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Hypoglycemic and α-amylase Inhibitory Effects of Polyherbal Aqueous Extract in Streptozotocin-Induced Diabetic Rats

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ABSTRACT
Diabetes mellitus is a long-term metabolic disease in which blood sugar is elevated, due to a deficiency of either insulin production or insulin function, or both. Conventional antidiabetic drugs have been found to be limiting, thus making medicinal plants an interest of study as alternative drugs. In this study, antihyperglycemic, α-amylase inhibitory and histopathological effects of polyherbal aqueous extract of Annona muricata, Zingiber officinale and Andrographis paniculata were assessed in streptozotocin induced diabetic rats. Thirty-nine male rats of Sprague-Dawley strain were grouped as diabetic rats treated with 50, 100 & 200 mg/kg of polyherbal extract, diabetic rats not treated, glibenclamide treated rats (10 mg/kg) and normal control rats. Streptozotocin (50 mg/kg) was used to induce diabetes. Seven-day oral treatments were given. The blood glucose level, α-amylase activity, and the histopathology of the pancreas and testicle were determined. The polyherbal extract significantly lowered the blood glucose level in a dose-dependent fashion, with an increase in the level of activity when there was an increase in the dose; significant inhibition of α-amylase activity was also recorded. Histological examination showed that the architecture of the pancreatic islets, presence of β-cell regeneration and structure of the seminiferous tubules were restored in the treated groups as compared to the untreated diabetic rats. Polyherbal aqueous extract showed potent antihyperglycemic and α amylase inhibitory effects and had the beneficial effect on diabetes-induced pancreatic and testicular damage. The results indicated that it could be considered as a therapeutic agent in the management of diabetes mellitus and its associated complications.

Keywords:
Diabetes mellitus,
Polyherbal extract,
Hyperglycemia,
α-amylase inhibition
Streptozotocin.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic metabolic conditions in the world, and is a significant health problem today because of its high prevalence, economic burden, and complications. It is defined as being characterised mainly by hyperglycemia, which is sustained by a deficiency of insulin secretion, insulin action or both (Mohd et al., 2025; Sapra & Bhandari, 2025). The insulin hormone is synthesized and secreted by the beta cells of the pancreas, and is crucial for the glucose uptake and utilization by cells and maintaining glucose homeostasis.

If impaired insulin production or function, then the blood glucose will be high, and if persistent, may cause serious metabolic and systemic complications (Lannon, 2024). Diabetes mellitus is a disease that affects carbohydrate, protein and lipid metabolism, and has chronic complications in multiple organs such as the nervous system, cardiovascular system, eyes and the kidney (Dilworth et al., 2021). Polyuria, polydipsia, polyphagia, loss of weight, fatigue and delayed wound healing are common clinical features. Diabetic nephropathy, neuropathy, retinopathy, cardiovascular diseases, diabetic ketoacidosis,

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and lower limb ulcers are potential complications of prolonged uncontrolled hyperglycemia (American Diabetes Association [ADA] 2009). Diabetes mellitus is divided into two types: Type 1 diabetes (T1D) and Type 2 diabetes (T2D). Type 1 diabetes is an autoimmune disorder that leads to a complete loss of pancreatic β-cells, which requires lifelong insulin therapy (Lucier & Mathias, 2024; David et al., 2026). Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes, representing the bulk of diabetes cases in the world, and is mainly characterized by insulin resistance coupled with gradual β-cell dysfunction and loss of insulin production over time (Galicia-Garcia et al., 2020; Adebayo et al., 2025). While diabetes was once thought to be a disease affecting adults, rising rates in children and adolescents are a growing worry worldwide (Shahid et al., 2025).

Diabetics are increasing in number worldwide at a staggering rate. The International Diabetes Federation (IDF) shows that in 2019 there were around 463 million people with diabetes and estimates that by 2045 the number of people with diabetes could be as high as 700 million (International Diabetes Federation [IDF], 2025). Type 2 Diabetes Mellitus (T2DM) is one of the most important health problems in Nigeria and has several risk factors. The nation's rapid urbanization, which promotes more sedentary lives and poor eating habits, is one of the main risk factors (Olamoyegun, 2024). Diabetes does not only have health-related impacts but also impacts in terms of productivity, cost of health services and quality of life of those affected (Okoronkwo et al., 2015).

