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Antidiabetic Activities of the Aqueous Root Bark and Flower Extracts of *Terminalia catappa* on Streptozotocin - Induced Diabetes in Male Wister Rats

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Authors' contributions

This work was carried out in collaboration between all authors. Authors CJP and LDC designed the study, wrote the protocol, managed the literature search and wrote the first draft of the manuscript. Author CJP performed the statistical analysis. Authors IYL and AJC managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Diabetes mellitus is a disease associated with the increase in Blood glucose level caused by the abnormalities of glucose receptors in the uptake of glucose or total destruction of the β pancreatic cell, with approximately 366 millions of people worldwide diagnosed with the disease in 2011. The aim of this study is to determine the antidiabetic activities of the aqueous Root bark and Flower extracts of *Terminalia catappa* on streptozotocin induced diabetic rats. The experiment consist of 25 male albino wister rats weighting about 250 – 300 g/bw divided into five groups of five rats each. Diabetic was induced by a single intraperitorial injection of streptozotocin (55 mg/kg). The aqueous Root bark and Flower extracts of *Terminalia catappa* (200 mg/kg) were administered orally for

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14 days, after which the blood glucose, Albumin, Total protein, electrolytes, antioxidants, haematological parameters were investigated. The results shows that diabetic control group have a significant ($p<0.05$) increase in the levels of glucose and bilirubin while a significant ($p<0.05$) decrease in body weight, albumin, total protein, electrolytes, haematological parameters and antioxidants when compared to normal control group. Oral administration of 200 mg/kg of aqueous Root bark and Flower extracts of *Terminalia catappa* for 14days to group C and D diabetes rats resulted in significant ($p<0.05$) decrease in blood glucose, total cholesterol, triglyceride, LDL, serum liver marker enzyme, kidney markers and bilirubin while a significant ($p<0.05$) increase in albumin, total protein, electrolyte, some haematological parameters and antioxidants. Results of the study indicates that aqueous Root bark and Flower extracts of *Terminalia catappa* possesses hypoglycemic and protective effects against ROS caused by streptozotocin induced diabetics rats. In Conclusion, the aqueous Root bark and Flower extracts of *Terminalia catappa* can be used in the management of diabetes mellitus at the said dose.

Keywords: Terminalia catappa; aqueous extract; streptozotocin; diabetics; hypoglycemic potentials.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by deficiency in production of insulin by the pancreas or by the ineffectiveness of the insulin produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerve. The two most common forms of diabetes are type I diabetes (T1D, known as insulin dependent diabetes IDDM) and type II diabetes (T2D, known as non-insulin-dependent diabetes NIDDM) [1]. Both are caused by a combination of genetic and environmental risk factors. However, there are other rare forms of diabetes that are directly inherited. These include Gestational diabetes (GD), maturity onset diabetes in the young (MODY), and diabetes due to mutations in mitochondrial DNA etc. [2] The number of diabetic cases has increased significantly worldwide in the last decade and it is the fifth leading cause of death worldwide, it has been noted that one in twenty adult deaths in developing countries is diabetes related [3]. [4] reported that Nigeria has the greatest number of people living with diabetes in Africa and its complications impose significant economic consequences on individuals, families, health system and countries. Medicinal plants have been found to contain bioactive compounds called phytochemicals or secondary metabolites that can be used to protect humans against diseases [5]. Some important groups of these phytochemicals (secondary metabolites) are involved in many in-vitro studies and assessment of haematological parameters, antioxidant activities, antidiabetic effect, anti-microbial effect and analgesic effect [6]. *Terminalia catappa Linn.* (Combretaceae) also known as tropical almond in Asia, umbrella tree in some part of Nigeria is a medium size deciduous medicinal plant. *Terminalia catappa Linn*. is known for its nutritional fruit and possesses medicinal benefits as well. All parts of the plant contains secondary metabolites that are used in traditional medicine such as the management of sickle cell disorders, cancer, rheumatism, diarrhea, dysentery, gonorrhea and stomach cramps, sexual dysfunction, diaphoretic, antidiabetic, anti-indigestion, anticlastogenic, antioxidant, antibacterial, stomatitis, skin diseases, arthritis, headache, colic and itching [7]. Other *Terminalia* species have notable ethno-medicinal utility. For example, *T. chebula* is used in the treatment of fever, cough, asthma, urinary diseases, piles and worms and *T. belerica* is used for the treatment of fever, cough, asthma, urinary diseases, piles, chronic diarrhea, dysentery, flatulence, vomiting, colic, enlarged spleen and liver [8]. The study seeks to investigate the effect of aqueous root bark and flower extracts of *Terminalia catappa* on streptozotocin induced diabetic rats and to provide some scientific basis if any, for the use of *Terminalia catappa* as antidiabetic agent.

