Kersen (*Muntingia calabura L.*) Leaf Extract Reduces Blood Glucose Levels and Restores Pancreatic Islets in Alloxan-Induced Mice

Maya Tejasari *, Listya Hanum , Zahra Nabila Latama

Histology Department, Faculty of Medicine Universitas Islam Bandung, Bandung, Indonesia.

mayatejasari4981@gmail.com

Abstract. Medicinal plants with hypoglycemic properties have long been used in traditional medicine for managing diabetes mellitus, although scientific evidence regarding their efficacy and mechanisms of action remains limited. *Muntingia calabura* L. (kersen) is a medicinal plant known to contain bioactive compounds with antioxidant and glucose-lowering potential. This study aimed to evaluate the antihyperglycemic effect of *M. calabura* leaf extract and its ability to repair damage to the pancreatic islets of Langerhans in hyperglycemic mice. A total of 24 male white mice (*Mus musculus* L.) were randomly divided into six groups: a normal control group, an alloxan-induced hyperglycemic control group, an alloxan plus glibenclamide group, and three treatment groups receiving kersen leaf extract at doses of 200, 400, and 800 mg/kg body weight, respectively. Hyperglycemia was induced using alloxan at a dose of 160 mg/kg body weight, and the extract was administered orally for 14 consecutive days. Blood glucose levels were measured, and pancreatic tissues were examined histologically to assess morphological changes in the islets of Langerhans. The results showed that mice treated with kersen leaf extract exhibited a significant reduction in blood glucose levels compared with the hyperglycemic control group ($p<0.05$). Histological analysis revealed substantial restoration of pancreatic architecture, characterized by increased islet size and β-cell density resembling those of normal mice. These findings suggest that kersen leaf extract possesses potent antihyperglycemic and β-cell regenerative properties, supporting its potential as a natural candidate for antidiabetic therapy.

Keywords: *antidiabetic, hyperglycemia, Muntingia calabura L., kersen leaf extract*

A. Introduction

Hyperglycemia is a pathological condition characterized by elevated blood glucose levels. Excessive glucose accumulation in the bloodstream leads to the generation of reactive oxygen species (ROS) within cells, which, in excessive amounts, can become cytotoxic (1–3). Although various synthetic drugs are available for the treatment of hyperglycemia, their long-term use is often associated with adverse side effects, including hepatotoxicity and gastrointestinal disturbances (4, 5). A range of pharmacological strategies has been developed to improve hyperglycemia, primarily by stimulating insulin secretion, enhancing glucose transport activity, inhibiting hepatic gluconeogenesis, or reducing intestinal glucose absorption (6, 7). Currently available therapies are administered either as monotherapy or in combination to achieve optimal glycemic control (8). In addition to dietary interventions, hypoglycemic agents remain the cornerstone of type 2 diabetes mellitus (T2DM) management (1). However, many of these agents demonstrate limited efficacy and cause mechanism-based adverse effects such as hypoglycemia, gastrointestinal irritation, and edema (9, 10). Consequently, there is an urgent need to identify safer and more effective hypoglycemic compounds derived from natural sources.

The management of diabetes mellitus continues to evolve as novel therapeutic agents and mechanisms are explored to enhance glycemic control and minimize complications. Fauchier *et al.* (11) reported that the use of certain antidiabetic drugs may influence the risk of new-onset atrial fibrillation, highlighting the importance of careful pharmacologic selection. Among newer classes of drugs, sodium–glucose cotransporter type 2 (SGLT2) inhibitors have gained attention for their renal glucose-lowering mechanism, offering improved metabolic regulation while providing cardiovascular and renal benefits (12). Furthermore, oxidative stress has been identified as a key pathogenic factor

* mayatejasari4981@gmail.com

in T2DM, as excessive ROS production contributes to β-cell dysfunction and insulin resistance. Panigrahy *et al.* (13) emphasized the potential of antioxidant-based therapies to counteract these effects. Complementarily, Chaudhury *et al.* (14) provided a comprehensive review of current antidiabetic drugs and underscored the importance of balancing efficacy and safety in long-term diabetes management.

