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Antilipidemic and Hepatorenal Effects of Aqueous Extracts of *Terminalia catappa* on Streptozotocin-induced Diabetic Rats

Japhet C.P. [a,b], Luka C.D. [a], Otitoju A.P. [c*] and Miri P [b]

[a] Department of Biochemistry, Faculty of Basic Medical Sciences, University of Jos, Nigeria.
[b] North Central Zonal Biotechnology Centre of Excellence, University of Jos, Nigeria.
[c] Medical Biotechnology Department, National Biotechnology Development Agency, Abuja, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Diabetes mellitus, a condition characterized by glucose receptor abnormalities affecting glucose uptake, affects approximately 600 million individuals globally as of 2021. This study aimed to assess the antilipidemic and renal effects of aqueous extracts from the root bark and flowers of *Terminalia catappa* on streptozotocin-induced diabetic rats.
Methodology: Twenty-five Albino rats weighing 160 – 300g were divided into five groups: A - normal control, B - diabetic control, C - diabetic treated with root bark extract, D - diabetic treated with flower extract, E - diabetic rats treated with glibenclimide. Diabetes was induced using streptozotocin (55mg/kg). The extracts (200mg/kg) were orally administered for 14 days, after which lipid profiles, renal and liver function tests were conducted.

**Corresponding author: E-mail: akinbobolapeace@gmail.com;*

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Results: There was a significant ($p<0.05$) increase in total cholesterol, serum liver enzymes, and kidney markers in the diabetic control group compared to the normal control group. Treatment with the *Terminalia catappa* extracts for 14 days resulted in more than 20% decrease in urea (from 18.58 Mmol/L to between 11.58 and 13.92 Mmol/L), creatinine (from 343.56 Mmol/L to between 223.94 and 266.30 Mmol/L) and uric acid (from 570.54 µmol/L to between 413.55 and 440.62 µmol/L) concentrations by more than 20%, with the root bark extract showing the most significant effect. Additionally, the *Terminalia catappa* extract-treated groups exhibited a substantial (around 40%) reduction in serum liver enzymes compared to the diabetic control group. The hepatoprotective capacity of the root bark extract was similar to the glibenclimide-treated group. Furthermore, the extracts led to a 3% reduction in total cholesterol, triglycerides, and low-density lipoproteins, along with a significant increase in high-density lipoproteins.
Conclusion: The aqueous root bark and flower extracts of *Terminalia catappa* demonstrate potentials for managing diabetes mellitus at the specified dosage.

Keywords: Diabetes mellitus; Terminanlia catappa; liver enzymes; kidney biomarkers; lipid profile.

1. INTRODUCTION

"Diabetes is a serious, chronic condition that occurs when raised levels of blood glucose occur because the body cannot produce any or enough of the hormone insulin or cannot effectively use the insulin it produces" [1]. "Diabetes results from a lack of insulin, which is needed for the conversion of glucose to energy, or stored, or the inability of cells to respond to insulin, thereby leading to high levels of blood glucose, a condition known as hyperglycaemia, which is a clinical indicator of diabetes. About 600 million people are suffering from diabetes globally today and this number is projected to reach 783 million by 2045" [1]. "As the disease progresses, it causes damage to the vascular tissues, leading to such complications as neuropathy, nephropathy, retinopathy, cardiovascular complications and ulceration" [2].

"There are several other types of diabetes, including the monogenic diabetes, type 1 and type 2 diabetes" [3]. "Monogenic diabetes, which represents about 2% of all diabetes cases, results from a single gene" [4]. "Type 1 diabetes is caused by an autoimmune process in which the body's immune system attacks the insulin-producing beta-cells of the pancreas. As a result, the body produces very little or no insulin" [5]. "Type 2 diabetes is considered the most prevalent type of diabetes, with over 90% of cases. It results from initially, the inability of the body's cells to respond fully to insulin, a condition termed insulin resistance. Thereafter, the insulin is less effective and, in due course, prompts an increase in insulin production. Over time, inadequate production of insulin can develop as a result of failure of the pancreatic beta cells to keep up with demand. Though, the causes of type 2 diabetes are not yet understood to the fullest, there is however, a strong relationship between factors of obesity, increasing age, ethnicity, and family history, with the onset of diabetes" [6]. "As with type 1 diabetes, contributors to type 2 diabetes risk are thought to include polygenic and environmental triggers" [1].

"The economic burden of diabetes on countries, health systems, people with diabetes, and their families is significant" [1, 7-10]. According to the International Diabetes Foundation Atlas report of 2021, it is estimated that the total diabetes-related health expenditure will reach USD 1.03 trillion by the year 2030. The increasing cost of treatment associated with modern medicine, coupled with the unsatisfactory outcome [11], has prompted many researchers to begin to look in the direction of medicinal plants for alternative therapeutic measures [12].

