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Phytotherapy for Diabetes: A Preclinical Study of Ethanol Extract of Winged Bean (*Psophocarpus tetragonolobus* L.) Leaves in Diabetic Rat (*Rattus norvegicus*) Models

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Abstract

*The long-term use of synthetic hypoglycemic agents is known to cause adverse side effects and induce drug resistance. Winged bean (*Psophocarpus tetragonolobus* L.), a traditional medicinal plant from the Maluku region, contains secondary metabolites such as flavonoids, saponins, and tannins, which are believed to have potential in lowering blood glucose levels. This study aimed to investigate the effect of an ethanolic extract of winged bean leaves on blood glucose reduction and β -cell regeneration in the pancreas of white rats (*Rattus norvegicus*), serving as a diabetic model. Thirty rats weighing between 150–200 g were divided into five groups: Group I (negative control), Group II (positive control), and Groups III, IV, and V (diabetic rats treated with ethanolic extract of winged bean leaves at doses of 2.52 mg/g BW, 5.04 mg/g BW, and 7.56 mg/g BW, respectively). Streptozotocin (STZ) was administered to Groups II–V to induce diabetes. Rats with blood glucose levels exceeding 200 mg/dL were subsequently treated with the designated doses of the extract in Groups III–V. On the final day, blood glucose levels were measured, and pancreatic organs were harvested for histological analysis. The results demonstrated that the ethanolic extract of winged bean leaves at a dose of 7.56 mg/g BW effectively reduced blood glucose levels in diabetic rats.*

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder caused by the inability of the pancreas to produce sufficient insulin, resulting in elevated blood glucose levels (Tofure *et al.*, 2021; Ukratalo *et al.*, 2023; Moniharapon *et al.*, 2023; Fidia *et al.*, 2025). Persistent hyperglycemia is a hallmark of DM and, over time, may lead to serious complications affecting vital organs such as the blood vessels, kidneys, eyes, heart, and nervous system (Ningrum & Imamah, 2022).

According to data from the International Diabetes Federation (2024), diabetes represents a growing global health burden. It is estimated that 10.5% of adults aged 20–79 years are living with diabetes, nearly half of whom remain undiagnosed. Projections for 2045 indicate that 1 in 8 adults approximately 783 million people will be affected by diabetes, representing a 46% increase in prevalence. Over 90% of type 2 DM cases are associated with socioeconomic, demographic, environmental, and genetic factors (Ningrum & Imamah, 2022). In Indonesia, the

Basic Health Research (Risikesdas) 2018 reported the highest prevalence of DM among individuals aged 55–64 years (6.3%), with women comprising the largest proportion of diagnosed cases (1.8%) (Ludong *et al.*, 2019; Novi *et al.*, 2025).

In healthy individuals, normal blood glucose levels typically range around 90 mg/dL, with fasting glucose levels between 80–125 mg/dL (Syuaib *et al.*, 2025). The American Diabetes Association (ADA) defines the diagnosis of DM based on several criteria, including fasting blood glucose, two-hour plasma glucose levels after an oral glucose tolerance test, and HbA1c levels. Various factors such as dietary habits, physical activity, medication use, and genetic predisposition can influence fluctuations in blood glucose levels (Care & Suppl, 2022).

Hyperglycemia in diabetic patients contributes to increased production of free radicals and a decline in the body's antioxidant defense systems, ultimately triggering oxidative stress (Yuslianti, 2018; Prawitasari, 2019; Kaliky *et al.*, 2025). According to Pratiwi *et al.* (2021), elevated plasma glucose levels beyond the normal threshold serve as a key diagnostic indicator of DM, as the primary metabolic disturbance lies in carbohydrate metabolism (Kaihena *et al.*, 2024). Prolonged hyperglycemia can result in chronic complications such as cardiovascular disease (e.g., myocardial ischemia and cardiomyopathy), gangrene, chronic kidney failure, retinopathy, and neuropathy (Febriani *et al.*, 2023).

Although hyperglycemia cannot be completely cured, DM management generally relies on four main pillars: education, dietary regulation, physical activity (exercise), and pharmacological therapy (Nurhikma *et al.*, 2025). However, these approaches have not significantly reduced the incidence of diabetes due to several limitations, including the need for long-term treatment, side effects of oral antidiabetic drugs (OADs), and limited access to optimal healthcare (Zakaria *et al.*, 2019). As a result, many patients have turned to alternative treatments using natural products, which are perceived as more affordable, accessible, and associated with fewer side effects (Wulandari *et al.*, 2021; Pangemanan *et al.*, 2023; Kaihena *et al.*, 2024a).