The current treatment of diabetes is mainly insulin and oral hypoglycemic drugs such as metformin, sulfonylureas, and DPP-4 inhibitors. While these therapies are effective at regulating blood glucose, their chronic administration can be restricted due to cost, availability, patient adherence, and potential side effects such as gastrointestinal upset, pancreatitis, renal problems, cardiovascular issues and hypoglycaemia (Al-Saleh et al., 2021; Gieroba et al., 2025). Therefore, the medicinal plants and herbal remedies are gaining popularity as alternative and complementary treatment methods.

Due to their availability, low cost and safety profile, medicinal plants are widely used in traditional medicine to treat and prevent many diseases for centuries (El-Saadony et al., 2025). Phytochemicals obtained from plants like flavonoids, alkaloids, terpenoids, steroids, tannins, and polyphenols have various biological properties including antioxidant, anti-inflammatory, antimicrobial, and antidiabetic (Ullah et al., 2020; El-Saadony et al., 2025). A total of 400 plant species with hypoglycemic activity have been identified through scientific investigations and over 1,200 medicinal plants with therapeutic potential against diabetes and its complications have been recorded from ethnobotanical sources (Patel et al., 2012; Kifle et al., 2020).

A plant that has been receiving a great deal of attention for its antidiabetic properties is *Annona muricata* (soursop), which is widely grown throughout Africa, South America and Southeast Asia. All parts of the plant have been used in traditional medicine for the treatment of diseases like fever, infection, pain, and inflammation. Experimental research has shown that *A. muricata* exhibits antidiabetic activity, mainly due to the presence of bioactive compounds such as acetogenins, alkaloids and flavonoids (Mutakin et al., 2022; Zubaidi et al., 2023).

Zingiber officinale (ginger) is also a medicinal plant of great value and it has been used traditionally in different medicine systems such as Ayurvedic, Chinese and Unani medicine. Some of the active ingredients present in ginger include gingerols and shogaols with antioxidant, anti-inflammatory properties, antimicrobial, antihyperlipidemic and antihyperglycemic effects (Ayustaningwarno et al., 2020). Ginger has been demonstrated to have beneficial effects on glycemic control and lipid metabolism by lowering blood glucose, triglycerides, total cholesterol, and low-density lipoprotein levels in experimental studies (Rahimlou et al., 2019).

Likewise, *Andrographis paniculata*, known as king of bitters or green chiretta, is known for its wide pharmacological activities. *A. paniculata* has been used in various countries including Nigeria, India, China and the Philippines for its anti-inflammatory, antimicrobial, hepatoprotective and antidiabetic activities in traditional medicine. Bioactive compounds such as andrographolides in A. paniculata have been reported (Naomi et al., 2022). Past research indicates that the plant could play a role in regulating glucose levels and improving overall metabolism.

Some of the recent studies indicated that polyherbal formulation containing combination of medicinal plants may have synergistic therapeutic effects better than the individual medicinal plants. It has been reported that polyherbal combinations are more effective, less toxic, less adverse and more effective at targeting multiple metabolic pathways (Kaelen, 2025). These compositions could thus be useful for the treatment of complicated diseases like Diabetes mellitus.

In this background, the present study aimed to explore the anti-glycemic and alpha-amylase inhibitory effects of a polyherbal aqueous extract of *Annona muricata*, *Zingiber officinale*, and *Andrographis paniculata* in diabetic rats. The aim of the study was to present scientific evidence that these medicinal plants are beneficial for potential therapeutic treatment in diabetes mellitus and help in the continuous search of inexpensive and effective plant-based remedies for diabetes.

MATERIALS AND METHODS

Plant Collection and Authentication

Fresh leaves of *Andrographis paniculata*, leaves of *Annona muricata*, and rhizomes of *Zingiber officinale* were collected from Benin City, Edo State, Nigeria. The plant materials were identified and authenticated at the Department of Plant Biology and Biotechnology, University of Benin, Edo State, Nigeria. Voucher specimens were deposited at the departmental herbarium with accession numbers UBH-A1402 (*Andrographis paniculata*), UBH-2711 (*Annona muricata*), and UBH-Z1012 (*Zingiber officinale*).

