

Anti-diabetic Effect of Ethanol Leaf Extract of *Ziziphusspina-christi* on Alloxan Induced Albino Rats

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Abstract

This study aimed to evaluate the impact of an ethanol extract obtained from the leaves of *Ziziphusspina-christi* on alloxan-induced diabetic rats using standard analytical procedures. Fifteen Albino Wistar rats were divided into five groups, each consisting of three rats. The groups included normal uninduced rats as control group, a diabetic untreated group as the diabetic control, a group treated with a dosage of 150 mg/kg body weight, a diabetic group treated with metformin as the standard drug, and another treatment group. The levels of liver marker enzymes, such as alanine transaminase (60.7 ± 3.25) and aspartate transaminase (69.5 ± 1.84), as well as liver function parameters like total protein (7.47 ± 0.02), were found to be higher in the diabetic control group compared to the normal control and other treatment groups. However, in all the treatment groups, there was a significant decrease observed in alanine transaminase, aspartate transaminase, and alkaline phosphatase. The level of kidney function markers such as blood creatinine (1.58 ± 0.07) and blood urea (43.50 ± 0.86) were significantly ($p > 0.05$) higher in the diabetic control group when compared to the normal control. However, significant ($p > 0.05$) reductions in blood creatinine and blood urea were observed in all the treatment groups. The presence of phytochemicals such as alkaloids, tannins, flavonoids, phenols, and cardiac glycosides in the ethanolic extract of sidr leaves were probably responsible for the anti-diabetic activities of the plant extract. In conclusion, the antidiabetic effect of ethanolic extract of sidr as observed in this study may be attributed to its antioxidant properties.

Keywords: Anti-oxidant, phytochemicals, *Ziziphusspina-christi*, marker

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Introduction

Diabetes Mellitus (DM) is a group of metabolic disorders characterized by disruptions in the metabolism of fuel molecules due to a deficiency of insulin. This inadequate secretion or inaction of insulin affects the body's ability to utilize glucose effectively. Insulin, a hormone produced by the pancreas, is responsible for transporting glucose from the bloodstream into cells, where it is utilized as fuel. Insulin is essential for the survival of individuals [1]. Diabetes is a prevalent endocrine disorder that poses significant health risks and can lead to mortality across all populations worldwide [2]. The International Diabetes Federation (IDF) estimated the global population with diabetes mellitus (DM) to be 463 million in 2019 and 700 million in 2045. Diabetic retinopathy remains a common complication of DM and a leading cause of preventable blindness in the adult working population [3]. The worldwide prevalence of type 2 diabetes is expected to reach 4.4% by 2030, with type 1 diabetes accounting for approximately 5-10% of diagnoses and type 2 accounting for 90% [2, 4]. The total number of

individuals affected by type 2 diabetes is projected to reach 366 million by 2030 [5, 6, 7].

Herbal medicine has been widely utilized in the treatment of diabetes and other ailments, especially among underprivileged individuals who cannot afford conventional medications. The use of many alternative treatments is limited by their serious side effects. Herbal medicine and plant-based compounds with low toxicity and minimal or no side effects have emerged as valuable therapeutic options for the treatment of diabetes worldwide [8]. Anti-oxidant properties of the herbal medicine are responsible for the curative properties of diabetes [9]. These plant-based therapies have been employed for over 5,000 years and continue to be relevant in the primary healthcare system in many communities [10]. Africa is abundant in medicinal plants, and approximately 60-80% of the population utilizes these plants for disease treatment [11, 12, 13] *Ziziphusspina-christi*, also known as sidr in Iran and Kandiida in the Hausa language of Northern Nigeria, is a wild tree characterized by its light grey bark, cracked and twisted trunk, flexible spiny branches, and small orange-yellow fruits.



