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Physicochemical Profile and Anti-Diabetic Property of *Clerodendrum splendens* G. Don Leaves (Verbenaceae) on Alloxan-Induced Diabetic Albino Wistar Rats.

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Abstract

C*lerodendrum splendens* G. Don (CS) is an African folk plant that is used in traditional medicine to manage diabetes. This study aimed to evaluate the physicochemical profile and antidiabetic properties of a CS ethanol extract and its solvent fractions in alloxan-induced diabetic albino rats. Dried powdered plant samples were extracted using cold maceration and fractionated using n-hexane, ethyl acetate, and water. Physicochemical and qualitative phytochemical profiling of CS leaves was performed using standard procedures. An acute toxicity study was also conducted. Diabetes was induced in albino rats by intraperitoneal injection of alloxan monohydrate (120 mg/kg). Diabetic rats were treated with 200 and 400 mg/kg of the crude extract and 200 mg/kg of each fraction. Glibenclamide (5 mg/kg) was used as a positive control, and untreated diabetic rats were used as negative controls. All treatments were administered orally once daily for 15 days, and the blood glucose levels of the rats were determined at 3 days interval after overnight fasting. A histopathological examination of the pancreas was performed. The physicochemical evaluation of the powdered sample indicated a total ash value of 4.88%, acidinsoluble ash ((0.32%), water-soluble ash (2.19%), moisture content (10.23%), ethanol extractive value of 13.16%, *n*-hexane extractive value of 1.76%, and ethyl acetate extractive of4.37%. Phytochemical analysis of the crude CS extract revealed the presence of phenols, alkaloids, flavonoids, tannins, glycosides, saponins, steroids, and terpenoids. The reduction in blood sugar levels by the CS extract at 200 mg/kg (54.05%) and 400 mg/kg (45.27%) was comparable to that of the glibenclamide group (58.07%). Histopathological examination of the pancreas revealed the regenerative potential of the extract for pancreatic islet atrophy. The CS ethanol extract has potential antidiabetic properties that could be explored for the development of new therapeutic agents.

Keywords: *Clerodendrum splendens,* Glibenclamide, alloxan, diabetes, acid-insoluble ash, moisture content.

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Introduction

Ethno-pharmacological uses of plants prevail among Nigerian people. Many drugs and chemotherapeutic agents have been developed from plants and many published reports have shown the effectiveness of traditional herbs in many diseases (Bhardwaj et al., 2023). Plants are a source of modern medicine (Obute 2005). Baker *et al.* (1995) indicated that plants continue to play a prominent role in primary health care of about 80% of the world's population. The existence of various species that bear a close resemblance in macro-morphological features but differ in micromorphology and phytochemical constituents has led to misidentification of plant species (Obi *et al*., 2021). Hence, there is a need to standardize and document the inherent and unshared characteristics of a particular plant species.

Diabetes is estimated to affect–2-3% of the world's population and is commonly referred to as diabetes mellitus (DM). It is a major emerging public health problem worldwide and is growing at an alarming rate. Diabetes is the fifth leading cause of death in the world (Mutlu *et al.* 2014). The World Health Organization (WHO) estimated that approximately 30 million people suffered from diabetes in 1985 and that this number will increase to over 366 million by 2030, with a large increase in developing countries, especially in people aged 45–64 years. The WHO Health Organization estimates that globally, 422 million adults aged over 18 years were living with diabetes in 2014 (Harreiter *et al.,* 2016).

Diabetes mellitus (DM) is an endocrine disorder characterized by hyperglycemia due to the altered metabolism of lipids, carbohydrates, and proteins caused by insulin deficiency, often combined with insulin resistance (Zhao *et al*., 2023). Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced glucose uptake by skeletal muscles with reduced glycogen synthesis (Ramasarma and Rafi, 2016).

