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Research Article

Curative Effects of Ethanol Leaf Extract of *Cnidoscolus aconitifolius* on Visceral Organs (Liver and Kidney) of Alloxan-Induced Diabetic Female Wistar Rats

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Abstract

Background: Diabetes mellitus is a chronic metabolic disorder often associated with oxidative stress, which can lead to cellular damage in key organs such as the liver and kidney. The search for natural remedies with antioxidant and antidiabetic properties has directed scientific attention toward medicinal plants such as *Cnidoscolus aconitifolius* (Chaya). The plant is traditionally used in managing diabetes, hypertension, and related metabolic complications.

Objective: This study aimed to evaluate the antidiabetic, hepatoprotective, and renoprotective effects of the ethanolic leaf extract of *Cnidoscolus aconitifolius* in alloxan-induced diabetic female Wistar rats, while assessing the phytochemical constituents responsible for these effects.

Methods: Phytochemical analysis of the ethanolic leaf extract was conducted to identify bioactive compounds. Experimental rats were divided into groups and induced with alloxan to develop diabetes, followed by oral administration of *C. aconitifolius* extract at doses of 100 mg/kg and 500 mg/kg for 14 days. Blood samples were analyzed for liver enzyme markers (ALT, AST, ALP), kidney function indices (urea, creatinine), and glucose levels. Histological examinations of the liver and kidney tissues were also carried out.

Results: Phytochemical screening revealed the presence of flavonoids, saponins, alkaloids, tannins, cardiac glycosides, and steroids, with flavonoids and saponins occurring in high concentrations. Administration of *C. aconitifolius* extract led to a dose-dependent reduction in blood glucose, confirming its antihyperglycemic potential. Liver enzyme assays showed a significant decrease in AST, ALT, and ALP levels in treated groups compared to untreated diabetic controls, indicating reduced hepatic injury and improved liver function. Similarly, urea and creatinine levels decreased significantly in treated groups, demonstrating improved kidney function and protection against diabetic nephropathy. Histological analyses supported these biochemical findings, showing fewer necrotic cells in the liver and kidney tissues of treated rats compared to untreated diabetic rats.

Conclusion: The ethanolic leaf extract of *Cnidoscolus aconitifolius* exhibits potent antidiabetic, hepatoprotective, and renoprotective effects in alloxan-induced diabetic rats. These effects are attributed to its high flavonoid and saponin content, which confer antioxidant, anti-inflammatory, and antihyperglycemic properties. The extract also enhances the functional recovery of the liver and kidney by reducing oxidative stress and cellular damage.

Keywords: *Cnidoscolus aconitifolius (C. aconitifolius); Visceral Organs (Liver and Kidney); Alloxan; Diabetic Female Wistar Rats*

Introduction

Physiologically, blood glucose serves as the key substrate for generating energy (adenosine biphosphate, ATP) required for metabolic processes. Maintaining glucose balance is crucial because organs such as the brain and testes depend on a steady glucose supply. Any disruption may lead to disorders that elevate or reduce glucose levels to pathological states. A continuous rise in fasting blood glucose above 6.9 mmol/L indicates hyperglycemia, clinically called diabetes mellitus. Diabetes is a major global health challenge [1]. Alarmingly, the rate of new cases appears to be increasing faster than expected [2]. Reports indicate most new cases are emerging from Asia and Africa due to lifestyle changes [3].

Diabetes mellitus (DM) results from genetic and environmental interactions. It is characterized by elevated blood glucose from inadequate insulin secretion, impaired action, or both. Global estimates show diabetes cases reaching 366 million-higher than earlier WHO projections-with over 4 million deaths linked to diabetes [4]. Global healthcare spending on diabetes in 2010 reached $320 billion [5]. Low- and middle-income countries record the fastest rise, especially ages 40-59 [6]. Preventive and therapeutic interventions are urgently needed [7]. Management must go beyond blood glucose control [8]. Although many medicinal plants show antihyperglycemic activity [9], *Cnidoscolus aconitifolius* has not been widely documented.

Conceptual framework

Environmental factors significantly affect homeostasis [10]. Disturbance of regulatory mechanisms may lead to metabolic disorders including hyperglycemia. Diabetes prevalence is rising in developing nations [11]. WHO estimates 437 million individuals with diabetes, with mortality expected to double between 2005 and 2030 [12]. Type 1 DM results from insulin deficiency, whereas Type 2 DM (90% of cases) involves insulin resistance [13]. Obesity and inactivity are major triggers. Gene IFIHI has been linked to T1DM [14]. T2DM involves β-cell dysfunction, increased hepatic glucose output, reduced insulin sensitivity, altered GI insulin response, and renal glucose reabsorption [15]. Due to cost and limited access to treatment, alternative therapy is needed [16]. WHO encourages scientific evaluation of antidiabetic plants [17]. *C. aconitifolius* phytochemical evaluation is therefore warranted. Study of alloxan-induced diabetes helps clarify mechanisms of pathological glucose elevation [10].

