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Original Research Article

Ethyl acetate Fraction of *Nypa fruticans* Wurmb Leaves Enhances Antihyperglycemic Activity, Insulin Secretion, Pancreatic *β*-cell Mass, and GLUT2 Expression

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ABSTRACT

Diabetes mellitus is a metabolic condition characterized by persistent hyperglycemia resulting from defective insulin production, resistance, or a combination of both. The objective of this study was to assess the antihyperglycemic impact of the ethyl acetate fraction (AEF) of *Nypa fruticans* Wurmb fronds in streptozotocin-induced diabetic rats. Male Wistar rats were administered AEF at dosages of 125, 250, or 500 mg/kg body weight, or glibenclamide at 0.45 mg/kg, for a duration of 21 days. Blood glucose and serum insulin levels were evaluated at intervals, and pancreatic tissues were examined for insulitis score, *β*-cell count, and GLUT2 expression using immunohistochemistry. Compared to diabetic controls, AEF at 250 and 500 mg/kg dramatically lowered blood glucose and raised insulin levels. Histopathological study demonstrated decreased insulitis and augmented *β*-cell mass, whilst immunohistochemistry indicated elevated GLUT2 expression in pancreatic islets. These findings indicate that AEF enhances glycemic control by promoting insulin secretion, regenerating *β*-cells, and increasing GLUT2 expression, hence confirming its potential as a candidate for antidiabetic therapy.

Keywords: *Nypa fruticans* Wurmb; Antihyperglycemic activity; Insulin secretion; *β*-cell regeneration; GLUT2 Expression

Introduction

Diabetes mellitus (DM) is a major global health burden, with an estimated 537 million people affected worldwide,[1] and Indonesia ranking fifth globally, with 19.5 million cases in 2021—expected to increase to 28.6 million by 2045.[2] Chronic hyperglycemia contributes to serious complications such as nephropathy, cardiovascular disease, and neuropathy, significantly impairing quality of life. DM is characterized by impaired glucose metabolism caused by insulin resistance, insufficient insulin secretion, or both. Dysfunctional pancreatic *β*-cells exhibit reduced insulin output and gradually diminish in mass, exacerbating hyperglycemia and lowering GLUT2 expression in islets.[3–5] Therefore, therapeutic strategies that restore *β*-cell function, stimulate insulin release, and regulate glucose transport are critical for effective diabetes management.[6] The mangrove plant *Nypa fruticans* Wurmb (commonly known as nipah) is traditionally used in Indonesia for the treatment of diabetes.[7] Its reported antidiabetic mechanisms include inhibition of intestinal glucose transporters and carbohydrate-hydrolyzing enzymes such as α-glucosidase and α-amylase, which contribute to the suppression of postprandial hyperglycemia.[8]

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Aqueous vinegar extracts of nipah have demonstrated blood glucose-lowering effects at doses of 1,000 mg/kg in diabetic rats, accompanied by a 13.6% increase in insulin secretion and evidence of *β*-cell repair based on histology and immunohistochemistry.[9-11] Additionally, methanol extracts of nipah leaves and twigs stimulated residual pancreatic function and peripheral glucose uptake,[12] while ethanol frond extracts reduced postprandial glucose in type 2 diabetic patients.[13] These effects are attributed to various bioactive flavonoids present in the plant, including quercetin, eriodictyol, catechin, hydroquinone, apigenin, kaempferol, anthocyanin, and rutin.[14–16] Among them, catechin is particularly noted for improving insulin sensitivity and secretion, promoting *β*-cell regeneration, enhancing glycogen synthesis, and modulating gut hormone activity.[17,18]

This study investigates the antihyperglycemic effects of the ethyl acetate fraction (AEF) of *N. fruticans* fronds, with specific focus on insulin secretion, pancreatic *β*-cell regeneration, and GLUT2 expression in diabetic rats. The findings aim to provide scientific support for the ethnopharmacological use of nipah and highlight its potential as an alternative therapeutic agent for diabetes.

