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Research Article

Apparent Restoration of Insulin Production in Alloxan-Induced Wistar Rats Using *Vernonia amygdalina* (Bitter Leaf) and Brick-Red *Terminalia catappa* (Almond Leaf) Leaves Extract

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ABSTRACT

Diabetes is a disorder resulting from a lack of insulin to manage glucose in the blood. This work aims to find a synergy between a combination of the leaves of *Vernonia amygdalina* and *Terminalia catappa* to determine whether it will produce results comparable to exogenous insulin administration in restoring insulin production. Phytochemical screening and acute toxicity tests were conducted. Wistar rats weighing 100-150 g were used, and Type 1 diabetes was induced using Alloxan (150 mg/kg) intraperitoneally. Body weight and blood glucose levels were monitored. A histopathological examination of the pancreatic tissues was also conducted. The phytochemical assay revealed the presence of saponins, tannins, alkaloids, cardiac glycosides, flavonoids, steroids, and polyphenols. The acute toxicity test indicated no mortality, suggesting the LD_{50} was above 5000 mg/kg. A significant body weight loss was observed in the Alloxan-induced diabetic rats in the first week compared to the normal control. Rats in groups administered with extracts exhibited an increase in body weight from week 2 compared to the untreated group. Daily administration of insulin and the single and combined extracts significantly reduced fasting blood glucose levels compared to the diabetic untreated group. There was no significant difference between the treated groups and the normal control. Histological examination showed moderate regeneration of islet cells in rats given the combined extract, while single extracts displayed slight restoration. The study concludes that single and combined extracts can potentially restore insulin production in Alloxan-induced diabetic Wistar rats.

Keywords: Antidiabetic effect; Blood glucose; Histopathology; Insulin; *Terminalia catappa; Vernonia amygdalina*

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INTRODUCTION

Diabetes mellitus is a severe metabolic condition resulting from insulin insufficiency, resistance, or both, leading to hyperglycemia (Oladoja *et al*., 2023). It is the seventh leading cause of death worldwide and is prevalent in both developing and developed countries (Shahadat *et al*., 2019). There are two common forms of hyperglycemia: Type 1 diabetes and type 2 diabetes. In Type 1 or insulin-dependent diabetes, the immune system destroys the beta cells of the pancreas. Both children and adults can develop Type 1 diabetes (Mazhar *et al*., 2022). Complications of hyperglycemia include neuropathy, cardiovascular disease, and kidney disease, all believed to be irreversible after they develop (Zainul *et al*., 2018).

In Nigeria, 11.2 million people are estimated to have diabetes, with a prevalence of 5.77% (Uloko *et al*., 2018). Conventional medicine aims to ensure optimal glycemic control using insulin, oral hypoglycemic agents, and other non-pharmacological approaches (Oladoja *et al*., 2023). Although much has been done to prevent diabetes using orthodox medicine, the outcomes of treatment in patients are still in vain, which comes with a lot of consequences, such as drug

resistance, cost implications, side effects, and toxicity (Oladoja *et al*., 2023).

Phyto-molecules as remedies for diabetes are increasing due to their minimal or no adverse effects (Shahadat *et al*., 2019). Plants, such as *Terminalia catappa* and *Vernonia amygdalina* leaves, have strong antidiabetic activities and have been used without apparent side effects.

As diabetes mellitus is projected to increase to 10.2% by 2030, treatment options are limited to insulin injections, conventional anti-diabetic medications, and lifestyle changes (Sukhikh *et al*., 2023). Drug combinations with differing mechanisms of action provide a treatment option in diabetes (Mohammed and Tajuddeen, 2022).

A combination of these plants (*Vernonia amygdalina* and *Terminalia catappa*) phytomedicine is being tested to see if it will produce a synergetic result in restoring insulin production comparable to exogenous insulin administration.

This study aims to evaluate the restoration of insulin production using *Vernonia amygdalina* and brick-red *Terminalia catappa* leaves extract in alloxan-induced Wistar rats.

MATERIALS AND METHODS

Plant collection and authentication

Vernonia amygdalina leaves and brick-red *Terminalia catappa* leaves were collected from a home garden in Kaduna State, Nigeria. The plants were botanically authenticated at the herbarium of the Biological Sciences Department, Nigeria Defense Academy, Kaduna State, Nigeria. They were identified with a voucher number, *Vernonia amygdalina* (NDA/BIOH/202525). Brick-red *Terminalia catappa* (NDA/BIOH/202526) and leaves samples were deposited at the herbarium unit.

