Jurnal Jamu Indonesia (2026) 11(5): 389–398
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.v11i5.467

# Effect of *Morinda citrifolia* L. Ethanolic Leaf Extract on Pancreatic Histopathology in Streptozotocin-Induced Diabetic Rats

## Efek Ekstrak Etanol Daun *Morinda citrifolia* L. terhadap Histopatologi Pankreas Tikus Diabetes yang Diinduksi Streptozotosin

**Yunlis S. Kenta[1]*, Niluh Puspita Dewi[1], Indah Kurnia Utami[1], Nur Ramadhani[2], Nani Astria Polontalo[3]**

[1]*Department of Pharmacology and Clinical Pharmacy, STIFA Pelita Mas Palu, Palu 94231, Central Sulawesi, Indonesia*
[2]*Department of Pharmaceutical Chemistry, STIFA Pelita Mas Palu, Palu 94231, Central Sulawesi, Indonesia*
[3]*Department of Pharmaceutical Technology, Academy of Pharmacy Bina Farmasi, Palu 94231, Central Sulawesi, Indonesia*

**ARTICLE INFO**

***Article history***
**Received on:** 2025-12-06
**Revised on:** 2026-01-18
**Accepted on:** 2026-08-18

**Keyword:**
Diabetes mellitus;
Histopathology;
*Morinda citrifolia*;
Pancreas;
Streptozotocin

**Kata kunci:**
Diabetes melitus;
Histopatologi;
Mengkudu;
Pankreas;
Streptozotosin

**ABSTRACT**

*Morinda citrifolia* L. (noni) is used in Indonesian jamu for diabetes, but evidence for its leaf is limited. This study evaluated its ethanolic leaf extract (MCLE) on pancreatic histopathology in streptozotocin (STZ)-induced diabetic rats. Thirty male rats were randomised into six groups (n = 5): normal and negative controls, glibenclamide (0.45 mg/kg BW), and MCLE at 250, 500 or 750 mg/kg BW orally for 28 days after confirmed diabetes (STZ 40 mg/kg BW). Haematoxylin–eosin-stained pancreata were graded on a 0–3 damage scale. Screening detected alkaloids, flavonoids, saponins, tannins and steroids. Pancreatic damage differed markedly among the groups ($p < 0.001$). Only the highest dose, 750 mg/kg BW, gave significantly less damage than the untreated diabetic control, reaching a condition indistinguishable from both healthy animals and glibenclamide. The 250 and 500 mg/kg BW doses did not differ from the untreated diabetic control. MCLE is therefore pancreatoprotective at 750 mg/kg BW only.

**ABSTRAK**

*Morinda citrifolia* L. (mengkudu) digunakan dalam jamu untuk diabetes, namun bukti mengenai daunnya masih terbatas. Penelitian ini mengevaluasi ekstrak etanol daunnya (MCLE) terhadap histopatologi pankreas tikus diabetes yang diinduksi streptozotosin (STZ). Tiga puluh tikus jantan diacak ke enam kelompok (n = 5): kontrol normal dan negatif, glibenklamid (0,45 mg/kg BB), serta MCLE 250, 500 atau 750 mg/kg BB per oral selama 28 hari setelah konfirmasi diabetes pascainduksi STZ (40 mg/kg BB). Pankreas terwarnai hematoksilin–eosin dinilai pada skala kerusakan 0–3. Skrining mendeteksi alkaloid, flavonoid, saponin, tanin dan steroid. Kerusakan pankreas berbeda nyata antarkelompok ($p < 0,001$). Hanya dosis tertinggi, 750 mg/kg BB, yang memberikan kerusakan lebih rendah secara signifikan dibandingkan kontrol diabetes tanpa perlakuan, serta mencapai kondisi yang tidak berbeda dari hewan sehat maupun glibenklamid. Dosis 250 dan 500 mg/kg BB tidak berbeda dari kontrol diabetes tanpa perlakuan. MCLE dengan demikian protektif terhadap pankreas hanya pada 750 mg/kg BB.

