Jurnal Jamu Indonesia (2026) 11(2): 111–118
https://jamu-journal.ipb.ac.id/index.php/JJI/index

ISSN 2407-7178
eISSN 2407-7763

Research Article
Doi: https://doi.org/10.29244/jji.v11i2.452

Therapeutic Effects of *Morus alba* Leaf Extract on Fasting Blood Glucose and Pancreatic β-Cell Restoration in HFD–STZ-Induced Diabetic Rats

Efek Terapeutik Ekstrak Daun *Morus alba* terhadap Glukosa Darah Puasa dan Restorasi Sel β Pankreas pada Tikus Diabetes Model HFD–STZ

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ARTICLE INFO

Article history
Received on: 2025-11-13
Revised on: 2026-01-07
Accepted on: 2026-03-03

Keyword:
Diabetes mellitus
Metabolic syndrome
Morus alba
Pancreatic β-cells

ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycemia caused by insulin resistance and pancreatic β-cell dysfunction. *Morus alba* leaves contain bioactive compounds with potential antidiabetic activity. This study evaluated the hypoglycemic and β-cell protective effects of ethanolic *M. alba* leaf extract (EMA) in diabetic rats. The extract was obtained through maceration, yielding 12.14%. Wistar rats were divided into normal control, negative control, positive control, EMA100 (100 mg/kg BW), and EMA200 (200 mg/kg BW). Diabetes was induced using a high-fat diet, 2% sucrose solution, and low-dose streptozotocin. Fasting blood glucose (FBG) and pancreatic histopathology were analyzed. EMA significantly reduced FBG and improved pancreatic β-cell morphology, particularly at 200 mg/kg BW. These findings suggest that EMA has potential as a therapeutic candidate for T2DM by improving glycemic control and preserving pancreatic β-cell integrity.

Kata kunci:
Diabetes melitus
Morus alba
Sel β pancreas
Sindrom metabolik

ABSTRAK

Diabetes melitus tipe 2 (DMT2) ditandai oleh hiperglikemia kronis akibat resistensi insulin dan disfungsi sel β pankreas. Daun *Morus alba* mengandung senyawa bioaktif yang berpotensi memiliki aktivitas antidiabetik. Penelitian ini bertujuan mengevaluasi efek hipoglikemik dan protektif sel β dari ekstrak etanol daun *M. alba* (EMA) pada tikus diabetes. Ekstrak diperoleh melalui metode maserasi dengan rendemen 12,14%. Tikus Wistar dibagi menjadi kelompok kontrol normal, kontrol negatif, kontrol positif, EMA100 (100 mg/kg BB), dan EMA200 (200 mg/kg BB). Diabetes diinduksi menggunakan diet tinggi lemak, larutan sukrosa 2%, dan streptozotosin dosis rendah. Parameter yang dianalisis meliputi glukosa darah puasa (GDP) dan histopatologi pankreas. EMA secara signifikan menurunkan GDP dan memperbaiki morfologi sel β pankreas, terutama pada dosis 200 mg/kg BB. Hasil ini menunjukkan bahwa EMA berpotensi sebagai kandidat terapi DMT2.

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Citation: Salampe, M., Widiasri, D. A. D., Wahyuddin, N., Agus, R. R., Imrawati, Awaluddin, A., & Wahyuni. (2026). Therapeutic Effects of *Morus alba* Leaf Extract on Fasting Blood Glucose and Pancreatic β-Cell Restoration in HFD–STZ-Induced Diabetic Rats. *Jurnal Jamu Indonesia*, *11*(2), 111–118. https://doi.org/10.29244/jji.v11i2.452

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia caused by impaired insulin secretion, reduced insulin sensitivity, or both (Banday et al., 2020; Yameny, 2024). Among its clinical forms, type 2 diabetes mellitus (T2DM) accounts for more than 90% of global diabetes cases and is closely associated with insulin resistance and progressive dysfunction of pancreatic β-cells (Strati et al., 2024). These metabolic disturbances are strongly linked to lifestyle-related factors, particularly high-fat dietary intake and sedentary behavior. Prolonged hyperglycemia contributes to the development of serious complications, including neuropathy, nephropathy, and cardiovascular disease, which substantially increase morbidity and mortality (Banday et al., 2020). Consequently, strategies that can simultaneously improve glycemic control and protect pancreatic β-cell function have become an important focus in diabetes research (Abdalla, 2024; Taneera et al., 2024).