Materials and Methods

Plant material and authentication

Fronds of *N. fruticans* were collected from Bugel Beach, Panjatan Sub-district, Kulon Progo Regency, Yogyakarta Special Region (–7.5833, 110.8173). A voucher specimen (no. 190/Lab.Bio/B/III/2023) was deposited in the Biology Laboratory of Ahmad Dahlan University. The fronds were washed, oven-dried at 40 °C, and ground into fine powder.

Extraction and fractionation

A total of 500 g of nipah frond powder was macerated in 96% ethanol (1:10 w/v) for 72 hours, with solvent replacement every 24 hours. The combined filtrate was concentrated under reduced pressure using a rotary evaporator and further dried at 60°C. The resulting crude ethanol extract was suspended in distilled water and successively partitioned with n-hexane and ethyl acetate (1:1, v/v). The ethyl acetate fraction (AEF) was collected and evaporated to dryness.

Experimental animals and ethics
Thirty male Wistar rats (180–250 g, aged 3–4 months) were obtained from the Pharmacology Laboratory, Faculty of Pharmacy, Universitas Muhammadiyah Surakarta. The animals were acclimatized for 3 days under a 12-hour light/dark cycle with free access to a standard diet and water. All animal procedures were approved by the Animal Ethics Committee, Faculty of Medicine, Islamic University of Indonesia (Approval No. 15/Ka.Kom.Et/70/KE/XII/2024).

Induction of diabetes
After overnight fasting, diabetes was induced by intraperitoneal injection of nicotinamide (230 mg/kg body weight), followed 15 minutes later by streptozotocin (65 mg/kg body weight) dissolved in cold 0.9% NaCl. To prevent hypoglycemia, rats were given 5% glucose solution for 24 hours. Fasting blood glucose was measured 96 hours post-induction using a GlucoDr. auto™ glucometer (Model AGM-4000), and rats with fasting blood glucose levels >200 mg/dL were included in the study.

Experimental design and treatment
The diabetic rats were randomly divided into six groups (n = 5 per group): (1) Normal control (vehicle: 0.5% sodium CMC, 10 mL/kg body weight); (2) Diabetic control (0.5% sodium CMC); (3) Positive control (glibenclamide 0.45 mg/kg body weight); (4) AEF 125 mg/kg body weight; (5) AEF 250 mg/kg body weight; and (6) AEF 500 mg/kg body weight. Treatments were administered orally twice daily (every 12 hours) for 21 days. Fasting blood glucose was measured on days 0, 7, 14, and 21. On day 22, rats were anesthetized with intramuscular ketamine (75 mg/kg body weight), and blood was collected via the orbital sinus for serum insulin analysis. Pancreatic tissues were harvested for histopathological and immunohistochemical evaluation.

Assessment of blood glucose and insulin
Fasting blood glucose was determined using the GlucoDr. auto™ glucometer. Serum insulin levels were quantified using a commercial ELISA kit (Rat-INS 96T, China) according to the manufacturer's instructions.

Pancreatic histopathology
Pancreatic tissues were fixed in 10% neutral-buffered formalin, processed through a graded ethanol series and xylene, embedded in paraffin, and sectioned at 3 µm thickness. The sections were deparaffinized, stained with hematoxylin and eosin, and examined under a light microscope to evaluate insulitis scores and β-cell counts.[19]

Immunohistochemistry for GLUT2
Paraffin-embedded sections (4–5 µm) were subjected to antigen retrieval using citrate buffer (pH 6.0) at 95°C for 20 minutes, followed by blocking of endogenous peroxidase activity with 3% hydrogen peroxide. The sections were then incubated with an anti-GLUT2 primary antibody (optimized dilution) for 1 hour at room temperature, followed by a horseradish peroxidase (HRP)-conjugated secondary antibody for 30 minutes. Visualization was achieved using DAB substrate, and hematoxylin was used as counterstain. Semiquantitative analysis of GLUT2 expression in β-cells was performed using QuPath software version 0.5.1.[20]

Statistical analysis
Data were expressed as mean ± standard error of the mean (SEM). Statistical comparisons were made using one-way ANOVA followed by Duncan's New Multiple Range Test (DNMRT) with SPSS software version 25. A p-value of less than 0.05 was considered statistically significant.