There are two types of diabetes mellitus. Type 1 and type 2 diabetes mellitus. Type 1 diabetes mellitus is also known as insulin-dependent diabetes mellitus (IDDM). It usually develops in childhood or early adulthood. Antibodies that destroy β-cells are also present. Macrophages and T lymphocytes mediate autoimmune processes by producing autoantibodies against β cell antigens (Barbara *et al.,* 2012). Normally, glucagon secretion is reduced during hyperglycemia. However, glucagon secretion is not suppressed by hyperglycemia in patients with IDDM (Bozadjieva *et al*., 2021). Therefore, inappropriately elevated glucagon levels exacerbate metabolic defects caused by insulin deficiency. In the absence of insulin, Patients with IDDM develop diabetic ketoacidosis rapidly. Insulin deficiency leads to uncontrolled lipolysis and elevated levels of

Free fatty acids in the plasma suppress glucose metabolism in peripheral tissues such as skeletal muscle (Raju and Raju, 2010). Type 2 Diabetes mellitus is also known as noninsulin-dependent diabetes mellitus (NIDDM). No autoimmune destruction of the pancreas was observed. Insulin resistance is caused by increased lipolysis and free fatty acid production, increased hepatic glucose production, and decreased glucose uptake in skeletal muscle (Dimitriadis *et al.,* 2011). Patients with diabetes mellitus are resistant to the action of insulin, and there is a high tendency to develop macrovascular and microvascular complications (Aljabery *et al*., 2020).

Clerodendrum splendens is commonly known as the glory tree, and belongs to the Verbenaceae family. It is a climbing evergreen bush plant with attractive red flowers produced during the dry season (Obi *et al.,* 2022). It is composed of small trees, shrubs, and herbs that are commonly used in the tropics as ornamental plants (Brickell and Zuk, 1997). The leaves were opposite, simple, long, and 2-6.5 cm broad, with an entire margin, dark green on the inner side, and pale green on the outside. The texture is smooth, and the leaf is petiolate (Sunil *et al.,* 2014). The leaves and bark of *C. splendens* are used in traditional medicine to treat many diseases including urinary tract inflammation, tumors, skin disorders, ulcers, abdominal pain, fibroids, gonorrhea, and syphilis (Okwu and Iroabuchi, 2008). Studies carried out by various researchers have shown that the plant has several properties, including hepatoprotective potential, lowering of plasma lipid levels (Obi *et al.,* 2021), antimicrobial and woundhealing properties (Gbedema *et al.,* 2010), and antipyretic and anti-inflammatory effects (Abouzid *et al.,* 2013). However, to the best of our knowledge, there is no information available on the antidiabetic properties of C. *splendens* leaves. This study was designed to investigate the physicochemical constituents and antidiabetic properties of C. *splendens* leaf extract.

Material and Method

Collection and Preparation of Plant Sample

The leaves of *Clerodendrum splendens* were collected from Nsukka in Enugu State, Nigeria, in August 2020 and authenticated by a taxonomist, Mr. A. O. Ozioko of the International Centre for Ethnomedicine and Drug Development (InterCEDD). A voucher specimen was preserved in

the herbarium of the Department of Pharmacognosy at Enugu State University of Science and Technology. The collected leaves were dried at room temperature under a shade for 10 days and pulverized into coarse powder form using a suitable grinder, and the powdered leaves sample was stored in an airtight container ready for extraction.

Physicochemical Evaluation of Plant Sample

The physicochemical evaluation of the leaves was performed using standard methods described by Evans (2009).

Extraction and Fractionation

The extraction process was carried out using 450 g of the pulverized leaves, macerated in 2500 ml of ethanol (analytical grade) for 72 h, and then filtered using Whatman (No1) filter paper. The extract was concentrated using a rotary evaporator at 40 °C and 120 resolutions per minute (rpm) until a dried extract was obtained and weighed. The dried ethanol extract was washed with *n*-hexane, ethyl acetate, and aqueous ethanol using a separating funnel (liquid – liquid fractionation), and the individual fractions were concentrated using a rotary evaporator set at 40 °C and 120 rpm. The resulting extracts were oven dried at 40 °C.

Chemicals

All chemicals and drugs used in this study were commercially obtained and of analytical grade. Alloxan monohydrate was purchased from Sigma–Aldrich (St. Louis, MO, USA). Louis, USA), glibenclamide (Aventis Pharma Ltd, Goa, India)

Phytochemical Screening

Phytochemical screening of the plant extracts was performed using the standard procedures outlined by Evans (2009) and Harborne (1973) for the presence of secondary metabolites, such as alkaloids, steroids, tannins, flavonoids, glycosides, and saponins.
Preparation of Experimental Animal

Adult albino Wistar Rats (150–200 g) of both sexes bred at the University of Nigeria were used throughout the study. The animals were housed in metallic cages for two weeks for acclimatization under standard environmental conditions, which included an ambient temperature of 22±2°C and–4555% relative humidity. The animals were fed a standard rat pellet diet and water *ad libitum,* except during the day of blood sampling when the animals were used after an overnight fast. The care and handling of animals were in accordance with internationally accepted principles for laboratory animal use and care, and the experimental protocols were in accordance with the ethics guidelines established by the Enugu State University of Science and Technology Ethics Committee (approval reference number: ESUT/AEC/0190/ AP114).