Empirical review

Carbohydrate metabolism

Glucose is the most vital carbohydrate [18]. Carbohydrates are classified into simple and complex forms. Carbohydrates provide quick energy, regulate insulin, and may be stored as glycogen or converted to fat. The general formula is CnH_2nOn; glucose is $C_6H1_2O_6$. Aerobic respiration equation:

$C_6H1_2O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$ + energy (ATP).

Metabolic processes

Major processes include photosynthesis, glycolysis, Krebs cycle, pentose phosphate pathway, glycogenesis, glycogenolysis and gluconeogenesis [19].

Regulation of blood glucose

Insulin regulates glucose uptake, glycogen synthesis, and metabolism. Glucagon promotes glycogen breakdown. Other hormones also support regulation [20]. Dietary carbohydrates are converted to glucose in the liver [20]. Glucose transport occurs via facilitated diffusion; insulin improves uptake [20].

Phosphorylation and fate of glucose

Glucose is phosphorylated to glucose phosphate by hexokinase or glucokinase. Glycogen is stored mainly in liver and muscle; excess glucose becomes fat [20].

Blood glucose concentration

Normal glucose is 4 - 6 mmol/L [21]. Regulation involves anabolic and catabolic hormones. Whole-blood glucose × 1.15 = plasma glucose [21].

Glycaemic index

GI measures carbohydrate effect on glucose. Low-GI foods aid glucose control.

Monitoring of blood glucose

Tests include FBS, 2-hour post-prandial, RBS, OGTT, IVGTT, HbA1c [21]. Hypoglycemia causes confusion and coma; chronic hyperglycemia causes complications [22].

Unit conversion

mg/dL ÷ 18 = mmol/L; mmol/L × 18 = mg/dL [21].

Blood and haematologic parameters

FBC measures blood components [23]. Haematologic indices monitor health [24].

Embryology of blood and haemopoiesis

Blood forms from yolk sac mesoderm; hematopoiesis later shifts to bone marrow [25].

Management of diabetes

DM has no permanent cure; management includes diet, exercise, insulin/OADs [26]. Lifestyle modification is key [27]. Metformin remains first-line [28]. Aspirin not routine in uncomplicated diabetes [29]. Telehealth care effective [30].

Oxidative stress and antioxidants

ROS damage tissues via lipid peroxidation and DNA damage [31]. Oxidative stress arises from imbalance of ROS and antioxidants [32]. Antioxidants include flavonoids, phenolics, etc. [33-35].

Medicinal plants and antidiabetic importance

Plant-derived compounds show antidiabetic effects [36]. Flavonoids and saponins may stimulate insulin secretion [37,38]. Diabetes burden rising [39,40]. Antioxidant plants protect against ROS [41]. Several plant extracts show hypoglycemic effects [42-44]. Lack of African data limits use [45].

Phytomedicine for diabetes

Many plants show hypoglycemic effects in animals and humans [46,47], containing glycosides, alkaloids, terpenoids, flavonoids, and saponins [48]. WHO encourages herbal evaluation [49]. Flavonoids have antioxidant benefits [50,51].

Cnidoscolus aconitifolius (Chaya)

Traditional antidiabetic plant [52,53]. Cyanogenic glycosides removed by boiling 20 minutes [54]. Known locally as efo iyana ipaja/ oguru obala/Hospital-too-far.

Health importance of *Cnidoscolus aconitifolius* (CA)

Cnidoscolus aconitifolius, commonly known as Chaya, is one of the most nutrient-dense leafy green vegetables (ECHOtech, n.d.). It is a rich source of protein, vitamins, calcium, iron, and antioxidants [55]. Studies show that its nutrient levels are two to three times higher than most land-based leafy vegetables. The plant also exhibits high fiber content and notable antibacterial activity [56].

Oladeinde., *et al*. (2007) reported significant antidiabetic properties in the leaf extract of *Cnidoscolus aconitifolius* when tested in type 2 diabetic mice [57]. Similarly, Oyagbemi., *et al*. (2008) observed that the plant ameliorates anemia and reduces osmotic fragility caused by protein-energy malnutrition. Collectively, these findings highlight the therapeutic and nutritional significance of Chaya as a functional food and medicinal plant [58].

Scientific classification of *Cnidoscolus aconitifolius*

Taxonomic Rank	Classification
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Euphorbiales
Family	Euphorbiaceae
Genus	Cnidoscolus
Species	Cnidoscolus aconitifolius (Mill.) I.M. Johnst.

