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Antidiabetic effect of aqueous stem bark extract of *Parinari macrophylla* in alloxan-induced diabetic Wistar rats

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Abstract

Background: Diabetes is a major public health problem with increasing prevalence globally. Plant-based medicines for diabetes are gaining popularity across the world due to perceptions of efficacy, safety and cost-effectiveness. The plant, *Parinari macrophylla*, has been widely reported to possess potent ethnomedicinal properties especially in the northern part of Nigeria. However, there has been no scientific documentation of this plant to be used as an antidiabetic agent. The objective of this study was to investigate the antidiabetic effect of aqueous stem bark extract of *P. macrophylla* in alloxan-induced diabetic Wistar rats. Phytochemical screening and acute toxicity studies were conducted. Wistar rats weighing between 100 and 150 g were used for the study and diabetes was induced using alloxan monohydrate (150 mg/kg) intraperitoneally. The animals were treated with different doses of aqueous stem bark extract of *P. macrophylla* (1000 mg/kg and 2000 mg/kg) for 2 weeks. Blood glucose levels and body weight were then monitored. Histopathological investigation of pancreatic tissue was also conducted.

Results: The phytochemical analysis revealed the presence of alkaloids, saponins, tannins, cardiac glycosides, carbohydrates, steroids, and triterpenes as secondary metabolites. The acute toxicity test revealed no mortality with a median lethal dose determined to be above 5000 mg/kg. Although the two different doses of aqueous stem bark extract of *P. macrophylla* decreased blood glucose levels at weeks 1 and 2, a statistically significant difference ($P < 0.05$) was only observed for the group treated with 2000 mg/kg dose compared to the diabetic control group at week 2. The histological investigation revealed that the two different doses of aqueous stem bark extract of *P. macrophylla* caused regeneration of pancreatic islet cells, with the 2000 mg/kg dose being more evident.

Conclusion: This study suggests that the stem bark extract of *P. macrophylla* possesses a potent antidiabetic effect and may potentially be used to treat diabetes and associated complications.

Keywords: Antidiabetic effect, Alloxan, Blood glucose levels, Pancreatic islet cells, *Parinari macrophylla*

Background

Diabetes is a major public health problem with increasing prevalence globally. Current estimates suggest that around 463 million adults in the world are suffering from diabetes and the figure is expected to escalate to 578 million by 2030 and 700 million by 2045 [1]. It is

considered to be one of the major causes of morbidity and mortality in both developed and developing countries. However, the prevalence of diabetes in low- and middle-income countries has been rising more rapidly compared to high-income countries. The impact is particularly more devastating in sub-Saharan Africa primarily due to lack of adequate funding for non-communicable diseases, lack of availability of studies and guidelines specific to the population, and lack of availability of medications to mention but a few [2]. About

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20 million adults aged 20–79 years are living with diabetes in sub-Saharan Africa, with about 60% of these undiagnosed. This figure is projected to increase to 28.6 million by 2030 and 47.1 million by 2045 [1]. The prevalence of diabetes in Nigeria was reported to be around 5.77%, with about 11.2 million people living with the disease [3].

Diabetes is a metabolic disorder primarily characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism as a result of defects in insulin secretion, insulin action, or both [4]. The most common type of diabetes is type II or insulin-independent diabetes and accounts for about 90–95% of all cases. Although type I or insulin-dependent diabetes is commonly seen in children, it may also occur in adults [5]. Most diabetes-related complications are due to high levels of glucose in the blood (hyperglycemia). The impact of persistent hyperglycemia in diabetes includes long-term damage, dysfunction, and failure of various organs, especially the eyes, heart, kidneys, nerves, and blood vessels [6]. Thus, diabetes is a complex chronic disorder necessitating continuous medical care with multifactorial risk-reduction strategies beyond glycemic control [7].

