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Original Research

Bidara Leaf Extract (Ziziphus mauritiana L.): A Natural Approach to Enhancing Pancreatic Function and Lowering Blood Sugar in Male Wistar Rats

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Abstract: Diabetes mellitus is a metabolic disorder characterized by insufficient insulin production, leading to elevated blood glucose levels. When pancreatic beta cells produce inadequate insulin to compensate for increased insulin resistance, chronic hyperglycaemia ensues. This study investigates the effect of Bidara leaf extract (*Ziziphus mauritiana*) on the pancreatic function of male Wistar rats and its efficacy in reducing blood sugar levels. The experimental design was a post-test only controlled group study. Six groups were included: a control group receiving 1% Na CMC and five treatment groups receiving Bidara leaf ethanol extract at doses of 50 mg/kg, 100 mg/kg, 300 mg/kg, and 500 mg/kg, with each group consisting of four rats. Data analysis involved normality tests, homogeneity tests, and ANOVA. Results indicated that the p-value for each group was less than 0.05. Specifically, the 50 mg/kg dose of Bidara leaf extract significantly reduced blood sugar levels ($p = 0.02$). The 100 mg/kg dose showed a p-value of 0.14, indicating effectiveness in lowering blood sugar levels, though less pronounced. Similarly, the 300 mg/kg dose ($p = 0.16$) and the 500 mg/kg dose ($p = 0.04$) demonstrated significant hypoglycaemic effects. In conclusion, Bidara leaf extract has a dose-dependent effect on lowering blood sugar levels in male Wistar rats, with significant results observed at varying concentrations. Further research is recommended to explore the mechanisms involved and potential therapeutic applications in humans.

Keywords: *Diabetes Mellitus; Bidara Leaf Extract; Ziziphus mauritiana; Blood Sugar Levels; Pancreatic Function.*

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that is unable to produce enough insulin, resulting in high glucose levels in the blood[1,2]. High levels of glucose in the blood are caused by the body not being able to convert glucose or carbohydrates into energy because the body no longer produces enough insulin or the body no longer produces insulin which causes glucose to not be able to enter the cells to be converted into energy and there is an increase in blood glucose levels, resulting in damage to various body tissues ranging from blood vessels, eyes, kidneys, heart, and also nerves[3,4].

Diabetes mellitus is a worldwide health problem and the number of sufferers continues to increase. The global status report issued by the World Health Organization (WHO) states that the prevalence of diabetes mellitus worldwide is estimated at 9%. Meanwhile, the proportion of deaths caused by diabetes mellitus from all deaths caused by non-communicable diseases is 4% [5]. Deaths caused by diabetes mellitus occur in low and middle income countries with a proportion of 80%. By 2030, it is estimated that diabetes mellitus will be the 7th leading cause of death in the world[6].

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Indonesia is the 7th country with the highest prevalence of diabetes, after China, India, the United States, Brazil, Russia and Mexico[7]. Asia states that out of 1,785 people in Indonesia who experience DM. The 2018 Riskesdas (Primary Health Research in Indonesia) report shows that the prevalence of DM diagnosed by doctors in the population aged ≥ 15 years is 2%. In 2021 Indonesia rose to 5th place with the highest number of DM cases with a prevalence of 19.5 [8].

One of the plants used as a medicine by the community is herbal bidara plant (*Ziziphus mauritiana Lam*.) is one of the plants found in Indonesia and its properties are not widely known[9,10]. Bidara leaves contain several compounds such as alkaloids, flavonoids, quercetin, phenols, rutin, and terpenoids that play a significant role in increasing antioxidant activity and are able to regenerate damaged pancreatic β cells[11]. Flavonoids are also thought to improve the sensitivity of insulin receptors, which is beneficial in DM[12].

Research conducted by Haeria, 2016 concluded that bidara leaf extract has strong antioxidant activity, this is due to the flavonoid content contained in it. Flavonoids are reducing compounds that can inhibit many oxidation reactions by transferring electrons to free radical compounds so that the free radical compounds become stable and without oxidation reactions occurring[13].