Results and Discussion

Fasting blood glucose, serum insulin, and body weight
The baseline fasting blood glucose (FBG) levels were comparable between diabetic groups (255–265 mg/dL; $p > 0.05$). On day 21, one-way ANOVA indicated a substantial treatment effect on fasting blood glucose (FBG) ($F_{(5,24)} = 45.12$, $p < 0.001$). Post hoc DNMRT revealed that AEF at dosages of 250 and 500 mg/kg decreased FBG to 129.4 ± 2.3 mg/dL (–47.6 %) and 120.0 ± 5.6 mg/dL (–49.5 %), respectively ($p < 0.05$ compared to diabetic control), which is equivalent to glibenclamide (113.8 ± 5.3 mg/dL; –56.9 %) (Table 1). AEF 125 mg/kg resulted in a slight, non-significant decrease (216.4 ± 13.8 mg/dL; –16.2 %). Serum insulin levels on day 21 varied among groups ($F_{(5,24)} = 32.84$, $p < 0.001$). Diabetic controls demonstrated hypoinsulinemia (1.46 ± 0.06 µg/L) compared to normals (3.04 ± 0.22 µg/L; $p < 0.05$). AEF at dosages of 250 and 500 mg/kg elevated insulin levels to 2.18 ± 0.05 and 2.79 ± 0.10 µg/L ($p < 0.05$ compared to diabetes), comparable to glibenclamide (2.88 ± 0.23 µg/L). AEF at a dosage of 125 mg/kg produced a concentration of 1.63 ± 0.07 µg/L ($p > 0.05$). Diabetic controls had weight loss by day 21 (152.0 ± 4.2 g) in contrast to normals (208.6 ± 7.3 g; $p < 0.05$). Glibenclamide and all AEF doses alleviated this loss (194–206 g), with no significant change from normal levels ($p > 0.05$), indicating maintained nutritional status.

Table 1: Effect of AEF on fasting blood glucose, serum insulin, and body weight after 21 days

Group	FBG day 21 (mg/dL)	% Δ FBG	Serum insulin (µg/L)	Body weight day 21 (g)
Normal control	75 ± 3.96[a]	–2.5 ± 3.34[a]	3.04 ± 0.22[c]	208.6 ± 7.25[b]
Diabetic control	260 ± 15.24[d]	–7.2 ± 10.38[a]	1.46 ± 0.06[a]	152.0 ± 4.21[a]
Glibenclamide	113.8 ± 5.31[b]	56.9 ± 1.98[c]	2.88 ± 0.23[c]	196.6 ± 2.75[b]
AEF 125 mg/kg	216.4 ± 13.77[c]	16.2 ± 2.29[b]	1.63 ± 0.07[a]	162.0 ± 1.95[a]
AEF 250 mg/kg	129.4 ± 2.32[b]	47.6 ± 1.82[c]	2.18 ± 0.05[b]	156.0 ± 4.85[a]
AEF 500 mg/kg	120.0 ± 5.59[b]	49.5 ± 2.30[c]	2.79 ± 0.10[c]	161.4 ± 4.63[a]

Data are mean ± SEM (n = 5). Superscripts within columns with different letters denote $p < 0.05$ (DNMRT). FBG, fasting blood glucose.

These data demonstrate that AEF produces a dose-dependent antihyperglycemic effect, closely resembling that of glibenclamide at elevated doses. The noted elevation in serum insulin indicates that the decrease in blood glucose may be ascribed to enhanced pancreatic β-cell functionality, aligning with prior findings regarding flavonoid-rich plant extracts like Moringa oleifera that promote both β-cell regeneration and glycemic regulation.[29] The maintenance of body weight indicates systemic metabolic advantages, potentially via reducing protein breakdown.[23]