The current management of diabetes includes diet, exercise, insulin injection, and oral glucose-lowering drugs [8]. However, synthetic medications are known to be associated with high cost and unpleasant side effects [9–11] and besides cannot cure diabetes since the oral medicines used are not capable of restoring normal glucose homeostasis or controlling all the pathological aspects of the disease [12]. Conversely, plant-based medicines for diabetes are gaining popularity across the world due to perceptions of efficacy, safety and cost-effectiveness [13]. In fact, traditional medicinal practitioners (herbalists) from different parts of the world claim to cure diabetes or at best reduce its major symptoms and progression through the administration of plant-based medicines [12]. In view of the foregoing, alternative treatments to contemporary pharmacotherapy of diabetes are highly needed especially in low-resource income settings where a number of patients cannot afford orthodox therapies.

Several varieties of medicinal plant species have been used traditionally to manage diabetes and many other ailments. There have been more than 400 medicinal plant species reported in the literature to possess antidiabetic properties even though only a few have been proven scientifically as effective antidiabetic agents [14, 15]. In Nigeria, many plant species have been documented to possess potent antidiabetic properties [16–18], thus are of significant importance in tackling diabetes in this context. One plant believed to possess potent ethnomedicinal properties is *Parinari macrophylla* (Sabine) also known as *Neocarya macrophylla*, which

belongs to the family *Chrysobalanaceae*. This plant is found abundantly in the tropical regions of Africa. The plant has been used extensively in the northern part of Nigeria for treating numerous diseases including asthma, dysentery, inflammations, pulmonary troubles, skin infections, eye and ear infections, and wounds [19]. Previous phytochemical screening of *P. macrophylla* plant [19, 20] suggests the presence of various secondary metabolites including carbohydrates, alkaloids, flavonoids, anthraquinones, saponins, tannins, glycosides, steroids, and triterpenes all of which may account for the potent pharmacological activities of the plant.

Although *P. macrophylla* has been reported to possess potent ethnomedicinal properties [19–21], there is no available scientific documentation of this plant to be used as an antidiabetic agent despite many testimonies by traditional medicinal practitioners for using it in the treatment of human diabetes (local communication). Thus, it is imperative to explore the scientific evidence of using this plant for potential safe consumption as an antidiabetic agent in humans as it was earlier claimed. This study, therefore, aimed at investigating the antidiabetic effect of aqueous stem bark extract of *P. macrophylla* in alloxan-induced diabetic Wistar rats. The plant may provide safe, cheap and effective treatment for patients suffering from diabetes especially in low-resource settings like rural Nigeria.

Methods

Plant material

The fresh stem bark of *P. macrophylla* was collected from Kufena village, Zaria, Kaduna State, Nigeria. Botanical authentication of the plant parts was carried out at the herbarium unit of Biological Sciences Department, Ahmadu Bello University, Zaria, Kaduna State, Nigeria. It was identified with a voucher specimen no.: 012341 and deposited at the herbarium unit.

Preparation of plant extracts

The fresh stem bark of *P. macrophylla* was air-dried and made into powder using pestle and mortar. The air-dried powdered plants (800 g) materials were extracted with water using soxhlets apparatus. The solvent was removed by vacuum evaporation using a rotary evaporator. A dark brown residue weighing 63.9 g was obtained and kept in a sealed container and stored in a refrigerator at about 4 °C until use.

Experimental animals

Thirty-two apparently healthy male Wistar strain albino rats (8–10 weeks old) weighing 100–150 g were obtained from Animal House, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna. The animals

were kept in well-aerated laboratory cages and were allowed to adjust to the laboratory conditions for a period of 2 weeks before the commencement of the experiment. They were fed with grower and starter mash from Vital Feeds Company and water was provided ad libitum during the stabilization period. The principles governing the use and care of laboratory animals, and the experimental protocol were strictly followed in accordance with the National Research Council, Guide on the Care and Use of Laboratory Animals [22]. The study was approved by the Research Ethics Committee of Nigerian Defence Academy, Kaduna, Kaduna State, Nigeria (Ref: NDA/PGS/FS/M/1826/14).