**Corresponding author:*
*Yunlis S. Kenta (yunliskenta@gmail.com)*

**Citation**: Kenta, Y. S., Dewi, N. P., Utami, I. K., Ramadhani, N., & Polontalo, N. A. (2026). Effect of *Morinda citrifolia* L. Ethanolic Leaf Extract on Pancreatic Histopathology in Streptozotocin-Induced Diabetic Rats. *Jurnal Jamu Indonesia*, *11*(5), 389–398. https://doi.org/10.29244/jji.v11i5.467

© 2026 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (http://creativecommons.org/licenses/by-nc-sa/4.0/)

## 1. INTRODUCTION

Diabetes mellitus is among the fastest-growing chronic diseases worldwide. The Global Burden of Disease Study estimated 529 million prevalent cases in 2021 and projects more than 1.31 billion by 2050, approximately 96% of which are type 2 diabetes (GBD 2021 Diabetes Collaborators, 2023). Indonesia carries a substantial share of this burden: successive national health surveys recorded a diabetes prevalence of 10.7% in 2013, 11.8% in 2018 and 11.3% in 2023, alongside a pre-diabetes prevalence approaching 39% (Muharram et al., 2025). The common pathological endpoint across diabetes subtypes is progressive dysfunction and loss of pancreatic β-cells. Because β-cells constitutively express low levels of catalase, superoxide dismutase and glutathione peroxidase, they are disproportionately vulnerable to oxidative injury. Reactive oxygen species (ROS) together with inflammatory signalling are now regarded as central drivers of β-cell failure rather than incidental consequences of hyperglycaemia (Dludla et al., 2023; Mukai et al., 2022; Wei et al., 2023). Interventions that limit oxidative damage to the endocrine pancreas are therefore of direct therapeutic interest.

Streptozotocin (STZ) is the most widely used chemical tool for modelling this injury in rodents. STZ enters the β-cell selectively through the GLUT2 transporter, where its nitrosourea moiety alkylates DNA, triggers overactivation of poly(ADP-ribose) polymerase-1 and depletes cellular $NAD^+$ and ATP. Concurrent liberation of nitric oxide and generation of superoxide and hydroxyl radicals culminates in β-cell necrosis (Lenzen, 2008; Ved et al., 2022). STZ is usually given intravenously or intraperitoneally; the intravenous route yields more stable hyperglycaemia, although intraperitoneal dosing is widely used and likewise produces partial islet destruction. The resulting lesion is readily quantified on haematoxylin–eosin-stained sections (Furman, 2021; Ghasemi & Jeddi, 2023). Sulfonylureas such as glibenclamide are conventionally used as the reference treatment in this model, although chronic sulfonylurea exposure itself promotes β-cell dedifferentiation and secondary failure, which limits their value as a long-term comparator (Watanabe et al., 2024).

Against this background, plant-derived antioxidants remain an actively investigated source of β-cell-protective agents (Dinić et al., 2022; Shehadeh et al., 2021). In Indonesia, where 33.6% of patients receiving treatment for diabetes also use traditional medicine (Pradipta et al., 2023), such candidates carry particular translational relevance. *Morinda citrifolia* L. (Rubiaceae), known locally as mengkudu or noni, is a long-established component of jamu practice and is used empirically for glycaemic complaints (Halimah et al., 2019; Nascimento Júnior et al., 2025). Its leaves accumulate flavonoids — notably catechin, epicatechin, quercetin and rutin — together with the coumarin scopoletin, anthraquinones, iridoids and triterpenes (Hou et al., 2025; Lima et al., 2022; Salleh et al., 2022), and ethanolic leaf preparations display high radical-scavenging capacity (Eelager et al., 2024; Wigati & Pratoko, 2016).