MATERIAL AND METHOD

This type of research is experimental using a pre-test and post-test control group design[14]. The research was conducted at the Pharmacology Laboratory of the Faculty of Pharmacy, University of North Sumatra from September 2023 to December 2023. The experimental animal research protocol was approved by the Prima Indonesia University Health Research Ethics Committee (012/KEPK/UNPRI/IX/2023). The test animals used in this study were healthy Wistar male rats obtained from Ellio Sains Laboratory. The 24 rats used were divided into 6 groups using bidara leaf ethanol extract 50, 150, 300 and 500 mg/KgBB and 1% Na-CMC as negative control and positive control was Metformin 500mg/KgBB.

Tools and Materials

The tools used in this research are measuring cup (Pyrex), drop pipette, sudip, analytical balance (*Mettler Toledo*), maceration vessel, stirring rod, rotary evaporator, jar. The materials used in this study are bidara leaves (*Ziziphus Mauritiana L*.), 96% ethanol, 1% Na CMC, Alloxan, Metformin, wistar male rats, husks for rat cages, rat feed, rat drinking water, and rat food.

Bidara leaf extraction (*Ziziphus mauritiana L*.)

Making bidara leaf extraction using maceration method. Maceration uses 96% ethanol solvent. Bidara leaf simplisia powder weighed 500 grams was soaked using 96% ethanol solvent as much as 3.75 liters for 3x24 hours while stirring occasionally at the same time, then the filtering process was carried out. The macerate was then filtered first using filter paper and evaporated using a waterbath at 60oC until a thick extract was obtained[15,16].

Blood Collection Process

Blood sampling is done by surgery to obtain blood from the heart of Wistar rats. Blood collection from the heart aims to get more blood volume compared to blood collection in the tail and eyes of rats. Before being dissected, the rats were first fed for 12 hours. Then the rats were euthanized until the rats lost consciousness (fainting). The rats were placed on a surgical tray (supine position) using a needle to puncture the legs so that the rats were spread-eagled. Make a midline incision in the abdominal wall muscle from the end of the stenum to the pubic symphysis. In the midline cut there will be a little bleeding. The cut in the abdominal muscle does not hit the diaphragm to avoid pneumothorax. Locate the

heart on the left side of the chest between the 3rd and 4th costae next to the sinister sternum. Insert the syringe into the heart 5 mm deep from the thorax towards the chin. The syringe forms an angle of 25-30° from the rat's chest. Blood was immediately drawn as much as 5 ml using a syringe and collected in a vacutainer[17].

Treatment Procedure

Animals in 1 group were placed together in 1 cage. Groups 3 to 6 were given ethanol extract of Bidara leaves (*Ziziphus Mauritiana L.*) orally according to the dose level while the negative control group was given 1% Na CMC solution and the positive control was given metformin 500 mg/KgBB. Grouping was divided into: Group I was given 1% Na CMC as a negative control, group II was given Metformin 500mg/KgBB as a positive control (*Ziziphus mauritiana* L), group III was given 50 mg/KgBB of bidara leaf ethanol extract (*Ziziphus mauritiana* L), group IV was given 150 mg/KgBB of bidara leaf ethanol extract (*Ziziphus mauritiana* L), group V was given 300 mg/KgBB of bidara leaf ethanol extract (*Ziziphus mauritiana* L) and group VI: 500 mg/KgBB of ethanol extract of bidara leaves (*Ziziphus mauritiana* L). Initial blood sugar checks were carried out on day 0, then after checking the blood glucose levels of normal rats, the rats were fed for 8 hours. Rats were induced alloxan intra peritoneally with a total dose of 24 mg on day 1, and diabetic blood sugar was checked on day 3. Rats were declared hyperglycemia if the blood glucose level was ≥ 135 mg/dL [18,19].