Acute Toxicity Study (LD_{50})

Acute toxicity of the plant extract in rats was determined using the standard method described by Lorke (1983).

Oral Glucose Tolerance Test (OGTT)

Oral glucose tolerance tests were performed according to the procedure described by Aguwa and Omole (2004). Overnight-fasted normal albino Wistar rats were administered an oral glucose load of 4 g/kg, and blood samples were collected at intervals of 0, 15, 30, 45, 60, and 120 min. A plasma glucose level of ≥ 200 mg, maintained for a longer period, was considered diabetic.

Induction of Diabetes in Rats

Diabetes was induced using the standard methods described by Odoh *et al.* (2014) and Obi *et al.* (2022). A single intraperitoneal injection of alloxan monohydrate solution (120 mg/kg body weight) was used to induce diabetes in albino Wistar rats that had fasted for 12–14 h. For three days, the alloxanized rats had unrestricted access to food and water. On the fourth day, the animals were fasted for 12-14 h but permitted free access to water and their fasted blood glucose levels were assessed using Acucheck Glucometer

Anti-diabetic Study

The animals were divided into nine groups (A-H) with four rats in each group. Group A consisted of normal non-diabetic rats that received normal saline, while Group B received normal saline, and Group C received 5 mg/kg glibenclamide (standard antidiabetic drug). Groups D, E, F, and G received 200 mg/kg each of n-hexane, ethyl acetate, aqueousethanol, and crude extracts, respectively, while Group H received 400 mg/kg of crude extract.

(a) Group A = Normal Rats that received normal saline (vehicle).
(b) Group B was used as a negative control and received normal saline.
(c) Group C = Positive Control and received glibenclamide 5 mg/kg (standard drug)
(d) The D = N-hexane fraction group was treated with 200 mg/kg of the n-hexane fraction.

(e) Group E = Ethyl acetate fraction group treated with 200 mg/kg ethyl acetate fraction.
(f) Group F = Aqueous ethanol fraction group treated with 200 mg/kg aqueous fraction.
(g) Group G = Crude extract group (I) treated with 200 mg/kg crude extract.
(h) Group H = Crude extract group (II) treated with 400 mg/kg crude extract.

The doses were administered orally once daily for 14 days, and the blood glucose levels of the rats were determined at 4-day intervals (days 0, 4, 8, 12, and 16) following overnight fasting. Blood samples were obtained from the tail vein, and blood glucose levels were determined using a One-Touch Acuchek Glucometer.

Preparation of Pancreas Tissue for Histopathological Examination

The pancreases of rats from each group were harvested and sections were prepared for histopathological examination following the methods described by Patrick *et al.* (2022).

Statistical Analysis

The results obtained from the study are presented as mean ± standard deviation, while the raw data were analyzed statistically using one-way analysis of variance (ANOVA), followed by Tukey's comparison test for significance. Statistical significance was set at $P < 0.05$.

RESULTS

Extractive yield

Ethanol produced an extractive value of (13.16 %), water extractive value (14.95 %), *n*-hexane extractive value (1.76 %), ethyl acetate extractive value (4.37 %), and aqueous ethanol (5 %) (Table 1). Water produced the highest extraction yield, followed by ethanol. Among these fractions, aqueous ethanol produced a higher yield than *the n*hexane and ethyl acetate fractions.

Physicochemical evaluation of the powdered sample

Physicochemical analysis of *C. splendens* powdered leaves, indicated total ash value of 4.88%, acid insoluble ash 0.32%, water-soluble ash 2.19%, and moisture content 10.23% (Table 2)

Preliminary phytochemical constituents of Clerodendrum splendens leaf

The crude ethanol extract contained glycosides, alkaloids, saponins, steroids, tannins, phenols and terpenoids (Table 3).

Acute toxicity test

The crude extract of *C. splendens* was safe up to a dose of 5000 mg/kg because no death or behavioral changes were observed in the rats 24 h after administration.