The utilization of medicinal plants and natural products as alternative or complementary therapeutic agents requires a rational and evidence-based approach. Given the complexity of drug interactions in biological systems, proper evaluation of such agents must consider medical, biochemical, and pharmacological aspects to ensure optimal bioavailability and therapeutic efficacy (6,7,15). Promising natural candidates for glycemic control can be identified through the assessment of biochemical parameters such as fasting blood glucose, lipid profiles, and liver enzyme activity, as well as histological evaluation of critical organs including the pancreas, liver, heart, and kidneys (7, 16–19).

Chronic hyperglycemia induces glucotoxicity in pancreatic β-cells, resulting in functional impairment and decreased β-cell mass, ultimately leading to diminished insulin secretion (20, 21). Histopathological alterations in the islets of Langerhans are characteristic features observed in both diabetic patients and experimental animal models. Previous studies have documented a reduction in the number and diameter of the islets, along with a decrease in pancreatic endocrine (β-cell) populations (22, 23). Elevated blood glucose levels have also been shown to stimulate oxidative phosphorylation, promote protein glycation, and impair mitochondrial function, thereby increasing ROS production and oxidative stress in pancreatic β-cells (3, 10, 24).

Alloxan is frequently employed in experimental models to induce diabetes due to its selective cytotoxicity toward pancreatic β-cells. The diabetogenic effect of alloxan is mediated by ROS, as both alloxan and its reduction product, dialuric acid, undergo redox cycling to generate superoxide radicals. The combined effects of oxidative stress and elevated cytosolic calcium concentrations lead to rapid β-cell necrosis. Antioxidant-rich compounds have been shown to protect against oxidative damage associated with diabetes and may play a role in promoting β-cell regeneration (25–27).

Kersen (*Muntingia calabura* L.), commonly known as the Jamaican cherry, has been reported to contain various phytochemicals, including flavonoids, tannins, saponins, triterpenes, and polyphenols, which exhibit potent antioxidant activity. Moreover, fractions of *M. calabura* have been found to contain alkaloids with hepatoprotective properties (28, 29). Despite these findings, scientific evidence demonstrating the potential of *Muntingia calabura* L. leaf extract to restore pancreatic islet integrity or lower blood glucose levels in hyperglycemic models remains limited. Therefore, the present study aimed to investigate the effect of *Muntingia calabura* L. leaf extract on blood glucose levels and pancreatic islet morphology in alloxan-induced hyperglycemic mice.

B. Method

Research Design

This study employed a true experimental design with a post-test-only control group approach to evaluate the effects of the ethanol extract of *Muntingia calabura* L. (kersen) leaf on hyperglycemic male white mice induced by alloxan. The research was conducted from August 2024 to December 2024 at the Biomedical Laboratory, Faculty of Medicine, Universitas Islam Bandung, Indonesia. Ethical approval for this study was obtained from the Research Ethics Committee of Universitas Islam Bandung (Ethical Clearance Number: 219/KEP-Unisba/VIII/2024).

Preparation of Kersen Leaf Extract

Kersen (*Muntingia calabura* L.) leaves were selected, weighed, and thoroughly washed with distilled water. The leaves were air-dried for 24 hours, sliced into small pieces, and then oven-dried at 70°C for another 24 hours. The dried leaves were reweighed and ground into a fine powder using a blender. The powdered leaves were macerated three times with 1 L of 96% ethanol for 24 hours each. The resulting macerate was filtered using a Buchner funnel to obtain the filtrate. The filtrate was then concentrated using a rotary evaporator at 50°C to yield a thick extract, which was subsequently dried to obtain a stable semi-solid extract and homogenized with 1% sodium carboxymethyl cellulose (Na-CMC).

Maintenance of Experimental Animal

Twenty-four healthy male white mice (*Mus musculus* L.), aged 2–3 months and weighing 30–40 g, were used in this study. The animals were obtained from the Biofarma Veterinary Center, Bandung, Indonesia. The experiment adhered to the ethical principles of the 3Rs (Replacement, Reduction, and Refinement). Mice were acclimatized for one week in clean cages lined with rice husks under standard laboratory conditions (temperature 22–25°C, 12 h light/dark cycle). During acclimation, the mice were provided with ad libitum access to food pellets and drinking water. The average feed intake was 3–4 g per mouse per day.