Preparation of Polyherbal Aqueous Extract

The leaves of *Annona muricata* and *Andrographis paniculata* were thoroughly washed and shade-dried for fourteen (14) days. The rhizomes of *Zingiber officinale* were similarly washed, sliced into smaller portions to facilitate drying, and shade-dried for the same duration. Following shade drying, all samples were further dried in a hot air oven at 45°C for 30 minutes to remove residual moisture.

The dried plant materials were separately pulverized into fine powder using an industrial blender. Equal portions of each powdered sample (300 g) were weighed and mixed in a ratio of 1:1:1 to obtain the polyherbal formulation.

Extraction was carried out using the hot aqueous maceration technique. The blended powdered samples were soaked in distilled water with intermittent stirring and shaking for 72 hours to enhance extraction efficiency. The resulting mixture was filtered using Whatman filter paper and concentrated to obtain a semi-solid extract. Percentage yield of extraction was calculated using the equation:

$$Formula\ yield = \frac{Extract\ weight}{Powdered\ sample} \times 100 \quad (1)$$

Experimental Animals

Thirty-nine (39) healthy adult male Sprague–Dawley rats weighing between 180 and 250 g were used for this study. The animals were obtained from the Animal House of the Department of Pharmacology, Faculty of Pharmacy, University of Benin, Nigeria.

The rats were maintained at the Animal and Environmental Biology Department Animal House, Faculty of Life Sciences, University of Benin under standard laboratory conditions including controlled temperature and humidity with normal photoperiod cycles. Animals were housed in clean cages and fed standard commercial rodent pellets with water provided *ad libitum*.

Animal care and handling were conducted according to institutional ethical guidelines and approved by the University of Benin Animal Ethics Committee (Ethical Approval Number: LS24317). Animals were marked appropriately for identification and randomly allocated into treatment groups.

Induction of Experimental Diabetes

Streptozotocin (STZ) was used to induce experimental diabetes. Fresh STZ solution was prepared in 0.1 M citrate buffer (pH 4.5) immediately before administration. Experimental rats were fasted for 24 hours before induction.

Diabetes was induced through a single intraperitoneal injection of STZ at a dose of 50 mg/kg body weight, while the non-diabetic control group received citrate buffer alone. To reduce the risk of immediate hypoglycemia, animals were supplied with 5% dextrose solution after STZ administration.

Seventy-two (72) hours after induction, fasting blood glucose levels were measured using Accu-Chek® Active glucose test strips (Roche Diagnostic Corporation, Germany). Rats with fasting blood glucose concentrations greater than 200 mg/dL accompanied by clinical symptoms including polyuria, increased water intake, and increased feed consumption were considered diabetic and included in the study.

Experimental Design

The thirty-nine experimental rats were randomly assigned into six groups:

- **Group I:** Diabetic rats treated with 50 mg/kg polyherbal aqueous extract
- **Group II:** Diabetic rats treated with 100 mg/kg polyherbal aqueous extract
- **Group III:** Diabetic rats treated with 200 mg/kg polyherbal aqueous extract
- **Group IV:** Diabetic rats treated with 10 mg/kg glibenclamide (positive control)
- **Group V:** Diabetic untreated rats (negative control)
- **Group VI:** Non-diabetic untreated rats (normal control)

The doses were selected based on previously reported pharmacological doses of the constituent plants/extracts and arranged to provide low, intermediate, and higher doses for evaluation of a dose-response relationship (Akhtar et al., 2016)

Treatment administration was carried out daily for seven (7) consecutive days.

Determination of Fasting Blood Glucose

Following induction and treatment administration, animals were fasted for eighteen (18) hours before fasting blood glucose determination. Blood glucose concentration was measured using a digital glucometer (Accu-Chek Advantage®, Roche Diagnostic, Germany) and glucose test strips.

Measurements were obtained at baseline (Day 0), Day 3, and Day 7 of the treatment period.