Pancreatic histopathology
STZ-nicotinamide resulted in significant β-cell depletion (22.6 ± 1.7 cells/islet) and insulitis (2.2 ± 0.37) compared to normal controls (153.6 ± 4.3 cells; score 0; $p < 0.001$) (Table 2 and Figure 1). AEF at dosages of 250 and 500 mg/kg reinstated β-cell counts to 95.6 ± 3.9 and 110.0 ± 2.4 cells/islet ($p < 0.05$ compared to diabetic controls) and decreased insulitis to 1.4 ± 0.55 and 0.8 ± 0.20, respectively ($p < 0.05$). AEF 125 mg/kg shown negligible impact (49.8 ± 3.1 cells; insulitis 1.9 ± 0.25). The histological findings validate the reparative impact of AEF on pancreatic β-cells and its capacity to mitigate inflammation in the islets. This is consistent with the scientific findings, as enhanced β-cell mass coincides with elevated insulin secretion. The effects are likely influenced by the antioxidant and anti-apoptotic characteristics of flavonoids—particularly catechin and quercetin—found in *N. fruticans*, which have demonstrated the ability to promote β-cell proliferation and neogenesis.[25-28]

GLUT2 immunohistochemistry
Immunostaining demonstrated robust (+++) GLUT2 expression in normal samples and diminished (+) expression in diabetic controls (Figure 2). AEF 125 mg/kg resulted in moderate (++) staining, but AEF 250 mg/kg, 500 mg/kg, and glibenclamide elicited robust (+++) GLUT2

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expression in β-cells ($p < 0.05$ compared to diabetes controls). Augmented GLUT2 expression indicates enhanced glucose sensing and absorption in pancreatic β-cells, a crucial mechanism for insulin secretion.[3–5,22] The increase aligns with findings from the combined extracts of *Vernonia amygdalina* and red onion peel, which enhanced insulin responsiveness through flavonoid-mediated augmentation of glucose transporter expression.[30] Furthermore, phytochemical examination of *Salacca zalacca* fruit demonstrated significant antidiabetic potential via the decrease of oxidative stress and the restoration of pancreatic tissue.[31] Flavonoid-rich extracts of *Orthosiphon aristatus* (Java tea) further substantiate the correlation between antioxidant capacity and antihyperglycemic activity.[32]

Table 2: Effect of AEF on pancreatic β-cell count and insulitis score

Group	β-Cell Count (cells/islet)	Insulitis Score
Normal control	153.6 ± 4.30^{e}	0.0 ± 0.00
Diabetic control	22.6 ± 1.69^{a}	2.2 ± 0.37^{a}
Glibenclamide	97.8 ± 1.69^{c}	0.6 ± 0.25^{c}
AEF 125 mg/kg	49.8 ± 3.11^{b}	1.9 ± 0.25^{a}
AEF 250 mg/kg	95.6 ± 3.95^{c}	1.4 ± 0.55^{b}
AEF 500 mg/kg	110.0 ± 2.45^{d}	0.8 ± 0.20^{c}

Data are mean ± SEM (n = 5). Superscripts within columns with different letters denote $p < 0.05$ (DNMRT).