Phytochemical screening

The preliminary phytochemical screening of the crude extracts of *P. macrophylla* was conducted at Pharmacognosy Department, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Kaduna to ascertain the presence of their constituents by utilizing standard conventional protocols [23]. The extracts were screened for alkaloids using Mayer's test and Wagner's test, saponins using Frothing test, tannins using Ferichloride test, anthracene derivatives using Bontrager's test, cardiac glycosides using Keller-Killiani test and NaOH test, flavonoids using Shinoda test and NaOH test, carbohydrates using Mollish test, and steroids and triterpenes using Liebermann-Burchard test. These tests were carried following the standard protocols reported in the literature [24–26].

Acute toxicity studies

The median lethal dose (LD₅₀) of the plant extract was determined by the modified method of Lorke [27] using 12 rats. In the first phase, rats were divided into 3 groups (3 rats per group) and were treated with the extract at doses of 10, 100, and 1000 mg/kg body weight orally. They were observed for 24 h for signs of toxicity. In the second phase, 3 rats were divided into 3 groups (1 rat per group) and were also treated with the same extract but at doses of 1600, 2900, and 5000 mg/kg body weight orally. The median lethal dose (LD₅₀) was obtained using the second phase.

Induction of experimental diabetes mellitus

Twenty rats were used for the experiment. The rats fasted for 24 h but they were allowed water ad libitum. Diabetes was induced in 15 of the 20 rats using a single intra-peritoneal injection of alloxan monohydrate at the dose of 150 mg/kg [28]. Because alloxan has the potential to produce fatal, hypoglycemia as a result of massive pancreatic release of insulin, the rats were kept for the next 24 h on 5% glucose solution bottles in their cages to prevent hypoglycemia [29]. After 72 h of alloxan

administration, the blood glucose levels (BGLs) of the rats were determined. The rats with BGL > 200 mg/dl were considered diabetic [30]. The body weight of the animals was monitored daily for 2 weeks.

Experimental design

The diabetic rats were randomly divided into three groups (B–D) comprising five rats per group ($n = 5$). Diabetes was not induced in group A, which represents the normal control group, but received 10 ml/kg of sterile distilled water orally. Group B which represents the diabetic control group received a standard oral hypoglycemic agent: 10 mg/kg of glibenclamide. Groups C and D (experimental groups) received oral dose of 1000 mg/kg and 2000 mg/kg body weight of aqueous stem bark extract of *P. macrophylla* respectively. All treatments were administered on daily basis for 2 weeks.

Determination of blood glucose levels

All blood samples were collected from the tail vein of the rats. BGL was determined at an interval of week 0 (0 day), week 1 (7th day), and week 2 (14th day). The determination of the BGLs was done by the glucose-oxidase method [31] using the digital glucometer (Accu-Check advantage, Roche Diagnostic, Germany), and results were reported in mg/dl.

Histological investigation of the pancreas

The animals in the normal control and the two experimental groups were sacrificed after the 2 weeks of treatment using chloroform inhalation as anesthesia. The rats were individually placed in an airtight plastic box containing drops of chloroform (37%) in cotton wool until they become unconscious (maximum time: 2 minutes). An incision was made in the abdomen and sections of their pancreatic tissue were removed and processed for histological examinations at the Gross Anatomy Research Laboratory, Department of Human Anatomy, Faculty of Medical Sciences, Ahmadu Bello University, Zaria, Kaduna State.

Statistical analysis

Data collected were summarized using descriptive statistics of mean and standard error of measurement (mean \pm SEM). One-way analysis of variance (ANOVA) was used to assess difference between the groups in BGLs and body weight. Where ANOVA showed a significant difference, a post-hoc test with Turkey HSD was applied for multiple pairwise comparisons. All statistical analyses were performed using SPSS version 23.0 (IBM Co., Armonk, NY, USA) with the level of significance set at $P < 0.05$.

Results

Phytochemical constituents

The phytochemical screening showed the presence of alkaloids, saponins, tannins, cardiac glycosides, carbohydrates, steroids, and triterpenes in the aqueous stem bark extract of *P. macrophylla*. However, anthraquinones and flavonoids were not detected in the plant's extract. The results of the phytochemical screening of the aqueous stem bark extract of *P. macrophylla* are presented in Table 1.

