.1.2 Determination of extract yield

The percentage yield of the ethanol root bark extract of *S. setigera was* calculated using the following formula:

$$\text{Percentage yield} = \frac{\text{Weight of concentrated extract}}{\text{Weight of dried root powder}} \times 100$$

3.1.3 Determination of the medial lethal dose (LD_{50}) of the plant extract

The LD_{50} of the extract was determined using the modified method of Lorke (1983) as described in Idrish and Nenge (2021). Nine albino rats (71-106 g) of either sex were divided into three groups of three rats each. They were first orally administered with *S. setigera* root bark extract. The extract was dissolved in normal saline and administered at doses of 500, 1000, and 2000 mg/kg body weight in the first phase. Gross behavior and mortality were monitored for 24 h.In the second phase, another set of nine rats were administered orally at doses of 2500, 3500, and 5000 mg/kg and monitored for 24 h for mortality and signs of toxicity. The LD_{50} was calculated as follows:

LD_{50}= $(a \times b)^{1/2}$ where a is the highest dose that gave no mortality and b is the least dose that produced mortality.

3.2 Experimental Protocol and Design of the Experiments

Thirty rats were assigned into six groups of five rats each for the diabetic study. The experimental protocol was approved by the Institutional Animals Ethics Committee (IAEC) and animal care was performed in accordance with the guidelines of the European convention for the protection of vertebrate animals and other scientific purposes ETS-124 (European Treaty Series, 2005).

3.3 Induction of Diabetes Mellitus

The rats were fasted for 12 hours. Diabetes was induced by intraperitoneal injection of 120 mg/kg body weight alloxan reconstituted in normal saline. Forty-eight hours later, diabetes was confirmed in rats with afasting blood glucose level (FBGL) of 230 mg/dL (Cennet & Ebubekir, 2010). FBGL was estimated using a one-touch Accu-check glucometer with blood obtained from the tail vein of the rats.

3.4 Treatment of Diabetic Rats

The rats were divided into six groups of five rats each with their tails marked to facilitate identification. The rats in the various groups were treated with drugs, except for groups A and B (which served as normal and diabetes control and were fed with feed and water only throughout the experimental period). Rats in groups C, D, and E were treated daily with the root bark extract of *S. setigera* at 300, 500, and 750 mg/kg weight doses, respectively, for 7days. Group F was also treated with the standard drug (Glibenclamide 5 mg/kg) for 7 days, as shown in Table 1. The drugs were orally administered.

Table 1: Experimental Design and Treatment Schedule for the Anti-hyperglycemic Study of *Sterculia setigera* Extract.

Group	Number of animals	Treatment	Dosage
A. Normal Control	5	Normal saline	-
B. Diabetic control	5	Normal saline	-
C. Diabetic treated	5	*S. setigera*	300 mg/kg
D. Diabetic treated	5	*S. setigera*	700 mg/kg
E. Diabetic treated	5	*S. setigera*	1000 mg/kg
F. Diabetic treated	5	The standard drug (glibenclamide)	5 mg/kg

3.5 Collection and Preparation of Serum Samples for Lipid Profile Analysis

Blood samples were collected from overnight fasted animals via cardiac puncture into plain tubes and were allowed to clot. The serum was separated by centrifugation using a Denley BS400 centrifuge (England) at 3000 rpm for 10 min. The serum was collected and then assayed for lipid profile.

3.5.1 Lipid profile assay

This was determined spectrophotometrically using enzymatic colorimetric assay kits (Randox, Northen Ireland). The following parameters were determined: serum total cholesterol**(**Stein, 1987); serum triglyceride **(**Tietz, 1990); serum high-density lipoprotein cholesterol (HDL-c) (the serum level was measured by the method of Wacnic& Albert, 1978). Determination of serum low-density lipoprotein cholesterol (LDL-C) levels (the serum level was measured according to the protocol of Friedewald *et al*. 1972).

3.6 Antioxidant Assay

This was performed to assess the free radical scavenging property of the extract. The assayed results were DPPH Radical Scavenging Activity as described by Blois (1958) andABTS Radical Scavenging ActivityDetermined according to Re *et al*. (1999).

3.7 Statistical Analysis of Data

The data were analyzed using the Graph Pad software. Glucose concentration results are expressed as mean ± Standard Error of the mean (SEM). The mean and SEM of the treatment groups were generated using the analysis of variance test. Significant differences between and within the treatment groups were considered significant at set value $p < 0.05$ using Dunnett's multiple comparison tests with appropriate control.

RESULTS AND DISCUSSION

4.1 Results

4.1.1 Percent yield

25.12% of the extract recovered from the root bark sample.