"Plants have formed the basis for the treatment of disease in traditional medicine for many years. Among these are the medicinal plants which possess compounds that have therapeutic properties or exert pharmacological effects on the human body" [13]. "Although, there are known antidiabetic drugs available in the market, herbal mixtures have become the go-to alternatives to treat diabetes" [14]. "The use of traditional medicine in developing countries have been attributed to multiple factors, such as accessibility, familiarity, and tradition, inadequate access to modern health care systems, high cost of modern medicine, and perceived safety or comparatively less toxicity to synthetic drugs, among other factors" [15]. Different parts of *Terminalia catappa*, a widely grown large tropical tree in the leadwood tree family, Combretaceae, native to Asia, Australia, the Pacific, Madagascar

and Seychelles [16] have been investigated for their physiological properties. “Different extracts of the leaves of this plant have been reported to possess anticancer, anti-HIV reverse transcriptase, hepatoprotective, and anti-inflammatory effects, among other biological effects” [2, 17]. “The antidiabetic activities of its fruit have also been reported in other study” [18]. Therefore, the current study was aimed to determine the antilipidemic and hepatorenal effect of T. *catappa* root bark and flower in an STZ-induced animal model.

2. MATERIALS AND METHODS

2.1 Plant Materials and Chemicals

Fresh *Terminalia catappa* root bark and flower were harvested from the compound of Old Jos University Teaching Hospital, Jos, Plateau state, Nigeria and authenticated at the Plant Science and Technology Department, University of Jos (identification number: UJH16000249). Streptozotocin was purchased from Sigma Chemical Co. (St Louis, MO, USA). A one-touch glucometer was purchased from Roche Diagnostics GmbH (Mannheim, Germany) for the analysis of blood glucose (BG). All other chemicals were of analytical grade.

2.2 Extraction of the Root Bark and Flower of *Terminalia catappa*

An amount of 100 g of root bark and flower of *Terminalia catappa* was separately soaked in 500 ml of water for 72 hours. The water was then sieved collecting the *Terminalia catappa* extract and the pellets discarded. The extract was stored at room temperature in a refrigerator within the laboratory of the Department of Biochemistry, University of Jos pending use.

2.3 Experimental Animal

Twenty-five (25) male albino rats were acquired from Animal House Unit, Department of Pharmacology, University of Jos. The rats acclimatized to the laboratory condition for two weeks before any experimental work was undertaken. At the time of experiment, the rats were weighing between 160 g and 300 g.

2.4 Experimental Design

Twenty-five male albino rats were distributed into five (5) groups. The groups are; Normal control (A), diabetic control (B), diabetic rats treated with root bark extract (C), diabetic rats treated with flower extract (D), and diabetic rats treated with glibenclimide (E).

2.4.1 Streptozotocin administration (STZ)

“A dose of 55 mg/kg of STZ was administered to four groups (via intra-peritoneal (IP) with the exception of normal control group. The blood glucose leveled was checked after 48hours using on call plus glucose strip” [19].

2.4.2 Plant extracts and glibenclimide (standard drug) administration

200 mg/kg/day of the extracts were administered for 14 days orally with constant feed and water ad libitum. 2.5 mg/kg of glibenclimide were administered orally for 14 days with constant feed and water.

2.5 Biochemical Analysis

After the 14 days of treatment, the blood glucose level was checked and weight of the experimental rats were taken before they were sacrificed. The blood was collected into two different bottles as described in Jiyil et al., 2019 [20]. Serum level of liver enzymes including ALT, AST and alkaline phosphatase (ALP) was estimated by using the commercially available test kits. Lipid profiles including, triglyceride, total cholesterol, low density lipoprotein, and high-density lipoprotein cholesterol were determined.

2.6 Statistical Analysis

All statistical analyses were conducted using the statistical package SPSS version 22.0 (Chicago, IL). Values were compared by one-way analysis of variance (ANOVA). Results were expressed as mean ± standard deviation with p value <0.05 considered significant.

3. RESULTS AND DISCUSSION

“For decades, several natural compounds obtained from different plants and found to possess significant pharmacological effects have been utilized in the treatment and management of various chronic diseases” [21]. “Today, more than 10,000 phytochemicals made up of tannins, flavones, triterpenoids, steroids, saponins, and alkaloids have been acknowledged, and many more are yet to be identified” [22]. The present study assessed the anti-diabetic and hepatorenal-protective effect of the flower and

root bark of T. *catappa* (200mg/kg) against STZ-induced diabetic model in experimental rats.

Terminalia catappa extracts possess a significant effect on some biochemical parameters and hematological assays as indicated from the Tables below:

As shown in Table 1, the aqueous extracts of the root bark and flower of *Terminalia catappa* induced a significant reduction in the serum protein when compared with the diabetic rats after the administration of *T. catappa* root bark or flower extract. The activities of these enzymes decreased gradually, suggesting an improvement in the streptozotocin-induced diabetic effect in rats. Furthermore, the study found that in streptozotocin-treated animals, there was an elevation in urea, uric acid, and creatinine levels (Table 1), indicating impaired renal function in response to streptozotocin treatment. Urea and creatinine are kidney markers that are raised under diabetic conditions [23]. High serum uric acid level has also been associated with metabolic syndrome in both normal subjects and diabetic patients [24]. However, since the levels of urea and creatinine were decreased in the *T. catappa* (200 mg/kg) treated groups, this suggests that *T. catappa* root bark and flower may have prevented the streptozotocin-induced biochemical alterations and did not cause renal damage. The root bark extract however produced the higher activity, when compared to the flower extract.