2. MATERIALS AND METHODS

2.1 Preparation and Processing of Samples

Terminalia catappa root bark and flower were collected within Jos area of plateau state Nigeria in December 2015 and identified at the department of plant science, university of Jos with the identification number of UJH16000249. The *Terminalia catappa* root bark and flowers are shade dry and the dried root bark and flower of *Terminalia catappa* were pounded using pestle

and mortar. 1.0 kg and 55.0g respectively of the powdered were poured into 1000 mL and 550 mL of distilled water respectively and placed on a hot plate. Mixture was heated for 20 minutes, allowed to cool and sieved with Whatman No.1 filter paper. Filtrate was then concentrated at 40℃ in oven and stored in an air tight container; the dried extract is then store in a desiccator which was later reconstituted to give the required dose of 200 mg/kg body weight [9].

2.2 Experimental Animals

Apparently healthy male albino wistar rats of average weight 250 g-300 g were obtained from the Jos University's Animal house. Twenty five (25) wistar Male rats were randomly distributed into five groups of five rats each and were fed with standard commercial feeds (vital feeds, Nigeria).The animals were handle and care based on the approved guidelines of institutional animal ethical committee.

2.3 Induction of Diabetes

Diabetes was induced in male wistar albino rats (250–300 g body weight) by intraperitoneal administration of Streptozotocin (STZ) (single dose of 55 mg/kg body weight) dissolved in freshly prepared 0.01 M citrate buffer, pH 4.5 [10]. After 48 h rats with marked hyperglycemia (fasting blood glucose >140 mg/dl) were selected and used for the study. All the animals were allowed free access to water and diet and maintained at room temperature in plastic cages [11].

2.4 Experimental Design

The rats are divided into five groups comprising of five animals in each group as follows:-

Group A: Normal control of 5 rats feed with standard diet for about 14 days.

Group B: Diabetic control rats (streptozotocin 55 mg/kg).

Group C: Diabetic rats treated with aqueous root extract of *Terminalia catappa* at 200 mg/kg.

Group D: Diabetic rats treated with aqueous flower extract of *Terminalia catappa* at 200 mg/kg.

Group E: Diabetic rats treated with glibenclimide at 2.5 mg/kg.

The administrations were done for 14 days. On day 14, bloods are collected by cardiac puncture under mild ether anesthesia from overnight fasted rats and fasting blood sugar are estimated.

2.5 Sample Collection

On the 14th day, the rats were anesthetised with diethyl ether, the neck area was quickly cleared. Venous blood was thus collected into a plain sample container and allowed to cloth and the serum was clearly remove and used for the assays. Blood sample was separately collected into an anti-coagulant and were used for haematological assay.