The global prevalence of diabetes continues to rise at an alarming rate. The International Diabetes Federation reported that approximately 537 million adults were living with diabetes worldwide in 2021, representing about 10.5% of the global population, with healthcare expenditures reaching USD 966 billion (Magliano & Boyko, 2021). This number is projected to increase to 783 million by 2045. Furthermore, nearly half of individuals with diabetes remain undiagnosed, particularly in low- and middle-income regions such as Southeast Asia, the Western Pacific, and Africa (Hossain et al., 2024). Indonesia is also experiencing a significant increase in diabetes prevalence, which is projected to rise from 9.19% (18.69 million cases) in 2020 to approximately 16.09% (40.7 million cases) by 2045, with diabetes-related mortality expected to more than double during the same period (Soeatmadji et al., 2023; Wahidin et al., 2024). These trends highlight the urgent need for effective and sustainable therapeutic strategies to address the growing global burden of T2DM.

Although several pharmacological treatments are available, long-term management of T2DM remains challenging. Many conventional antidiabetic drugs are associated with adverse effects, declining efficacy over time, and limited ability to prevent progressive β-cell deterioration (Gieroba et al., 2025). These limitations have stimulated increasing interest in natural products as potential complementary or alternative therapeutic agents for diabetes management (Pereira & Valado, 2023). Natural compounds derived from plants and other biological sources contain diverse bioactive metabolites with antioxidant, anti-inflammatory, and antihyperglycemic activities (Tran et al., 2020; Tsivileva et al., 2022). Several medicinal plants have demonstrated antidiabetic effects through multiple mechanisms, including improvement of insulin signaling, activation of AMP-activated protein kinase (AMPK), and protection of pancreatic β-cells from oxidative stress and inflammation (Sayem et al., 2025). Among these plants, *Morus alba* L. (white mulberry) has attracted growing attention because its leaves contain flavonoids, alkaloids, and phenolic compounds that contribute to glucose regulation, antioxidant activity, and pancreatic β-cell protection (Chen et al., 2023; Trimarco et al., 2025). Previous studies have suggested that *M. alba* may improve glucose metabolism and support β-cell regeneration (Porasar et al., 2025; Salampe et al., 2025; Suthamwong et al., 2020; Tricase et al., 2025).

However, despite increasing evidence regarding the antidiabetic potential of *M. alba*, the protective effect of ethanolic *M. alba* leaf extract on pancreatic β-cell restoration and fasting blood glucose regulation in a combined high-fat diet (HFD) and streptozotocin (STZ)-induced diabetic model remains insufficiently investigated. The HFD–STZ model is widely recognized as a reliable experimental approach that closely mimics the pathophysiological characteristics of human T2DM, including insulin resistance and β-cell dysfunction (Brito et al., 2025; Huang et al., 2024; Pratiwi et al., 2021). Therefore, this study hypothesized that ethanolic *M. alba* leaf extract could reduce fasting blood glucose levels while simultaneously preserving or restoring pancreatic β-cell structure in diabetic conditions. Based on this hypothesis, the present study aimed to evaluate the hypoglycemic effect and β-cell restorative potential of ethanolic *M. alba* leaf extract in rats with diabetes induced by a high-fat diet and streptozotocin.

2. METHODS

2.1. Plant Materials and Extraction

Leaves of *Morus alba* L. were collected from Wajo Regency, South Sulawesi, Indonesia. The plant material was cleaned, air-dried, and ground into powder before extraction. The dried leaf powder was extracted using the maceration method with 70% ethanol as the solvent (Bitwell et al., 2023; Lee et al., 2024). Briefly, the powdered material was first moistened and immersed in the solvent, then stored in a dark environment at room temperature for 72 hours with occasional stirring to facilitate the extraction process. After filtration, the remaining plant residue underwent a second maceration using the same solvent to maximize the recovery of bioactive compounds.

The combined filtrates were concentrated under reduced pressure using a rotary evaporator (Rotavapor R-80) at 60 °C and 75 rpm until a viscous extract was obtained. The concentrated extract was subsequently frozen at −20 °C for approximately 24 hours prior to lyophilization. Freeze-drying was carried out using a Lyovapor L-200 system for 24 hours to produce a stable dry extract. This process was employed to preserve the stability of thermolabile bioactive compounds and reduce moisture content, thereby improving the extract's stability and shelf life (Coşkun et al., 2024).

