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THE EFFECT OF ETHANOL EXTRACT OF *Passiflora Foetida* L. LEAVES ON FASTING BLOOD GLUCOSE LEVELS AND PANCREATIC HISTOPATHOLOGY IN ALLOXAN-INDUCED WHITE RATS (*Rattus Norvegicus*)

Angelica Febriyanti[1*], Hendro Pranoto[2]
*) *Corresponding Author*
[1,2] Universitas Negeri Medan
*Email: febriyantiangelica4@gmail.com

ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder characterized by elevated blood glucose levels. Alloxan is commonly used in antidiabetic research to induce diabetes in white rats (Rattus norvegicus). Passiflora foetida L. leaves contain bioactive compounds with potential antioxidant properties. This study aimed to evaluate the effects of ethanol extract of Passiflora foetida L. leaves (EEDR) on fasting blood glucose levels and pancreatic histopathology in alloxan-induced white rats. The research employed a completely randomized design (CRD) with six treatment groups: normal control, negative control, positive control (metformin), and three EEDR dosage groups (100, 200, and 400 mg/kg BW), each consisting of five rats. Data were analyzed using ANOVA followed by Duncan's test. The results indicated that EEDR at a dose of 400 mg/kg BW significantly reduced fasting blood glucose levels, though its efficacy was lower than metformin. Flavonoids in EEDR functioned as antioxidants, inhibited α-amylase enzymes, and enhanced insulin secretion. Additionally, EEDR protected pancreatic islet cells from necrosis and demonstrated regeneration of pancreatic beta cells.

Keywords: Antioxidants, Blood Glucose, Diabetes mellitus, *Passiflora foetida*.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by elevated blood glucose levels. Known as "the great imitator," DM affects multiple organs, causing a wide range of symptoms (Hastuti & Fatimah, 2018). According to the International Diabetes Federation (IDF), approximately 240 million individuals live with undiagnosed diabetes globally. Indonesia has shown an increasing prevalence of undiagnosed diabetes cases annually, attributed to unawareness of their condition (Kemenkes, 2014). Contributing factors include irregular dietary habits and lifestyle choices (Murtiningsih et al., 2021), leading to excessive blood glucose levels surpassing pancreatic capacity and decreased insulin production (Astutisari et al., 2022).

Sustained insulin compensation failure can result in progressive beta-cell damage in the pancreas (Budianto et al., 2022). Persistent hyperglycemia may cause macrovascular and microvascular complications (Rahmawati et al., 2015). Common microvascular complications include nephropathy, which may necessitate kidney transplants or dialysis if untreated (Tim Bumi

Medika, 2017). Effective prevention and management of DM are crucial to avoid these complications.

DM treatment strategies include pharmacological interventions and medical nutrition therapy. Metformin, a biguanide drug, enhances insulin sensitivity but may cause nervous system disorders with long-term use (Putra et al., 2017). Non-pharmacological alternatives, such as herbal medicines, are gaining popularity due to lower risks of side effects (Farlina et al., 2021). Herbal remedies, promoted by the Indonesian government, contain bioactive compounds like flavonoids, alkaloids, terpenoids, tannins, and saponins, which show potential in managing diabetes (Ernawati, 2015; Sinulingga et al., 2020).

Passiflora foetida L., known as rambusa, is an alternative antidiabetic plant used by communities in Central Kalimantan (Mulyani et al., 2022). Traditionally regarded as a wild plant, rambusa is utilized in Hutatinggi Village, Samosir, where its leaves are boiled and consumed for diabetes management. The leaves contain bioactive compounds, including flavonoids and saponins, known for their antioxidant properties, which influence glucose metabolism, lipid profiles, and liver enzyme activity, thereby enhancing insulin secretion (Pratiwi et al., 2023).

Parameters for evaluating antidiabetic efficacy include blood glucose levels and pancreatic histopathological assessments. Studies have shown that aqueous and ethanol extracts of Passiflora foetida L. effectively lower alloxan-induced hyperglycemia in Wistar rats (Asir et al., 2014). Similar studies reported the efficacy of rambusa leaf ethanol extract in lowering blood glucose in mice (Khaerati et al., 2015). These findings support rambusa's potential as an antidiabetic treatment, with mechanisms involving glucose regulation and pancreatic histopathology protection.

Based on the above, this study aims to determine the effects of ethanol extract of *Passiflora foetida* L. leaves on fasting blood glucose levels and histopathological changes in necrotic Langerhans islet cells in alloxan-induced Wistar rats (Rattus norvegicus).

MATERIALS AND METHODS

This study was conducted from August to October 2024 at the Biology Laboratory and Animal House, Faculty of Mathematics and Natural Sciences, Universitas Negeri Medan (UNIMED). Male Wistar white rats (Rattus norvegicus) were housed at the Animal House and treated according to experimental protocols, while pancreatic histological analyses were performed at the Biology Laboratory. A total of 24 male Wistar rats aged 2–3 months, weighing 175–200 g, were selected using purposive sampling.