Blood and Tissue Sample Collection

At the end of the treatment period, animals were sacrificed under appropriate handling procedures. Blood samples were collected through cardiac puncture into 5 mL vacutainer tubes containing clot activators. Samples were allowed to clot and centrifuged using a Hettich centrifuge (Model EBA-21, Germany) to obtain serum.

The pancreas and testes were excised and fixed immediately in 10% buffered formalin for histopathological analysis.

Histopathological Examination

Histological analysis was performed on preserved tissue samples. Fixed tissues were processed through dehydration, cleared with xylene, embedded in paraffin wax, sectioned, and stained using hematoxylin and eosin (H&E).

Prepared slides were examined microscopically to evaluate structural and pathological changes associated with diabetes and treatment effects.

Statistical Analysis

Data obtained were expressed as mean ± standard error of mean (SEM). Statistical analysis was performed using one-way Analysis of Variance (ANOVA) to determine differences among experimental groups.

Values of $p < 0.05$ were considered statistically significant. Statistical analyses and graphical presentations were carried out using GraphPad Prism version 10.

RESULTS AND DISCUSSION

Table 1: Fasting blood sugar level (mg/dl) of rats treated with poly-herbal (PAE) mixture for 7days

Groups	Doses (mg/kg)	Fasting Blood Sugar Level Day 1 (mg/dl)	Fasting BloodSugar Level Day 3 (mg/dl)	Fasting Blood SugarLevel Day 7 (mg/dl)
Streptozocin	50 mg/kg	376.50± 55.50^{a}	243.00± 117.00^{a}	210.50 ± 19.50^{a}
Glibenclamide	10 mg/kg	527.50± 72.50^{c}	484.00±116.00^{b}	103.00 ± 20.00^{b}
Normal control	5 ml/kg	89.00±7.00^{c}	90.00± 3.00^{c}	64.00 ± 9.00^{c}
PAE	50 mg/kg	131.50±12.50^{c}	180.50± 20.50^{b}	71.50 ± 0.50^{c}
PAE	100 mg/kg	215.00± 63.00^{b}	132.00± 20.00^{b}	82.50 ± 8.50^{c}
PAE	200 mg/kg	519.50± 80.50^{c}	600.00± 0.00^{c}	302.50 ± 96.50^{a}

Values are Mean ± SEM, n=5; Mean with similar superscripts when compared against the control group within a column are not significantly different (P > 0.05). PAE: Polyherbal Aqueous Extract. Normal control: Distilled water.

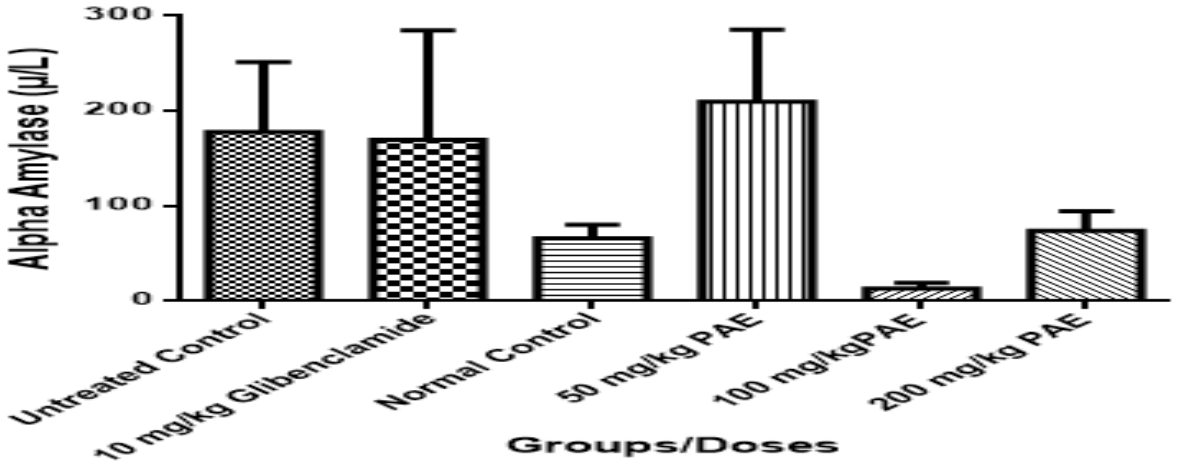


Figure 1: Effect of the polyherbal aqueous extract (PAE) on alpha-amylase in streptozotocin induced diabetes in rats