Acute toxicity studies

The results of the acute toxicity test revealed no mortality in the first and the second phase; hence, the LD₅₀ was determined to be above 5000 mg/kg.

Effect of aqueous stem bark extract of *P. macrophylla* on body weight

Table 2 shows an increase in body weight in all the groups across the weeks except for the groups treated with 1000 mg/kg and 2000 mg/kg of aqueous stem bark extract of *P. macrophylla* at week 1. However, there was no significant difference ($P > 0.05$) in body weight between the groups across the weeks.

Effect of aqueous stem bark extract of *P. macrophylla* on blood glucose levels

The effect of aqueous stem bark extract of *P. macrophylla* on weekly change in BGLs in the alloxan-induced diabetic Wistar rats is presented in Table 3. The diabetic control group and the groups treated with 1000 mg/kg and 2000 mg/kg of aqueous stem bark extract of *P. macrophylla* had a significantly greater increase ($P < 0.05$) in BGLs at week 0 compared to the normal control group. Although the two different doses of aqueous stem bark extract of *P. macrophylla* exhibited hypoglycemic activity in a dose-dependent manner, the group treated with 1000 mg/kg dose did not significantly reduce BGLs

at week 1 and 2 ($P > 0.05$) compared to the diabetic control group and the group treated with 2000 mg/kg. Similarly, the group treated with the 2000 mg/kg of aqueous stem bark extract of *P. macrophylla* did not significantly reduce BGLs at week 1 ($P > 0.05$) but at week 2 ($P < 0.05$) compared to the diabetic control group. Also, the diabetic control group had a significantly greater increase ($P < 0.05$) in BGLs compared to the normal control group at weeks 0 and 1 (Table 3).

Pancreatic histology

The histology study of the pancreatic islet cells of the normal control, 1000 mg/kg and 2000 mg/kg groups is shown in Figs. 1, 2 and 3, respectively.

In the normal control group, the histology shows a normal pancreatic structure which was uniform throughout. The islets were full of centrally placed beta cells, appeared very compact, and surrounded by seroacinar cells. The nuclei capillaries were also normal. These findings indicate that the pancreatic islets cells are normal with no sign of atrophy (Fig. 1).

In the group treated with 1000 mg/kg of aqueous stem bark extract of *P. macrophylla*, the histology shows a slight restoration of the pancreatic islet cells. The nuclei of centrally placed cells were normally stained with hematoxylin and eosin (Fig. 2).

In the group treated with 2000 mg/kg of aqueous stem bark extract of *P. macrophylla*, the histology shows a moderate restoration of the pancreatic islet cells. There was no manifestation of inflammation. The nuclei of the centrally placed cells were normally stained with hematoxylin and eosin. No infiltrative changes were observed (Fig. 3).

Discussion

With the rising prevalence of diabetes in developing countries and the adverse effects associated with commonly used allopathic drugs such as biguanides and sulfonylureas, the use of herbal diabetic preparations as alternative treatment has therefore been gaining much attention among many scientists. This study is the first to explore the antidiabetic effect of aqueous stem bark extract of *P. macrophylla* in alloxan-induced diabetic Wistar rats. The results suggest that the plant stem bark extract possesses a potent antidiabetic effect, which may be used in the management of diabetes.

In this study, the phytochemical screening of the aqueous stem bark extract of *P. macrophylla* indicates the presence of alkaloids, saponins, tannins, cardiac glycosides, carbohydrates, steroids, and triterpenes but anthraquinones and flavonoids. The presence of these secondary metabolites in this plant may be attributed to the potent antidiabetic activity observed in the diabetic Wistar rats. In the study by Yusuf and colleagues [19] to

Table 1 Phytochemical screening of aqueous stem bark extract of *P. macrophylla*

Phytochemicals	Presence of phytochemicals
Alkaloids	+
Saponins	+
Tannins	+
Anthraquinones	-
Cardiac glycosides	+
Flavonoids	-
Carbohydrates	+
Steroids	+
Triterpenes	+