Ziziphusspina-christi belongs to the Rhamnaceae family and has been used in traditional medicine for various ailments, including digestive disorders, weakness, liver complaints, obesity, urinary problems, diabetes, skin infections, loss of appetite, fever, pharyngitis, bronchitis, anemia, diarrhea, and insomnia [14]. The main bioactive components of *Ziziphusspina-christi* include cyclopeptide alkaloids, steroids, tannins, triterpenoids, and saponins [14, 15]. However, there is limited scientific documentation on the potential use of *Ziziphusspina-christi* in the treatment of diabetes mellitus. Therefore, this study aims to scientifically investigate the antidiabetic activity of *Ziziphusspina-christi* in alloxan-induced diabetic rats and provide evidence in supporting the traditional use of the plant by practitioners for diabetes treatment using the leaves of the plant.

Materials and Methods

Collection and preparation of plant materials

The leaves of *Ziziphusspina-christi* were purchased in one of the markets in Lafia metropolis, Nasarawa State, Nigeria, identified by a plant technologist in the Botany Department of Federal University Lafia, Nasarawa state, Nigeria. The sample of the plant was kept in the Herbarium. The plant leaves were air-dried in the laboratory, pulverized using mortar and pestle and then sieved.

Sample preparation

50 g of powdered *Ziziphusspina-christi* plant material was dissolved in 250 mL of 50% ethanolic solvent in a sterile bottle and shaken vigorously at interval. The mixture was then left to stand overnight for 48 h at room temperature. The mixtures were then filtered using a clean muslin cloth and then with Whatman No 1 filter paper. The filtrate was evaporated in a waterbath at 75°C. The resulting slurry was weighed and reconstituted in to distilled water to administer required dose.

Reagent and chemicals

The chemicals used in this study were of analytical grade.

Phytochemical analysis

The qualitative and Quantitative analysis of the plant constituents was assessed using standard procedure to identify the preliminary phytochemicals constituent; Alkaloids, Flavonoids, Tannins, Phenols, Saponins, Steroids, Coumarins and Cardiac glycoside.

Experimental animals

Fifteen (15) male albino rats were obtained from animal unit of the Veterinary Institute Vom, Jos Plateau State, Nigeria. The animals were acclimatized for a period of seven days. Rats were housed in a wooden cage where they will have access to adequate ventilation, with 12 h of natural light darkness. They were allowed free access to food and water. Good hygiene was maintained by constant cleaning and removal of feces and spilled feeds from the cages on a daily basis.

Ethical approval

Approval for the use of animals was obtained from the Ethical Review Committee of the Department of Biochemistry, Federal University of Lafia, Nasarawa State, Nigeria.

Preparation of standard drug

A standard diabetic drug (Metformin) was purchase from one of the top 10 (Ten) Pharmacy store in Lafia, Nasarawa State. The drug was dissolved in 1 ml distilled water as a dose of 150 mg/kg per body weight and administered intraperitoneally.

Experimental design

A total of 15 rats were divided in to 5 groups and each group containing three (3) rats each.

Group 1: Normal control (NC) - not induced with diabetes.

Group 2: Diabetic Control (DC) – induced but no treatment.

Group 3: Diabetic with known drug (DD) – induced and treats with diabetic drug Metformin at 150 mg/kg body weight on daily basis.

Group 4: Diabetic with Extract (DE) – diabetic rats treated with plant extract (150 mg/kg body weight)

Group 5: Normal with extract (NE) Non-Diabetic rat treated with plant extract (150 mg/kg body weight)

Induction of diabetes

Diabetes Mellitus was induced in the animals through interperitoneal administration of Alloxan, which was dissolved in distilled water and then injected at a dosage of 150 mg/kg body weight after an overnight fast for 7 – 8 h. Diabetes was confirmed by the elevation of blood glucose level, determined after 72 h using Accu-check glucometer.

Sample analysis

The blood was collected on the 14th day of experimental period through chloroform anesthesia. The rats were dissected laterally and blood sample were collected using sterile needle from the heart while its beats and pumps blood and store in plain sample bottle for biochemical analysis. Experimental animals were later sacrificed and buried.

Serum anti-oxidant enzymes analysis

All the serum anti-oxidant enzymes were measured using enzymatic colorimetric method with Agape reagent. Manufacture instruction was strictly adhered to.