2.2. Experimental Animals

Fifteen healthy male Wistar rats aged 2–3 months and weighing 200–250 g were used in this study. The animals were obtained from the Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia. Prior to the experiment, the rats were acclimatized for one week under standard laboratory conditions, including a 12-hour light–dark cycle, controlled temperature, and free access to food and water. Only animals that maintained or increased their body weight during the acclimatization period were included in the experiment.

All experimental procedures were conducted in accordance with ethical guidelines for the care and use of laboratory animals. Ethical approval for this study was granted by the Research Ethics Committee of Sekolah Tinggi Ilmu Farmasi (Approval No. 06.126/KOMETIK/STIFA/VI/2025).

2.3. Experimental Design and Induction of Diabetes

After the acclimatization period, the rats were randomly divided into five groups (n = 3 per group): normal control (NC), negative control (NEC), positive control (PC), and two treatment groups receiving ethanolic *Morus alba* leaf extract (EMA) at doses of 100 mg/kg body weight (EMA100) and 200 mg/kg body weight (EMA200).

Baseline fasting blood glucose (FBG) levels were measured after 5–8 hours of fasting. Blood samples were obtained from the tail vein, and glucose levels were determined using an EasyTouch glucometer.

To induce a diabetic condition resembling type 2 diabetes mellitus, rats in the NEC, PC, EMA100, and EMA200 groups were fed a high-fat diet (HFD) and a 2% sucrose solution for four weeks. The HFD consisted of acid-casein, corn flour, maltodextrin, microcrystalline fructose, soybean oil, and lard (BioCalorix, Faculty of Pharmacy, Universitas Katolik Widya Mandala, Surabaya, Indonesia). In the fifth week, the rats received a single intraperitoneal injection of streptozotocin (STZ) (Sigma-Aldrich, USA; Cat. No. S0130) at a dose of 35 mg/kg body weight as a diabetogenic agent (Brito et al., 2025; Huang et al., 2024).

Following STZ administration, treatments were initiated according to the experimental design. The positive control group received metformin (HEXpharm, Indonesia), the negative control group received Na-CMC, and the treatment groups were administered EMA at doses of 100 mg/kg BW and 200 mg/kg BW. The high-fat diet and sucrose administration were continued throughout the treatment period. At the end of the sixth week, animals were fasted again prior to the final measurement of fasting blood glucose levels.

2.4. Histopathological Examination

At the end of the experimental period, all rats were euthanized, and pancreatic tissues were collected for histopathological evaluation. The tissues were fixed in 10% neutral buffered formalin for 24–48 hours, followed by dehydration through a graded alcohol series, clearing in xylene, and embedding in paraffin.

Paraffin-embedded tissues were sectioned at a thickness of 5 µm using a microtome and mounted on glass slides. The sections were then stained with hematoxylin and eosin (H&E) following standard histological protocols (Wickramasinghe et al., 2024). The stained sections were examined under a light microscope (Olympus CX33) to assess morphological alterations and degeneration of pancreatic β-cells. Histological images were captured using an HDMI digital camera (Indomicro) for documentation and analysis.

2.5. Statistical Analysis

Fasting blood glucose data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using SPSS version 24. Differences among groups were analyzed using one-way analysis of variance (ANOVA), followed by the Least Significant Difference (LSD) post hoc test. Statistical significance was defined at $p < 0.05$. Additionally, paired *t*-tests were conducted to compare fasting blood glucose levels before and after treatment within each experimental group.

3. RESULTS AND DISCUSSION

3.1. Effect of *M. alba* Extract on Fasting Blood Glucose

The antidiabetic potential of ethanolic *M. alba* leaf extract (EMA) was evaluated in rats with diabetes induced by a high-fat diet (HFD) and streptozotocin (STZ). Extraction of the plant material using the maceration method produced a yield of 12.14%. Changes in fasting blood glucose (FBG) levels during the experimental period are presented in **Figure 1**.