Key: +ve represents the presence of phytochemicals, -ve represents the absence of phytochemicals

Table 2 Effect of aqueous stem bark extract of *P. macrophylla* on body weight in alloxan-induced diabetic Wistar rats

Group (n = 5)	Treatment given	Dose	Body weight (g)		
			Week 0	Week 1	Week 2
1	Normal control (distilled water)	10 ml/kg	118.00 ± 4.77 ^a	135.02 ± 3.37 ^a	147.20 ± 5.95 ^a
2	Diabetic control (glibenclamide)	10 mg/kg	129.00 ± 7.59 ^a	144.00 ± 9.41 ^a	147.20 ± 5.95 ^a
3	PMAE	1000 mg/kg	138.00 ± 15.36 ^a	137.00 ± 11.93 ^a	145.50 ± 11.89 ^a
4	PMAE	2000 mg/kg	140.50 ± 11.75 ^a	137.50 ± 11.58 ^a	143.00 ± 8.26 ^a

Values are presented in mean ± SEM; PMAE *Parinari macrophylla* aqueous stem bark extract; values in the same column having different letters of alphabets are statistically significant ($P < 0.05$)

explore the phytochemical composition and antimicrobial properties of the methanol stem bark extract of *P. macrophylla*, the presence of alkaloids, saponins, tannins, cardiac glycosides, carbohydrates, steroids, triterpenes, anthraquinones, and flavonoids were revealed as the secondary metabolites similar to the findings of the current study except for the absence of anthraquinones and flavonoids. Additionally, in line with our findings, previous studies [32–35] exploring the antidiabetic effects of different plant origins in animal model, also reported the presence of one or more of these promising compounds.

The presence of saponins in the aqueous stem bark extract of *P. macrophylla* is specifically relevant, as these phytochemicals are known to regulate BGLs and prevent diabetic complications owing to their antioxidant activity [36]. Additionally, they are reported to possess a hypocholesterolemic effect which may help to reduce the risk of atherosclerosis and cardiovascular disease in diabetes [37]. Thus, the presence of these metabolites may support the use of *P. macrophylla* plant in diabetes management considering their ability to lessen metabolic burden that would have been placed on the liver [38]. Similarly, tannins such as epigallocatechin-3-gallate have been reported to exhibit hypoglycemic activity [39]. The mechanisms underlining tannin therapeutic activity may include iron deprivation, hydrogen bonding, or specific interactions with vital proteins such as enzymes that bring about their roles as stable and potent antioxidants [40].

Regarding the results of the body weight across the study periods, the treatment with aqueous stem bark

extract of *P. macrophylla*, irrespective of the two different doses, did not result in significant weight gain in the studied animals between week 0 and 1 but a slight increase in body weight was observed between week 1 and 2. However, there was a trend showing an increase in body weight between week 0 and 2 in the control and diabetic control groups. Even though there was no significant difference between the groups, our finding is somewhat comparable to the finding of Gupta and Sharma [40] who reported a significant decrease in body weight of diabetic rats receiving an aqueous extract of some medicinal plants compared to controls. The pattern of body weight changes observed across the groups treated with aqueous stem bark extract of *P. macrophylla* might be due to differences in the dosage administered to each group. However, this was done to ascertain the appropriate dosage required to induce a significant antidiabetic effect. Thus, it can be inferred that the daily oral administration of the aqueous stem bark extract of *P. macrophylla* to the study rats in addition to their regular feeds could be attributed to the changes in body weight observed.