Histopathologic Examination

Pancreas samples were taken on the 28th day of the test animals. The pancreas obtained was then cleaned and fixed with 10% (Buffer Formaline Bio Analitika Pro Analysis) solution for at least 24 hours, then the pancreas samples were dehydrated with graded alcohol concentrations, followed by clearing using xylol, impregnation and embedding using paraffin. Blocks were cut to 5µm thick with a microtome, then Hematoxylin-Eosin (HE) general staining was performed[20,21].

Data Analysis

The research data were analyzed using statistical program. Data normality test was analyzed by Shapiro Wilk test ($p > 0.05$). Further analysis were carried out using paired Sample T - Test to see the relationship between each dose to reduce blood sugar levels[22,23].

RESULTS AND DISCUSSION

Phytochemical screening test results of bidara leaf (*Ziziphus mauritiana* L.)

Phytochemical screening is a qualitative test used as an initial stage carried out on bidara leaf extract (Ziziphus mauritiana L.). The purpose of phytochemical screening is to determine the secondary metabolite compounds contained in bidara leaf extract. The results of phytochemical screening can be seen in Table 1.

Table 1. Compounds contained in Bidara Leaf (*Ziziphus mauritiana* L.)

Secondary Metabolite Compounds	Reagents	Result
Alkaloid	Bouchardart	-
	Maeyer	-
	Dragendroff	+
	Wagner	+
Terpenoids/steroids	Salkowsky	-
	Lieberman-Burchad	-
Saponins	Aquadest + 96% Alcohol	+
Flavonoids	$Mg_{(s)}+HCl_{(p)}$	+
Tannin	$FeCL_3$ 1%	+
Glycosides	Mollish	+

Effectiveness of Bidara Leaf Extract at a Level of 50, 150, 300 and 500 mg/KgBW in Reducing Blood Sugar Levels

The statistical analysis results for the effectiveness of Bidara leaf extract at concentrations of 50, 150, 300, and 500 mg/kgBW in reducing blood sugar levels reveal significant p-values of 0.002, 0.014, 0.016, and 0.004, respectively. This indicates a statistically significant reduction in blood sugar levels at all tested concentrations. The lowest concentration of 50 mg/kgBW demonstrated a highly significant effect with a p-value of 0.002, suggesting that even minimal doses of the extract can effectively lower blood sugar levels. At 150 mg/kgBW, the extract continued to show significant hypoglycemic effects with a p-value of 0.014, likely due to the presence of bioactive compounds such as flavonoids that enhance insulin sensitivity and provide antioxidant benefits. The concentration of 300 mg/kgBW also maintained its effectiveness in reducing blood glucose levels, with a p-value of 0.016, indicating a consistent beneficial impact across varying dosages. The most substantial effect was observed at the highest concentration of 500 mg/kgBW, with a p-value of 0.004, underscoring the extract's potent hypoglycemic properties at higher doses. This dose-dependent response highlights the potential of Bidara leaf extract as a therapeutic agent for diabetes mellitus, demonstrating significant efficacy in lowering blood sugar levels across all tested concentrations.