At baseline, all experimental groups showed fasting blood glucose levels within the normal physiological range. The mean FBG values were 64 ± 8.02 mg/dL for the normal control group, 77.67 ± 17.8 mg/dL for the negative control group, 77.7 ± 12.4 mg/dL for the positive control group, 77 ± 19.1 mg/dL for the EMA100 group, and 73 ± 5.2 mg/dL for the EMA200 group. Statistical analysis indicated no significant differences among the groups ($p > 0.05$), confirming that the animals had comparable metabolic conditions prior to induction.

Following induction with HFD and STZ, rats in the negative control, positive control, EMA100, and EMA200 groups exhibited a marked elevation in fasting blood glucose levels exceeding 200 mg/dL, whereas the normal control group maintained normal glucose levels. Statistical analysis showed that induction with HFD–STZ significantly increased fasting blood glucose levels in the diabetic groups compared with the normal control group ($p < 0.05$). These findings confirm the successful establishment of a diabetic model. The combined HFD–STZ induction method is widely used to reproduce the metabolic characteristics of type 2 diabetes mellitus, particularly insulin resistance accompanied by partial pancreatic β-cell dysfunction (Brito et al., 2025; Huang et al., 2024; Pratiwi et al., 2021).

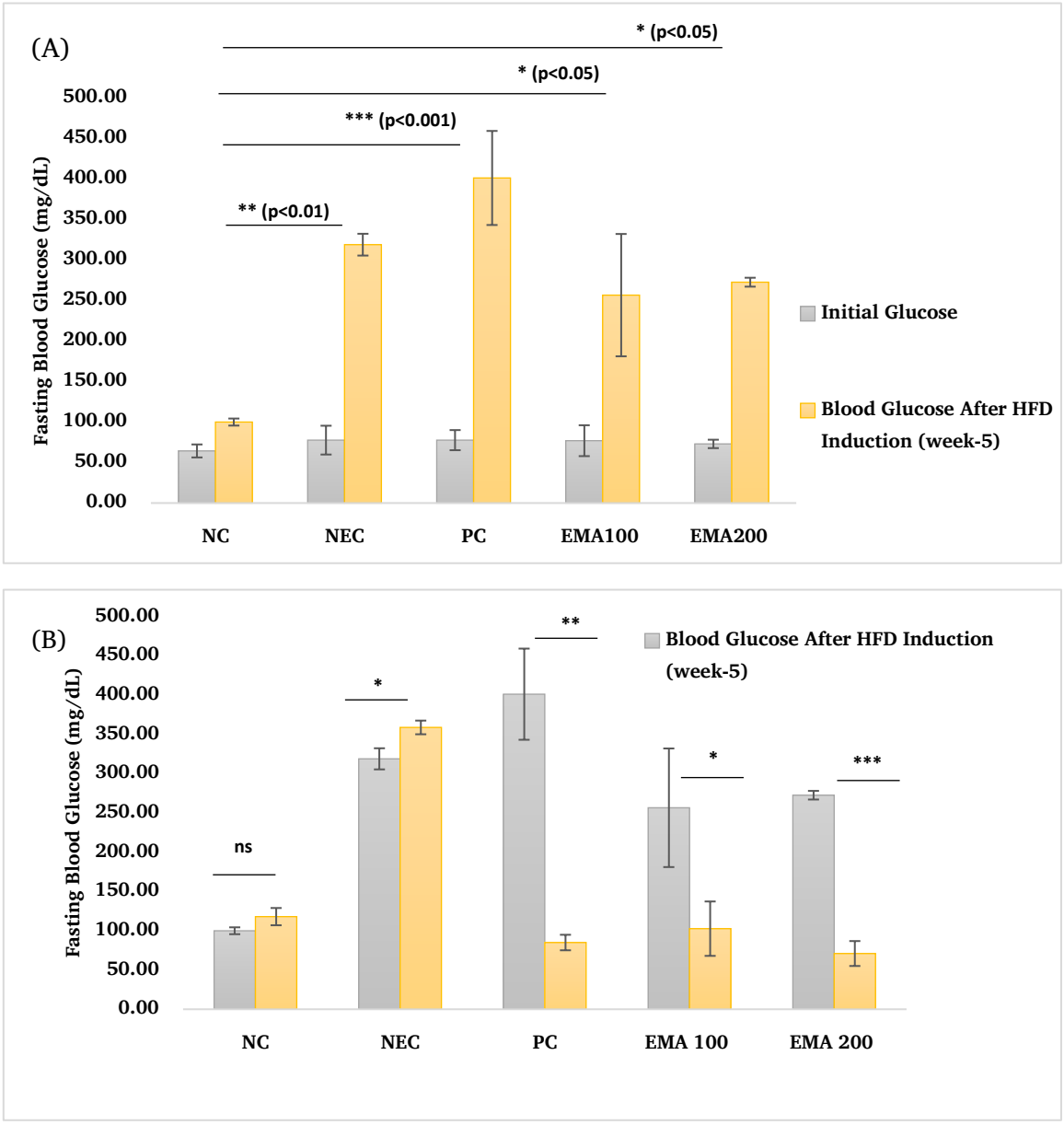

Figure 1. Effects of ethanolic *Morus alba* leaf extract (EMA) on fasting blood glucose (FBG) levels in HFD–STZ–induced diabetic rats. (A) Baseline FBG levels and FBG levels after induction with a high-fat diet (HFD) and streptozotocin (STZ). All groups exhibited comparable baseline glucose levels prior to induction ($p > 0.05$). Following HFD–STZ administration, rats in the negative control (NEC), positive control (PC), EMA100, and EMA200 groups showed a marked increase in