The results of our study demonstrated potent antidiabetic activity of different doses of the aqueous stem bark extract of *P. macrophylla* evidenced by the lower BGLs observed across the weeks. This effect could be attributed to the antioxidant activities of the polyphenolic compounds present in the plant stem bark extract. At week 0, the groups treated with 1000 mg/kg and 2000 mg/kg had more increase in BGLs compared to the diabetic control group. However, at weeks 1 and 2, the different doses had a decrease in BGLs with the 2000 mg/kg dose exhibiting a greater reduction in BGLs at week 2

Table 3 Effect of aqueous stem bark extract of *P. macrophylla* on blood glucose levels in alloxan-induced diabetic Wistar rats

Group (n = 5)	Treatment given	Dose	Blood glucose levels (mg/dl)		
			Week 0	Week 1	Week 2
1	Normal control (distilled water)	10 ml/kg	85.40 ± 0.60 ^a	88.20 ± 1.98 ^a	88.00 ± 8.00 ^a
2	Diabetic control (glibenclamide)	10 mg/kg	277.25 ± 60.82 ^b	179.00 ± 20.61 ^{ab}	188.25 ± 40.68 ^a
3	PMAE	1000 mg/kg	281.25 ± 23.17 ^b	152.25 ± 6.31 ^{ac}	149.75 ± 6.93 ^a
4	PMAE	2000 mg/kg	250.50 ± 29.83 ^b	171.50 ± 24.36 ^b	102.25 ± 6.96 ^a

Values are presented in mean ± SEM; PMAE, *Parinari macrophylla* aqueous stem bark extract; values in the same column having different letters of alphabets are statistically significant ($p < 0.05$)

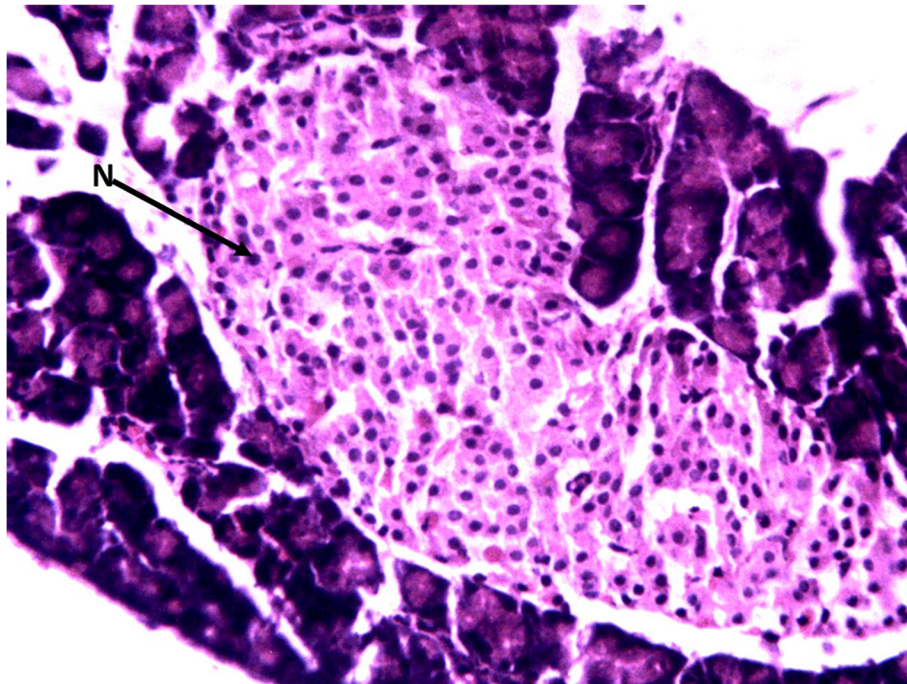


Fig. 1 Histology of the pancreas section stained with hematoxylin and eosin in the normal control group, x 250. N, normal pancreatic islet cells