In Indonesia, traditional medicine remains widely practiced and trusted by many communities as an alternative therapy for various health conditions (Tuhumury & Ukratalo, 2023; Loilatu *et al.*, 2024; Ukratalo, 2025; Hasan *et al.*, 2025). Traditional remedies typically consist of formulations made from natural ingredients such as plants, animal-derived substances, minerals, and other natural extracts. Knowledge of the medicinal properties of traditional remedies has been passed down through generations (Tuhumuri *et al.*, 2025). Due to their natural origins, these treatments are also commonly referred to as herbal medicines. For centuries, local communities have utilized a wide variety of plants for therapeutic purposes, underscoring the importance of ethnobotanical knowledge as a foundation for modern drug development (Amin & Cahya, 2025).

One traditional plant with promising medicinal potential is the winged bean (*Psophocarpus tetragonolobus* L.), which is commonly found and utilized in the Maluku region of Indonesia. This plant contains various secondary metabolites such as flavonoids, saponins, and tannins, particularly in its leaves and seeds (Kaihena & Samson, 2019; Henaulu & Kaihena, 2020; Ratulewen *et al.*, 2023; Sianipar *et al.*, 2025). Flavonoids possess notable pharmacological activities, especially in diabetes treatment, as they enhance insulin secretion

from pancreatic β -cells in the islets of Langerhans by regulating calcium (Ca^{2+}) metabolism and stimulating β -cell regeneration (Nubatonis *et al.*, 2015). In addition, flavonoids act as antioxidants, inhibit erythrocyte aggregation, and stimulate nitric oxide production, which plays a role in vasodilation (Ulpa *et al.*, 2022).

Local communities have long used winged bean leaves as an anti-hyperglycemic remedy, typically preparing them by boiling. The decoction is believed to extract active compounds with antidiabetic properties. However, exposure to high temperatures during boiling may degrade some bioactive compounds, potentially reducing therapeutic efficacy. Therefore, this study aims to investigate the effects of an ethanol extract of *Psophocarpus tetragonolobus* L. leaves on blood glucose reduction in diabetic rat models (*Rattus norvegicus*).

RESEARCH METHODS

Type of Research

This study was a laboratory-based experimental research.

Research Design

A Completely Randomized Design (CRD) with a factorial pattern was employed in this study, consisting of four treatments with three replications. A total of 20 rats were randomly assigned to five groups, with each group comprising four rats. Four groups, excluding the negative control group (i.e., the positive control, Treatment I, Treatment II, and Treatment III), were induced with Streptozotocin (STZ) at a dose of 30 mg/rat/day. Following STZ induction, the rats' blood glucose levels were measured. Subsequently, different treatments were administered: Treatment Group I received 2.52 mg/rat/day of ethanol extract of winged bean leaves, Treatment Group II received 5.04 mg/rat/day, and Treatment Group III received 7.56 mg/rat/day. The ethanol extract was administered daily for 15 consecutive days. The factorial design was selected to observe the interaction between two factors: Factor A (treatment groups) and Factor B (observation times of blood glucose levels in STZ-induced rats).

Tools and Materials

Equipment: The list includes writing tools, a rotary evaporator, an OHAUS digital balance, a hotplate, cover glass, a separating funnel, a syringe, an oral gavage (sonde), animal cages, an autocheck glucometer, measuring cylinders, pipettes, erlenmeyer flasks, a blender for grinding, cloth, a centrifuge, and a digital camera.

Materials: Winged bean leaves, filter paper, white rats (test animals), Streptozotocin (STZ), distilled water (aquadest), aluminum foil, tissue, rice husks, standard feed (bran), and water.

Experimental Procedure

Animal Preparation

The test animals used were male white rats (*Rattus norvegicus*), aged 8–10 weeks and weighing 150–200 grams, totaling 30 animals. Selection criteria included healthy physical characteristics: clean and shiny fur, absence of ectoparasites, pink and clear eyes, no excessive mucus or saliva discharge from the nose or mouth, normal and solid feces, active behavior,

normal food and water intake, and no visible signs of illness. All rats were acclimatized for one week before the experimental procedures began.