FBG levels exceeding 200 mg/dL, confirming successful induction of diabetes. (B) FBG levels after the treatment period. Administration of ethanolic *M. alba* leaf extract resulted in a significant reduction in FBG levels compared with the negative control group, with the EMA200 group demonstrating a greater hypoglycemic effect. The positive control group treated with metformin exhibited the greatest decrease in blood glucose levels. Data are presented as mean ± standard deviation (SD). Statistical significance is indicated as *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$; ns = not significant. NC = normal control; NEC = negative control; PC = positive control; EMA = ethanolic *M. alba* leaf extract; EMA100 = 100 mg/kg body weight; EMA200 = 200 mg/kg body weight.

After the treatment period, both EMA-treated groups demonstrated a reduction in fasting blood glucose levels compared with the negative control group. Statistical analysis indicated that FBG levels in the EMA-treated groups were significantly lower than those in the negative control group ($p < 0.05$). The reduction was more pronounced in the EMA200 group, suggesting a dose-dependent hypoglycemic effect of the extract. Although the positive control group treated with metformin exhibited the greatest decrease in blood glucose levels, the improvements observed in the EMA groups indicate that *M. alba* leaf extract possesses significant glucose-lowering activity. These findings suggest that the extract may contribute to improved glycemic regulation in diabetic conditions.

3.2 Histopathological Changes in Pancreatic β-Cells

To further evaluate whether EMA exerted protective effects on pancreatic tissue, histopathological examination of pancreatic β-cells was performed. Representative microscopic images of pancreatic tissue are presented in **Figure 2**.