Alloxan Administration to induce Hyperglycemia

Administration of alloxan at a dose of 160 mg/kg body weight has been shown to induce hyperglycemia in mice. Therefore, this dose was used in the present study to establish a diabetic model. Prior to induction, the mice were fasted for 6–8 hours with free access to water. After fasting, baseline blood glucose levels were measured using a glucometer, and body weight was recorded using a digital scale. Subsequently, a small puncture was made at the tail vein using a sterile needle to facilitate glucose measurement. Alloxan, freshly dissolved in 0.3 mL of *aqua pro injectione*, was administered subcutaneously at the nape of the neck approximately two hours after the tail wound had dried.

Twenty-four hours after alloxan administration, each mouse received 0.3 mL of 5% glucose solution orally to prevent hypoglycemia. Blood glucose levels were re-evaluated five days after induction. Mice with fasting blood glucose levels exceeding 125 mg/dL were classified as hyperglycemic, according to the criteria of the International Diabetes Federation. Hyperglycemic mice were subsequently treated orally with *Muntingia calabura* L. leaf extract for 14 consecutive days.

Treatment with Kersen Leaf Extract

The kersen leaf extract was administered orally once daily at doses of 200, 400, and 800 mg/kg body weight. These doses were selected based on previous evidence demonstrating their potential efficacy in lowering blood glucose levels.

Animal Dissection and Organ Sampling

At the end of the 14-day treatment period, the mice were anesthetized with chloroform prior to dissection. Each mouse was placed in a glass chamber containing cotton soaked with chloroform (0.67 mL per mouse), and anesthesia was maintained for approximately 60 seconds. After cessation of movement, a midline incision was made along the ventral surface to expose the abdominal cavity. The pancreas was carefully excised and immediately fixed in 10% neutral buffered formalin at a specimen-to-fixative ratio of 1:10. Fixed pancreatic tissues were then processed for histopathological evaluation at the Laboratory of Anatomical Pathology, Faculty of Medicine, Universitas Islam Bandung.

Preparation of Histological Sections

Pancreatic tissues were processed following standard histological procedures and stained with hematoxylin and eosin (H&E). The process included fixation, dehydration through graded alcohols, clearing, paraffin infiltration, embedding, sectioning, mounting, deparaffinization, staining, cover-slipping, and labeling.

Assessment of Pancreatic Damage

The degree of pancreatic damage was evaluated microscopically by examining the histological structure of the pancreas in each treatment group. The assessment focused on the morphology and area of the islets of Langerhans to determine the extent of damage and potential regeneration.

Data Analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) with SPSS software version 18. A confidence level of 95% ($\alpha = 0.05$) was applied. A *p*-value greater than 0.05

indicated no statistically significant difference, while a *p*-value less than 0.05 indicated a significant difference. Post hoc comparisons were performed using the Bonferroni test to identify specific group differences.

C. Result and Discussion

Blood Glucose Levels

The mean blood glucose levels of mice across all experimental groups are presented in Table 1.

Table 1. Mean Blood Glucose Levels of Mice in Each Experimental Group

No.	Group	Mean Blood Glucose Level (mg/dL)	p-value
1	NG (Normal Group)	83.50	
2	AG (Alloxan Group)	562.75	
3	GG (Alloxan + Glibenclamide)	142.25	<0.001
4	T1 (Alloxan + *M. calabura* Extract 200 mg/kg bw)	101.25	
5	T2 (Alloxan + *M. calabura* Extract 400 mg/kg bw)	121.50	
6	T3 (Alloxan + *M. calabura* Extract 800 mg/kg bw)	115.75	
	ANOVA Test		p < 0.05

Source: Processed Research Data, 2024.