Preparation of Test Material

Winged bean leaves were harvested from self-cultivated plants. Ten leaves were taken from the apex of each branch. The leaves were washed under running water, chopped, and air-dried. Once dried, the leaves were ground using a blender to produce a fine powder (simplicia), which was then used for the extraction process.

Extraction Procedure

Extraction followed the maceration method described by Kakisina & Ukratalo (2011), with the following steps:

1. A total of 250 grams of powdered simplicia was weighed and placed in an Erlenmeyer flask.
2. One liter of 70% ethanol was added, and the mixture was left to stand for 24 hours for maceration.
3. After 24 hours, the mixture was filtered using Whatman filter paper (0.2 μm pore size) to separate the ethanol extract from the residue. The extraction process was repeated three times to maximize yield.
4. The liquid extract was concentrated using a rotary evaporator to remove the ethanol solvent.
5. The resulting product was a thick ethanol extract of winged bean leaves, ready for subsequent experimental use.

Determination of Dosage

The initial dose was based on traditional human use, approximately 100 mg for a 50 kg individual. For a 70 kg human, the equivalent dose would be $70/50 \times 100 \text{ mg} = 140 \text{ mg}$. Using the conversion factor from human to rat (0.018, according to Laurence and Bacharach, 1964), the equivalent dose for a 200 g rat was $0.018 \times 140 \text{ mg} = 2.52 \text{ mg}$. Based on this, three doses were used:

- Dose I: 2.52 mg/rat/day
- Dose II: 5.04 mg/rat/day
- Dose III: 7.56 mg/rat/day

Induction of Diabetes in Rats

Diabetic induction followed the procedure described by Purwanto and Liben (2014). The required STZ dose was 150 mg/kg body weight. For a 200 g rat:

$$200 \times 150 / 1000 = 30 \text{ mg STZ}$$

STZ was dissolved in citrate buffer at a concentration of 22.5 mg/mL:

$$30 \text{ mg} / 22.5 \text{ mg/mL} = 1.3 \text{ mL}$$

An additional 0.1 mL was added as a minimal dose increment, resulting in a total volume of 1.4 mL/200 g body weight. Each rat received two intracardiac injections of 1.4 mL. Blood glucose levels were subsequently measured.

Testing Procedure

Administration of Ethanol Extract

A total of 20 male white rats were divided into five groups (4 rats per group). Their body weight and fasting blood glucose levels were measured before treatment. Three treatment groups received the ethanol extract of winged bean leaves for 15 consecutive days: treatment I: 2.52 mg/rat/day, treatment II: 5.04 mg/rat/day and treatment III: 7.56 mg/rat/day. The negative and positive control groups did not receive the extract.

Measurement of Blood Glucose Levels

Blood glucose levels were measured three times: before STZ injection, after STZ injection, and after administration of the extract, to assess the changes in glucose levels (Siscawati & Baszary, 2025). Blood glucose was measured using an Autocheck glucometer. The procedure involved cutting the tip of the rat's tail, allowing a blood drop to emerge, placing the blood onto a test strip, and recording the results.

Data Analysis

Blood glucose data were statistically analyzed using factorial pattern analysis of variance (ANOVA). A post-hoc test was performed if the ethanol extract showed a significant effect at $\alpha = 0.05$ (Kaihena *et al.*, 2023). Data analysis was conducted using SPSS version 25.0.

RESULTS AND DISCUSSION

Blood Glucose Levels in White Rats with Diabetes Mellitus

The mean blood glucose levels of the rat groups, including the negative control, positive control, and treatment groups administered with different doses of ethanol extract of winged bean leaves (2.52 mg/rat/day, 5.04 mg/rat/day, and 7.56 mg/rat/day), are presented in Table 1.