Nevertheless, the antidiabetic literature on *M. citrifolia* is dominated by the fruit and by fermented fruit juice (de Oliveira Fernandes et al., 2023; Zhang et al., 2022), whereas *in vivo* work on the leaf has addressed lipid and energy metabolism (Salleh et al., 2022) or renal endpoints (Tandi et al., 2023). To the best of our knowledge, no study has reported the effect of an ethanolic *M. citrifolia* leaf extract on pancreatic histoarchitecture in an STZ-induced model, leaving the organ most directly injured in this model uncharacterised for this plant part. The present study therefore had two objectives: (i) to determine the secondary-metabolite profile of the ethanolic leaf extract of *M. citrifolia* (MCLE), and (ii) to evaluate, against both a vehicle control and a glibenclamide comparator, whether and at what dose MCLE limits pancreatic histopathological damage in STZ-induced male rats.

## 2. METHODS

### 2.1. Study Design and Ethical Approval

This was a randomised, controlled, parallel-group laboratory experiment in rats, conducted at the Phytochemistry–Pharmacognosy Laboratory and the Biopharmaceutics Laboratory, Sekolah Tinggi Ilmu Farmasi Pelita Mas (STIFA-PM), Palu, and the Balai Besar Veteriner Maros Laboratory between July and September 2021. Reporting follows the ARRIVE 2.0 guidelines (Percie du Sert et al., 2020). All procedures involving animals were approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Tadulako (approval number 5115/UN28.1.30/KL/2021).

### 2.2. Plant Material and Extract Preparation

Fresh leaves of *M. citrifolia* were collected from Jalan Anoa II, North Tatura Sub-district, South Palu District, Palu City, Central Sulawesi, Indonesia -0.911591, 119.875574. The material was taxonomically verified at the Technical Implementation Unit for Biological Resources, Tadulako University, and assigned voucher specimen No. 304/UN.28.UPT-SDHS/LK/2019. The leaves were washed, air-dried (avoiding direct sunlight), ground, and sieved through a 40-mesh sieve. The dried powder (1,000 g) was macerated in 96% ethanol at a ratio of 1:3 (w/v) for 72 hours at room temperature, protected from light and with occasional stirring. The filtrate was concentrated using a rotary evaporator at 40–60°C, followed by evaporation in a water bath at 60°C until a viscous extract was obtained. Aqueous-ethanolic systems were selected because they give the highest recovery of leaf flavonoids and phenolics among food-grade solvents (Miao et al., 2023; Yeasmen & Orsat, 2023). Extract yield was expressed as a percentage of the dry powder mass.

### 2.3. Chemicals and Instruments

Streptozotocin (≥ 98%), glibenclamide and sodium carboxymethylcellulose (Na-CMC, pharmaceutical grade) were obtained from Sigma-Aldrich (St Louis, MO, USA). Ethanol (70% and 96%), citric acid, sodium citrate, phytochemical screening reagents and haematoxylin–eosin staining solutions were of analytical grade (Merck, Darmstadt, Germany). Distilled water

was used throughout. Blood glucose was measured with a glucometer and matching test strips (Accu-Chek, Roche Diagnostics, Mannheim, Germany). Extracts were concentrated on a rotary evaporator (Heidolph, Schwabach, Germany), masses were determined on an analytical balance (Ohaus, Parsippany, NJ, USA), sections were cut on a rotary microtome (Leica, Wetzlar, Germany) and examined on a light microscope (CX-21, Olympus, Tokyo, Japan). Dosing used oral and injection syringes (One Med Health Care, Bekasi, Indonesia) and a surgical instrument set (Renz, South Jakarta, Indonesia).

### 2.4. Phytochemical Screening

Qualitative screening was performed on the crude extract using standard colour and precipitation reactions: alkaloids with Dragendorff's reagent (orange-red precipitate); flavonoids by the Shinoda test using magnesium turnings and concentrated HCl (yellow to red colour); saponins by persistent foam after vigorous shaking followed by addition of 2 N HCl; tannins with $FeCl_3$ (dark blue-black colour); and steroids by the Liebermann–Burchard reaction (green colour). Each test was performed in triplicate, and the results were recorded as detected (+) or not detected (−).