Preparation of aqueous extracts

Fresh leaves of *Vernonia amygdalina* and brick-red *Terminalia catappa* were collected. After collection, the leaves were shade-dried individually at room temperature for one week. The dried leaves were ground into a fine powder using the electric grinding machine. Each powdered form was extracted with distilled water. The samples were soaked in distilled water for 48 hours before filtering through Whatman filter paper. The extract obtained was then dried at 45 °C in a water bath till a semi-solid form was obtained, reserved in a closed container and then stored in a refrigerator, about 4 °C until use (Iwuji *et al*., 2021).

Phytochemical screening

The plant extracts were subjected to preliminary phytochemical screening at the Biochemistry Department, Faculty of Sciences, Kaduna State University, Kaduna, to establish their constituents using standard conventional methods. The extracts were screened for alkaloids using Mayer's test, tannins using the Ferichloride test, saponins using the Frothing test, anthracene derivatives using the Bontrager's test, cardiac glycosides using the Keller-Killiani test, flavonoids using the Shinoda test, triterpenes and steroids using the Liebermann-Burchard test (Gul *et al*., 2017).

Experimental animal

For this study, 30 healthy adult Wistar rats, each weighing between 100-150g, were sourced from the Nigerian Institute for Trypanosomiasis Research (NITR) in Kaduna. The animals were housed in well-ventilated laboratory cages under controlled conditions (temperature: 25-27°C, relative humidity: 40-45%, and regulated dark-light cycles) and allowed a five-day acclimatisation period before the experiment began. They were provided with grower and starter mash from Vital Feeds Company, along with unrestricted access to water. All procedures adhered strictly to the ethical guidelines outlined in the National Research Council's *Guide on the Care and Use of Laboratory Animals* (brahim *et al*., 2021).

Acute Toxicity Assessment

The acute toxicity (LD_{50}) of the combined plant extract was evaluated following the modified Lorke (1983) method, using 12 rats. In the first phase, the rats were divided into three groups and administered the extract orally at doses of 50, 300, and 2000 mg/kg body weight. Their responses were monitored over 24 hours for any signs of toxicity. In the second phase, three rats were assigned to separate groups and given the same extract at higher doses of 1500, 2500, and 5000 mg/kg body weight. The LD_{50} value was determined based on observations from the second phase.

Diabetes Mellitus Induction using Alloxan

Thirty Wistar rats, each weighing between 100-150 g, were subjected to a fasting period of 24 hours, during which they were provided only water. Before administering Alloxan, their fasting blood sugar levels were measured. Diabetes was induced in 25 of the rats via a single intraperitoneal (I.P.) injection of Alloxan at a dose of 150 mg/kg, dissolved in normal saline (NaCl) and a 5% dextrose solution. After 48 hours, fasting blood sugar levels were reassessed to confirm Type 1 diabetes induction. Rats with fasting blood glucose levels exceeding 200 mg/dl (11.1 mmol/dl) were classified as diabetic. Throughout the experiment, their body weight was monitored daily (Ighodaro *et al*., 2017).

Experimental design

The rats were randomly divided into six groups of 5 rats: group A received distilled water and served as the normal control, group B received insulin (4 IU/kg subcutaneous), Group C was left untreated, group D received aqueous extract of *Vernonia amygdalina* (400

mg/kg), group E received aqueous extract of *Terminalia catappa* (400 mg/kg) and group F received the combined extract of *Vernonia amygdalina* and *Terminalia catappa* **(**400 mg/kg). Plant extracts were administered orally.

Histopathological Examination

After two weeks of therapy, the experimental animals were put down under anesthesia from chloroform inhalation. The rats were kept in an airtight plastic cage with drips of 37% chloroform in cotton wool until they passed out. Sections of their pancreas tissue were extracted and prepared for histological analysis at the Gross Anatomy Research Laboratory, Department of Human Anatomy, Faculty of Medical Sciences, Ahmadu Bello University, Zaria, Kaduna State, following an abdominal incision.