Table 1. Mean Blood Glucose Levels of White Rats Throughout the Study

Treatment	Blood Glucose Measurement Time (Day)						Mean Blood Glucose \pm SD (mg/dL)	
	Initial	Day 7 (post-STZ induction)	Treatment with the extract					
			Day 10	Day 13	Day 16	Day 19	Day 22	
K (-)	91,3	90,6	91,7	90,7	91,0	91,3	95,0	91,65 \pm 1,68 ^a
K (+)	91,7	304,7	351,3	425,7	429,7	496,7	573,3	381,87 \pm 147,9 ^b
Dosis 2,52	90,3	444,3	425,7	267,3	119,7	115,3	103,3	223,7 \pm 148,2 ^c
Dosis 5,04	91,7	401,6	329,3	288,3	111,7	106,3	105,0	204,84 \pm 123,9 ^d
Dosis 7,56	90,7	496,3	354,7	105,7	102,0	101,7	96,7	192,54 \pm 155,9 ^e
Mean	91,1 \pm 0,92^a	347,5 \pm 148,1^b	270,53 \pm 118,1^c	235,5 \pm 129,1^d	170,8 \pm 134,3^e	182,3 \pm 162,9^f	195,1 \pm 196,8^g	218,92 \pm 157,8^f

Note: Values in the same row followed by different superscript letters indicate statistically significant differences ($p < 0.05$), whereas those followed by the same letter are not significantly different ($p > 0.05$).

Based on the results shown in Table 1, the initial blood glucose levels were relatively uniform across all groups, ranging from 90.3 to 91.7 mg/dL, indicating that the baseline condition of the rats was normal and there were no significant differences among groups. After induction with streptozotocin (STZ) on day 7, a significant increase in blood glucose levels was observed in the positive control group (K (+)) and all three treatment groups receiving ethanol extract of winged bean leaves. The positive control group exhibited a drastic rise from 91.7 mg/dL to 304.7 mg/dL, confirming the successful induction of hyperglycemia. The groups treated with doses of 2.52 mg, 5.04 mg, and 7.56 mg showed increased blood glucose levels of 444.3 mg/dL, 401.6 mg/dL, and 496.3 mg/dL, respectively, with the highest level observed in the 7.56 mg dose group.

From day 10 to day 22, blood glucose levels in the negative control group remained stable and low, ranging between 90.6 and 95.0 mg/dL, indicating no hyperglycemic effect in normal rats. The positive control group showed a continuous increase in blood glucose, peaking at 573.3 mg/dL on day 22, indicating severe, untreated hyperglycemia. Conversely, the groups administered the ethanol extract of winged bean leaves demonstrated a gradual decrease in blood glucose levels following extract administration. At a dose of 2.52 mg/rat/day, blood glucose decreased from 444.3 mg/dL on day 7 to 103.3 mg/dL on day 22. The 5.04 mg/rat/day dose also showed a significant reduction from 401.6 mg/dL to 105.0 mg/dL on the last day. Similarly, the highest dose of 7.56 mg/rat/day reduced blood glucose levels from 496.3 mg/dL to 96.7 mg/dL on day 22, indicating the strongest hypoglycemic effect compared to the other two doses.

The average blood glucose measurements presented in Table 1 are illustrated more clearly in Figure 1.