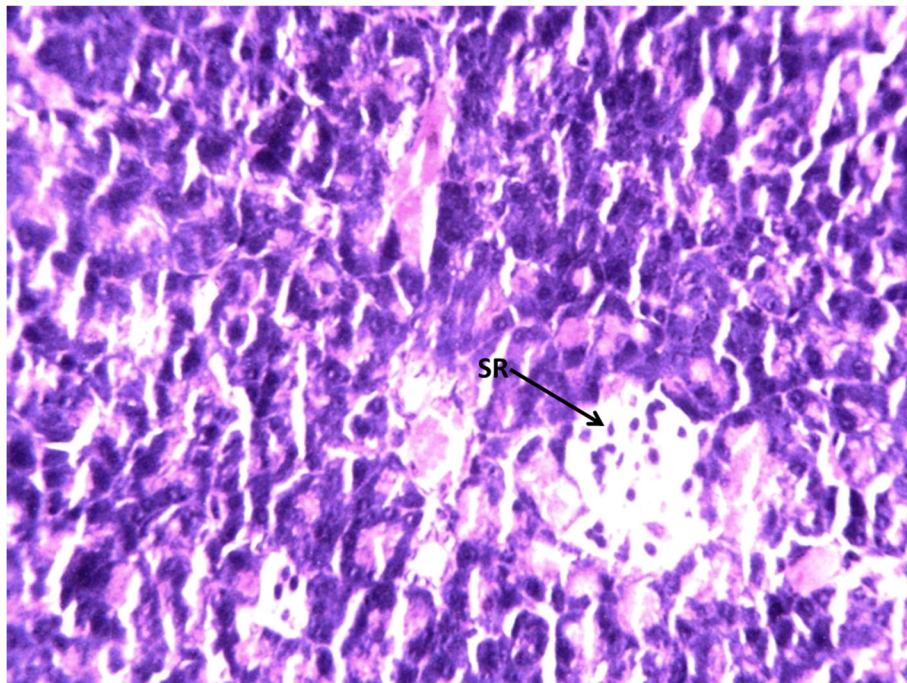


Fig. 2 Histology of the pancreas section stained with hematoxylin and eosin in the group treated with 1000 mg/kg of aqueous stem bark extract of *P. macrophylla*, x 250. SR, slightly restored pancreatic islet cells

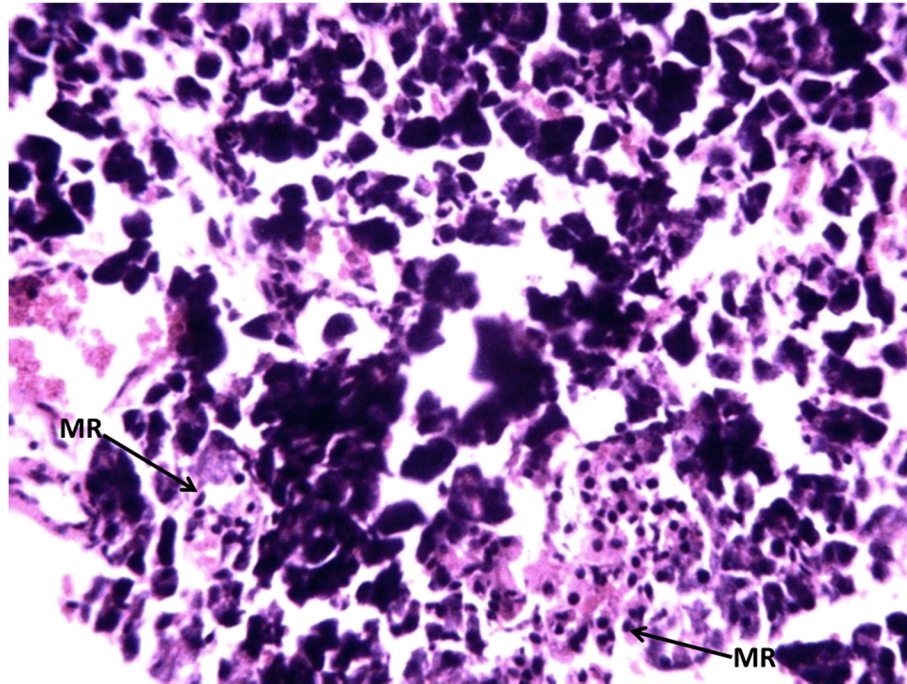


Fig. 3 Histology of the pancreas section stained with hematoxylin and eosin in the group treated with 2000 mg/kg of aqueous stem bark extract of *P. macrophylla*, $\times 250$. MR, moderately restored pancreatic islet cells

compared to the diabetic control group. By implication, the 2000 mg/kg dose proved to be more effective in the management of diabetes.