2.6 Biochemical Estimation

Glucose in serum was determined by the method of Trinder [12], Total Protein content of the serum was determined by using biuret method [13], Albumin level was determined as describe by Grant and Kacchman [14], Billirubin was determined using Colormetric method based on that described by Jendrassik and Grorf [15]. Electrolyte was determined using Flame photometer. Haematological parameters: Red blood cells (RBC), packed cell volume (PCV), haemoglobin concentration (Hb), white blood cell count (WBC) and its differential counts (neutrophil, eosinophil, basophil, lymphocyte and monocyte), were determined by Haematology analyser using the method of Dacie and Lewis [16]. The method by Beutle et al. [17] was used to estimate reduced glutathione (GSH), Catalase activity was determined according to the method described Sinha [18], The level of SOD activity was determined by the method described by Mistra and Fridovich [19], Glutathione-S-transferase activity was determined according to Habig [20], Lipid peroxidation was determined by measuring the thiobarbituric acid reactive substance as described by Rice and Evans [21].

2.7 Statistical Analysis

The result values were expressed as mean ± standard deviation. Analysis of variance (ANOVA) for comparison is used. Differences are considered significant when values of $p \leq 0.05$.

3. RESULTS AND DISCUSSION

Treatment of diabetes with the agents devoid of any side effects is still a challenge to the medical system. This has led to an increase in the

demand for natural products with hypoglycemic activity and fewer side effects. Prolonged exposure to hyperglycemia is now recognized as the primary causal factor in the pathogenesis of diabetic complications as well as induces a large number of alterations in vascular tissue that potentially promote or accelerated atherosclerosis [9]. The Aqueous Root bark and flower extracts of *Terminalia catappa* exhibited antidiabetic properties at 200 mg/kg. The results supported the claims by Traditional healers as folklore medicine for the treatment of diabetes mellitus. In the present study, diabetes induced in the experimental animal by Streptozotocin Produced significant decrease in body weight of the diabetic rats. The destruction of the pancreas by Streptozotocin results in the utilization of non-carbohydrate moieties such as protein for the synthesis of glucose. The loss of structural proteins in increased gluconeogenesis together with increased lipolysis and increased synthesis of ketone bodies results in severe weight loss. However, administration of the aqueous root bark and flower extracts of *Terminalia catappa* was found to be effective in ameliorating the weight loss observed in the diabetic rats compared with the control rats [22].

The aqueous root bark and flower extracts of *Terminalia catappa* significantly ($p<0.05$) reduced the blood glucose levels of the Diabetic treated groups when compared with the Diabetes control group. Previous work has indicated that plant extracts possess hypoglycemic properties, possible insulin release stimulatory effects and uptake of peripheral glucose, which in turn reversed streptozotocin induced hyperglycemia [1]. Other studies also reported that *Phaseolus vulgaris L* [23], *Vitex doniana* [9], *Moringa Oleifera* seed [24] has significant antidiabetic activities.

Albumin is a major protein of human plasma and represents about 25% of total hepatic protein synthesis and half its secreted proteins. Its synthesis is depressed in variety of diseases, particularly those of the liver. Table 2 shows that there was a significant decrease in the concentration of albumin and total serum protein of the diabetic control group when compared with the control and the treated groups. This observation may be attributed to numerous effects of hyperglycemia in the diabetic group. Hyperglycemia increases gluconeogenesis which leads to excess protein breakdown as well as excess loss of nitrogen resulting to negative nitrogen balance [25]. A decline in total protein level in diabetic rats can be attributed to inhibition of oxidative phosphorylation which leads to decrease in protein synthesis, increase in catabolic processes and reduction in protein absorption [26]. Also, decrease in the total protein of diabetic control, might may due to decrease due to microproteinurea which are important clinical markers of diabetic nephropathy [27], and/or may be due to increased protein catabolism as a result of insulin deficiency from free radical generation due to streptozotocin induction, since it has been established that insulin stimulates the incorporation of amino acids into protein [28]. The results showed that administration of the root bark and flower extracts of *Terminalia catappa* caused a remarkable increase in the serum total protein and albumin levels in the diabetic treated groups. These observations may be due to the presence of some compounds which help in provision of a reserved store of protein [29] Bilirubin is an endogenous compound that can be toxic, especially in neonates. However, it has recently been recognized that unconjugated bilirubin (UCB) exerts a strong anti-oxidant activity, and that mild hyperbilirubinaemia might have positive health effects. Bilirubin is the ultimate breakdown product of haemoglobin and serves as a diagnostic marker of liver and blood disorders. It has a complex metabolism, which is important in relation to several processes involved in drug metabolism [30]. Table 3 shows the concentration of Total Bilirubin and Direct Bilirubin found to be significantly ($p<0.05$) increased in Group B diabetic control rats when compared to Group A normal control rats. When Root bark and Flowers was administered to Group C and D rats, the above parameters were reversed.