Histopathology of pancreatic β-cells in Wistar Rat

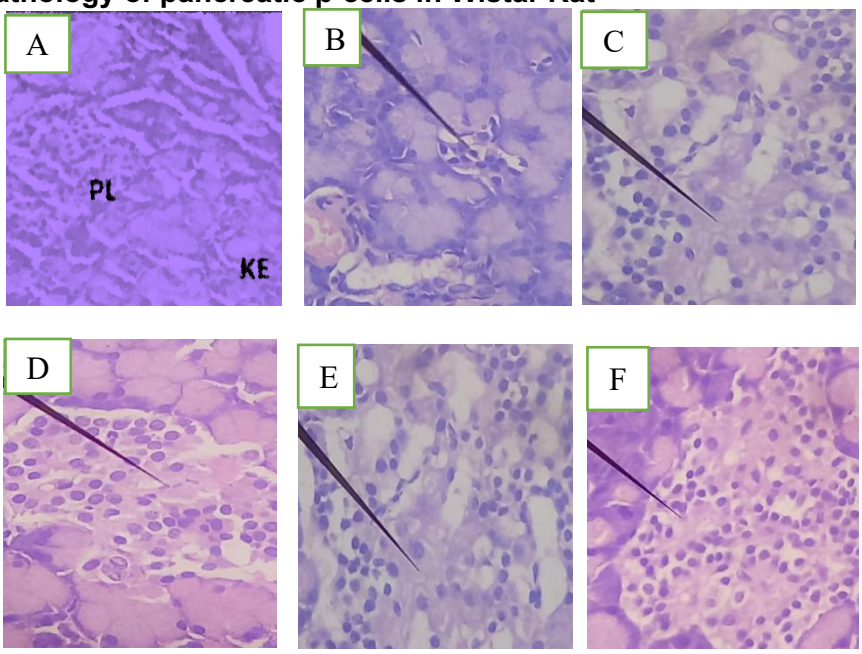

Figure 1. Positive Control (A); Negative Control (B); Dose 50 mg/KgBB (C); Dose 150 mg/KgBB (D); Dose 300 mg/KgBB (E); Dose 500 mg/KgBB (F)

The study investigates the effects of various doses of Bidara leaf extract on the Langerhans islets and histopathological changes in the pancreas of male Wistar rats, with comparisons to positive and negative controls. For the Positive Control group (A), diffuse expansion between the interlobular septum was observed, accompanied by inflammation around the ductal periphery. However, there was no vascularization, and necrosis was limited to 5-10 necrotizing cells per low-power field (LPF), indicating a relatively mild degree of pancreatic damage.

In the Negative Control group (B), the Langerhans islets value at 10x10 magnification was 7. Histopathological analysis at 10x40 magnification revealed

significant damage, with 50% necrosis and 70% degeneration of the pancreatic tissue, indicating substantial pancreatic impairment without any treatment.

At a dose of 50 mg/kgBW (C), the Langerhans islets value decreased to 5 at 10x10 magnification. Histopathological examination showed 80% necrosis and 70% degeneration at 10x40 magnification, suggesting that this low dose was not sufficient to protect the pancreas and may have contributed to increased tissue damage. For the 150 mg/kgBW dose group (D), the Langerhans islets value further decreased to 3 at 10x10 magnification. Necrosis remained at 80%, and degeneration increased to 80% at 10x40 magnification, indicating persistent and severe pancreatic damage at this intermediate dose. In the 300 mg/kgBW dose group (E), the Langerhans islets value improved to 7 at 10x10 magnification, matching the negative control group. Histopathological analysis revealed 50% necrosis and 70% degeneration at 10x40 magnification, showing that this dose reduced necrosis but did not significantly affect degeneration compared to the negative control.

At the highest dose of 500 mg/kgBW (F), the Langerhans islets value significantly increased to 12 at 10x10 magnification. Histopathological results showed 50% necrosis and 70% degeneration at 10x40 magnification, indicating that this dose provided the most substantial protection against pancreatic damage, evidenced by a higher number of Langerhans islets and reduced necrosis compared to lower doses and the negative control.

In summary, the results suggest that Bidara leaf extract exhibits a dose-dependent effect on pancreatic protection. Lower doses (50 and 150 mg/kgBW) were associated with higher necrosis and degeneration, while higher doses (300 and 500 mg/kgBW) showed improved pancreatic health, with the 500 mg/kgBW dose being the most effective in preserving Langerhans islets and reducing necrosis. These findings indicate that higher doses of Bidara leaf extract may have therapeutic potential in mitigating pancreatic damage and managing diabetes mellitus. Further research is needed to elucidate the mechanisms underlying these protective effects and to confirm their applicability in clinical settings.