Statistical Analysis

The collected data were analyzed using descriptive statistics, including the mean and standard error of measurement (mean ± SEM). To evaluate differences between groups in body weight and blood glucose levels, a one-way analysis of variance (ANOVA) was conducted. And Tukey HSD post-hoc testing was applied for multiple pairwise comparisons. All statistical analyses were done using SPSS (IBM Co., Armonk, NY, USA), with a significance level set at $P < 0.05$.

RESULT

Phytochemical Composition of Aqueous Leaves Extract of *Vernonia amygdalina,* brick-red *Terminalia catappa,* and the Combined Extract

The qualitative phytochemical composition showed the presence of alkaloids, saponins, tannins, cardiac glycosides, flavonoids, steroids, polyphenols, and triterpenes in the aqueous extract of *Vernonia amygdalina* and *Terminalia catappa* leaves. The combined extract contains terpenoids, which are absent in brick-red *Terminalia catappa* leaf extract. The results of the phytochemical screening of the aqueous *V. amygdalina, T. catappa,* and the combined extract are presented in Table 1.

Results obtained from the quantitative evaluation showed that *Vernonia amygdalina* aqueous extract had a moderate presence of Tannins (11.32mg/100g), polyphenols (4.63mg/100g) followed by alkaloids (3.82mg/100g), saponins(4.59mg/100g), and Flavonoids (1.90mg/100g). While *Terminalia catappa* has Polyphenols (4.01mg/100g), Alkaloids (1.78mg/100g), flavonoids (0.77mg/100g), and Saponins (1.53mg/100g).

Acute Toxicity

The results of the acute toxicity test revealed no mortality or behavioural change in the first and second phases; thereby, the LD_{50} was determined to be above 5000 mg/kg.

Effect of the Treatments on the Body Weight of Animals

Table 2 presents the differences observed in the body weight of the diabetic rats and controls during the treatment. All diabetic rats experienced a weight reduction in the first week. There was a significant body weight loss in the alloxan-induced diabetic rats in the first week compared to the normal control. Whereas rats in groups administered with insulin, *Vernonia amygdalina*, and combined extract showed a significant increase in body weight from week 2 compared to the untreated group. The diabetic control group presented the highest body weight reduction.

Effect of Treatments on the Blood Glucose Levels of Animals

The fasting blood glucose levels of the rats were elevated 48 h after alloxan induction. The diabetic control group and the groups treated with *Vernonia amygdalina,* brick-red *Terminalia. catappa* leaves extract, and the combined extracts had a significantly greater increase ($P < 0.05$) in fasting blood glucose at week 0 compared to the normal control group. The assessment of the fasting glucose levels of diabetic rats through the treatment shows a drop in blood glucose levels in animals receiving *Vernonia amygdalina* and *Terminalia catappa* at week 2. Also, daily administration of insulin and the combined extract significantly reduced FBGL compared to the untreated group in the second week. The untreated group had a significantly greater increase in blood glucose levels when compared to all the treated and control groups in weeks 1 and 2. (Table 3).

Effect of Treatment on Histology of the Pancreatic Tissues

The histological examination of the pancreatic tissue for the various treatments is shown in Figure 3-8. The normal control group shows a normal pancreatic structure. The islets were full of centrally placed beta cells and appeared very compact. These indicate that the pancreatic islet cells are normal with no sign of atrophy compared to the untreated diabetic rats, which showed damaged and shrunken islets of the pancreas. The histological examination of the pancreatic islet cells in the group treated with *Vernonia amygdalina* and brick-red *Terminalia catappa* showed a slight restoration. In the standard control group and the group treated with the combined extract, the histology shows a moderate restoration.

Table 1: Phytochemical composition of the Aqueous leaves Extract of *Vernonia Amygdalina*, Brick-Red *Terminalia catappa*, and the Combined Mixture

Phytochemical	Plant Extract		
	V. amygdalina	***T. catappa***	**Combined mixture**
Alkaloid	++	+	+++
Tannins	++	+	++
Saponin	++	+	++
Flavonoid	++	++	+++
Steroids	+	+	+
Polyphenols	+++	++	+++
Cardiac glycoside	+	+	+
Terpenoids	+	-	+

Note: (-) = Absent, (+) = Present, (++) = Present in moderate concentration, (+++) = Present in high concentration

Table 2: Effect of Extracts on Body Weight in Alloxan-induced Diabetic Wistar Rats