Statistical analysis

Data obtained were subjected to statistical analysis expressed as mean± standard deviation (SD). Data were analyzed using Microsoft Excel 2013 (Redmond, Woshington, USA) Graph Pad Prism version 5 (Graph Pad Software, Inc., USA) all the data from the treatment group (including Diabetic + Metformin) were compared with the result from the diabetic control groups. A *p* value of less than 0.05 was considered statistically significant.

Results and Discussion

Phytochemical composition

The phytochemical analysis of the ethanol extract of leaves of *Ziziphusspina-christi* indicate the presence of alkaloids, tannins, flavonoids, phenolics and cardiac glycosides in the plant leaf extract as shown in Table 1

Table 1: The qualitative and quantitative phytochemical composition of *Ziziphusspina-christi* ethanol extract

Phytochemicals	Concentration (MG/KG)
Alkaloids	74.47±0.64
Tannins	203.20±0.78
Flavonoids	48.28±0.02
Phenols	6.14±0.03
Cardiac glycoside	772.62±1.22

Body weight

The trend of body weight gain/loss in the experimental animals is shown in Table 2. The results showed that there was no significant ($p < 0.05$) difference in body weight among all groups at the start of the experiment. Untreated diabetic groups (DC) shows a significant ($p > 0.05$) decrease in body weight during the

experimental period as against what was observed in normal control group (NC) where a significant ($p > 0.05$) increase in body weight was noticed. All treated diabetic groups recorded a significant ($p > 0.05$) elevation in body weight as the experiment period progressed, showing body weight gain compare with untreated diabetic group, while metformin alone has lowest final body weight gain value.

Fasting blood glucose

Table 3 shows elevated level of fasting blood glucose in alloxan-induced rats. The results showed that the diabetic control group records a significant ($p > 0.05$) increase in serum glucose level as compared with normal control group. In contrast, serum insulin level as well as glycogen content in the liver tissue homogenate also showed a significant decrease as compare to the untreated diabetic group. All treated groups showed significant ($p > 0.05$) decrease in serum glucose. However, metformin treated group showed the most significant ($p > 0.05$) glucose lowering effect. Also, treatments of diabetic rats with *Ziziphusspina-christi* leaf methanol extract efficiently decrease blood glucose level of diabetic rats.

Table 2: Trend of body weight gain/loss in the experimental rats

Groups	Day 3(G)	day 6(G)	Day 9(G)	Day 12(G)	Day 14 (G)
N P-value = 0.0016	126.0±1.41 ^a	129.5±0.71 ^b	133.0±2.83 ^c	138.0±1.41 ^d	141.0±1.41 ^e
DC P-value = 0.0001	155.5±2.12 ^a	147.0±4.24 ^b	135.5±3.54 ^c	125.0±2.82 ^d	90.0±7.07 ^e
DD P-value = 0.0002	101.10±4.24 ^a	123.5±0.71 ^b	127.0±1.41 ^c	131.0±2.83 ^d	137.0±1.41 ^e
NE P-value = 0.0002	97.0±0.00 ^a	100.5±3.54 ^a	112.0±2.83 ^c	121.5±2.12 ^d	126.5±0.71 ^e
DE P-value = 0.0001	128.0±1.41 ^a	125.5±0.71 ^b	134.0±2.83 ^c	151.1±2.12 ^d	156.5±0.71 ^e

Values are presented as means ± standard deviations (SD) of three replicates. Means with different superscript(s) across rows are significantly ($p < 0.05$) different.

N= normal, DC = Diabetic Control, DD = Diabetic with known Drug, NE = Normal with Extract, DE = Diabetic with Extract.

Table 3: Impact of *Ziziphusspina-christi* leaf extract on blood glucose level in alloxan-induced diabetic wistar rats