### 2.5. Animals, Housing and Husbandry

Thirty healthy male white rats (*Rattus norvegicus*) of the Wistar strain, aged 3–4 months with a body weight of 200–250 g, were obtained from the STIFA Pelita Mas research laboratory (in-house colony), Palu. Male animals were used because male rats are more susceptible to the diabetogenic effect of STZ than females (Ghasemi & Jeddi, 2023). The animals were acclimatized for 14 days prior to the start of the experiment and housed in standard polypropylene cages (5 animals per cage) with rice husk and wood shaving bedding—replaced twice weekly—at a temperature of 22–25°C and a relative humidity of 50–60%, under a 12-hour light/dark cycle. Standard rat chow and drinking water were provided *ad libitum*.

### 2.6. Sample Size, Randomisation, Blinding and Exclusion Criteria

A group size of five animals was adopted following the resource-equation approach, which gives an acceptable error degrees of freedom for a six-group design when no prior variance estimate for the damage score is available; the study was consequently powered to detect large effects only, and this constraint is revisited in the Limitations. Animals were allocated to the six groups by simple randomisation: each rat was given an identification number and numbers were drawn by lot. Histological scoring was performed by a single observer blinded to group allocation. Animals failing to reach a fasting blood glucose ≥ 200 mg/dL after STZ administration were to be excluded and replaced; no animal was excluded and no mortality occurred; all 30 rats (five per group) completed the protocol. The primary outcome was the pancreatic histopathological damage score on day 28.

### 2.7. Induction of Diabetes and Confirmation

Streptozotocin was dissolved in 0.1 M citrate buffer (pH 4.5) immediately prior to use and administered as a single intraperitoneal injection at a dose of 40 mg/kg body weight to all groups except the normal control group, which received only citrate buffer. Fasting blood glucose levels were measured on day 7 post-injection using blood samples collected from the lateral tail vein. Rats with fasting blood glucose levels ≥ 200 mg/dL were classified as diabetic and proceeded to the treatment phase.

### 2.8. Experimental Design and Treatment

Following confirmation of diabetes, animals received their assigned treatment by oral gavage once daily for 28 consecutive days. The normal control received 0.5% Na-CMC without STZ induction; the negative control received 0.5% Na-CMC after STZ induction; the positive control received glibenclamide 0.45 mg/kg BW suspended in 0.5% Na-CMC; and the three treatment groups received MCLE at 250, 500 or 750 mg/kg BW suspended in 0.5% Na-CMC. The Na-CMC vehicle was prepared by dispersing 0.5 g of Na-CMC in warm distilled water, homogenising, and adjusting to 100 mL with distilled water. Doses were selected to match those used for the same extract and the same STZ model in an earlier study by our group (Tandi et al., 2023). The dosage was adjusted daily according to each animal's body weight.

### 2.9. Euthanasia and Tissue Collection

On day 28 of treatment, and in accordance with the approved ethical protocol, rats were anaesthetised by inhalation of diethyl ether in a closed chamber containing ether-soaked cotton wool. Depth of anaesthesia was verified by loss of the pedal withdrawal reflex in response to stimulation of the footpad; absence of a response was taken to indicate surgical anaesthesia. Animals were then euthanised by cervical dislocation and placed supine on a dissection board. The pancreas was excised immediately and immersion-fixed in 10% neutral buffered formalin at a fixative-to-tissue volume ratio of at least 10:1 for 48 h.

### 2.10. Histological Processing and Semi-Quantitative Scoring

Fixed tissues were dehydrated through graded ethanol, cleared, embedded in paraffin, sectioned at 5–6 µm and stained with haematoxylin and eosin. For each animal, five non-overlapping fields per section were examined at 400× magnification. Damage was graded on a four-point ordinal scale applied jointly to the endocrine and exocrine compartments: 0 = islets of Langerhans and exocrine acinar cells of normal appearance; 1 = swelling and degeneration of islet cells with normal exocrine cells; 2 = necrosis of 25–50% of islet cells with lysis of 25–50% of exocrine cells; 3 = necrosis of more than 50% of islet cells with lysis of more than 50% of exocrine cells. Grade criteria were defined *a priori* and applied uniformly across all groups, consistent with published principles for valid histopathological scoring (Gibson-Corley et al., 2013). A comparable ordinal scheme has previously been applied

to pancreatic sections from this model (Dewi et al., 2018). One score was assigned per animal, giving five scores per group. Representative fields illustrating each grade are shown in **Figure 1**.