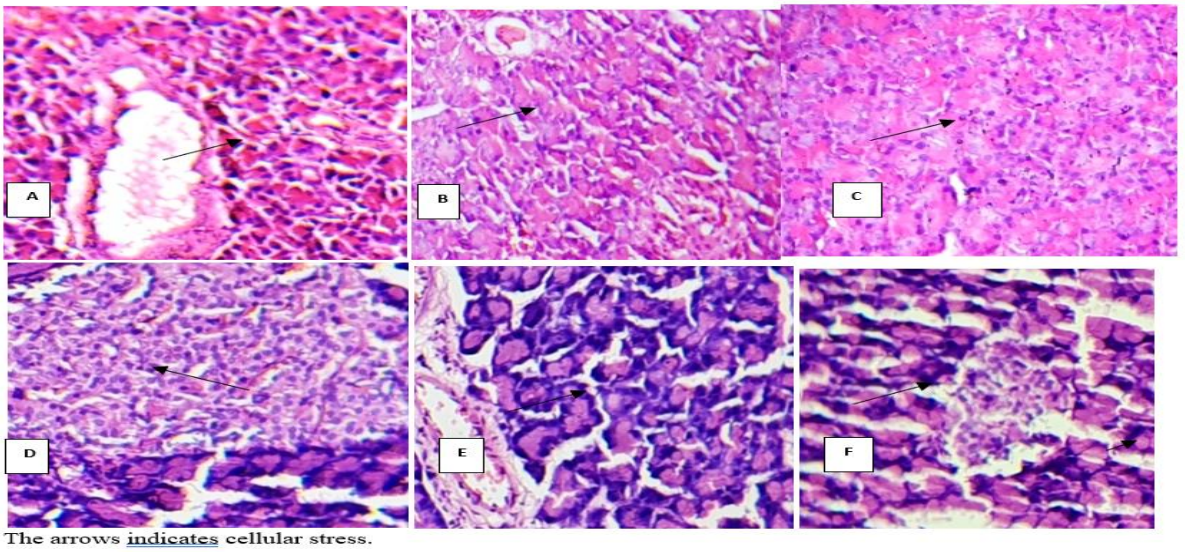


Plate 1: Effect of the Polyherbal extract on the pancreas of Rats.

A. Untreated group: Pancreas features had several acinar cells with mildly despaired pyknotic infiltrates nuclei and intralobular duct appeared fatty. There were some cellular damage and fat accumulation in the pancreas of this group.

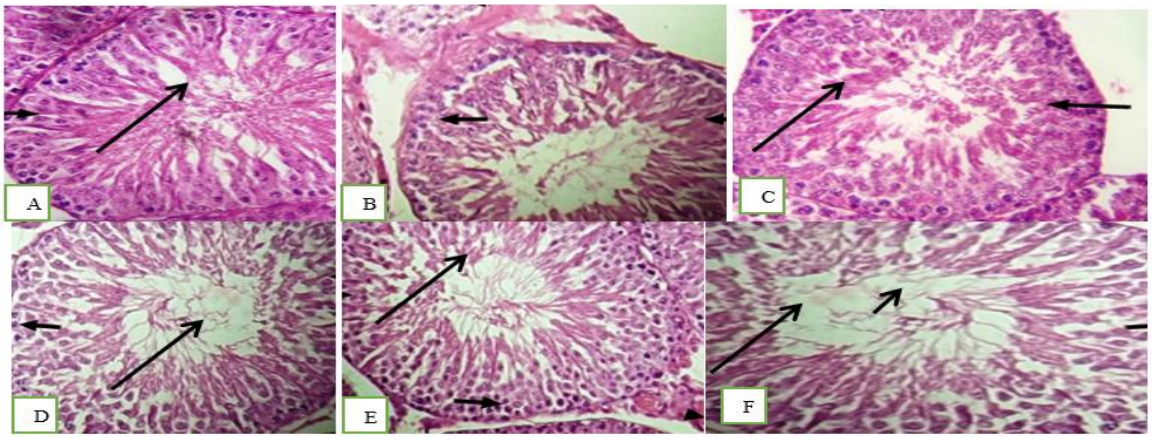
B. 10 mg/kg Gliberclamide: Pancreas reveals features with acinar cells having despaired pyknotic nuclei. There were some cellular damage and fat accumulation in the pancreas of this group.