The one-way ANOVA test revealed a statistically significant difference in blood glucose levels among all groups ($p < 0.05$). To determine which groups differed significantly, a Post Hoc Bonferroni test was subsequently performed.

Table 2. Post Hoc Bonferroni Test Results for Blood Glucose Levels

Group	Compared With	p-value
NG	AG	<0.001
	GG	0.080
	T1	1.000
	T2	0.832
	T3	1.000
AG	NG	<0.001
	GG	<0.001
	T1	<0.001
	T2	<0.001
	T3	<0.001
GG	NG	0.080
	AG	<0.001
	T1	0.605
	T2	1.000
	T3	1.000
T1	NG	1.000
	AG	<0.001
	GG	0.605
	T2	1.000
	T3	1.000
T2	NG	0.832

Group	Compared With	p-value
	AG	<0.001
	GG	1.000
	T1	1.000
	T3	1.000
T3	NG	1.000
	AG	<0.001
	GG	1.000
	T1	1.000
	T2	1.000

Source: Processed Research Data, 2024.

NG: Normal Group; AG: Alloxan Group; GG: Alloxan + Glibenclamide Group;
T1: Alloxan + *Muntingia calabura* Extract (200 mg/kg bw);
T2: Alloxan + *M. calabura* Extract (400 mg/kg bw);
T3: Alloxan + *M. calabura* Extract (800 mg/kg bw).

The results of the Post Hoc Bonferroni test showed that there was no significant difference in blood glucose levels between the normal group (NG) and the treatment groups (T1, T2, and T3) ($p > 0.05$). This indicates that mice induced with alloxan and subsequently treated with kersen leaf extract achieved blood glucose levels comparable to those of normal, non-diabetic mice. These findings demonstrate that administration of kersen leaf extract effectively reduced blood glucose levels in hyperglycemic mice to near-normal levels. Furthermore, the treatment groups (T1, T2, T3) did not show any significant difference compared with the glibenclamide-treated group (GG) ($p > 0.05$). This suggests that kersen leaf extract exhibited a glucose-lowering effect comparable to that of glibenclamide, a standard antidiabetic drug.