Table

Nutritional composition of *Cnidoscolus aconitifolius*

S/N	Nutritional Component	Percentage (%)
1	Water	85.3
2	Protein	5.7
3	Fat	0.4
4	Crude Fiber	1.9
5	Calcium	1.99
6	Phosphorus	0.39
7	Potassium	2.17
8	Iron	0.11
9	Vitamin C	1.65
10	Carotenoids	0.085

Table 1: *Nutritional value of Cnidoscolus aconitifolius (CA).*

These nutrient levels are consistent with previous reports [59], showing that Chaya's nutritional value surpasses that of other common leafy vegetables such as spinach (6.4%), amaranth (11.3%), Chinese cabbage (7.0%), and lettuce (5.4%) [30].

Chaya leaves are rich in essential minerals necessary for human health. Potassium helps control hypertension and reduce the risk of stroke [42], calcium supports bone formation, and iron is essential for hematopoiesis [32]. Vegetables with high vitamin C content, like Chaya, enhance non-heme iron absorption, further contributing to its nutritional value [21].

Alloxan

Alloxan (2,4,5,6-pyrimidinetrone) is an oxygenated pyrimidine derivative that exists as alloxan hydrate in aqueous form. It was first isolated in 1818 by Brugnatelli and later named by Wöhler and Liebig in 1838, derived from "Allantoin" and "Oxalic acid".

Biological effects of alloxan

Alloxan and streptozotocin are cytotoxic glucose analogues that selectively destroy pancreatic β-cells, leading to insulin-dependent diabetes mellitus in experimental animals [33]. This process resembles type 1 diabetes in humans. In the presence of intracellular thiols, alloxan undergoes redox cycling with its reduced form, dialuric acid, generating reactive oxygen species (ROS). These free radicals mediate the cytotoxic action of alloxan on pancreatic cells.

Impact on beta cells

Alloxan induces diabetes by selectively targeting insulin-producing β-cells in the pancreas due to its structural similarity to glucose and preferential uptake via the GLUT2 transporter. The result is irreversible damage to β-cells and the onset of hyperglycemia in experimental models.

Due to the increasing challenges associated with poor preventive practices, rapid shift from traditional diets to Western fast foods, poverty and adverse effects of most synthetic drugs/chemicals, the incidence of diseases and organ/tissue dysfunctions is on the rise [22]. Considering the reported physiological benefits of phytomedicinal compounds from various plants over time, there is immediate need to explore alternative therapies by utilizing nutrient-rich plant products in managing these conditions. Many of these plant-based remedies possess antioxidant and antihyperglycemic properties, have fewer side effects, and are affordable and readily accessible making them potential alternative therapies that will likely be in higher demand by patients [37].

Materials and Methods

Materials

The materials used for this study include: Beakers, Measuring cylinders, Dissecting set, Anaesthetics (chloroform), Wooden cages with wire gauze, Weighing balance, Glucometers, Glucose test strips, Surgical gloves, Syringes, Normal saline, Distilled water, EDTA sample bottles, Electric grinding machine, Soxhlet extractor (Model No. 3587, Austria), Rotary evaporator (Gallenkamp, UK), Alloxan, Ethanol leaf extract of *Cnidoscolus aconitifolius.*

Source and identification of plant material

Fresh leaves of *Cnidoscolus aconitifolius* (CA) were collected from residential areas in Owerri and Isiala Mbano, Imo State, Nigeria. The plant was authenticated and identified by Mr. Finian Iroka of the Department of Botany, Nnamdi Azikiwe University, Awka, Anambra State**,** and assigned the herbarium number NAUH-321c.

Preparation and storage of leaf extract

Extraction was conducted following the method described by Okigbo., *et al*. (2005). The fresh leaves of *Cnidoscolus aconitifolius* were air-dried and pulverized using an electric grinding machine. Ethanol extraction was carried out using a Soxhlet extractor (Model No. 3587, Austria). The resulting extract was filtered through Whatman No. 1 filter paper, and the filtrate was concentrated under reduced pressure using a rotary evaporator (Gallenkamp, UK) at 45°C. The concentrated extract was stored at 4°C until use.

Ethical approval

Ethical approval for the study was obtained from the University Ethics Committee, Faculty of Basic Medical Sciences, Abia State University, Uturu, Nigeria.

Source and maintenance of experimental animals

Healthy adult female Albino Wistar rats were procured from Amaka Farm, Uturu, and housed in the Animal House of the Faculty of Basic Medical Sciences, Chukwuemeka Odumegwu Ojukwu University, Uli, Anambra State. The animals were allowed to acclimatize for two weeks under standard laboratory conditions. They were maintained on vital livestock grower mash (Grand Cereals Ltd., Jos, Plateau State) and provided clean tap water *ad libitum*. Sawdust bedding was changed every three days to maintain hygiene. The rats used for the experiment weighed between 150 - 250g.