Group Treatment (mg/kg)	Body Weight (g)		
	Week 0	**Week 1**	**Week 2**
Normal Control	121.90±0.95^{b}	135.27±0.58^{b}	136.33±0.79^{e}
Diabetics + Insulin	122.70±0.31^{b}	122.03±0.54^{c}	123.28±0.09^{d}
Diabetic Untreated	115.13±0.62^{a}	105.97±0.34^{a}	98.27±0.49^{a}
Diabetic + *V. amygdalina* (400)	120.93±0.55^{b}	118.93±0.93^{c}	120.03 ± 0.92^{bc}
Diabetic + *T. catappa* (400)	100.60±0.12^{a}	115.27 ± 0.55^{b}	117.50± 0.35^{b}
Diabetic + *V. amygdalina* + *T. Catappa* (400)	108.60±0.25^{a}	120.90±0.25^{c}	122.53±0.18^{cd}

Key: n = Number of rats in each group

All values are expressed as mean ± SEM. Superscript shows post hoc analysis. Mean that shares the same superscript symbol are not statistically different, while means with different superscript symbol (s) indicate statistical difference (P<0.05)

Table 3: Effect of Extracts on Fasting Blood Glucose Level of Alloxan-induced Wistar Rats

Group Treatment (mg/kg)	Fasting Blood Glucose Level (Mmol/dl)		
	Week 0	**Week 1**	**Week 2**
Normal Control	5.07±0.20^{a}	5.13±0.15^{a}	5.13±0.17^{a}
Diabetics + Insulin	9.03±0.62^{b}	7.50±0.21^{a}	7.20±0.17^{a}
Diabetic Untreated	12.20±0.64^{c}	12.73±4.18^{a}	13.67±5.32^{b}
Diabetic + *V. amygdalina* (400)	10.20±0.52^{b}	9.63±0.32^{a}	9.20±0.21^{a}
Diabetic + *T. catappa* (400)	9.83±0.15^{b}	9.30±0.15^{a}	8.53±0.29^{a}
Diabetic + *V. amygdalina* + *T. Catappa* (400)	10.00±0.25^{b}	8.80±0.23^{a}	7.50±0.23^{a}

Key: n = Number of rats in each group

All values are expressed as mean ± SEM. Superscript shows post hoc analysis. Mean which share the same superscript symbol are not statistically different, while Mean with different superscript symbol(s) indicate statistical difference (P<0.05)

Pancreatic Histopathology

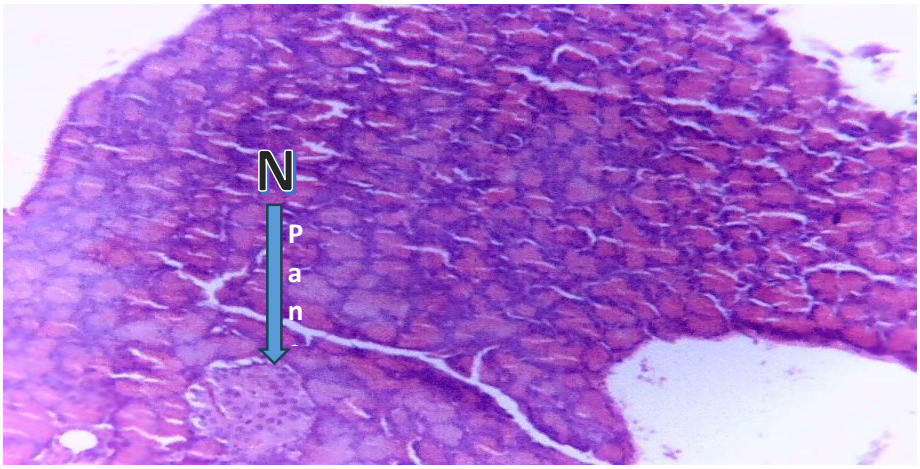

Plate 1: Histopathology of the pancreas section in the control group, × 250. N, normal pancreatic islet cells