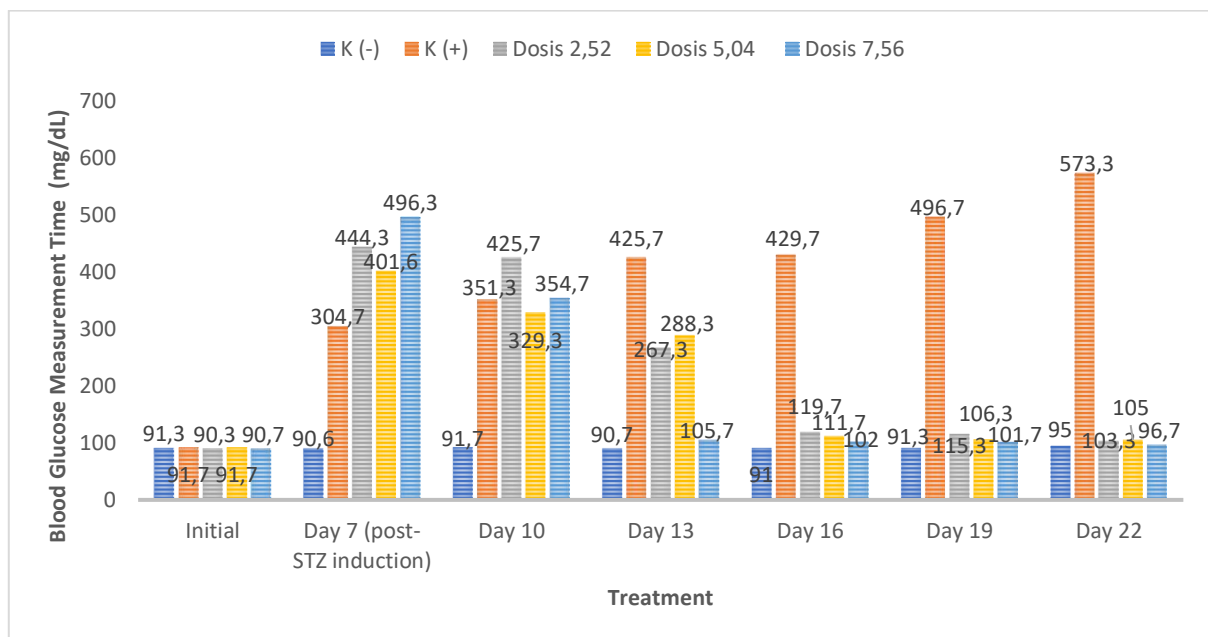


Figure 1. Histogram depicting the mean blood glucose levels during the study period

Based on the factorial Analysis of Variance (ANOVA) conducted using SPSS version 16.0 (Appendix 2), the calculated F-value was greater than the critical F-value, indicating that the

administration of ethanol extract of winged bean leaves significantly affected the reduction of blood glucose levels in diabetic rats. Similarly, the measurement time and the interaction between dose and measurement time also had significant effects ($P < 0.05$).

The post hoc analysis using Duncan's Multiple Range Test (DMRT) at a 95% confidence level showed that the mean blood glucose level in the negative control group was significantly different from those in the positive control group and the diabetic rat groups treated with ethanol extract of winged bean leaves at doses of 2.52 mg/rat/day, 5.04 mg/rat/day, and 7.56 mg/rat/day. The mean blood glucose level in the positive control group was significantly different from that in all treated diabetic groups. Furthermore, the mean blood glucose level in the group treated with 2.52 mg/rat/day differed significantly from those treated with 5.04 mg/rat/day and 7.56 mg/rat/day, and the group treated with 5.04 mg/rat/day differed significantly from the group treated with 7.56 mg/rat/day. In addition, the blood glucose measurement periods showed significant differences between the initial measurement and those taken on days 10, 13, 16, 19, and 22.

Streptozotocin (STZ) is an alkylating agent that acts by breaking the DNA strands in the cells of the Langerhans islets in the pancreas of rats. Although its use is restricted due to side effects that can cause permanent pancreatic damage, this toxic effect makes STZ a commonly used agent in experimental diabetes animal models (Purwanto and Liben, 2014). Studies have shown that STZ toxicity is mediated by nitric oxide (NO) produced during STZ metabolism (Alfisyahri, 2015). In this study, STZ injection in white rats successfully induced diabetes mellitus, as STZ directly caused degeneration of pancreatic β cells by altering the shape of their nuclei, thereby inhibiting insulin production and secretion (Kintoko *et al.*, 2018). STZ acts through the glucose transporter GLUT2 in pancreatic β cells due to its structural similarity to glucose. The STZ molecule consists of two functional groups: glucopyranosyl and nitrosourea. The glucopyranosyl group reduces the affinity of GLUT2, facilitating the entry of STZ into β cells (Ghasemi & Jeddli, 2023). The nitrosourea group can damage DNA via alkylation, leading to DNA fragmentation. This condition triggers poly ADP-ribosylation (PARP) activity to repair the DNA damage; however, PARP activity can inhibit the enzyme aconitase in the Krebs cycle, thereby disrupting cellular metabolism through reduced ATP production.

STZ is also a nitric oxide (NO) donor, contributing to β -cell damage. In addition, STZ generates superoxide radicals that can form hydrogen peroxide (H_2O_2) and hydroxyl radicals ($\cdot OH$) via xanthine oxidase reactions. NO, and these free radicals can produce peroxynitrite, which is toxic to pancreatic β cells (Kim, 2020). As a result, β cells may undergo apoptosis, leading to decreased insulin secretion and subsequent hyperglycemia (Husna *et al.*, 2019). Blood glucose levels in rats increase significantly during the first week following an STZ injection at a dose of 45 mg/kg body weight (Utami *et al.*, 2025).