Experimental design

A total of 41 Wistar rats were used and randomly divided into four groups after acclimatization:

1. **Group 1 (Positive Control):** Received distilled water only (non-diabetic).
2. **Group 2 (Negative Control):** Induced with alloxan but received no extract.
3. **Group 3 (Treatment A):** Induced with alloxan and administered 100 mg/kg of *Cnidoscolus aconitifolius* ethanolic leaf extract.
4. **Group 4 (Treatment B):** Induced with alloxan and administered 500 mg/kg of *Cnidoscolus aconitifolius* ethanolic leaf extract.

Blood glucose levels were measured every two days for 14 days using a glucometer before feeding.

Feeding and husbandry

All animals were fed vital livestock grower mash and supplied fresh water *ad libitum*. Feed and water containers were cleaned and replaced daily. The experimental environment was maintained at room temperature with adequate ventilation throughout the study period.

Phytochemical screening of the extract

Phytochemical screening was conducted at Springboard Research Laboratory, Awka, Anambra State, Nigeria, using the ethanol (1:4 v/v) extract of *Cnidoscolus aconitifolius* leaves. Standard procedures described by Harborne (1973) and Pearson (1974) were followed to test for the presence of tannins, saponins, alkaloids, steroids, cardiac glycosides, and flavonoids.

Acute toxicity test (LD_{50})

The acute toxicity test of the ethanolic leaf extract of *Cnidoscolus aconitifolius* was conducted in the Department of Human Anatomy, College of Health Sciences, Chukwuemeka Odumegwu Ojukwu University, Uli**,** following the method of Lorke (1983).

Phase I: Nine (9) rats were divided into three groups (3 rats each):

1. Group 1: 50 mg/kg body weight.
2. Group 2: 500 mg/kg body weight.
3. Group 3: 5000 mg/kg body weight.

The animals were observed for 24 hours for signs of toxicity or mortality.

Phase II: Based on phase I results, four (4) rats were used in phase II (one per group):

1. Group 1: 6000 mg/kg body weight.
2. Group 2: 7000 mg/kg body weight.
3. Group 3: 8000 mg/kg body weight.
4. Group 4: 9000 mg/kg body weight.

Animals were again observed for 24 hours for any signs of toxicity or death.

Results

Quantitative analysis of phytochemicals carried out on the dry ethanolic leaves extract of *Cnidoscolus aconitifolius* CA showed the presence of tannins, saponins, cardiac glycosides, alkaloids, flavonoids and steroids. The results are showed in the table 2 below.

Test	Results
Saponins	5.7%
Tannins	8.8%
Alkaloids	6.2%
Cardiac Glycosides	3.9%
Flavonoids	4.4%
Steroid	2.7 mg/ml

Table 2: *Quantitative analysis of phytochemicals.*

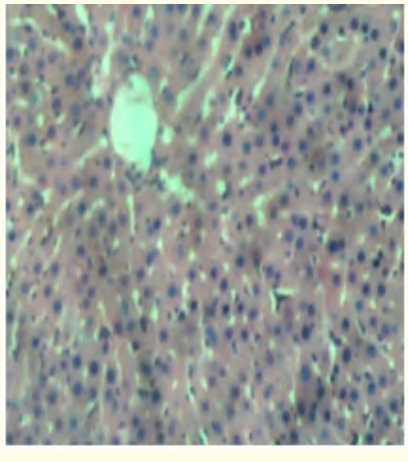

Figure 1: *Photomicrograph of the liver, positive control group (non diabetic group) stained h and e tissue section showing a central vein with normal hepatocytes (h) radiating towards the central vein. X400.*

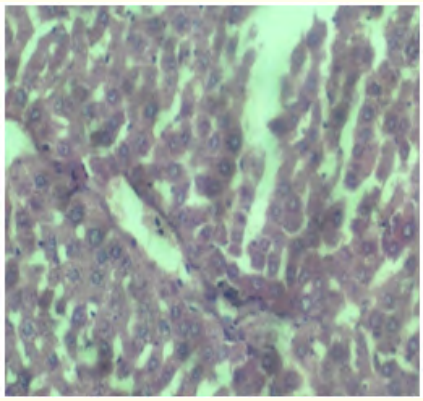

Figure 2: *Photomicrograph of the liver on the negative (control diabetics group): liver: an h and e stained tissue section showing a dilated central vein with hepatic plates radiating and some tissue section showing a deranged hepatocytes (circle) towards it. x400.*

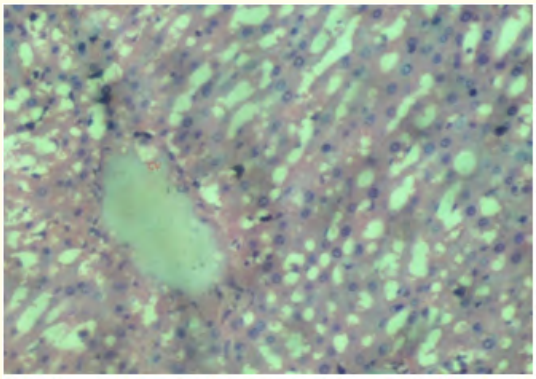

Figure 3: *Photomicrograph of the liver on the diabetic group treated with 100 mg/kg of ca extract on the liver: an h and e stained tissue section showing a central vein with normal hepatocytes with oedematous stroma, dilated central canal with few fat cells. x400.*