C. Normal control: Pancrease reveals secretory acini islet with intralobular duct on low power. This group retained their normal histological features.

D. 50 mg/kg extract: Pancrease reveals secretory acini with reveals intralobular duct. This group retained their normal histological features.

E. 100 mg/kg extract: Pancrease have acinar cells having islet-cells with pyknotic nuclei. There was some level of cellular stress with the dose of the extract.

F. 200 mg/kg extract: Pancrease reveals secretory acini with the nucleus appears pyknotic. There was some level of cellular stress with the dose of the extract



The long arrow indicates circular outline of seminiferous tubules, while the short arrow indicates pyknotic Sertoli and Leydig cells and spermatogenic series cells

Plate 2: Effect of the polyherbal extract on the testicular cells of the testes

A. **Untreated control Testis:** The seminiferous tubules that are circular in outline (long arrow).and pyknotic Sertoli cells Leydig cells and other cells of spermatogenic series (short arrow).

B. **100 mg/kg Glibenclamide Sildenafil citrate Testis:** The seminiferous tubules that are circular in outline (long arrow), pyknotic Sertoli cells Leydig cells, and other cells

of spermatogenic series (short arrow), and congested dilated vessel (arrowhead).

C. **Normal controll Testis:** The seminiferous tubules that are circular in outline (long arrow).and pyknotic Sertoli cells Leydig cells and other cells of spermatogenic series (short arrow).
D. **50 mg/kg extract Testis:** The atrophied seminiferous tubules that are circular in outline (long arrow).and pyknotic Sertoli cells Leydig cells and other cells of spermatogenic series (short arrow).
E. **100 mg/kg extract Testis:** The seminiferous tubules that are circular in outline (long arrow) and pyknotic Sertoli cells Leydig cells and other cells of the spermatogenic series (short arrow).
F. **200 mg/kg extract Testis:** The seminiferous tubules that are circular (long arrow) and pyknotic Sertoli cells Leydig cells and other cells of spermatogenic series (short arrow) with a mildly thickened congested vessel (arrowhead).

The present study showed that the polyherbal aqueous extract of *Annona muricata*, *Zingiber officinale*, and *Andrographis paniculata* is effective in reducing the hyperglycemic condition in streptozotocin induced diabetic rats. The extract showed significant reduction in the fasting blood glucose level, with the highest reduction seen at 100 mg/kg, suggesting that it is beneficial in terms of glycemic control. Hyperglycemia is induced by streptozotocin and is mainly caused by selective damage of the pancreatic β-cells due to oxidative stress, which causes impaired insulin secretion and chronic hyperglycemia (Al Syaad et al., 2019). The decrease in blood glucose levels thus, indicates that the polyherbal extract can be useful in improving residual β-cell function, insulin secretion, peripheral glucose utilization, or insulin-sensitizing. The antihyperglycemic activity can also be explained by a synergic effect of phytochemicals such as flavonoids, alkaloids, tannins and terpenoids, which are reported to have antidiabetic properties (Firdous et al., 2025; Situmarang et al., 2025).

The gradual decrease of fasting blood glucose level recorded during the treatment period is in line with earlier works that have proved the antidiabetic activity of polyherbal formulation on experimental diabetic rats. Comparable results were found by other researchers Suvarna et al., (2021) Ikechukwu et al., (2026) Kıran et al., (2026) and Dey & Dutta (2026) on the administration of different polyherbal extracts to streptozotocin induced diabetic rats, which showed significant reductions in blood glucose concentrations. The present study showed that the antihyperglycemic activity of the extract is similar to the glibenclamide, indicating that the formulation may have a good therapeutic potential. In addition, the treated animals did not have any significant weight loss, suggesting that the extract was safe in the long term and has the potential to maintain the normal metabolism.