According to Birru *et al.*, (2015), normal blood glucose levels in male white rats range between 60 and 150 mg/dL. Initial measurements in this study indicated that blood glucose levels across all treatment groups remained within the normal range. However, measurements taken on days 3, 6, 9, 12, and 15 revealed distinct differences: the negative control group maintained stable blood glucose levels without significant increases (i.e., did not develop

diabetes mellitus), whereas the positive control group exhibited highly significant increases in blood glucose on these days.

The diabetic rat groups treated with ethanol extract of *Psophocarpus tetragonolobus* (kecipir) leaves at doses of 2.52 mg/g BW, 5.04 mg/g BW, and 7.56 mg/g BW also showed elevated blood glucose on day 10, indicating the onset of diabetes mellitus. This increase occurred because STZ administration raised blood glucose levels and caused toxicity that damaged β cells. The destruction of β cells led to the loss of the body's natural insulin production capacity, making it heavily reliant on external insulin (Rahman *et al.*, 2021). This condition was characterized by fasting blood glucose levels in rats reaching or exceeding 300 mg/dL.

Several hypotheses regarding mechanisms of increased oxidative stress due to high blood glucose levels include the polyol pathway in peripheral nerves, increased production of Advanced Glycation End Products (AGEs), activation of protein kinase C (PKC), and the hexosamine pathway associated with excessive protein modification by N-acetylglucosamine. Additionally, glucose autoxidation in diabetes mellitus (Garg & Gupta, 2022) and oxidative phosphorylation (Siahaan, 2020) also contribute to oxidative stress.

In diabetes mellitus patients, oxidative stress impairs glucose uptake by muscle and adipose cells and reduces insulin secretion by pancreatic β cells. Moreover, oxidative stress directly affects the vascular wall, playing a significant role in the pathophysiology of type 1 diabetes complications (Pertiwi & Perdhana, 2023).

Factorial ANOVA results demonstrated that administration of ethanol extract of kecipir leaves at varying doses significantly influenced blood glucose levels in diabetic rats. This was evident from the pattern of blood glucose increase post-STZ induction, followed by a gradual decrease on days 10, 13, 16, 19, and 22 after administering ethanol extract doses of 2.52 mg/rat/day, 5.04 mg/rat/day, and 7.56 mg/rat/day.

The 2.52 mg/rat/day dose reduced blood glucose by 341 mg/dL, the 5.04 mg/rat/day dose by 296.6 mg/dL, and the 7.56 mg/rat/day dose achieved the greatest reduction of 399.6 mg/dL. Furthermore, the timing of glucose measurements significantly affected the decrease in blood glucose levels. For example, at the 7.56 mg/rat/day dose, blood glucose normalized (105.7 mg/dL) by day 13, whereas at 2.52 mg/rat/day and 5.04 mg/rat/day doses, normalization occurred by day 16, with levels of 119.7 mg/dL and 111.7 mg/dL, respectively.

The reduction in blood glucose following ethanol extract administration is attributed to the active compounds contained within, namely secondary metabolites such as saponins, tannins, and flavonoids (Raharjo *et al.*, 2025). According to Veiko *et al.* (2020), flavonoids protect cell membranes from oxidative stress induced by free radicals by increasing membrane fluidity and preventing the entry of harmful molecules, thereby maintaining membrane integrity. Flavonoids also enhance glucose metabolism and convert glucose into energy (Budianto *et al.*, 2022), which increases cellular insulin sensitivity and lowers blood glucose levels.

Flavonoids act in diabetes mellitus by inhibiting glucose absorption and improving glucose tolerance (Dewi *et al.*, 2022). Moreover, flavonoids regulate blood glucose reduction and improve the distribution of insulin-producing β cells in the islets of Langerhans, as

demonstrated by Hematoxylin-Eosin (HE) staining. Increased insulin receptor sensitivity is supported by flavonoid activity in enhancing both the affinity and number of insulin receptors, activating insulin receptor tyrosine kinase (IRTK), and inhibiting insulin receptor tyrosine phosphatase (Decroli *et al.*, 2022).