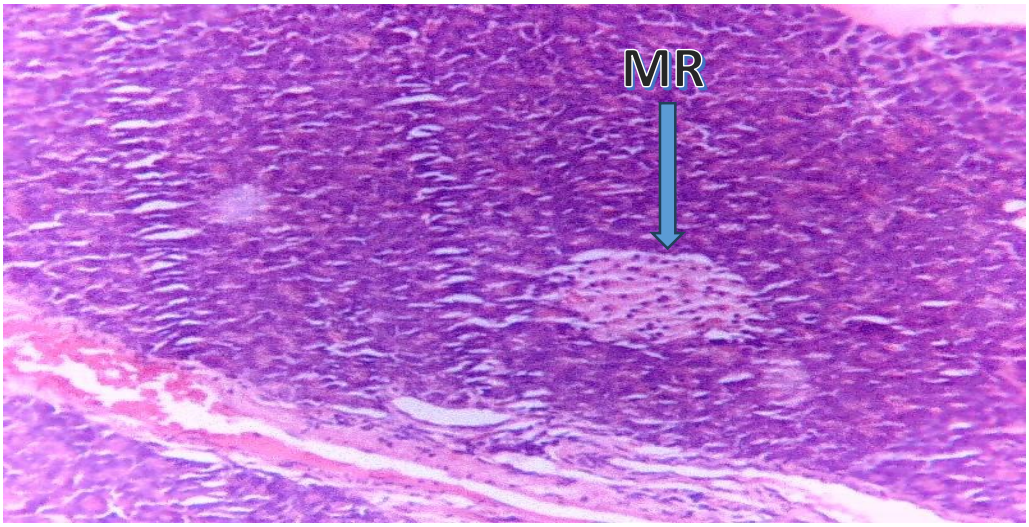

Plate 2: Histopathology of the pancreas section in the group treated with exogenous insulin, × 250. MR, moderate restored pancreatic islet cells

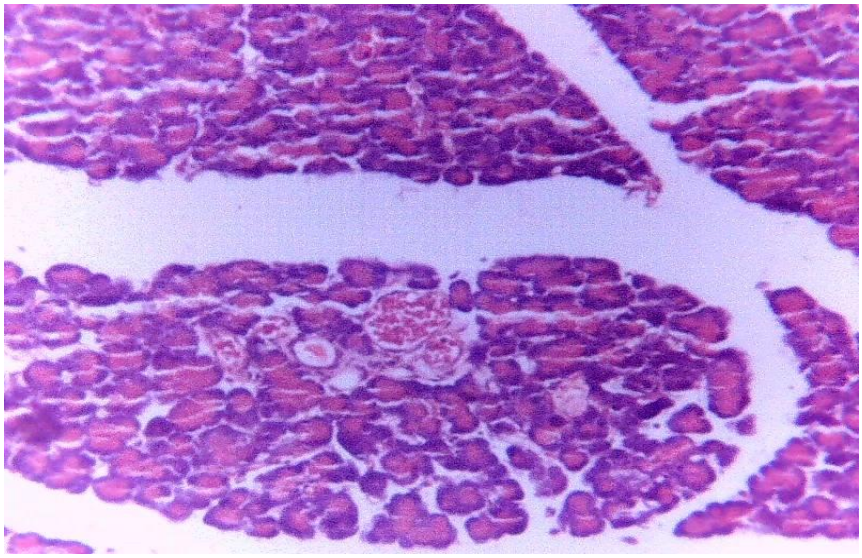

Plate 3: Histopathology of the pancreas section in the diabetic control group of the pancreas shows shrunken and sparsely populated islet cells

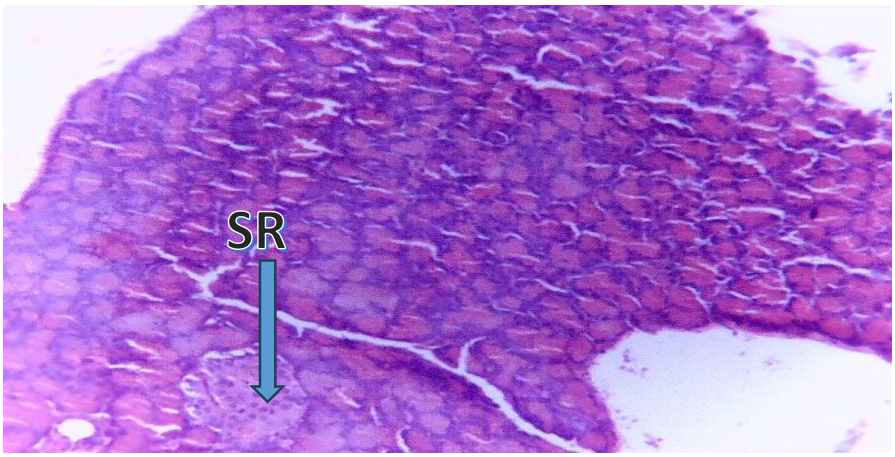

Plate 4: Histopathology of the pancreas section in the group treated with *V. amygdalina* aqueous leaves extract, × 250. SR, slightly restored pancreatic islet cells