Alloxan is one of the cytotoxic glucose analogs prominently used as diabetogenic agents to induce diabetes in experimental animals. Two distinct mechanisms by which alloxan-induced diabetes involve selective inhibition of glucose-induced insulin secretion through specific inhibition of glucokinase (the glucose sensor of the beta cell), and generation of reactive oxygen species (ROS) which lead to inadequate secretion of insulin or a state of insulin-dependent diabetes, resulting in sequential necrotic beta cells death [41]. The actions of the aqueous stem bark extract of *P. macrophylla* on the BGLs in this study could have been from direct mopping out of the ROS generated from alloxan toxicity thereby restoring a balance between the pro-oxidants and the antioxidants within the system. The activities of the extracts could also have been from upregulation or augmentation of endogenous antioxidants enzymes leading to the mitigation of oxidative stress. Diabetic patients do not only tend to have increased levels of ROS and reactive nitrogen species but also reduced antioxidant defenses [42]. The action of the extracts from this study could also have been from the direct stimulatory activity of these extracts on surrounding pancreatic beta cells, resulting in insulin secretion

and subsequent tissue utilization of blood glucose and decreased BGLs.

Histomorphological evaluation of the pancreatic tissue in this study revealed normal islet cells in the pancreas in the normal rats. Alloxan destroyed the islet cells of pancreas as observed in the diabetic Wistar rats relative to the normal control. However, treatment with aqueous stem bark extract of *P. macrophylla* led to the regeneration of pancreatic islet cells. This is more evident in the group treated with the 2000 mg/kg dose. The restoration of pancreatic islet cells is believed to increase insulin secretion. Accumulation of glucose in tissues could have precipitated into reduction of the glucose to sorbitol and activation of the polyol pathway. These actions could cause subsequent osmosis and apoptosis of the pancreatic cells in hyperglycemic conditions. Treatment with the aqueous stem bark extract of *P. macrophylla* could have interrupted such pathway, stopping the progressive damage of the islet cells and activation of healing mechanisms as shown from the histology. In light of the foregoing, *P. macrophylla* plant could be considered in the treatment of insulin-dependent diabetic conditions.

Conclusion

In conclusion, aqueous stem bark extract of *P. macrophylla* was found to possess a potent antidiabetic effect. Moreover, the plant can cause regeneration of pancreatic

islet cells thereby improving insulin secretion. Based on these findings, *P. macrophylla* plant may potentially be used to treat human diabetes and associated complications. Future studies should be conducted on leaves and roots of this plant to further explore its potential antidiabetic properties. Additionally, exploring hematological and lipidemic activities of aqueous stem bark extract of *P. macrophylla* in future studies would be useful.

Abbreviations

NaOH: Sodium hydroxide; LD50: Median lethal dose; BGL: Blood glucose level; PMAE: *Parinari macrophylla* aqueous stem bark extract; SEM: Standard error of measurement; ANOVA: Analysis of variance; ROS: Reactive oxygen species

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Plant authentication

Botanical authentication of the plant parts was carried out at the herbarium unit of Biological Sciences Department, Ahmadu Bello University, Zaria, Kaduna State, Nigeria (voucher specimen no.: 012341).

Authors' contributions

AAI Sr, MSA, and JA conceptualized and design the study. AAI Sr and AHU executed the experiments and analyzed the data. AAI Sr and AAI Jr were responsible for drafting the final manuscript. MSA and JA supervised the study. AAI Jr and KDD were responsible for reviewing the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author.

Declarations

Ethics approval and consent to participate

All animal procedures and experimental protocol were strictly followed as per the National Research Council, Guide for the Care and Use of Laboratory Animals. The study was approved by the Research and Ethical Committee on the use of laboratory animals of Nigerian Defence Academy, Kaduna, Kaduna State, Nigeria (Ref: NDA/PGS/FS/M/1826/14).

Consent for publication

Not applicable

Competing interests

All authors declare that they have no competing interests.

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