Saponins in the ethanol extract of kecipir leaves act as glycosides that reduce blood glucose by inhibiting the release of the α -glucosidase enzyme in the small intestine. This inhibition reduces the breakdown of polysaccharides into simple sugars, effectively decreasing carbohydrate digestion and absorption (Ukratalo *et al.*, 2022). Consequently, glucose release into the bloodstream occurs more slowly, and blood glucose levels rise gradually, preventing postprandial glucose spikes (Putri *et al.*, 2024). Tannins, as polyphenolic compounds, also play an important role by reducing oxidative stress and acting as antibodies through their protein-binding and precipitating abilities.

Microscopic Overview of Pancreatic β Cells in White Rats with Diabetes Mellitus

The histological profiles of the pancreas in negative control, positive control, and groups administered with ethanol extract of *Vigna unguiculata* leaves at doses of 2.52 mg/rat/day, 5.04 mg/rat/day, and 7.56 mg/rat/day are presented in Figure 2.

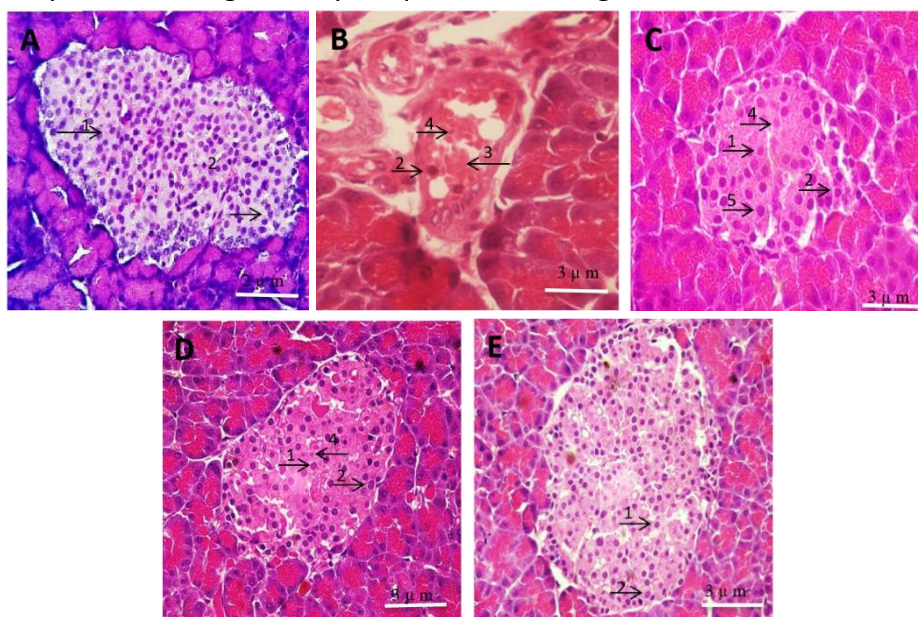


Figure 2. Photomicrograph of the pancreas of white rats: (A) Negative control group, (B) Positive control group, (C) Group administered with *Vigna unguiculata* leaf extract at a dose of 2.52 mg/rat/day, (D) Group administered with leaf extract at 5.04 mg/rat/day, and (E) Group administered with leaf extract at 7.56 mg/rat/day; (1) β cells, (2) α cells, (3) Karyopyknosis, (4) Necrosis, and (5) Atrophy. Magnification: 400 \times

The microscopic profiles of the pancreas in negative control, positive control, and groups administered with ethanol leaf extract at doses of 2.52 mg/rat/day, 5.04 mg/rat/day, and 7.56 mg/rat/day, as observed using Hematoxylin-Eosin (HE) staining, are presented in Figure 2. In the positive control group, damage to the pancreatic islets of Langerhans was observed (Figure 2B). In the group treated with 2.52 mg/rat/day of the ethanol leaf extract (Figure 2C), necrosis,

edema, and enlargement of the pancreatic islets were still observed. Meanwhile, in the groups treated with 5.04 mg/rat/day (Figure 2D) and 7.56 mg/rat/day (Figure 2E), necrosis and edema were still present; however, the size of the pancreatic islets had returned to normal.

The study results indicated that injection of streptozotocin (STZ) at 1.4 mL/200 g body weight caused damage to the pancreatic islets, where the cells appeared to lack nuclei or exhibited karyopyknosis, and the individual cells were indistinguishable (Figure 2B). This damage occurs because STZ undergoes redox metabolism, generating free radicals that induce β -cell injury. Consequently, the β -cell mass in the islets of Langerhans was reduced. Damage to these cells impaired insulin production, resulting in elevated blood glucose levels.