### 2.11. Statistical Analysis

The pancreatic damage score is an ordinal variable and is summarised as the median with interquartile range (IQR); the mean ± standard deviation is reported alongside for comparability with earlier reports. Because ordinal severity grades do not satisfy the assumptions of parametric analysis, non-parametric methods were used throughout (Mata & Milner, 2021). Overall differences among the six groups were tested with the Kruskal–Wallis test, and the effect size was expressed as epsilon-squared ($\varepsilon^2$), interpreted as small (0.01), medium (0.08) or large (0.26). Pairwise comparisons used Dunn's test with the Benjamini–Hochberg false-discovery-rate correction for the 15 possible comparisons. Groups that did not differ after adjustment share a common letter in **Figure 3**. Two-sided $p < 0.05$ was taken as statistically significant. Analyses were performed in IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA).

## 3. RESULTS AND DISCUSSION

### 3.1. Extract Yield and Phytochemical Profile

Maceration of 1,000 g of dried *M. citrifolia* leaf powder in 96% ethanol yielded 90 g of viscous extract, corresponding to a yield of 9.0% (w/w). This falls within the range expected for aqueous-ethanolic extraction of leaf biomass, in which ethanol concentrations of roughly 60–75% maximise flavonoid recovery while limiting co-extraction of chlorophyll and waxes (Miao et al., 2023; Yeasmen & Orsat, 2023).

Qualitative screening detected alkaloids, flavonoids, saponins, tannins and steroids (**Table 1**). This profile is consistent with the compound classes catalogued for *M. citrifolia*, which include flavonols and flavan-3-ols such as quercetin, rutin, catechin and epicatechin, the coumarin scopoletin, anthraquinones and iridoids (Hou et al., 2025; Lima et al., 2022; Salleh et al., 2022). It also reproduces the profile obtained previously from the same plant part and solvent by our group (Tandi et al., 2023), supporting the reproducibility of the preparation. Screening was qualitative only; the absence of quantification is addressed in the Limitations.

### 3.2. Pancreatic Histopathology

Photomicrographs illustrating each grade of the scoring scale are presented in **Figure 1**, and representative fields for each experimental group are shown in **Figure 2**. Pancreatic tissue from the normal control group displayed intact architecture, with clearly demarcated islets of Langerhans and regular exocrine acini. STZ-induced animals receiving vehicle alone showed the opposite picture: islet cells were shrunken and necrotic, islet boundaries were poorly defined, and adjacent exocrine acini showed cytoplasmic lysis. Animals receiving glibenclamide or MCLE showed intermediate appearances, with the 750 mg/kg BW group retaining islet outlines and largely preserved exocrine tissue.

**Table 1.** Phytochemical screening of the ethanolic leaf extract of *M. citrifolia*

| No. | Metabolite class | Reagent / test | Observation | Result |
|---|---|---|---|---|
| 1 | Alkaloids | Dragendorff's reagent | Orange-red precipitate | + |
| 2 | Flavonoids | Mg turnings + concentrated HCl (Shinoda) | Yellow colour | + |
| 3 | Saponins | Vigorous shaking + 2 N HCl | Persistent foam | + |
| 4 | Tannins | $FeCl_3$ solution | Dark blue-black colour | + |
| 5 | Steroids | Liebermann–Burchard reagent | Green colour | + |

Note: + = detected; − = not detected. Screening was qualitative and no quantitative determination of total phenolic or flavonoid content was performed.

### 3.3. Semi-Quantitative Scoring and Group Comparisons

Individual damage scores for all 30 animals are shown in **Figure 3**. No damage was recorded in any animal of the normal control group (median 0, IQR 0). The negative control group recorded the highest scores (median 2, IQR 0.5; mean 2.2 ± 0.45), while the glibenclamide-treated positive control recorded the lowest scores among STZ-induced groups (median 1, IQR 1; mean 0.6 ± 0.55). Among MCLE groups, the 250 and 500 mg/kg BW doses produced identical distributions (median 1, IQR 1; mean 1.4 ± 0.55 in both), and the 750 mg/kg BW dose produced the lowest scores (median 1, IQR 0.5; mean 0.8 ± 0.45).