Derangement of water and electrolyte balance may occur in subjects with diabetes mellitus, resulting from insulin deficiency, hyperglycemia, and hyperketonemia. The kidneys work to keep the electrolyte concentrations in the blood constant despite changes in the body. So plasma electrolyte values are usually indicative of the renal functions or dysfunctions. The present study showed a significant reduction in serum Na^+, Ca^{2+}, HCO_3^- and Cl^- levels and an elevation in serum PO_4^{3-} and K^+ in the Diabetic group were observed [31]. This result was consistent with those reported by previous studies. Treatment with aqueous root bark and flower extracts of *Terminalia catappa* improved the abnormalities in serum electrolyte concentrations

caused by streptozotocin induced diabetes. This result is an indication of the ability of aqueous root bark and flower extracts of *Terminalia catappa* to improve on the compromise of the kidneys and restore both acid-base balance and renal functions in the diabetes rats.

Fig. 1. Showing *Terminalia catappa* plant

Table 1. Effect of aqueous root bark and flower extracts *Terminalia catappa* on body weight of both normal and streptozotocin induced diabetic rats

Groups	Weight variation (g)		
	Final	Initial	Difference
Normal control	324.40±35.89	266.80±39.96	58.00±9.49
Diabetic control	199.40±42.05	251.00±38.98	-52.60±6.58
Diabetic treated RB	227.20±16.32	260.60±12.12	-33.40±4.34
Diabetic treated F	233.00±16.14	259.80±17.57	-26.80±5.07
Glibenclimide	250.60±23.29	273.60±22.46	-23.60±14.59

Values are expressed as Mean ± SD, n= 5 for each group

Table 2. Effect of aqueous root bark and flower extract of *Terminalia catappa* on blood glucose, protein and albumin of both normal and streptozotocin induced diabetic rats

Group	Treatment	Glucose (mmol/L)	Protein (g/L)	Albumin (g/L)
A	Normal control	3.92±0.32	77.89±0.91	38.36 ±0.50
B	Diabetic control	19.06±0.57[a]	59.46±0.12[a]	28.36±0.60[a]
C	Diabetic treated RB	8.18 ±0.14[ab]	75.51±1.26[ab]	36.10±1.05[ab]
D	Diabetic treated F	10.04±0.14[ab]	70.71± 0.97[ab]	31.27±0.71[ab]
E	Glibenclimide	9.37±0.37[ab]	74.93±0.93[ab]	37.68±0.62[ab]

Values are expressed as Mean ± SD, n= 5 for each group.
[a]Values are significantly different when compared with normal control (p<0.05).
[b]Values are significantly different when compared with diabetic control (p<0.05).
RB = Root bark; F = Flower

Table 3. Effect of aqueous root bark and flower extracts of *Terminalia catappa* extracts on total bilirubin and direct bilirubin of both normal and streptozotocin induced diabetic rats

Group	Treatment	Total bilirubin (µmol/L)	Direct bilirubin (µmol/L)
A	Normal control	8.06 ±0.64	3.94± 0.26
B	Diabetic control	29.70±0.93[a]	10.41±0.41[a]
C	Diabetic treated RB	14.46 ±0.77[ab]	5.46±0.33[ab]
D	Diabetic treated F	25.69±0.52[ab]	9.60±1.29[ab]
E	Glibenclimide	15.21±0.74[ab]	5.61±0.44[ab]