According to Samarghandian (2016), in vivo administration of STZ also increases malondialdehyde (MDA) levels. Elevated plasma MDA indicates increased lipid peroxidation in β -cells, disrupting insulin secretion and leading to hyperglycemia through the following mechanisms: (1) STZ causes DNA strand breaks in pancreatic islets, stimulating poly(ADP-ribose) polymerase (PARP) and reducing intracellular NAD⁺ and NADP⁺ levels, thereby inhibiting proinsulin synthesis and inducing hyperglycemia, and (2) activation of reactive oxygen species (ROS), such as superoxide (O₂⁻), hydroxyl radical (\cdot OH), and hydrogen peroxide (H₂O₂).

Pancreatic damage occurs because STZ impairs the cellular antioxidant defense system through oxidative stress (Eguchi *et al.*, 2021). Oxidative stress induces lipid peroxidation, leading to membrane damage. Cell membranes regulate passive and active transport and serve as attachment sites for enzymes. Loss of membrane integrity causes fluid accumulation in cells (edema), which may progress to cell death (necrosis). Empty spaces in the islets of Langerhans result from β -cell necrosis. Cytotoxic agents can induce shrinkage of pancreatic islets, β -cell depletion, degranulation, and vacuolization (Folli *et al.*, 2018). Additionally, some cells undergo swelling as a pre-necrotic phase (Hidayah, 2008), demonstrating that STZ-induced free radicals lead to β -cell necrosis through lipid peroxidation.

According to Engwa *et al.* (2022), antioxidants donate one or more electrons to free radicals, forming stable, harmless molecules and preventing radical-induced damage. This mechanism contributes to the observed reduction in blood glucose levels in diabetic rats, as β -cell regeneration improves alongside inhibited glucose absorption. Substances containing antioxidants have been shown to protect pancreatic islets from STZ-induced damage (Anastasiou *et al.*, 2021).

In the present study, the group administered 2.52 mg/rat/day of ethanol leaf extract (Figure 2C) exhibited minimal necrosis, edema, and β -cell atrophy. Rats treated with 5.04 mg/rat/day (Figure 2D) and 7.56 mg/rat/day (Figure 2E) still showed some necrosis, edema, and atrophy; however, β -cell numbers had increased, indicating that ethanol leaf extract promotes β -cell regeneration and enhances pancreatic β -cell mass.

The observed β -cell regeneration in diabetic rats is attributed to natural antioxidants in the ethanol leaf extract, including flavonoids, saponins, and tannins. Antioxidants prevent damage to injured cells by neutralizing free radicals before they can induce cell injury. Sulistyorini *et al.* (2015) reported that flavonoids capture free radicals, regulate blood glucose, and improve β -cell distribution in the pancreatic islets of Langerhans as observed via HE

staining. Flavonoids inhibit α -glucosidase through hydroxylation and β -ring substitutions, tannins enhance glucose and lipid metabolism, preventing excessive accumulation in the blood, and tannins also exhibit antioxidant and anti-tumor activity. According to Liu *et al.* (2021), saponins promote pancreatic regeneration, increasing β -cell and islet numbers, thus enhancing insulin secretion.

CONCLUSION

Ethanol leaf extract of *Vigna unguiculata* at different doses (2.52 mg/rat/day, 5.04 mg/rat/day, and 7.56 mg/rat/day) was sufficient to stimulate a reduction in blood glucose levels in diabetic rats and to promote regeneration of pancreatic β cells in a dose-dependent manner. The most effective dose for lowering blood glucose and regenerating pancreatic β cells in diabetic rats was 7.56 mg/rat/day.

DECLARATIONS

Author Contributions

P.I.T. designs research, collects and analyzes data, and prepares draft publications. M. M. and M. K contributed to proofreading the manuscript.

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Ethical Statement

The use of test animals and the implementation of this research procedure have fulfilled the laws and regulations relating to using test animals in the Republic of Indonesia.

Declaration of Interest

The author declares that they have no financial or personal relationships that could positively or negatively influence the use of data or the research topic.

Data Sharing Statement

The datasets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

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