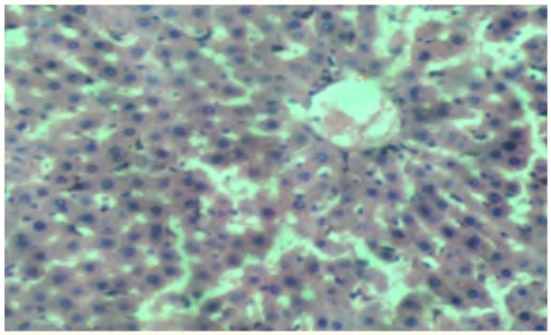

Figure 4: *Photomicrograph of the liver on the diabetic group treated with 500 mg/kg of ca extract on the liver: an h and e stained tissue section showing a central vein with hepatocytes with mucin globes and fats cells necrosis with brown materials deposits (bmd) and mild restoration of hepatocytes. x400.*

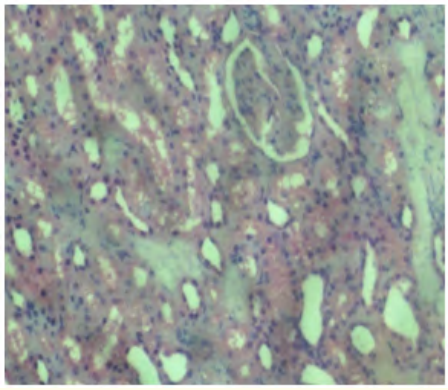

Figure 5: *Photomicrograph of the kidney on the positive (non diabetics group): an h and e stained tissue section showing intact architecture with glomerulus inside the bowman's capsule (arrow) and the renal tubules; dct/pct preserved. x400.*

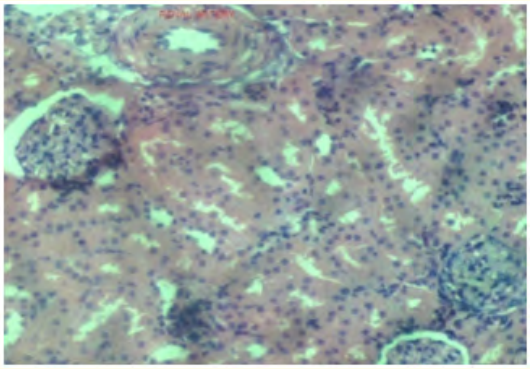

Figure 6: *Photomicrograph of the kidney on the negative (control diabetics group): kidney an h and e stained tissue section showing possible areas of necrosis, nephron destroyed with glomerular capsule partly destroyed, cellular details lost. x400.*

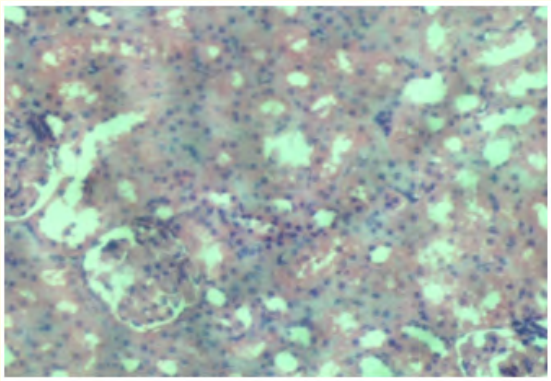

Figure 7: *Photomicrograph of the kidney treated with 100 mg/kg of ca an h and e stained tissue section showing glomerulus inside the Bowmans capsule and renal tubules (rt) with areas of possible derangement. x400.*

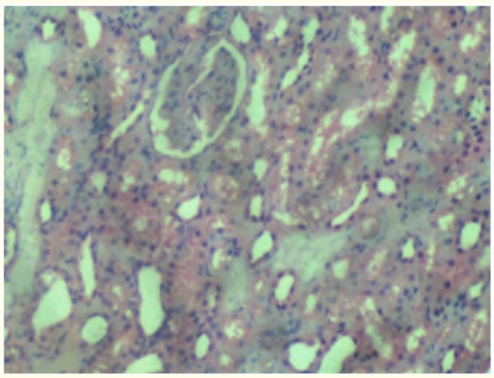

Figure 8: *Photomicrograph of the kidney treated with 500 mg/kg of ca an h and e stained tissue section showing mild restoration of glomerulus inside the Bowmans capsule and renal tubules with areas of possible derangement. x400.*