4.1.2 Acute Toxicity Study

Sterculia setigera root bark showed neither mortality nor sign of toxicity, even at doses as high as 5000 mg/kg body weight.

4.1.3 Phytochemical Screening Results

Table 2: Qualitative and quantitative phytochemical screening of *S. setigera* Root bark extract

Class	Qualitative	Quantitative
Alkaloids	+	11.08 ± 0.99 %
Carbohydrate glycosides	+	ND
Saponnins	+	28.00 ± 4.00 %
Phytosterols	+	ND
Phenols	+	4.75 ± 0.30 mg/g
Tannins	+	0.26 ±1.50 mg/100g
Flavonoids	+	8.27 ± 0.46
Protein and Amino acids	+	ND
Diterpenes	+	ND

Values are expressed as mean ± SD(n = 3); **+ =** present**,** ND **=** not determined

4.1.4 Antioxidant results

Table 3: Antioxidant properties of *S. setigera* root bark extracts

Concentration, µg/mL	ABTS Assay		DPPH Assay	
	Sterculia setigera	Vitamin C standard	*Sterculia setigera*	Vitamin C standard
25	3.08±0.10[b]	33.16±0.02	3.58±0.02[b]	29.29±0.01
50	17.90±0.01[b]	55.39±0.14	21.32±0.01[b]	62.43±0.02
75	11.16±0.35[b]	80.90±0.05	36.09±0.02[b]	80.27±0.00
150	43.02±0.05[b]	88.10±0.05	65.37±0.03[a]	86.66±0.01
300	73.52±0.09[a]	95.44±0.00	82.90±0.00[a]	92.08±0.00

Values are expressed as mean ± SEM; b = significant, a = not significant at $p < 0.05$ compared with standard (Vitamin C).

4.1.5 Results of antidiabetics

Table 4: Effect of *S. setigera* root extract and standard drug on blood glucose level (mg/dl) in alloxan-induced diabetic rats

Group	Day0	Day1	Day2	Day3	Day4	Day5	Day6	Day7
A	78.75±4.89	552.50±9.25	77.25±4.66	76.50±4.03	81.00±2.12	90.00±3.72	89.21±2.05	90.01±3.75
B	334.25±17.55*	379.00±9.42*	420.75±20.13*	450.75±17.67*	447.00±19.66*	515.00±8.53*	516.23±10.50*	514.00±7.53*
C	536.36±12.20	416.91±4560^{b}	488.22 ±21.70^{b}	517.41±20.14	493.98±26.64	465.55±35.77^{a}	465.19±33	426.27±43.59^{a}
D	473.49±37.40^{b}	411.51±63.87^{b}	414.76±58.75^{ab}	440.00±69.06^{ab}	427.02±68.91^{a}	395.66±73.83^{a}	377.29±46.55^{a}	372.24±23.17^{a}
E	493.33±31.38^{b}	427.71±54.57^{b}	509.18±22.02	532.95±21.29	491.51±36.84	425.94±45.74^{a}	425.94±45.74^{a}	442.88±40.44^{a}
F	552.50±9.25	568.75±7.57	501.12±13.65	469.75±19.88	419.67±15.60^{a}	369.00±10.68^{a}	342.58±30.05^{a}	294.75±4.2^{a}

Results expressed in mean±SEM, n=5, *= significant at $p < 0.05$ compared with A (normal control); a = significant compared with diabetic control; b = significant compared with standard drug. A = Normal control/Positive control; B = Diabetic control; C = Diabetic treatment (300 mg/kg); D = Diabetic treatment (500 mg/kg); E = Diabetic treatment (750 mg/kg); F = Standard drug (Glibenclimide, 5 mg/kg) .

4.1.6 Lipid profile assays

Table 5: Effect of *S. setigera* ethanol root extraction the lipid profile of alloxan-induced diabetic rats

Groups	Cholesterol, mg/dL	Triglyceride, mg/dL	HDL, mg/dL	LDL, mg/Dl
Positive control	51.71±0.81^{b}	178.78±0.51^{b}	63.12±0.60^{b}	77.31±1.91^{b}
Diabetic control	95.48±0.56^{c}	190.16±4.08^{c}	56.81±0.10	87.50±0.55^{c}
Diabetic treatment (300 mg/kg)	65.28±8.75	132.40±14.71^{bc}	52.99±2.03	78.59±6.23^{b}
Diabetic treatment (500 mg/kg)	90.95±13.80	81.04±12.58^{bc}	43.35±4.91	48.02±8.53^{bc}
Diabetic treatment (750 mg/kg)	35.67±12.24	92.00±0.71^{bc}	38.04±1.96	76.30±13.84^{bc}
Standard drug (5 mg/kg)	54.12±0.23^{b}	170.20±0.76^{bc}	67.37±0.28^{bc}	69.40±0.24^{bc}

Results are expressed as mean ± SEM (n = 5) and significant at $p < 0.05$; a = significant compared with the standard drug; b = significant compared with the negative control; c = significant compared with the positive control.