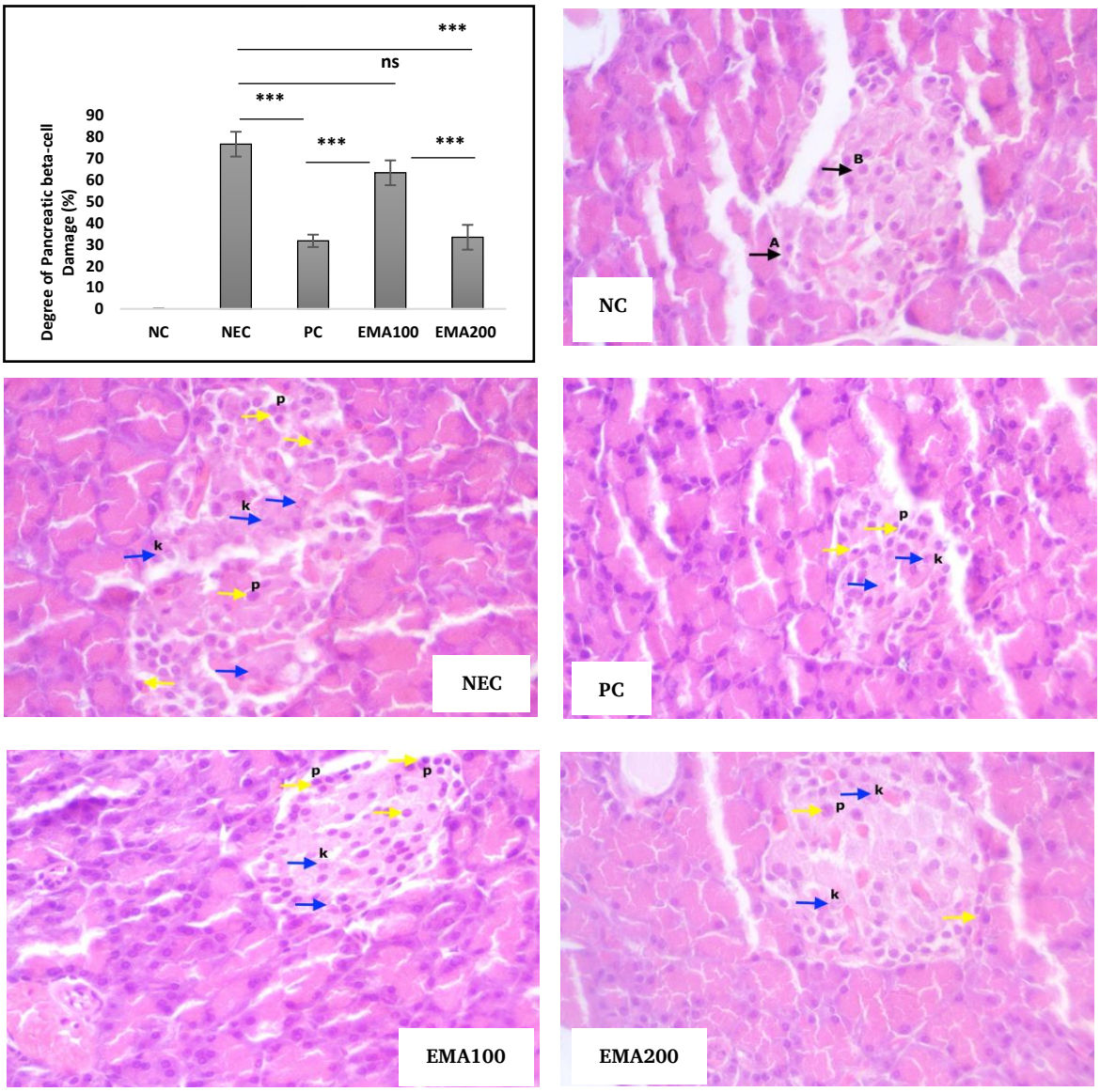

Figure 2. Histopathological changes in pancreatic β-cells of HFD–STZ–induced diabetic rats after treatment with ethanolic *M. alba* leaf extract (EMA). Representative hematoxylin and eosin (H&E)–stained pancreatic sections showing morphological alterations in the islets of Langerhans. Severe β-cell degeneration characterized by nuclear pyknosis and karyolysis was observed in the negative control group. Treatment with EMA improved islet morphology and reduced cellular degeneration, particularly at the dose of 200 mg/kg BW. Statistical significance is indicated as ***$p < 0.001$; ns = not significant. NC = normal control; NEC = negative control; PC = positive control; EMA = ethanolic *M. alba* leaf extract; EMA100 = 100 mg/kg BW; EMA200 = 200 mg/kg BW; A = α-cells; B = β-cells; P = pyknotic nuclei; K = karyolytic nuclei.

In the normal control group, the islets of Langerhans displayed normal histological architecture with intact α-cells and β-cells and well-organized cellular structures. In contrast, the negative control group demonstrated severe pancreatic damage, with approximately 77% of cells categorized as severely damaged. The pancreatic islets showed irregular cell distribution, structural disorganization, and nuclear abnormalities such as pyknosis and karyolysis, indicating advanced cellular degeneration and necrosis. These structural alterations reflect pancreatic β-cell injury caused by metabolic stress and streptozotocin toxicity, which ultimately impairs insulin secretion and contributes to persistent hyperglycemia.

Treatment with *M. alba* extract resulted in substantial improvements in pancreatic histoarchitecture. The EMA100 group exhibited moderate cellular damage (approximately 60%), characterized by partial nuclear degeneration and mild disruption of islet structure. In contrast, the EMA200 group showed only mild histological alterations and demonstrated structural features comparable to those observed in the positive control group. The restoration of cellular organization, reduced nuclear degeneration, and normalization of islet morphology observed in the EMA-treated groups indicate that the extract contributed to the preservation or recovery of pancreatic β-cell integrity.