Under diabetic conditions induced by streptozotocin, liver marker enzymes such as AST, ALP, and ALT were elevated (Table 2). “These enzymes, which are key indicators of hepatic function, are found in various tissues including the liver, cardiac muscle, skeletal muscle, kidney, brain, pancreas, lungs, leukocytes, and erythrocytes” [25]. “The increase in enzyme activity in the blood suggests increased permeability and damage, or necrosis of liver cells” [26]. “The liver is a vital organ for glucose regulation in physiological and pathological states such as diabetes mellitus. Dyslipidaemia in diabetes mellitus has been considered to play an important role in the accumulations of free fatty acids and lipids in the liver that leads to excessive ROS production and lipid peroxidation. These processes enhance the oxidative stress and damage in liver resulting to increase in the amount of the liver function enzymes that are found in the serum of diabetic subjects” [27]. However, following the administration of *T. catappa* root bark or flower extract, the concentration of these enzymes decreased gradually, suggesting an improvement in the streptozotocin-induced diabetic effect in rats.

Table 1. Effect of administration of extract of *Terminalia catappa* on some level of biochemical parameter

Group	Treatment	Urea (Mmol/L)	Creatinine (Mmol/L)	Uric Acid (µmol/L)
A	Normal Control	4.61±0.15	80.19±1.20	199.01±0.46
B	Diabetic control	18.18±0.50a	343.56±12.72a	570.54±9.37a
C	Diabetic treated RB	11.58 ±0.40ab	223.94±15.54ab	413.55±15.26ab
D	Diabetic treated F	13.92±0.75ab	266.30±30.18ab	440.62±40.00ab
E	Glibenclimide	12.71±0.73ab	233.00±134.18ab	438.90±017.43ab

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: Terminalia catappa root bark; F: Terminalia catappa flower

Table 2. Effect of administration of *Terminalia catappa* extract on serum level of liver function enzymes

Group	Treatment	ALT (U/L)	AST (U/L)	ALP (U/L)
A	Normal Control	12.61±0.54	17.52±0.52	158.93±0.96
B	Diabetic control	36.96±0.73[a]	58.56±0.68[a]	493.12±5.36[a]
C	Diabetic treated RB	15.52±0.71[ab]	19.25±0.81[ab]	188.50±5.00[ab]
D	Diabetic treated F	25.98 ±3.67[ab]	43.45±1.50[ab]	365.08±13.80[ab]
E	Glibenclimide treated	6.24±0.57[ab]	19.51±0.52[ab]	204.29±6.54[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: Terminalia catappa root bark; F: Terminalia catappa flower

Table 3. Effect of aqueous root bark and flower extracts of *Terminalia catappa* extracts on serum lipid profile of both normal and streptozotocin induced diabetic rats

Group	Treatment	Total chol. (mmol/L)	TRIG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
A	Normal Control	3.73±0.16	0.89±0.64	1.23 ± 0.07	1.83±0.07
B	Diabetic control	5.80 ±0.21[a]	2.41±0.03[a]	0.41± 0.03[a]	2.41±0.03[a]
C	Diabetic treated RB	4.43±0.32[ab]	1.57±0.15[ab]	0.66±0.03[ab]	2.34±0.09[ab]
D	Diabetic treated F	4.96±0.49[ab]	1.75±0.15[ab]	0.58±0.04 [ab]	2.32±0.16[ab]
E	Glibenclimide-treated	4.55±0.24[ab]	1.44± 0.15[ab]	0.83±0.04[ab]	2.26 ±0.12[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: Terminalia catappa root bark; F: Terminalia catappa flower

Furthermore, Table 3 shows the result of the analysis of biochemical lipid profile parameters (Total cholesterol, triglyceride, high density lipoproteins and low-density lipoproteins) on experimental rats. “Lipid profiles have been demonstrated to be another significant predictor of many diseases, including diabetes” [28-29]. In this study, administration of aqueous extract of *T. catappa* root bark and flower caused antihyperlipidaemia, as the serum total cholesterol, triglyceride and low density lipoproteins, were significantly reduced, coupled with a significant increase in high density lipoprotein, when compared with the diabetic control group. Our results corroborate the findings of previous investigations within our laboratory regarding the antidiabetic effects of plant extracts [29-31], and shows the efficacy of *T. catappa* root bark and flower extracts in ameliorating the diabetes-induced damages in rat models.

4. CONCLUSION

Administration of the aqueous extracts of *Terminalia catappa* root bark, and flower demonstrated hypolipidemic and hepatoprotective properties in streptozotocin-induced diabetic rats. The phytochemicals inducing the reported effects need to be elucidated and their mechanisms of action evaluated.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The experimental design was conducted in accordance with the guidelines approved by the institutional animal ethical committee of University of Jos, Nigeria.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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