Values are expressed as Mean ± SD, n= 5 for each group.
[a]Values are significantly different when compared with normal control (p<0.05)
[b]Values are significantly different when compared with diabetic control (p<0.05)

Table 4. Effect of aqueous root bark and flower extracts of *Terminalia catappa* extracts on electrolyte of both normal and streptozotocin induced diabetic rats

Parameter treated	(mmol/L)				
	A Normal control	**B Diabetic control**	**C Diabetic treated RB**	**D Diabetic treated F**	**E Glibenclimide**
Sodium (Na^+)	147.20±3.96	133.20 ±1.30[a]	141.20±1.30[ab]	137.80±1.92[ab]	138.20±0.84[ab]
Potassium (K^+)	3.73±0.02	5.81±0.08[a]	4.27±0.36[ab]	18±0.034[ab]	4.73±0.06[ab]
Chloride (Cl^-)	125.40±16.99	102.80±0.84[a]	11.20±1.3[ab]	108.0±1.92[ab]	107.60±1.14[ab]
Biocarbonate ($HCO3^-$)	24.20±0.84	17.20±0.84[a]	23.60±0.89[ab]	19.60±1.82[ab]	21.80±0.84[ab]
Phosphate ($PO43^-$)	1.13±0.01	2.05±0.24[a]	1.20±0.86[ab]	1.62± 0.20[ab]	1.38±0.10[ab]
Calcium (Ca2+)	2.46±0.01	1.62±0.18[a]	2.13± 0.14[ab]	1.91±0.09[ab]	1.90±0.08[ab]

Values are expressed as Mean ± SD, n= 5 for each group.

[a]*Values are significantly different when compared with normal control (p<0.05)*

[b]*Values are significantly different when compared with diabetic control (p<0.05)*

Table 5. Effect of aqueous root bark and flower extracts of *Terminalia catappa* extracts on haematological parameters of both normal and streptozotocin induced diabetic rats

Parameter treated	(mmol/L)				
	A Normal control	**B Diabetic control**	**C Diabetic treated RB**	**D Diabetic treated F**	**E Glibenclimide**
PCV (%)	47.80 ±0.45	31.20±2.17[a]	38.40±1.14[ab]	37.60±1.67[ab]	37.20 ±0.84[ab]
HB (g/dl)	15.60±0.55	10.80±0.84[a]	13.59±0.80[ab]	12.31±0.53[ab]	12.74±0.54[ab]
RBC (mm3)	9.58±0.37	4.74±0.13[a]	7.80±0.61[ab]	6.64±1.13[ab]	7.23±0.45[ab]
WBC (mm3)	6520.00±83.67	10300.00±418.33[a]	7000.00±316.23[ab]	7960.00±867.76[a]	7360.00±207.36[ab]
NEU (%)	29.00±2.24	17.80±1.30[a]	26.20±1.30[ab]	24.60±3.05[ab]	25.20±1.30[ab]
LYM (%)	66.80±2.17	75.80±5.07	70.00± 5.00	72.20±3.35	68.00±1.58
EOS (%)	2.00±0.00	0.60±0.55	1.20±0.84	1.40±0.55	1.60±0.55
BAS (%)	0.00±0.00	0.80±0.45	0.40± 0.55	0.40±0.55	0.60±0.55
MONO (%)	3.00±0.00	2.00±0.00[a]	1.20±0.45[ab]	1.40±0.55[ab]	2.80±0.84[ab]
PLT (mm3)	167800.00±2774.88	267000.00±18275.67[a]	221400.00±21824.30[ab]	231800.00±21475.57[ab]	244000.00±20651.88[ab]

Values are expressed as Mean ± SD, n= 5 for each group.