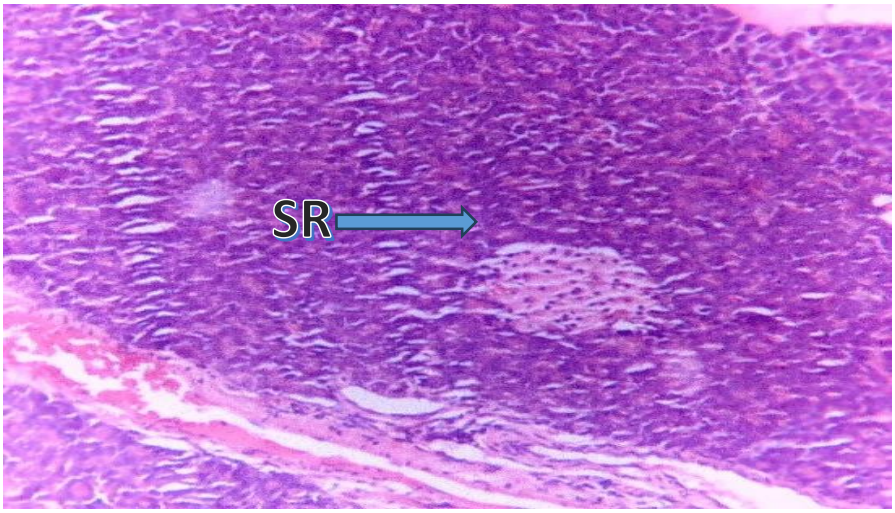

Plate 5: Histopathology of the pancreas section in the group treated with brick red *T. catappa* aqueous leaves extract, × 250. SR, slightly restored pancreatic islet cells

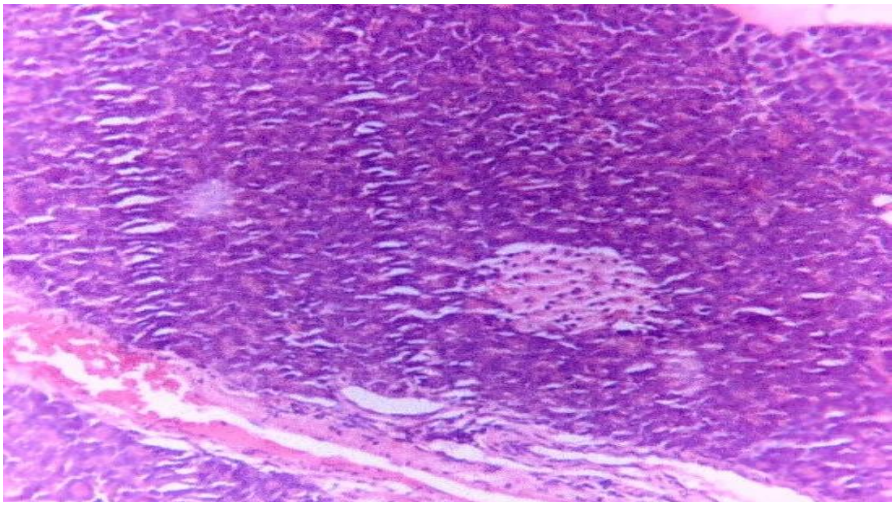

Plate 6: Histopathology of the pancreas section in the group treated with the combined extract of *V. amygdalina* and *T. catappa* aqueous leaves extract, × 250. MR moderately restored pancreatic islet cells