Figure 9: *Graphical illustration of the hypoglyceamic effect of ethanolic extract of CA on the glucose level of female albino wistar rats. From the above graph, it shows that as the dose of the CA increase from 100 mg/kg to 500 mg/kg from the first day (Day 0) of administration to the fourteen day (Day 12), there is statistically significant decrease in the blood glucose level.*

Days	Day 0 Mean ± SEM	Day 2 Mean ± SEM	Day 4 Mean ± SEM	Day 6 Mean ± SEM	Day 8 Mean ± SEM	Day 10 Mean ± SEM	Day 12 Mean ± SEM
Positive Control	92.2 ± 0.60	90.40 ± 0.92	87.25 ± 0.60	94.50 ± 0.58	92.28 ± 0.45	90.45 ± 0.75	89.52 ± 0.05
Negative Control	297.25 ± 0.25	275.45 ± 0.52	283.45 ± 0.25	321.42 ± 0.62	301.30 ± 0.58	301.25 ± 0.06	304.62 ± 0.58
100mg/kg Group	298.46 ± 1.95	287.25 ± 0.92	287.40 ± 0.82	272.45 ± 0.72	220.24 ± 0.54	304.48 ± 0.05	189.45 ± 0.09
500mg/kg Group	292.0.5 ± 0.91	284.48 ± 0.85	272.45 ± 0.35	271.58 ± 0.62	192.45 ± 0.65	201.52 ± 0.08	162.48 ± 0.51

f- value	2285.212	2974.718	3916.378	2982.518	3462.416	2485.313	1256.524
p- value	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Table 3: *Showing the hypoglyceamic effect of levels of glucose from day 0 to day 12 on various groups of female albino wistar rats.*

Data was analysed using one way ANOVA and values was considered significant at P < 0.05, (SEM) Standard Error Mean.

Table 3 the one way ANOVA was computed to determine the hypoglyceamic effect of level glucose from day 0 to day 12 of the various groups.

Groups	ALP (U/L) Mean ± SEM	ALT (U/L) Mean ± SEM	AST (U/L) Mean ± SEM	Urea (mg/dl) Mean ± SEM	Creatinine (mg/dl) Mean ± SEM
Positive control	498.60 ± 0.60	67.80 ± 1.13	58.50 ± 0.71	28.65 ± 0.92	0.55 ± 0.01
Negative control	525.50 ± 2.12*	130.40 ± 0.57*	159.50 ± 0.71*	38.75 ± 0.35*	0.73 ± 0.01*
100 mg/kg group	243.65 ± 1.91*	96.40 ± 0.60*	112.30 ± 0.42*	34.50 ± 0.71*	0.53 ± 0.01*
500 mg/kg group	236.25 ± 1.06*	64.40 ± 5.09*	62.25 ± 0.35*	30.15 ± 0.21*	0.56 ± 0.01*
f-value	19867.116	270.217	13946.313	109.759	152.524
p-value	0.000	0.000	0.000	0.000	0.000

Table 4: *Showing the effects of CA on of some liver enzymes and kidney marker in various groups.*

*Data was analysed using one way ANOVA and values was considered significant at P<0.05, *statistically significant, (SEM) Standard Error Mean.*

The one way ANOVA was computed to determine the effect of ethanol extract of CA on some liver enzymes (ALP, ALT and AST) and kidney makers (Creatinine and Urea) in various groups on female albino wistar rats.

The ANOVA computation revealed a statistically significant different between the positive control group and in values when compared with the treatment groups (100 mg/kg and 500 mg/kg) in values, and between the negative control group and the treatment groups (100 mg/kg and 500 mg/kg) as well.

On urea and creatinine, table 4 shows statistically decrease in value as the dose of the extract increase from 100 mg/kg to 500 mg/kg when compared with the untreated diabetic negative control group, but increase in value when compared with the untreated non diabetic positive control group.

Discussion

Oxidative stress resulting from environmental factors or drug exposure during diabetes and its treatment often elevates liver enzyme levels [43]. In this study, three hepatic enzymes were assessed Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP). Elevated concentrations of these enzymes usually indicate cellular injury in organs such as the liver, kidney, heart, or skeletal muscles.