[a]*Values are significantly different when compared with normal control (p<0.05).*

[b]*Values are significantly different when compared with diabetic control (p<0.05)*

Table 6. Effect of aqueous root bark and flower extracts of *Terminalia catappa* extracts on antioxidant parameters of both normal and streptozotocin induced diabetic rats

Group	Parmeter treated	Catalase (umol/mg)	SOD (%)	MDA/LPO (nm/mg)	GP_X (umol/protein)	GST (umol/protein)
A	Normal control	6.18±0.23	9.42±0.37	2.55±0.20	7.42±0.31	89.88 ±1.53
B	Diabetic control	1.32±0.11[a]	3.43±0.38[a]	11.07±0,76[a]	2.56±0.56[a]	4.85±1.33[a]
C	Diabetic Treated RB	3.77±1.38[ab]	5.99±0.71[ab]	4.03±0.48[ab]	4.15±0.80[ab]	59.87±4.41[ab]
D	Diabetic treated F	3.36±0.61[ab]	5.11±0.37[ab]	4.26±0.58[ab]	4.13±0.70[ab]	50.58±5.73[ab]
E	Glibenclimide	3.65±0.44[ab]	5.51±0.38[ab]	5.03±0.40[ab]	3.73±0.45[ab]	56.71±2.02[ab]

Values are expressed as Mean ± SD, n= 5 for each group.
[a]Values are significantly different when compared with normal control (p<0.05)
[b]Values are significantly different when compared with diabetic control (p<0.05)

Assessment of haematological parameters can be used to determine the extent of deleterious effect on blood constituents of an animal. It can also be used to explain blood relating functions of chemical compounds in plant extract. Table 5 shows that the mean values of Red Blood Cell, Haemoglobin and Packed Cell Volume for the diabetic groups are lower than the values of control group, indicating anaemia. Research by [32] reported that the occurrence of anaemia in diabetes mellitus may be due to the increased non-enzymatic glycosylation of RBC membrane proteins, which correlates with hyperglycemia or might be due to the destruction of matured red blood cells by the effect of Reactive oxygen species which have been implicated in the mechanism of red blood cells damage produced by streptozotocin leading to the low haemoglubin counts accompanied by the fall in the red blood cell and packed cell volume in diabetic untreated groups. The reversal of this derangement in diabetic rats administered with aqueous Root bark and Flower extracts of *Terminalia catappa* may signify the protective effect of the extracts against the effect of streptozotocin induced diabetics in rats.

Superoxide dismutase, Catalase, Glutathione-s-transferase, malonaldehyde and Gluthione peroxidase constitute a mutually supportive team of defense against Reactive Oxygen Species (ROS) [32,33]. SOD is a metalloprotein and is the first enzyme involved in the antioxidant defense by lowering the steady state level of O_2^-. In hyperglycemia, glucose undergoes auto oxidation and produces superoxide and free radicals that in turn leads to lipid peroxidation in lipoproteins. This study shows, decrease in the activities of these enzymes in the Streptozotocin (STZ) induced diabetes rats and an increase in the activities of the enzymes to a significant ($p<0.05$) level, after the administration of Aqueous Root bark and flowers extracts of *Terminalia catappa.* The result indicates that the oxidative stress elicited by Streptozotocin (STZ) [23] had been reverse, this may be attributed to the presences of Flavonoids a group of phytochemicals found in the plants which have been frequently implicated to have a potential anti-oxidant activity against superoxide and free radicals [34,35].

4. CONCLUSION

In conclusion, the study showed the antidiabetic activity of the aqueous Root bark and Flower extracts of *Terminalia catappa* on streptozotocin induced diabetics in rats and the plant extracts are as effective as the standard drug (glibenclimide). The ability of *Terminalia catappa* to reduce blood glucose level in the animals may inform the usage of the plant parts by traditional medical practitioners in the management of diabetes. Further studies are required to determine the exact phytochemical component responsible for the action and it mechanism of action in stabilizing blood glucose.

CONSENT

It is not applicable.

ETHICAL APPROVAL

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

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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