Oral glucose tolerant test (OGTT) of the experimental rats

All experimental animals in all treatment groups showed normal glucose tolerance levels within 2 h of monitoring (Figure 2).

Antidiabetic effects of the extract and fractions

The results showed an increase in blood sugar levels from day 0 to day 5; however, from day 10 -21 reduction of, blood sugar reduction was evident in all treated animals. The n-hexane fraction showed the highest percentage reduction in blood sugar level (58.51 %), which was comparable to that of the positive control group (58.07%) on day 21 (Fig 3 and Table 4).

Table 1: Results of extractive values using solvents of different polarities

S/N	Solvents	% Yield
1	Ethanol	13.16
2	Aqueous/water	14.15
3	n-hexane	1.76
4	Ethyl acetate	4.37
5	Aqueous ethanol	5.00

Table 2: Results of the Physicochemical evaluation of *Clerodendrum splendens* leaf

S/N	PARAMETER	RESULT (%)
1	Moisture content	10.23
2	Total ash	4.88
3	Acid insoluble ash	0.32
4	Water soluble ash	2.19

Table 3: Results of Phytochemical Screening of the Extract

Phytochemical	Ethanol extract
Glycosides	+
Flavonoids	-
Alkaloids	+
Saponins	+
Steroids	+
Tannins	+
Terpenoids	+
Phenols	+

Keys: – = Absent; + = Present

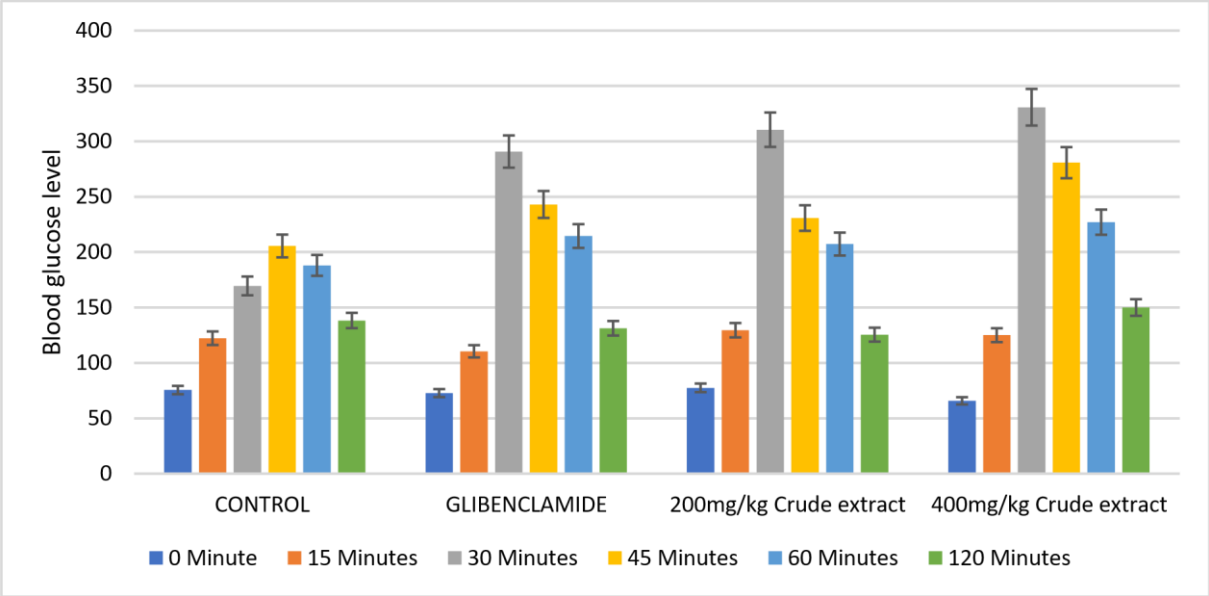

Figure 2: Effect of crude ethanol extract on blood glucose levels in the OGTT of normal rats.