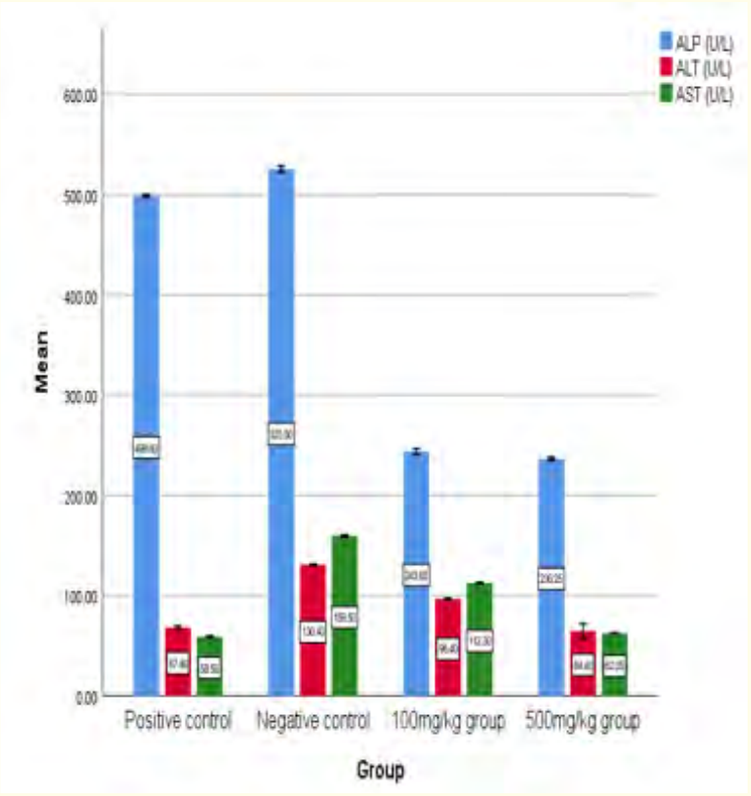

Figure 10: *Graphical illustration of mean plot of ALP, ALT, AST.*

The graph shows the effects of ethanol leaves extract of CA on some biochemical parameters of enzymes ALP, ALT, and AST level of female albino wistar rats.

The above graph illustrated that there is decrease in values of the treatment group (100 mg/kg and 500 mg/kg) when compared with the value of the negative control group of the various liver enzymes.

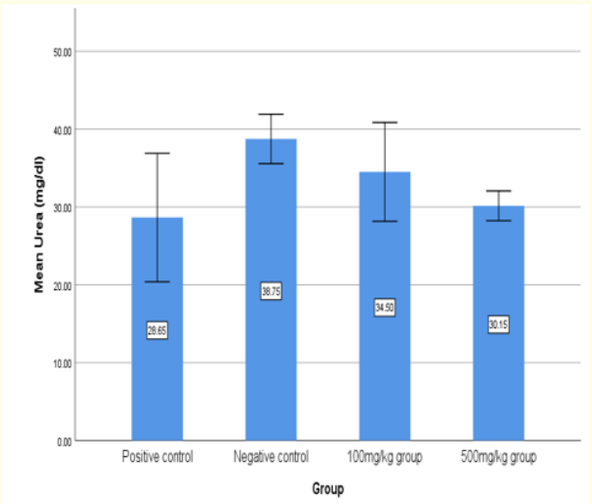

Figure 11: *Graphical illustration of mean plot of urea.*

The graph shows the effect of ethanolic leaves extract of CA on urea of female albino wistar eats, indicating a decrease in value of the treatment group (100 mg/kg and 500 mg/kg) when compared with untreated diabetic negative control group in value, but slight increased in value urea when compared with untreated non diabetic positive control group in value.

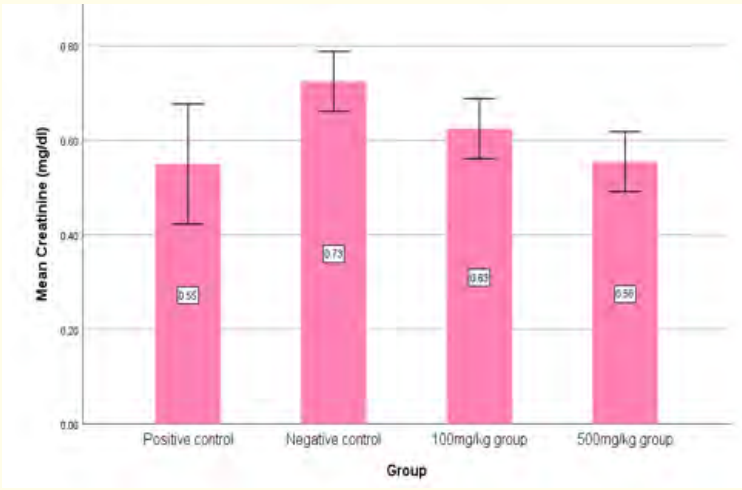

Figure 12: *Graphical illustration of mean plot of creatinine.*

The graph shows the effect of ethanol leaves extract of CA on creatinine of female albino wistar eats, indicating a decrease in value of the treatment group (100 mg/kg and 500 mg/kg) when compared with untreated diabetic negative control group in value, but slight increased in value creatinine when compared with untreated non diabetic positive control group in value.

The AST/ALT ratio can also serve as a diagnostic indicator for differentiating various causes of liver injury [48]. According to table 3, treatment with *Cnidoscolus aconitifolius* ethanolic extract significantly reduced ALT and AST levels in diabetic rats (96.40 and 64.40; 112.30 and 62.25, respectively) when compared with untreated diabetic controls (159.50 and 130.40). However, there was a slight, statistically significant increase relative to the non-diabetic control group (67.80 and 58.50, respectively).