Groups	Day 3(G)	Day 6(G)	Day 9(G)	Day 12(G)	Day 14 (G)
N P-value = 0.5869	3.70±0.14 ^a	3.75±0.07 ^a	3.85±0.07 ^a	3.85±0.07 ^a	3.80±0.14 ^a
DC P-value = 0.0015	6.65±0.212 ^a	7.00±0.0 ^b	7.35±0.212 ^c	8.75±1.06 ^d	11.25±0.35 ^e
DD P-value = 0.0001	7.40±0.4 ^a	6.25±0.07 ^b	5.70±0.41 ^c	4.95±0.07 ^d	3.90±0.14 ^e
NE P-value = 0.0002	6.35±0.21 ^a	5.80±0.14 ^b	4.55±0.07 ^c	6.20±0.14 ^a	5.25±0.07 ^d
DE P-value = 0.0001	8.40±0.14 ^a	7.40±0.14 ^b	6.00±0.14 ^c	5.60±0.14 ^d	5.00±0.14 ^e

Values are presented as means ± standard deviations (SD) of three replicates. Means with different superscript(s) across rows are significantly ($p < 0.05$) different.

N= normal, DC = Diabetic Control, DD = Diabetic with known Drug, NE = Normal with Extract, DE = Diabetic with Extract.

Table 4: Impact of *Ziziphusspina-christi* leaf extract on Serum anti-oxidant markers in alloxan-induced diabetic wistar rats

Sample	UREA mmol/L	CR μmol/L	AST μmol/L	ALT μmol/L	CHOL μmol/L	TC mmol/L	HDL mmol/L
A - NC	4.27±0.25 ^d	205.10±0.49 ^d	24.27±0.50 ^a	74.08±0.63 ^b	3.53±0.15 ^c	2.50±0.10 ^c	1.40±0.20 ^c
B - DC	8.53±0.31 ^e	230.70±0.92 ^e	78.20±0.65 ^d	167.00±0.20 ^e	5.73±0.15 ^d	6.00±0.20 ^d	0.72±0.07 ^a
C - DD	2.67±0.15 ^c	193.30±0.36 ^c	23.4±0.25 ^a	95.67±0.40 ^c	3.30±0.17 ^b	1.90±0.20 ^b	1.62±0.02 ^e
D - NE	1.96±0.20 ^a	120.20±0.36 ^a	26.9±0.30 ^b	72.63±0.45 ^a	2.67±0.12 ^a	1.73±0.15 ^a	1.54±0.02 ^d
E - DE	2.13±0.15 ^b	127.40±0.45 ^b	30.23±0.30 ^c	120.90±0.51 ^d	3.53±0.15 ^c	1.63±0.10 ^a	1.30±0.02 ^b

Values are presented as means ± standard deviations (SD) of three replicates. Means with different superscript(s) down the columns are significantly ($p < 0.05$) different.

N= normal, DC = Diabetic Control, DD = Diabetic with known Drug, NE = Normal with Extract, DE = Diabetic with Extract.



Assessment of some biochemical parameters

At the end of fourteen (14) days treatment period, blood sample of all the experimental animals were collected for analysis of some serum biochemical makers. The results of the analysis as presented in Table 4 showed that untreated diabetic group of rats recorded a significant ($p>0.05$) increase in serum level of triglyceride (TG) and total cholesterol (TC) as compared to negative control group. However, serum high density lipoprotein, cholesterol (HDL-C) were significantly ($p>0.05$) decreased compared to the diabetic control group. It was also observed that the serum TG and TC in all treatment groups were significantly ($p>0.05$) reduced. However, a significant ($p>0.05$) elevation of serum TG and TC as well as significant ($p>0.05$) rise in serum HDL-C were observed.

It was also noted that not treated diabetic control group recorded a significant ($p>0.05$) increase in the activities of serum transaminases (AST and ALT) as compared with normal group. Also, when compared to the diabetic group, all treated groups showed a significant ($p>0.05$) decrease in the activities of serum transaminases except for the group treated with metformin as it recorded no significant ($p <0.05$) change in the serum alanine aminotransferase (ALT) activity. Administration of *Ziziphusspina-christi* leaf methanol extract to diabetic rats was observed to cause a more significant ($p>0.05$) reduction in the activity of serum ALT suggesting an improved anti-oxidant status in liver tissue homogenate.