Table 4: Effect of the extracts and fractions on fasting blood glucose levels in diabetic rats

Groups	Initial FBG	FBG After Diabetes Induction				
		FBG day 0	FBG day 5	FBG day 10	FBG Day 15	FBG Day 21
Normal Rats	75.66± 2.31	94.00 ± 1.47	101.75 ± 5.27	89.50 ± 6.29	92.50 ± 4.01	105.00 ± 3.72
Negative control	70.50 ± 3.20	216.80 ±	274.76 ± 23.29	391.02 ± 9.00	498.73 ± 63.82	-
Glibenclamide	61.33 ± 1.87	251.25 ± 30.26	203.00 ± 29.29* (19.20%)	166.75 ± 7.95* (33.63%)	111.00 ± 29.55* (55.82%)	105.35 ± 25.84* (58.07%)
N-hexane 200 mg/kg	66.5 ± 3.11	258.50 ± 27.28	208.75 ± 22.44* (19.25%)	163.75 ± 20.38* (36.65%)	115.00 ± 2.27* (55.51%)	107.25 ± 4.61* (58.51%)
Ethylacetate 200 mg/kg	95.75 ± 1.90	263.75 ± 30.55	249.00 ± 43.33 (5.59%)	222.75 ± 42.92* (15.54%)	262.50 ± 52.05* (0.47%)	208.25 ± 100.9* (21.04%)
Aqueous ethanol 200mg/kg	58.75 ± 1.82	267.00 ± 32.92	232.50 ± 13.60* (12.92%)	164.75 ± 15.11* (38.30%)	189.75 ± 63.57* (28.93%)	258.00 ± 89.92* (3.37%)
Crude extract 200 mg/kg	65.50 ± 2.61	242.00 ± 14.47	207.50 ± 29.88* (14.26%)	192.42 ± 11.41* (20.49%)	101.17 ± 5.68* (58.19%)	111.21 ± 3.22* (54.05%)
Crude extract 400 mg/kg	63.75 ± 2.62	224.09 ± 50.11	202.14 ± 54.16* (9.80%)	144.30 ± 7.35* (35.61%)	106.29 ± 5.17* (52.56%)	122.65 ± 24.12* (45.27%)

Results are expressed as mean ± SEM. n = 4. Statistical significance was set at *P < 0.05