4.2 Discussion

Phytochemical analysis of *S. setigera* root bark extract revealed the presence of alkaloids, flavonoids, saponins, tannins, cardiac glycosides, phenols, and phytosterols (Table 2). The extract was low in saponins (28.00 ± 4.00 %) but rich in phenols (37.5 ± 0.30 mg/g), which is in line with the findings of Tchoucbou*et al.,* (2023), who reported a high quantity of polyphenol (80.77 ± .12 gEAG/100 g) but a low quantity of saponin (13.01 ± .04 gEG/100 g) in the leaves of the same plant. These classes of phytochemicals have antihyperglycemic properties (Switi *et al*., 2014). Previous studies reported the inhibition effect of glycosides on carbohydrates metabolic enzymes (such α-amylase) and its ability to raise the level of serum insulin. In addition to their antioxidant properties, flavonoids could reduce glucose absorption (Idris and Nenge, 2021). Alkaloids have a stimulatory action on insulin secretion (Ujah *et al*., 2015). Thus, the improved glycemic level of the experimental rats

(Table 4) recorded from this extract could be attributed to the actions of these phytochemicals contained therein.

Acute toxicity (LD_{50}) of the *root* extract did not cause death even at a dose of 5000 mg/kg, indicating that the plant was well tolerated by the rats.

The measurement and use of plant antioxidants for scientific and industrial purposes are of increasing interest Maury *et al*., 2020). These compounds (such as phenolics and alkaloids) protect cells against the damaging effects of reactive oxygen species (ROS) (Frie, 1995; Liu, 2003) and are relatively safe and economical compared with many synthetic antioxidants that are believed to promote carcinogenesis (Suhaj, 2006; Tadhani *et al.,* 2007). These compounds made up the list of phytochemicals of *S. setigera* root bark extract under investigation. The extract showed remarkable ABTS and DPPH antioxidant inhibitory activity in a concentration-dependent manner (Table 3). The value was significantly lower at 75 µg/ml (11.16±0.35) compared with the standard (80.90±0.05) in the ABTS assay. However, the extract was more active against the DPPH agent, as evidenced by a higher inhibition percentage at various concentrations (25-300 µg/ml) compared to vitamin C (used as a standard). These results agreed with of Tchoubou *et al.*, (2023) on the leaf extract.

Alloxan partially damages the beta cells in the pancreas, thus hampering insulin synthesis. This principle was used to effectively induce hyperglycemia in the experimental rats through intraperitoneal (i.p.) administration of 120 mg/kg alloxan (Table 4). However, upon administration with *S. setigera* root extract, their glucose levels were significantly ($p \leq 0.05$) lowered within 7 days of treatment. This result indicated that the root extract possesses active principles capable of regenerating the beta cells to restore insulin production.

It has been established that complications arose from diabetes due to reactive molecules released from abnormal biochemical reactions in the cells (Otang *et al*., 2012). Thus, the antihperglycemic effect of the extract on the experimental rats could be attributed to the presence and actions/activities of these active phytochemicals (flavonids, alkaloids, saponins, etc.) with antioxidant properties (Manisha *et al*., 2017) contained in the plant.

Findings in the existing research agreed with previous report (Akah *et al.*, 2009) that diabetes mellitus development usually alters lipid profile parameters (Table 5). There was a marked increase in blood total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-c), and high-density lipoprotein (HDL-c).Excess TC and TG can increase blood lipoprotein levels and promote atherosclerosis formation (Hasty *et al*., 2001), which is a, risk factor for cardiovascular complications in patients with diabetes.However, upon treatment of the diabetic rats with *S. setigera* root extract, these conditions were reversed (Table 5) at all doses compared with the diabetic control.

5.0 CONCLUSION

Plants are sources of biomolecules vital to other living organisms, especially humans, where they are used for nutritional, economic, and health benefits. In the present study, *S. setigera* root extract was investigated for its antioxidant and antihyperglycemic potentials. The results indicated that the root extract contains phytochemicals with remarkable antioxidant and antihyperglycemic properties; therefore, it could be a potent agent for the management of diabetes mellitus. Meanwhile, studies on the extract targeted at isolating bioactive compounds responsible for these properties are ongoing.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare. The study was conducted in harmony with the authors.

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