Diabetes is characterized by dehydration, hyperglycemia, insulin deficiency or resistance, increased glycogenolysis, lipolysis, and gluconeogenesis. These metabolic changes lead to muscle wasting and loss of tissue protein [16]. In the present study, metformin, known to increase insulin sensitivity [17], resulted in increased body weight in diabetic rats. However, due to its appetite-reducing effect as reported by [18], the weight gain in the metformin-treated rats was the lowest compared to the rats treated with the extract. Ethanol extract of *Ziziphusspina-christi* showed hypoglycemic effect. This effect along with its ability to improve loss of appetite, explains its impact on the body weight of diabetic rats in this study. This finding is in tandem with reports from other researchers who observed body weight enhancement of the plant [19, 20, 21].

The manifestation of diabetes mellitus in the control group confirmed the cytotoxic action of alloxan on pancreatic β -cells [22, 23]; reducing insulin secretion and causing hyperglycemia. Metformin's hypoglycemic effect was attributed to improved insulin sensitivity, antioxidant activity, inhibition of gastrointestinal glucose absorption, and modulation of inflammatory parameters.

The hypoglycemic effect of metformin observed in this study has been attributed to its ability to improve insulin sensitivity. Insulin, in turn, stimulates glucose uptake by muscles and the liver while decreasing glucose production. Metformin also strengthens the

antioxidant status, inhibits gastrointestinal glucose absorption, and restores inflammatory parameters in diabetic patients [24, 25].

Several studies have reported the anti-diabetic effect of plants and plant materials, suggesting that phenols, alkaloids, terpenoids, and glycosides present in the plant leaves are responsible for their anti-hyperglycemic properties [26]. Michel revealed that oral administration of *Ziziphusspina-christi* leaf extract increases serum insulin and c-peptide levels [6].

The hypolipidemic effect of metformin observed in this study is supported by research suggesting that metformin may alleviate diabetic nephropathy symptoms by modulating lipid metabolism and dyslipidemia [27]. Metformin reduces the rate of lipolysis through increased insulin sensitivity, slowing the conversion of free fatty acids into lipoprotein precursors in the liver [28]. By lowering plasma glucose levels, metformin decreases the fraction of glycated LDL-C, which is inefficiently removed from the body [29].

Similarly, the hypolipidemic effect of *Ziziphusspina-christi* extract observed in this study aligns with [30], who demonstrated that the administration of crude extract of sidr leaves significantly ameliorated oxidative stress by lowering hepatic antioxidant enzymes in rats with streptozotocin injection.

The increased activities of AST and ALT in the serum may be attributed to the leakage of these enzymes from liver cells into the bloodstream, indicating the hepatotoxic effect of alloxan [31]. Diabetic hyperglycemia also leads to elevated plasma levels of urea and creatinine, significant markers of renal dysfunction [32]. These abnormalities may result from the body's failure to excrete metabolic end-products of protein breakdown, as protein metabolism increases in diabetes due to increased gluconeogenesis [33].

Treatment with *Ziziphusspina-christi* extract reduced AST and ALT activity, possibly due to its phenolic content exerting antioxidant effects on liver tissue, consistent with previous studies on sidr leaves [5].

Research suggests that plant compounds like phenols, alkaloids, terpenoids, and glycosides contribute to the anti-hyperglycemic properties of plants. *Ziziphusspina-christi* leaf extract was shown to increase serum insulin and c-peptide levels, supporting its anti-diabetic effects. Both metformin and the extract exhibited hypolipidemic effects, potentially through modulation of lipid metabolism.

Regarding kidney function markers, Al-Ghamdi *et al.* argued that the sidr leaf extract showed promise in reducing serum creatinine and uric acid levels [5]. Also, suggesting renal protective effects likely mediated by its antioxidant properties [34]. These findings underscore the potential therapeutic benefits of *Ziziphusspina-christi* and its constituents in managing diabetes-related complications, particularly liver and kidney dysfunction.



Conclusion

In summary, the research findings demonstrate that the ethanol extract of *Ziziphusspina-christi* leaves possesses anti-diabetic effects in alloxan-induced diabetic rats. These results provide support for the traditional use of *Ziziphusspina-christi* as an oral remedy for diabetes and suggest that it could be a promising source for the development of new drugs for the management of diabetes and its complications.

Conflict of interest: Authors hereby declare that no conflicting interest exists in publishing this work.

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