DISCUSSION

Most studies have linked the antidiabetic effects of various medicinal plants to bioactive components, including tannins, phenolics, alkaloids, and flavonoids (Ojo *et al*., 2022). This study identified the presence of flavonoids, tannins, terpenoids, alkaloids, steroids and phenols in *V. amygdalina*, brick-red *Terminalia catappa* leaf extract, and their combination. The phytochemicals present in these plants play a role in the therapeutic antidiabetic effects noted. These substances are recognized for their anti-inflammatory, antidiabetic, and antioxidant properties. The combined extract contains the highest levels of alkaloids, polyphenols, and flavonoids, followed by *Vernonia amygdalina*, with *Terminalia catappa* exhibiting the lowest levels. The higher concentration of the combined extract may result from potential synergistic mechanisms in combination treatment, which include an enhanced yield of bioactive compounds. *Vernonia amygdalina* exhibits a high concentration of alkaloids, which possess various pharmacological properties, including anti-inflammatory and analgesic effects. The antioxidant properties of flavonoids may reduce the impact of free radicals that harm pancreatic beta cells, facilitating their regeneration, which could enhance insulin production and lower blood glucose levels (Utomo *et al*., 2023).

The extract from *Terminalia catappa* leaves, characterised by its brick-red colour, exhibited moderate levels of saponins, tannins, terpenoids, phenols, and steroids. Mishra *et al*. (2024) reported analogous findings in their assessment of the phytochemical composition of *Terminalia catappa*. *Vernonia amygdalina* leaves exhibited moderate concentrations of steroids, tannins, glycosides, and saponins. This is consistent with the findings of Utomo *et al*. (2023), Nwaoguikpe (2010), and Zainul *et al*. (2018).

The normal control group exhibited stability in body weight, serving as a baseline for comparison with the effects of other treatments. Diabetic rats administered extracts and insulin exhibited a minor reduction in body weight from week 0 to week 1, followed by a slight increase by week 2. The weight loss is due to the alloxan. Alloxan induced weight loss by disrupting glucose metabolism, resulting in protein catabolism and the utilization of body fat. This was managed by the daily insulin and extracts administration. Insulin therapy is known to help manage glucose levels, which can prevent severe weight loss associated with diabetes. The diabetic control group experienced a significant decrease in body weight from week 0 to week 2 compared to the normal control group. The weight loss is consistent with the hyperglycemic effect of alloxan, leading to reduced body weight due to uncontrolled diabetes. The aqueous leaf extracts of *Vernonia amygdalina* showed a decrease ($p<0.05$) from week 1, but a slight recovery by week 2. This suggests that *V. amygdalina* might have protective or restorative effects against alloxan-induced weight loss. The group treated with brick-red *T. catappa* and the combined extract showed an increase in body weight from week 1 to week 2; the combination of both plant extracts appears to have a synergistic effect in counteracting the weight loss induced by alloxan. Alloxan is a cytotoxic glucose analogue commonly utilised as a diabetogenic agent to induce diabetes Type 1 in experimental animals. Alloxan-induced diabetes operates through two distinct mechanisms: the selective inhibition of glucose-induced

insulin secretion via specific glucokinase inhibition, and the generation of reactive oxygen species (ROS), which contribute to insufficient insulin secretion or a state of insulin-dependent diabetes, ultimately leading to sequential necrotic death of beta cells (Ighodaro *et al*., 2017).

The rats treated with alloxan monohydrate had considerably higher Fasting Blood Glucose levels than the normal control rats. In this study, basal fasting blood glucose levels in the diabetic control and treated groups were not significantly different from those in the normal control group prior to induction and treatment of diabetes mellitus. This indicates that all animals in the diabetic control and treated groups had a basal blood glucose level before induction. The standard control group has significantly lower blood glucose levels from week one to week two, showing that diabetes is being managed well. *Vernonia amygdalina* has long been claimed to have the capacity to decrease blood glucose levels in diabetics (Nwaoguikpe, 2010). Fasting blood glucose concentrations in untreated diabetic rats showed a significant increase in blood glucose, highlighting the hyperglycemic effect of alloxan-induced diabetes when compared to normal control, as a result of diabetes mellitus not being managed, resulting in an increase in blood glucose over time.

The results from group A, the normal control, indicate that groups administered *Vernonia amygdalina, Terminalia catappa,* and the combined extract exhibited no statistically significant differences when compared to one another at week 2. This experiment confirmed that both *V. amygdalina* and *T. catappa*, whether used individually or in combination, are effective in managing diabetes. This finding aligns with Zainul's report, which indicated that *Vernonia amygdalina* aqueous extract significantly reduced HDL cholesterol, triglycerides, and fasting blood glucose levels (Zainul *et al*., 2018). Additionally, polyphenols present in *Terminalia catappa* exhibit anti-inflammatory and antihyperglycemic properties, contributing to improved insulin sensitivity and reduced blood glucose levels.