Similarly, ALP levels decreased significantly with increasing extract doses from 100 mg/kg to 500 mg/kg (243.65 and 236.25) compared with both control groups (498.60 and 525.50). These results suggest that *C. aconitifolius* may possess hepatoprotective properties in diabetic conditions by reducing oxidative stress-induced enzyme elevation. Nevertheless, the extract should not be misused by non-diabetic individuals, as inappropriate use may cause biochemical imbalances.

The observed enzyme reductions also imply that the extract may help preserve the integrity of tissues such as the liver, kidney, skeletal muscles, and erythrocytes since damage to these organs often results in elevated serum AST levels.

Chronic hyperglycemia is known to cause severe complications, including cardiovascular damage and renal impairment [24]. Diabetic nephropathy affects approximately 25 - 40% of diabetic patients (Parving, 1998) and remains a leading cause of end-stage renal disease (ESRD) in developed nations [17]. Assessing kidney function is therefore crucial in diabetic conditions.

The glomerular filtration rate (GFR) is considered the most accurate indicator of renal performance [28]. Serum creatinine and urea levels are inversely related to GFR and are commonly used to estimate renal dysfunction [49]. While serum creatinine serves as an indirect marker of GFR, it may be influenced by diet and muscle mass [11]. Urea formation is affected by liver function, protein intake, and metabolic rate [39]. Elevated creatinine levels typically indicate renal impairment and tend to rise later than urea, signifying chronic conditions [15].

In this study, *C. aconitifolius* extract produced a significant dose-dependent decrease in serum urea levels (34.50 and 30.15 at 100 mg/kg and 500 mg/kg, respectively) compared with untreated diabetic rats (38.75). However, values remained slightly higher than in the non-diabetic control group (28.65). A similar pattern was observed for creatinine, which decreased significantly from 0.73 in untreated diabetic rats to 0.53 and 0.56 in extract-treated groups.

These findings indicate that *C. aconitifolius* exerts a protective effect on renal function by reducing urea and creatinine accumulation, thereby mitigating early signs of diabetic nephropathy. The mild elevation in urea and creatinine levels suggests that while some renal dysfunction was present, it had not progressed to chronic kidney disease. If unchecked, alloxan-induced diabetes can impair GFR, leading to the retention of nitrogenous wastes such as urea and creatinine.

Conclusion

The findings of this study indicate that the antidiabetic properties of the ethanolic leaf extract of *Cnidoscolus aconitifolius* (CA) are primarily attributed to its rich content of flavonoids and saponins, both known for their potent antioxidant and antidiabetic effects. The extract's relatively high crude fiber and low fat composition contribute to its anti-obesity potential, while its considerable iron content supports anti-anemic activity.

Daily administration of the extract for fourteen days resulted in reduced cellular necrosis in vital organs, including the liver and kidney, as well as the pancreas and ovary. It also significantly lowered blood glucose levels in diabetic rats. The antihyperglycemic effect observed demonstrates both therapeutic and preventive (prophylactic) capabilities. Additionally, the extract exhibited antihyperlipidemic and antiatherogenic activities, alongside restorative and functional enhancement of the liver, kidney, pancreas, and ovary.

Overall, the results provide phytochemical, biochemical, histological, and physiological evidence supporting the antidiabetic efficacy of *Cnidoscolus aconitifolius* ethanolic leaf extract. These findings justify further exploration and potential development of the plant extract as a safe, effective, and minimally toxic natural therapy for diabetes and its associated complications.

Recommendations

Based on the analysis and interpretation of the study's results, the following recommendations are made:

1. Phytochemical analysis: Further detailed isolation and identification of bioactive fractions in the ethanolic leaf extract of *Cnidoscolus aconitifolius* using high-performance thin-layer chromatography (HPTLC) should be conducted to ensure clearer characterization and improved reproducibility of results.
2. Compound investigation: Identified compounds within the extract should undergo additional pharmacological evaluation to determine the specific constituents responsible for the highest antidiabetic potency and safety profile.
3. Hormonal and histological studies: Future research should include hormonal assays, hematological, and histopathological studies to clarify the direct effects of the extract on hormone secretion and organ function, particularly the liver and kidney.
4. Regulatory control: The consumption and dosage of *C. aconitifolius* extract should be appropriately regulated to prevent possible dose-dependent or fraction-related adverse effects.
5. Collaborative development: Traditional healers, pharmaceutical industries, research institutions, government bodies, and non-governmental organizations should collaborate to provide materials, equipment, and expertise for proper extraction, evaluation, and utilization of this plant extract. Such collaboration will aid in mitigating diabetes prevalence, especially in resource-limited regions.

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