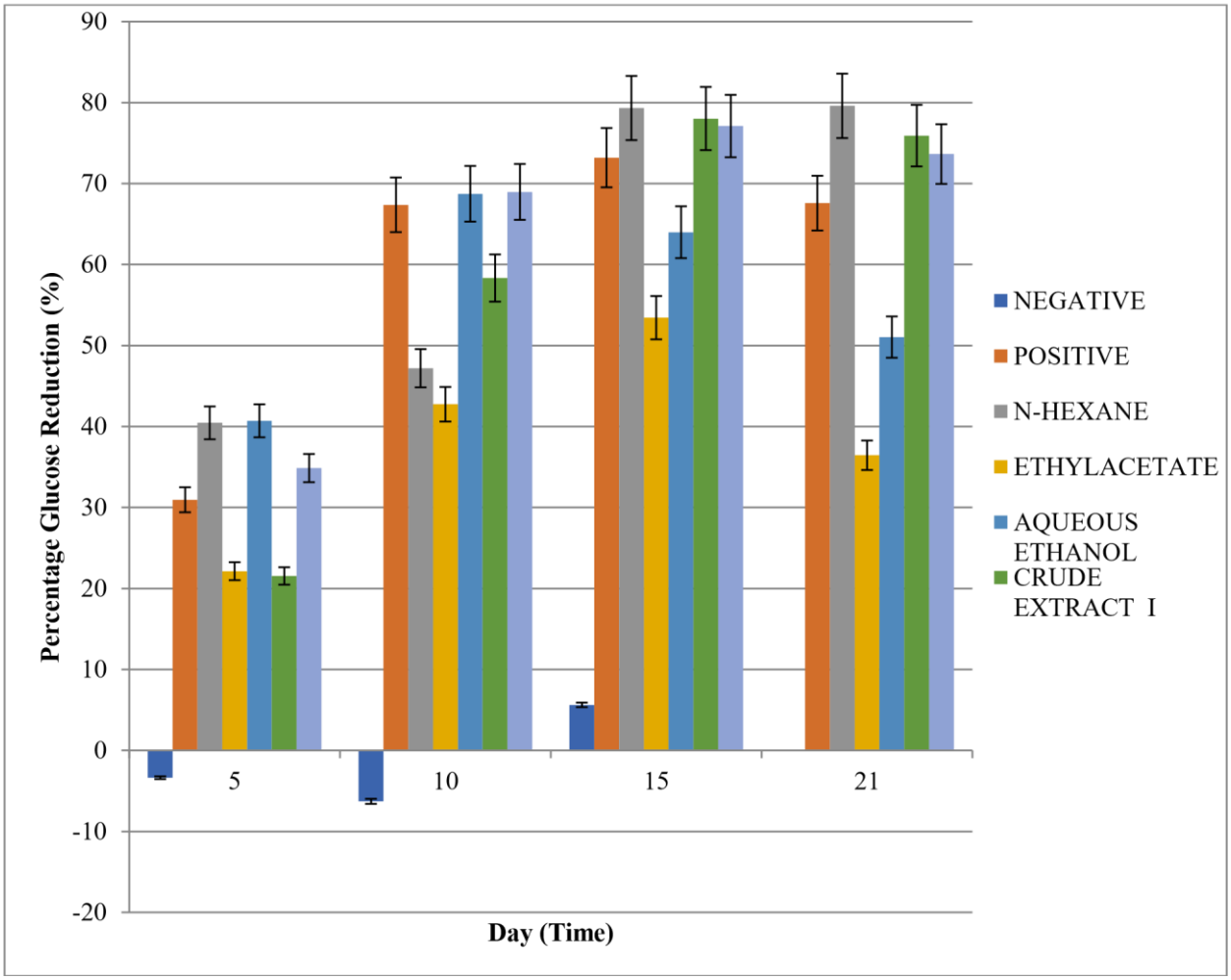

Figure 3: Percentage reduction of fasting blood glucose levels in diabetic rats treated with 200 mg/kg and 400 mg/kg extracts and 200 mg/kg of each fraction.

Histopathology of pancreatic sections from rats treated with the extract.

Histopathological examination of the pancreas revealed that untreated rats had normal histomorphology of the endocrine pancreas. Large pancreatic islets (P) consisting mostly of beta cells, which are pale polygonal cells with single centrally located nuclei, were observed. Islets were frequent and varied in size (Figure 4). In Figure 5, the pancreatic section is marked by widespread atrophy of pancreatic islets. Figure 6 shows a section of the pancreas with regeneration of pancreatic islets (P). Figure 7 shows a section of the pancreas with regeneration of pancreatic islets (P). However, the islets were mostly small. Additionally, Figure 8 shows pancreatic sections with regeneration of the pancreatic islets (P).

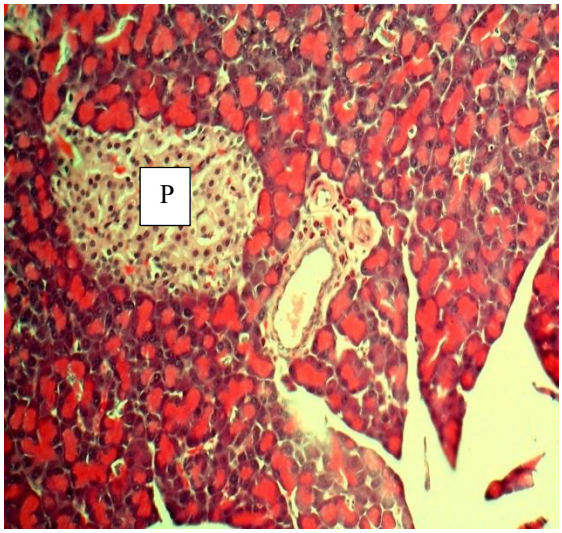

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Figure 4: Photomicrograph of pancreas section of the untreated rat.

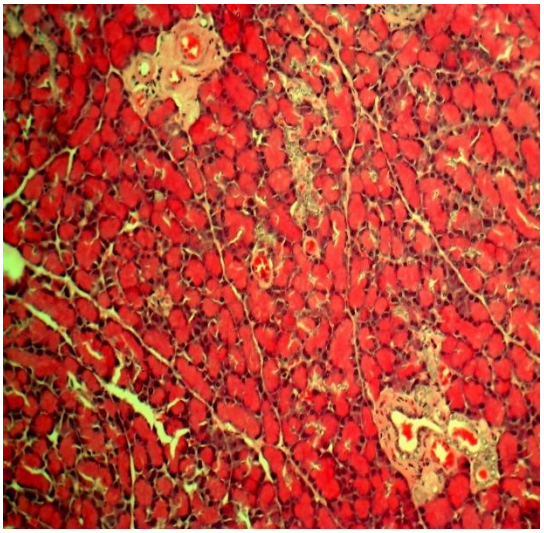

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Figure 5: Photomicrograph of pancreas section of the rat treated with normal saline (negative control).