The polyherbal extract was also highly effective at inhibiting α-amylase, especially at the doses of 100 and 200 mg/kg, suggesting that this is another mechanism by which the formulation could help regulate glucose levels. α-Amylase converts dietary starch into absorbable sugars and high levels of the enzyme are associated with rapid postprandial hyperglycemia (Quazi et al., 2022). This enzyme's inhibition slows down the digestion of carbohydrates, which will hinder glucose absorption and moderate the postprandial glucose spike, respectively (Kashtoh & Baek, 2022). The α amylase inhibitory activity has been previously reported in some medicinal plants and poly herbal formulations (Safamansouri et al., 2014; Quazi et al., 2022). The inhibitory effect seen in the present study thus suggests that the extract has the potential to be used as a natural enzyme inhibitor in the management of diabetes mellitus.

The biochemical results were confirmed by histopathological examination of the pancreas. The diabetic rats produced with streptozotocin showed islet of Langerhans distortion, pancreatic cells degeneration, and decreased cellular density, indicating the severe damage of β cells by hyperglycemia. The treatment, however, with polyherbal extract led to the acceptable restoration of the pancreatic architecture with enhanced islet organization and reduced cell degeneration especially at 100 mg/kg. It was observed that the extracts have cytoprotective and regenerative properties which could help maintain the integrity of pancreatic β-cells. Restoration of the pancreatic histoarchitecture has been also reported after treatment with polyherbal formulations with antioxidant and anti-inflammatory properties (Madić et al., 2021; Anushree, 2025). This observed protection of the pancreas could therefore directly be responsible for the better glycemic control seen in these treated groups.

Oxidative stress, inflammation and dysfunction of endocrine pathways contribute significantly to diabetes induced reproductive dysfunction and are associated with a negative impact on spermatogenesis and testicular architecture. The present study revealed the degeneration of seminiferous tubules and decreased spermatogenic activity in the untreated diabetic rats while the polyherbal extract significantly corrected the structure of testes and maintained the spermatogenic cells in the untreated diabetic rats. The results in this study show that the extract protected from diabetes-associated testicular injury and possibly could normalize the reproductive function. Protective effects in the present study have been found to be similar to those reported earlier that polyherbal formulations reduce the damage to testicles in diabetic rats by antioxidant and anti-apoptotic activities (Chatterjee et al., 2013; Zhang et al., 2025). The current study further confirmed the protective effect of the polyherbal extract on the organs vulnerable to the chronic

hyperglycemic injury as observed from the improvement in the testicular histology.

The aqueous polyherbal formulation shows multiple complementary effects in streptozotocin induced diabetes by its antihyperglycemic, α-amylase inhibitory and histopathological effects. The synergic effect of the combined activity of *A. muricata*, *Z. officinale*, and *A. paniculata* seems to offer better glycemic control, maintain the integrity of pancreatic tissues/β-cells, and prevent any damage to the reproductive tissues caused by diabetes. The results obtained are consistent with those of other reports indicating that polyherbal formulations are potential good therapeutic alternatives for diabetes mellitus and its related complications as they are affordable, novel, and have multi-target activity.

CONCLUSION

The present study revealed that the polyherbal aqueous extract of *Annona muricata*, *Zingiber officinale*, and *Andrographis paniculata* possesses significant antihyperglycemic and α-amylase inhibitory activities in streptozotocin induced diabetic rats. The extract showed a beneficial effect on reducing the fasting blood glucose level and inhibiting α-amylase activity while improving the histoarchitecture of the pancreas and testicles when compared to untreated diabetic rats, mainly at 100 mg/kg. The synergistic effect of these phytochemicals may be responsible for better glycemic control, preservation of pancreatic β-cells and mitigation of reproductive tissue injury caused by diabetes in the polyherbal formulation, which accordingly suggests that the latter may be beneficial. The study thus gave scientific evidence for therapeutic potential of plant-based intervention (Polyherbal Aqueous extract) in the management of diabetes mellitus and associated complications. It is recommended that the plant should be subjected to further studies for chronic toxicity evaluation, phytochemical characterisation, mechanism of action and clinical trials to ascertain the safety, efficacy and suitability for therapeutic use in human.

CONFLICT OF INTEREST

There is no conflict of interest to be disclosed.

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