Histopathological Features of the Pancreatic Islets of Langerhans

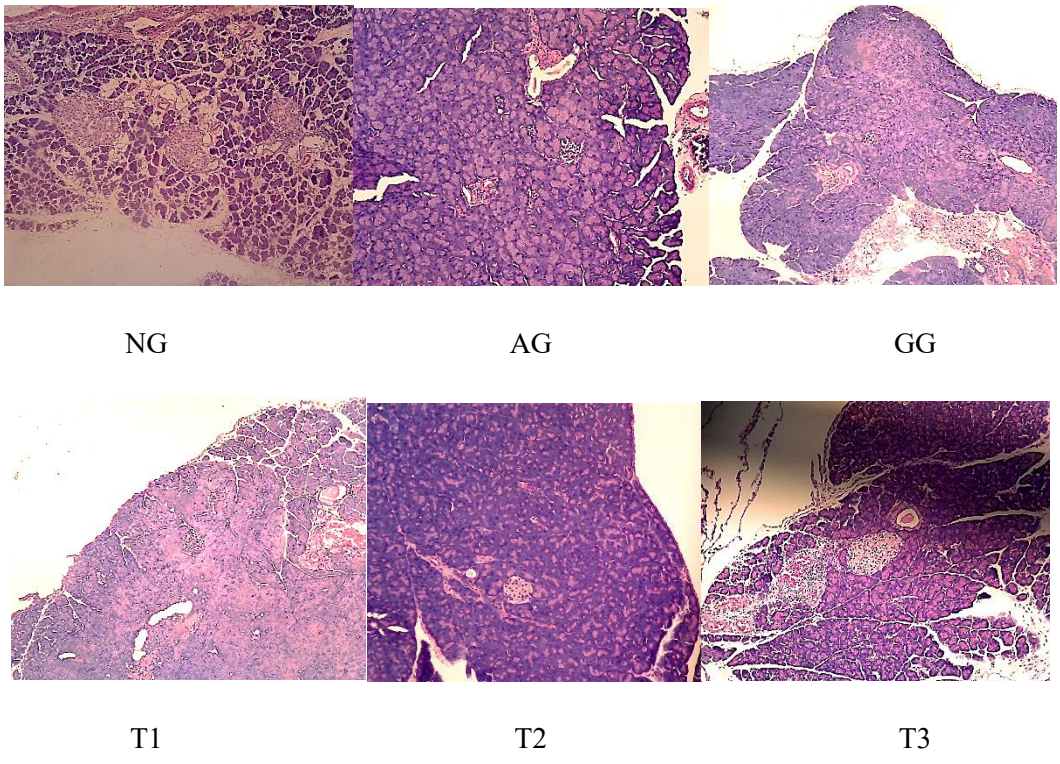

Figure 1. Histopathological features of the pancreatic islets of Langerhans in different experimental groups.

NG: Normal Group; AG: Alloxan Group; GG: Alloxan + Glibenclamide Group;
T1: Alloxan + *Muntingia calabura* Extract (200 mg/kg bw);
T2: Alloxan + *M. calabura* Extract (400 mg/kg bw);
T3: Alloxan + *M. calabura* Extract (800 mg/kg bw).

Histopathological examination of pancreatic tissue revealed distinct differences in the islets of Langerhans among the experimental groups. In the normal control group (NG), the islets of Langerhans exhibited normal morphology with clearly defined boundaries and a dense population of pancreatic β-cells arranged uniformly. In contrast, the alloxan-induced diabetic group (AG) showed marked histopathological damage, including shrinkage of the islets of Langerhans, cellular disorganization, vacuolization, and decreased β-cell density. These findings confirm the cytotoxic effect of alloxan on pancreatic β-cells through oxidative stress mechanisms. The glibenclamide-treated group (GG) demonstrated substantial regeneration and restoration of the islet architecture, with cell density and morphology closely resembling that of the normal group. Similarly, the treatment groups receiving kersen leaf extract (T1, T2, and T3) showed notable improvement in islet structure, characterized by reappearance of regular islet contours and partial to complete restoration of β-cell populations. The histological appearance of the islets in these groups was comparable to that of the glibenclamide-treated group, particularly in T2 and T3, indicating a dose-dependent reparative effect. These observations suggest that kersen leaf extract effectively ameliorated alloxan-induced pancreatic damage, likely due to its antioxidant constituents that mitigate oxidative stress and promote β-cell regeneration. Furthermore, the degree of histological recovery observed in the kersen-treated groups was comparable to the therapeutic effect of glibenclamide, a standard antidiabetic drug. Thus, kersen leaf extract shows strong potential for development as a natural antidiabetic agent capable of protecting and restoring pancreatic β-cell integrity.

Analysis and Discussion

Glycemic homeostasis refers to the physiological regulation of blood glucose levels within a narrow range. Diabetes mellitus significantly disrupts this homeostasis, resulting in chronic hyperglycemia that contributes to long-term complications such as retinopathy, nephropathy, and neuropathy. These complications are major contributors to diabetes-related morbidity and mortality. Several studies have demonstrated the significant potential of natural compounds and molecular mechanisms in improving glycemic regulation and insulin function. Fuangchan *et al.* (30) reported that *Momordica charantia* (bitter melon) exhibited a hypoglycemic effect comparable to metformin in newly diagnosed type 2 diabetes patients, suggesting its therapeutic potential as a natural alternative or adjunct to conventional therapy. Similarly, White *et al.* (31) observed that bitter melon supplementation, in combination with chromium propionate, improved insulin sensitivity and reduced symptoms of insulin resistance in diabetic rat models, reinforcing its metabolic benefits. At the molecular level, glucose homeostasis is critically dependent on the activity of glucose transporter 2 (GLUT2), which facilitates glucose uptake in pancreatic β-cells and hepatocytes. Structural and protein–ligand interaction studies by Duddela *et al.* [32] revealed key insights into GLUT2 function, while research by Guillam *et al.* (33) demonstrated that the absence of GLUT2 leads to early-onset diabetes and abnormal postnatal pancreatic islet development in mice, highlighting the transporter's essential role in glucose sensing and insulin regulation. Complementing these findings, Mahrosh *et al.* (34) identified hypoglycemic peptides derived from conserved regions of adMc1 with potent antidiabetic activity, further supporting the potential of bioactive natural molecules in modulating glucose metabolism. Collectively, these studies underscore the growing evidence that both plant-derived bioactive compounds and specific molecular targets such as GLUT2 and hypoglycemic peptides play pivotal roles in developing effective, natural, and mechanism-based therapies for diabetes mellitus.