Other findings indicate that a combination of the extract from the leaves of *Vernonia amygdalina* and Metformin, utilizing a larger proportion of the extract and a reduced dosage of Metformin, is effective and safe for managing diabetes mellitus (Michael *et al*., 2010). A prior study demonstrated that aqueous and cold extracts from fresh, tender leaves of Indian almonds can reduce elevated blood glucose levels and lipids in alloxan-induced animal models. The anti-hyperglycemic effect may result from an insulin-potentiating mechanism that stimulates the remaining pancreatic islets to release insulin, or potentially from the regeneration of beta cells induced by the aqueous extract. Furthermore, *Vernonia amygdalina* may significantly contribute to the management of both insulin-dependent and non-insulin-dependent diabetes. This is evident, as it is frequently utilized as a dietary approach that plays a crucial role in the management of diabetes. Additional researchers have observed that *V. amygdalina* leaf extract may exert a direct insulin-like influence on glucose metabolism (Michael *et al*., 2010). The blood glucose levels in the normal control group of rats administered distilled water remained stable throughout the experiment. The untreated diabetic rats exhibited persistent hyperglycemia throughout the 14-day treatment period with distilled water, indicating that the hyperglycemia in this group resulted from the administration of alloxan.

Normal glucose levels facilitate effective bodily function and serve as an essential energy source for cellular activity. Elevated blood sugar levels can lead to complications by gradually harming pancreatic cells, thereby inhibiting insulin production, which is essential for the body's utilization of glucose from food as energy (Todd *et al*., 2017).

No deaths or behavioural changes were observed in Wistar rats following the oral administration of combined extracts at doses of 300, 2000, and 5000 mg/kg during acute toxicity testing. No effects were observed on the animals' skin, gastrointestinal, sensory, or nervous systems. No mortality or indications of acute toxicity were observed. This suggests that the LD_{50} of the extract exceeds 5000 mg/kg, indicating reduced toxicity. The findings indicated that the combination of the two phytomedicines effectively restored insulin production at an LD_{50} exceeding 5000 mg/kg, surpassing the theoretical LD_{50} of *V. amygdalina* and brick-red *T. catappa* when evaluated individually. A non-toxic substance may exhibit toxicity at elevated doses, while a highly toxic substance can be considered safe at low doses. Overdose during treatment is likely to present safety concerns (Mensah *et al*., 2019). Toxicity studies conducted on animals do not inherently yield equivalent effects in humans.

The pancreatic histopathology of the normal control group of rats exhibited well-differentiated and normal pancreatic architecture, with intact pancreatic islets, pancreatic acini, and interlobular connective tissue. The results indicate that the pancreatic islet cells in the untreated diabetic group were sparse, suggesting a depletion of these cells. This is likely a consequence of the effects of alloxan monohydrate on the pancreas. The group administered *Vernonia amygdalina* extract exhibited no histological alterations across all pancreatic characteristics. The brick-red *Terminalia catappa* extract exhibits minor degeneration of pancreatic islets, acini, and interlobular connective tissue. However, histopathological analysis indicates that these extracts can restore pancreatic β-cell activity

and improve insulin sensitivity (Mishra *et al*., 2024). This may result from the bioactive components found in the plant extract. The histopathological analysis of pancreatic tissues conducted by Zahira *et al* (2023) corroborates these findings, demonstrating that T. catappa extract can enhance β-cell function and decrease β-cell apoptosis (Zahira *et al*., 2023). This study suggested that extracts from *Vernonia amygdalina* and *Terminalia catappa* leaves exhibit antidiabetic properties. The combined extract demonstrates greater efficacy in enhancing pancreatic islet cells in alloxan-induced Wistar rats, as indicated by histopathological examination, revealing moderate restoration of the pancreatic islets.

CONCLUSION

This study highlights the potential of *Vernonia amygdalina* and *Terminalia catappa* leaves extract, both individually and in combination, as effective, with blood glucose results comparable to or not significantly different from exogenous insulin administration. The extracts may induce islet cell regeneration, indicating potential for restoring insulin production in Alloxan-induced Wistar rats.

An increase in the intake of the leaves of *Vernonia amygdalina* as part of the diet by diabetic patients, and further research to explore these findings is recommended

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