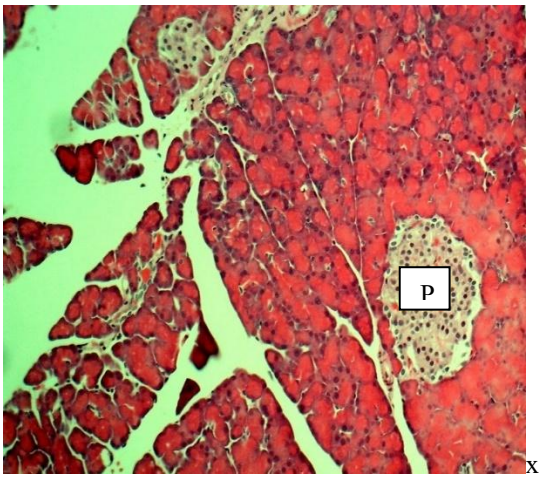

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Figure 6: Photomicrograph of pancreas section of rat that received glibenclamide 5mg/kg (standard drug).

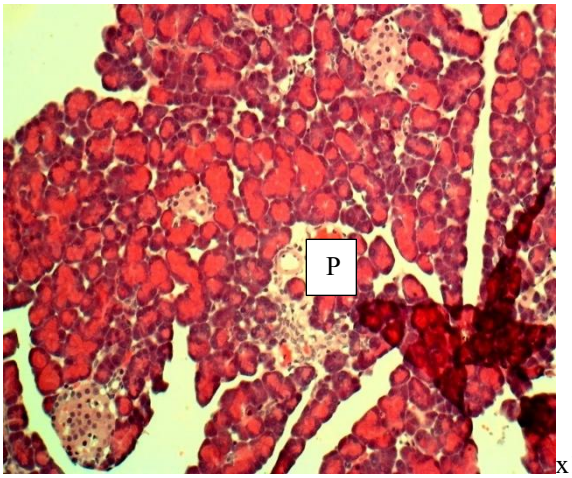

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Figure 7: Photomicrograph of pancreas section of rat treated with 400 mg/kg crude extract of *C. splendens*.

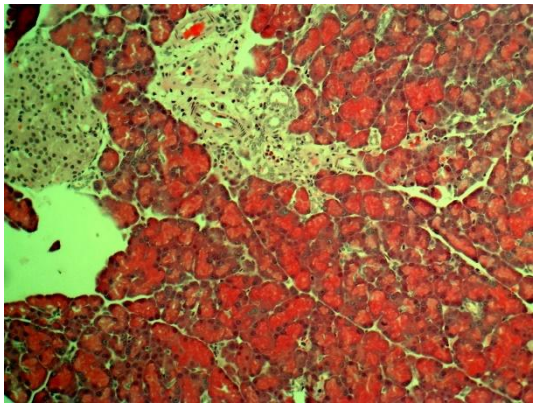

Figure 8: Photomicrograph of pancreas section of rat that received 200 mg/kg of *C. spledens*