The sample size was calculated using the Federer formula $(t-1)(r-1) \geq 15$ (t−1)(r−1)≥15, where t 6 t=6 groups and r4 r=4 replications, resulting in 24 rats divided equally into six groups. An experimental study using a Completely Randomized Design (CRD) was conducted with six groups: normal control (P), negative control (P-), positive control (P+), and treatment groups (P1, P2, P3) receiving ethanolic extract of Passiflora foetida (EEDR) at doses of 100, 200, and 400 mg/kg BW, respectively. Diabetes was induced in Groups P-, P+, P1, P2, and P3 by intraperitoneal injection of alloxan at 120 mg/kg BW after fasting for 18 hours, with diabetic status confirmed by fasting blood glucose levels >200 mg/dL. Treatments were administered daily for 14 days, followed by blood glucose measurement and pancreas dissection for histological evaluation.

Passiflora foetida leaves were prepared into ethanolic extract using the maceration method. The leaves were washed, dried at 40°C to retain bioactive compounds, and ground into a fine powder. The powder was macerated with 96% ethanol in a 1:10 (w/v) ratio for 3 days at room temperature, with periodic shaking. The mixture was filtered, and the filtrate was evaporated using a rotary evaporator at 40°C to obtain a concentrated extract.

Data were collected through fasting blood glucose measurements on days 0, 7, and 14 using a glucometer and histological analysis of pancreatic islets to evaluate necrosis based on established scoring criteria. Quantitative data were analyzed using ANOVA and post hoc tests, with significance set at $p < 0.05$ p<0.05. Statistical analysis aimed to assess the effects of EEDR on blood glucose levels and pancreatic histopathology compared to controls.

RESULT AND DISCUSSION

The effect of ethanol extract of rambusa leaves (EEDR) on fasting blood glucose (FBGL) levels and pancreatic islet necrosis was evaluated in rats induced with alloxan. Blood glucose levels were significantly elevated in the negative control group (P2) compared to the normal group (P1). The 400 mg/kg EEDR treatment (P6) significantly reduced blood glucose levels to 144.8 ± 5.5, though still less effective than metformin (P3, 111.2 ± 5.5 (Table 1.).

Table 1. Blood Glucose Levels (mg/dL) in Rats

Treatments	**Fasting Blood Sugar Levels ($\bar{x} \pm$ SD)**		
	Day to		
	0	**7**	**14**
P1 (Normal)	$87{,}8 \pm 1{,}9^{a}$	$86{,}4 \pm 1{,}9^{a}$	$87{,}2 \pm 3{,}1^{a}$
P2 (Negative)	$230{,}0 \pm 4{,}3^{b}$	$242{,}0 \pm 1{,}8^{b}$	$261{,}6 \pm 1{,}8^{b}$
P3 (PositiveMetformin)	$222{,}4 \pm 2{,}4^{c}$	$146{,}6 \pm 3{,}0^{c}$	$111{,}2 \pm 5{,}5^{c}$
P4 (EEDR 100 mg)	$227{,}0 \pm 3{,}0^{bc}$	$219{,}6 \pm 1{,}1^{d}$	$207{,}6 \pm 3{,}7^{d}$
P5 (EEDR 200 mg)	$225{,}0 \pm 4{,}3^{bc}$	$189{,}2 \pm 1{,}9^{e}$	$178{,}6 \pm 2{,}6^{e}$
P6 (EEDR 400 mg)	$226{,}5 \pm 4{,}0^{bc}$	$156{,}6 \pm 4{,}6^{f}$	$144{,}8 \pm 5{,}5^{f}$

Histopathological analysis revealed that the negative control group exhibited the most significant islet necrosis (3.6 ± 0.08), while EEDR-treated groups (P4, P5, P6) showed lower necrosis scores, with the 400 mg/kg dose having the lowest score (3.3 ± 0.16) (Table 2. and Figure 1).

Table 2. Histopathological Necrosis Scores of Pancreatic Islets

Treatments	**Necrosis Cell Scoring ($\bar{x} \pm$ SD)**
P1 (Normal)	$0.2 \pm 0{,}08^{a}$
P2 (Negative)	3.6 ± 0.08^{c}
P3 (Positive/Metformin)	3.6 ± 0.12^{c}
P4 (EEDR 100 mg)	3.3 ± 0.20^{b}
P5 (EEDR 200 mg)	3.3 ± 0.13^{b}
P6 (EEDR 400 mg)	3.3 ± 0.16^{b}