In experimental research, alloxan-induced hyperglycemia is a widely used model to study diabetes pathophysiology and potential therapeutic interventions. Alloxan exerts its diabetogenic effect through two main pathogenic mechanisms: first, it selectively inhibits glucokinase, the glucose sensor enzyme of pancreatic β-cells, thereby reducing glucose-induced insulin secretion; and second, it generates reactive oxygen species (ROS), which cause oxidative stress leading to β-cell necrosis and insulin deficiency. Under physiological conditions, ROS play an essential role as signaling

molecules in various metabolic and regulatory pathways. However, excessive ROS production overwhelms endogenous antioxidant defenses, resulting in oxidative stress and subsequent cellular injury. The imbalance between ROS generation and antioxidant protection has been implicated in the pathogenesis of several chronic diseases, including diabetes mellitus, cancer, asthma, pulmonary hypertension, and diabetic retinopathy. To counteract the oxidative stress induced by alloxan, an antioxidant-rich extract was administered. *Muntingia calabura* L., commonly known as kersen or Jamaican cherry, contains abundant bioactive compounds such as flavonoids, tannins, and polyphenols—potent natural antioxidants with strong free radical scavenging activity. Given the increasing prevalence of hyperglycemia and the limitations of current antidiabetic therapies, natural products with high antioxidant potential, such as flavonoids, represent promising therapeutic alternatives for managing diabetes.

In this study, alloxan administered at a dose of 160 mg/kg body weight effectively induced hyperglycemia by causing structural and functional damage to the pancreatic islets of Langerhans, the endocrine regions responsible for insulin secretion. As a result, β-cell dysfunction led to persistent hyperglycemia. Treatment with the ethanol extract of *M. calabura* leaves demonstrated a remarkable ability to lower blood glucose levels and restore islet morphology toward normal conditions. The antihyperglycemic effect observed may be attributed to the extract's antioxidant constituents, which neutralize ROS and protect β-cells from oxidative damage. Moreover, these compounds may promote β-cell regeneration and repair by enhancing endogenous antioxidant enzyme activity and stabilizing cellular membranes. Additionally, flavonoids and polyphenols in *M. calabura* have been reported to protect DNA from oxidative damage, reducing genetic instability and preventing β-cell apoptosis (27, 28).

Histopathological findings in this study corroborated the biochemical results, showing that treatment with *M. calabura*extract at doses of 200, 400, and 800 mg/kg bw markedly improved the architecture of the islets of Langerhans, with cellular integrity comparable to that of normal control mice. These results suggest that *M. calabura* leaf extract exerts both protective and reparative effects on pancreatic tissue, likely through its antioxidative and cytoprotective mechanisms. Taken together, these findings indicate that *Muntingia calabura* leaf extract has substantial potential as a natural antidiabetic agent, capable of mitigating oxidative stress, enhancing β-cell recovery, and improving glycemic control comparable to standard drug therapy. Further studies are recommended to isolate the active compounds and elucidate their molecular mechanisms of action.

D. Conclusion

The extract of *Muntingia calabura* (kersen) leaf demonstrated a significant ability to reduce blood glucose levels and repair damage to the pancreatic islets of Langerhans in hyperglycemic mice. These findings indicate that kersen leaf extract possesses potent antihyperglycemic and pancreatic cytoprotective properties. Therefore, kersen leaves represent a promising natural source for the development of safe and effective plant-based antidiabetic agents. Further research is warranted to isolate the active phytoconstituents and elucidate their mechanisms of action at the molecular level.

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