The results of the study after being given standard feed plus induced Alloxan intraperitonially or intravenously once for 7 days and increased body weight and blood glucose. The mean blood glucose level in white rat before hyperglycemia was 165.2 mg/dL, while the mean blood glucose level in white rat after hyperglycemia was 308 mg/dL. This shows that there is an increase in blood glucose levels in white wistar rats by 163.8 mg/dL. The increase in blood glucose levels on alloxan administration can be caused by two processes, namely the formation of free radicals and damage to cell membrane permeability resulting in damage to pancreatic beta cells that function to produce insulin[24]. The toxic action of alloxan on beta cells is initiated by free radicals formed by redox reactions. Alloxan and its reduction product, dialuric acid, form a redox cycle with the formation of superoxide radicals[25]. This radical undergoes dismutation to hydrogen peroxide. Hydroxyl radicals with high reactivity are formed by the Fenton reaction [26]. Free radical action with high excitability increases cytosolic calcium concentration leading to rapid destruction of pancreatic beta cells. The increased cytosolic calcium concentration is also due to alloxan inducing calcium release from the mitochondria which then leads to disruption of the oxidation process of pancreatic beta cells[27].

Examination of blood glucose levels was carried out before and after the administration of bidara The examination of blood glucose levels was carried out before and after the administration of bidara leaf ethanol extract using six treatment groups of bidara leaf ethanol extract 50, 150, 300 and 500 mg/KgBB and Na-CMC 1% as negative control and positive control is Metformin 500mg/KgBB which has the effect of lowering blood sugar levels in rats. The decrease in blood glucose levels can be caused by the anthocyanins contained in bidara leaves. Anthocyanins include flavonoid group pigments that produce orange, red and blue

colors that are soluble in water and easily degraded. Anthocyanin degradation can be caused by pH, light, temperature, and the addition of sugar. Anthocyanins are high enough as antioxidants that can reduce the risk of diabetes mellitus. It is known that dietary antioxidants, including anthocyanins, protect β-pancreatic cells from glucose induced oxidative stress[28,29].

According to Maulana's research, 2020 bidara leaf extract contains antidiabetic activity. Bidara leaf extract is obtained through the mechanism of inhibiting enzymes that break carbohydrates into glucose found in the gastrointestinal tract, two groups of enzymes that are inhibited are α-Amylase and α-Glucosidase. The α-amylase enzyme group is produced by the salivary glands and pancreas whose main function is to break down amylum (salivary amylase) and break down glycogen (pancreatic amylase), inhibition of its activity will inhibit the breakdown of carbohydrates in the gastrointestinal tract and in the body, thus affecting the availability of glucose in the blood plasma. The α-Glucosidase group, including maltase, isomaltase, glucomaltase, and sucrase, has the function of hydrolyzing oligosaccharides that enter the small intestine, so if inhibited, it will affect the digestion of carbohydrates and their absorption so as to prevent an increase in blood glucose levels after eating[30].

CONCLUSION

The study on Bidara leaf extract's effects revealed significant findings regarding its potential as a therapeutic agent for diabetes mellitus. The extract demonstrated dose-dependent hypoglycemic effects across concentrations of 50, 150, 300, and 500 mg/kgBW, with all doses showing statistically significant reductions in blood glucose levels. Particularly notable was the substantial efficacy at the lowest dose of 50 mg/kgBW, indicating potent hypoglycemic properties. Histopathological analysis showed that higher doses (300 and 500 mg/kgBW) preserved Langerhans islets and reduced pancreatic necrosis compared to lower doses and controls, suggesting protective effects against diabetes-induced pancreatic damage. These results highlight Bidara leaf extract's potential in enhancing insulin sensitivity, scavenging free radicals, and protecting pancreatic beta cells from oxidative stress. Further research is needed to fully understand its mechanisms and confirm its clinical applicability in managing diabetes. Bidara leaf extract stands out as a natural remedy with promising therapeutic benefits, warranting continued investigation into its pharmacological properties and safety profile.

AUTHORS' CONTRIBUTIONS

Musdayani Nasution prepared the samples, designed the protocols, executed the protocols, and wrote the manuscript. Ali Napiah Nasution and Maya Sari Mutia reviewed and supervised the manuscript. All authors have read and approved the final manuscript

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigastion are available from the corresponding author on reasonable request

DISCLOSURE STATEMENT

There is no conflict of interest.

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