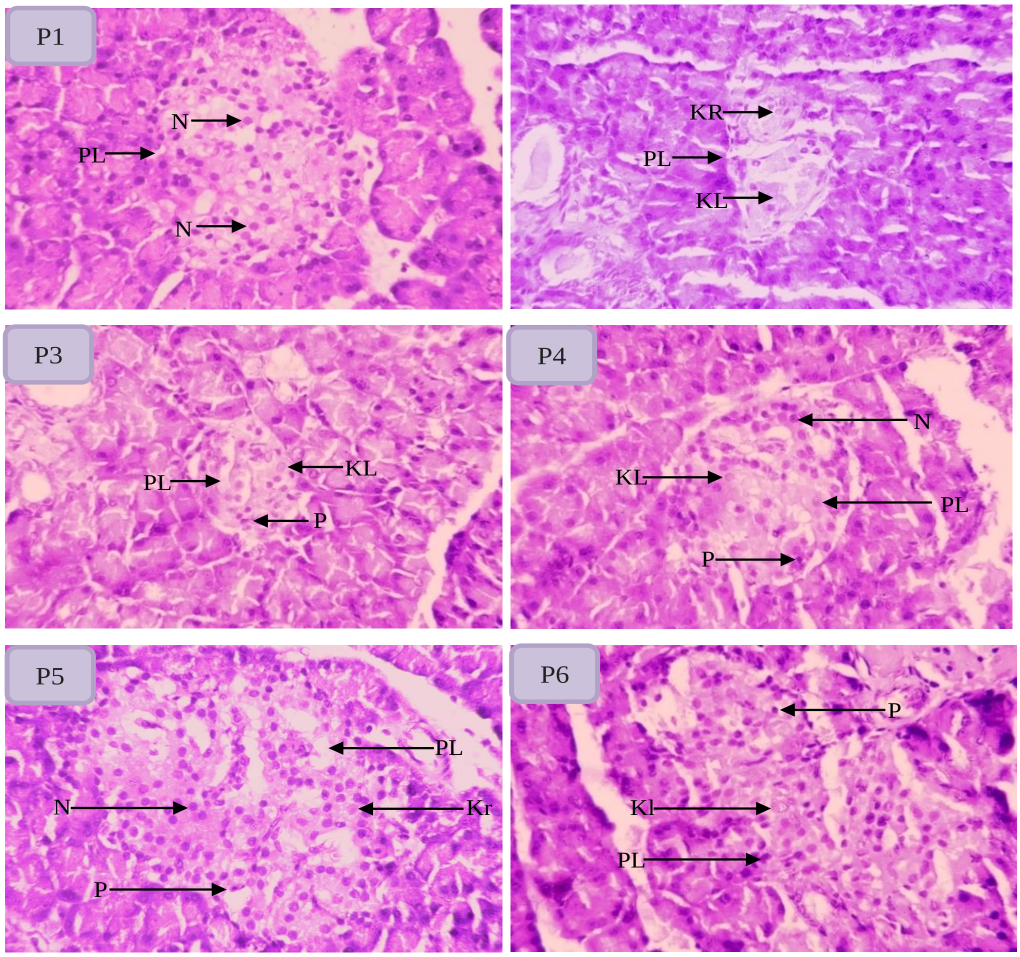

Figure 1. Histology of the pancreatic islets of Langerhans in rats from groups P1 (Normal), P2 (Negative Control), P3 (Positive Control/Metformin), P4 (EEDR 100 mg), P5 (EEDR 200 mg), and P6 (EEDR 400 mg) under 400x magnification (HE staining). PL = Islet of Langerhans, N = Normal, P = Pyknosis, Kr = Karyorrhexis, Kl = Karyolysis.

Alloxan induces hyperglycemia by damaging insulin-producing beta cells. EEDR, particularly at 400 mg/kg, demonstrated a significant reduction in blood glucose levels. This effect is likely due to the antioxidant properties of flavonoids in EEDR, which neutralize free radicals and protect beta cells. Flavonoids may also enhance insulin secretion and glucose uptake (Yi et al., 2023). Although EEDR showed promising results, metformin remained more effective in reducing blood glucose levels, likely due to its well-documented mechanism of enhancing insulin sensitivity and inhibiting hepatic glucose production (Musi et al., 2002).

Histological analysis revealed that EEDR treatment significantly reduced pancreatic islet necrosis, especially at the 400 mg/kg dose. Flavonoids like quercetin may help regenerate beta cells and protect against cellular damage, aligning with findings from previous studies (Mulia et al., 2019). In contrast, metformin showed limited efficacy in protecting pancreatic islet morphology, as its effects are more focused on improving insulin sensitivity rather than directly repairing beta cells (Yanti et al., 2019).

CONCLUSIONS

EEDR demonstrated potential as an anti-diabetic agent by lowering blood glucose levels and reducing pancreatic islet necrosis. The 400 mg/kg dose was the most effective, though it was less potent than metformin. Future studies should explore the regenerative potential of EEDR on beta cells and investigate its long-term effects on diabetes management.

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