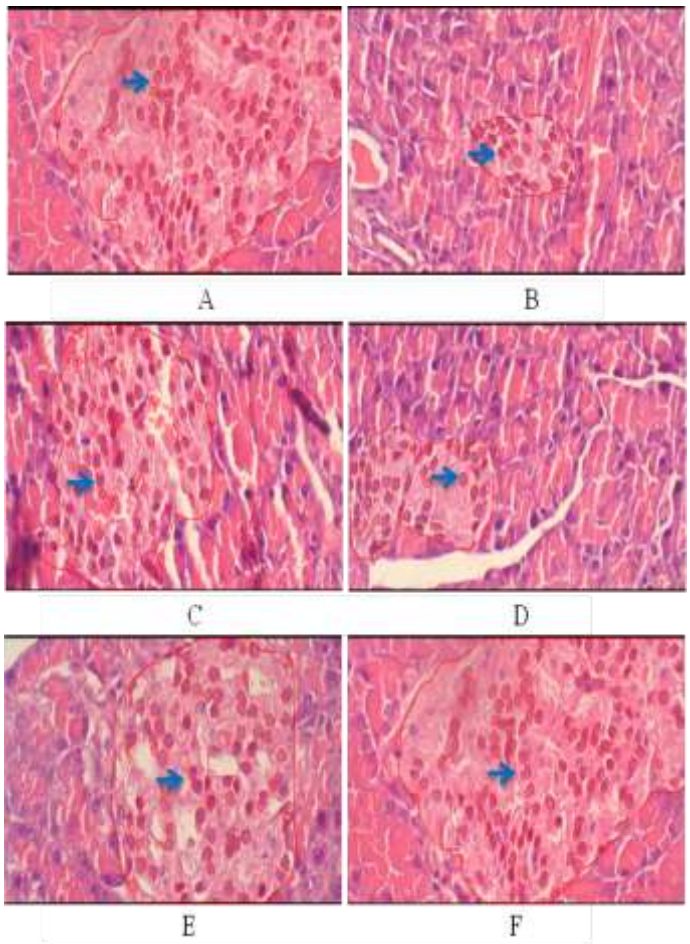

Figure 1: Histopathology of pancreatic islets (HE, 400×). (A) Normal control; (B) Diabetic control; (C) Glibenclamide 0.45 mg/kg; (D) AEF 125 mg/kg; (E) AEF 250 mg/kg; (F) AEF 500 mg/kg. Red circles indicate β-cells.

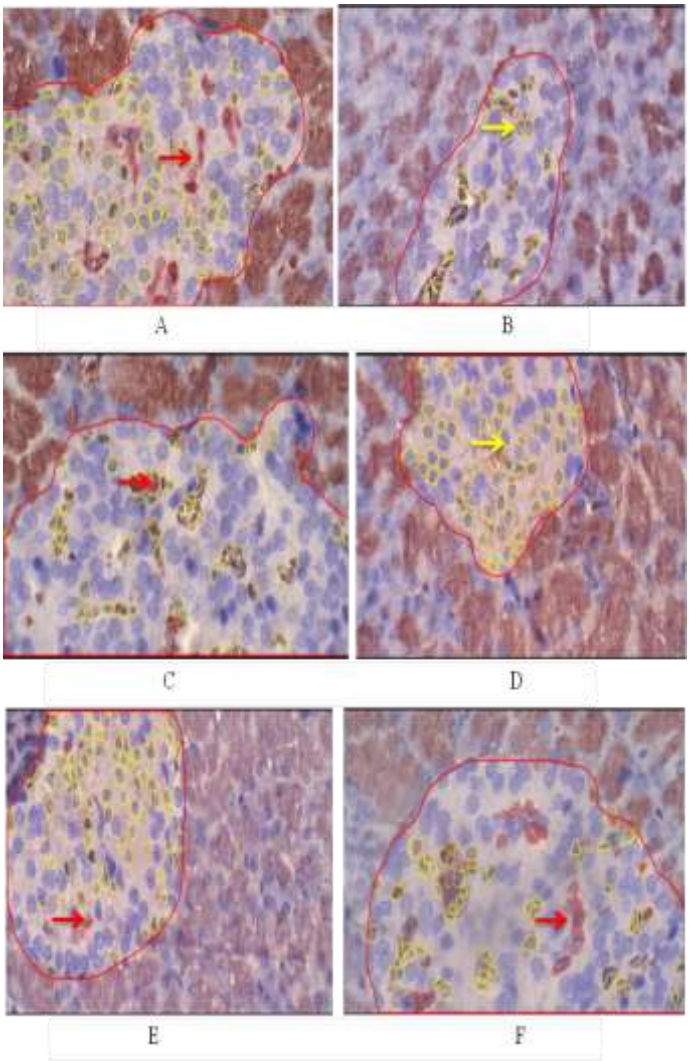

Figure 2: IHC of GLUT2 in pancreatic islets (DAB, 400×). (A) Normal control; (B) Diabetic control; (C) Glibenclamide 0.45 mg/kg; (D) AEF 125 mg/kg; (E) AEF 250 mg/kg; (F) AEF 500 mg/kg. Blue circles: negative; yellow: weak (+); orange: moderate (++); red: strong (+++).

Conclusion

This study demonstrates that the ethyl acetate fraction of *N. fruticans* fronds exerts dose-dependent antihyperglycemic effects in STZ–nicotinamide-induced diabetic rats. The fraction significantly lowered fasting blood glucose, restored serum insulin levels, preserved body weight, promoted pancreatic β-cell regeneration, and enhanced GLUT2 expression in islets. These findings highlight the potential of *N. fruticans* AEF as a promising candidate for antidiabetic therapy and justify further pharmacological and mechanistic investigations.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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