Discussion

Diabetes is one of the largest global health emergencies of the 21st century (Standl *et al*., 2019). There is a need for safer, more effective, and less costly treatments, as currently available evidencebased complementary and alternative drug regimens for Diabetes Mellitus have limitations. Thus, investigating plant-derived compounds for diabetes mellitus is an attractive research area because they are believed to be safe, easily accessible, and do not require laborious pharmaceutical synthesis (Rahman *et al.,* 2022).
Preliminary phytochemical screening was performed using a color-forming test and precipitating chemical reagents to detect the presence of plant constituents in the extracts. The results revealed that the plant contains many secondary metabolites, such as alkaloids, saponins, tannins, phenols, steroids, and terpenoids in the absence of flavonoids. Thus, the significant antidiabetic effects of *C. The observed splenens* could be due to the presence of the above-mentioned components in the extracts, which could act synergistically or independently to enhance glycolytic enzyme activity. According to Wang *et al. (*2010), some alkaloids are hypoglycemic agents. For instance, berberine, a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids, has been successfully used in experimental models of diabetes mellitus and clinical studies (Behl *et al*., 2022). Therefore, further studies should be carried out to isolate and evaluate the antidiabetic properties of *Clerodendrum splendens* leaves. The results of the moisture content analysis show that the powdered drug has a low moisture content (10.23%) and therefore will have high stability during storage and will not be prone to some storage factors due to high water activities. The high-water activity in pharmaceutical products encourages microbial infestation, which eventually leads to microbial degradation. Therefore, powdered leaves can be stored for extended periods. There is an insignificant amount of extraneous earth matter, such as siliceous earth matter, sand, and water-soluble salts in the powder leaf, based on the results obtained from the total ash, acid-soluble, and water-soluble ash. These parameters can help to identify any adulteration in the product, and this insignificant amount is evidence that the plant sample was properly handled.
An acute toxicity study showed that the administration of graded doses of 70% ethanol leaf extracts of *C. splendens* did not generate any observable signs of toxicity up to a dose of 5000 mg/kg after 24 h of administration; they were physically active. This was confirmed by the absence of significant changes in behavior, such as alertness, motor activity, sluggishness, paralysis, tachycardia, restlessness, diarrhea, convulsions, and even coma. The results showed that the plant extracts had no observable adverse effects at the doses tested, which implies that the lethal dose (LD50) was greater than 5000 mg/kg body weight in mice. A single dose of alloxan (120 mg/kg) induces diabetes in animals by elevating FBG levels above 200 mg/dl. Alloxan is a beta cytotoxin. It induces diabetes in a wide variety of animal species by damaging insulin-secreting pancreatic beta cells, which results in a decrease in endogenous insulin release, paving the way for the decreased utilization of glucose by the tissues (Ighodaro et al., 2017). Therefore, this leads to various metabolic aberrations in animals, such as increased blood glucose levels, as observed in the study after administration. Alloxan monohydrate was chosen as the diabetes-inducing agent because it is known to produce diabetes mellitus irreversibly

with a single dose administration by selective necrotic action on the beta cells of the islets of Langerhans, leading to relative insulin deficiency. The significant lowering of FBG levels in alloxan-induced diabetic animals after administration of the extract and fractions, especially n-hexane fractions, is an indication of the hypoglycemic activity of C. splendens leaf extract. The results of the antidiabetic studies suggest that the extract and all its fractions possess varying degrees of hypoglycemic potency, since all produced at least a 25 % reduction in the FBG of the animals on a given day after three days of treatment. Kahn and Shechter (1991) suggested that a 25 % reduction in blood glucose levels is a significant hypoglycemic effect. Although the exact mechanism of action of the test samples has not been investigated, they possibly act by potentiating the insulin effect, either by increasing pancreatic secretion of insulin from beta cells of the pancreatic islets of Langerhans or by increasing peripheral glucose uptake. Pancreatic α-amylase is a vital enzyme that hydrolyzes starch into smaller oligosaccharides that are further broken down into glucose by α-glucosidase. The resulting glucose enters the bloodstream upon absorption, leading to increased postprandial hyperglycemia (PPHG). Hence, plant extracts with the potential to inhibit these two enzymes may be valuable in lowering PPHG-associated complications in type 2 diabetes (Sudha *et al.,* 2011). They can act similar to glibenclamide, which secretes insulin from beta cells in type II cells. Type II diabetes is characterized by reduced pancreatic insulin secretion, insulin resistance, or both. Since the standard drug glibenclamide, as well as the tested plant samples, was found to be effective in lowering blood glucose levels in alloxan-induced diabetic rats, it is possible that alloxan did not completely destroy pancreatic cells, suggesting a model of type II diabetes in this study.

Treatment of alloxan-induced diabetic animals with the extract and its various fractions produced a decline in FBG levels, which was generally sustained throughout the 16 days of treatment. This indicated that the extracts and fractions had hypoglycemic activity. The n-hexane fraction showed the highest antidiabetic activity, but the ethyl acetate fraction was more consistent, which may be a result of secondary metabolites such as terpenoids, which are mostly found in the ethyl acetate fraction of the plant extract. Terpenoids in *C. splendens* have been implicated in most of the biological activities reported in previous studies. Terpenes are a large class of plant secondary metabolites, with a large percentage of their members having antioxidant and antidiabetic activities in several research publications.

Conclusion

This study has demonstrated the anti-hyperglycemic potential of the ethanol extract of *Clerodendrum splendens* leaf and provided justification for its ethnomedical use. The general results of this study can be a base reference standard for further work on the plant because there is enough evidence to support the claim based on the results obtained.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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