The beneficial effects observed in this study are consistent with previous findings describing the pharmacological properties of *M. alba*. Mulberry leaves contain a wide range of bioactive compounds, including flavonoids, alkaloids, polysaccharides, and phenolic compounds, which are associated with antidiabetic

activity. Alkaloids such as 1-deoxynojirimycin (DNJ), fagomine, and N-methyl-1-deoxynojirimycin inhibit α-glucosidase activity, thereby reducing intestinal glucose absorption and attenuating postprandial hyperglycemia. Flavonoids, including morusin, kuwanon C, and morusyunnansin L, interact with key metabolic regulators such as AKT1, PPARγ, GSK3β, and ADORA1, which contribute to improved insulin signaling and suppression of insulin resistance (Lv et al., 2022; Ramos et al., 2021).

In addition, phenolic compounds such as chlorogenic acid, rutin, isoquercitrin, and quercitrin have been shown to enhance pancreatic islet function and protect β-cells against oxidative stress–induced injury. These compounds may activate the AMPK/mTOR signaling pathway and promote protective autophagy, thereby helping maintain β-cell viability under diabetic conditions (Ji et al., 2021). The combined action of these phytochemicals may explain the improvements observed in both glycemic control and pancreatic tissue structure following treatment with *M. alba* extract.

Importantly, the present study provides evidence that ethanolic *M. alba* leaf extract not only reduces fasting blood glucose levels but also contributes to the restoration of pancreatic β-cell morphology in an HFD-STZ-induced diabetic model. While previous studies have mainly focused on the hypoglycemic properties of *M. alba*, the current findings highlight its potential role in preserving pancreatic islet integrity under diabetic conditions. These results suggest that *M. alba* may exert dual therapeutic effects by improving glucose metabolism while simultaneously protecting pancreatic β-cells, thereby supporting its potential development as a complementary therapeutic agent for the management of type 2 diabetes mellitus.

4. CONCLUSION

Ethanolic *M. alba* leaf extract demonstrated significant antihyperglycemic activity and protective effects on pancreatic β-cells in rats with HFD-STZ-induced diabetes. Treatment with the extract reduced fasting blood glucose levels and improved pancreatic islet morphology, indicating partial restoration of β-cell integrity, with the 200 mg/kg BW dose showing the most pronounced effect. These findings suggest that *M. alba* may exert dual therapeutic benefits by improving glycemic control while preserving pancreatic β-cell structure. Consequently, *M. alba* represents a promising natural candidate for the development of complementary therapeutic strategies for type 2 diabetes mellitus, although further molecular and clinical studies are required to confirm its mechanisms and therapeutic potential.

AUTHOR CONTRIBUTIONS

Conceptualization, M.S.; methodology, M.S. and D.A.D.W.; software, N.W.; validation, M.S., A.A., and W.; formal analysis, M.S. and N.W.; investigation, M.S., D.A.D.W., N.W., R.R.A., and I.; resources, M.S.; data curation, N.W.; writing—original draft preparation, M.S. and A.A.; writing—review and editing, M.S. and A.A.; visualization, W.; supervision, M.S.; project administration, M.S.; funding acquisition, M.S. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

The animal study protocol was approved by the Research Ethics Committee of Sekolah Tinggi Ilmu Farmasi (protocol code 06.126/KOMETIK/STIFA/VI/2025).

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

FUNDING

This research was funded by the Ministry of Higher Education, Science, and Technology through the Fundamental Grant program.

ACKNOWLEDGMENT

The authors gratefully acknowledge the Ministry of Higher Education, Science, and Technology for financial support through the Fundamental Grant program. The authors also thank Universitas Almarisah Madani for institutional support and research facilities. Appreciation is extended to all research team members and colleagues who contributed to the completion of this study.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ROLE OF FUNDERS

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

During the preparation of this manuscript, the author(s) used ChatGPT (OpenAI) to assist in improving the clarity, structure, and readability of the text. After using this tool, the author(s) thoroughly reviewed, edited, and verified the entire content to ensure that it accurately represents their own ideas and interpretations. The author(s) take full responsibility for the integrity and originality of the published work.

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