The Kruskal–Wallis test confirmed that the six groups did not derive from a common distribution ($H = 21.66$, $df = 5$, $p < 0.001$), with a large effect size ($\varepsilon^2 = 0.69$). Dunn's test with Benjamini–Hochberg adjustment localised these differences (**Figure 3**). Relative to the negative control, a significant reduction in damage score was obtained only with MCLE at 750 mg/kg BW ($p = 0.029$); the 250 and 500 mg/kg BW doses did not differ from the negative control (both $p = 0.253$). Glibenclamide likewise differed from the negative control ($p = 0.019$). None of the three MCLE doses differed from glibenclamide ($p = 0.203$, 0.203 and 0.737 for 250, 500 and 750 mg/kg BW, respectively). Compared with the normal control, the 250 and 500 mg/kg BW groups remained significantly more damaged (both $p = 0.019$), whereas the 750 mg/kg BW group did not ($p = 0.203$), as was also the case for glibenclamide ($p = 0.263$).

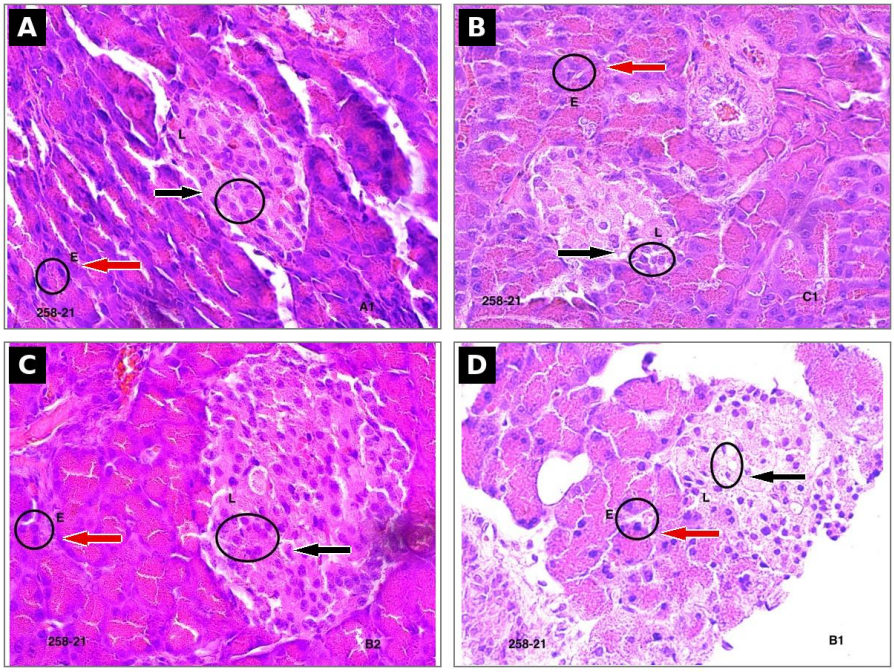



**Figure 1.** Reference photomicrographs defining the pancreatic damage scoring scale in male rats (haematoxylin–eosin, 400× magnification). (A) Score 0 — no damage; islets of Langerhans (L) and exocrine acinar cells (E) of normal appearance. (B) Score 1 — mild damage; islet cells swollen and degenerative, exocrine cells normal. (C) Score 2 — moderate damage; 25–50% of islet cells necrotic and 25–50% of exocrine cells lysed. (D) Score 3 — severe damage; more than 50% of islet cells necrotic and more than 50% of exocrine cells lysed. Black arrows indicate islets of Langerhans (L); red arrows indicate exocrine acinar tissue (E). Panels A and B show the same microscopic fields as Figure 2A and Figure 2C respectively, reproduced here as reference examples of scores 0 and 1.

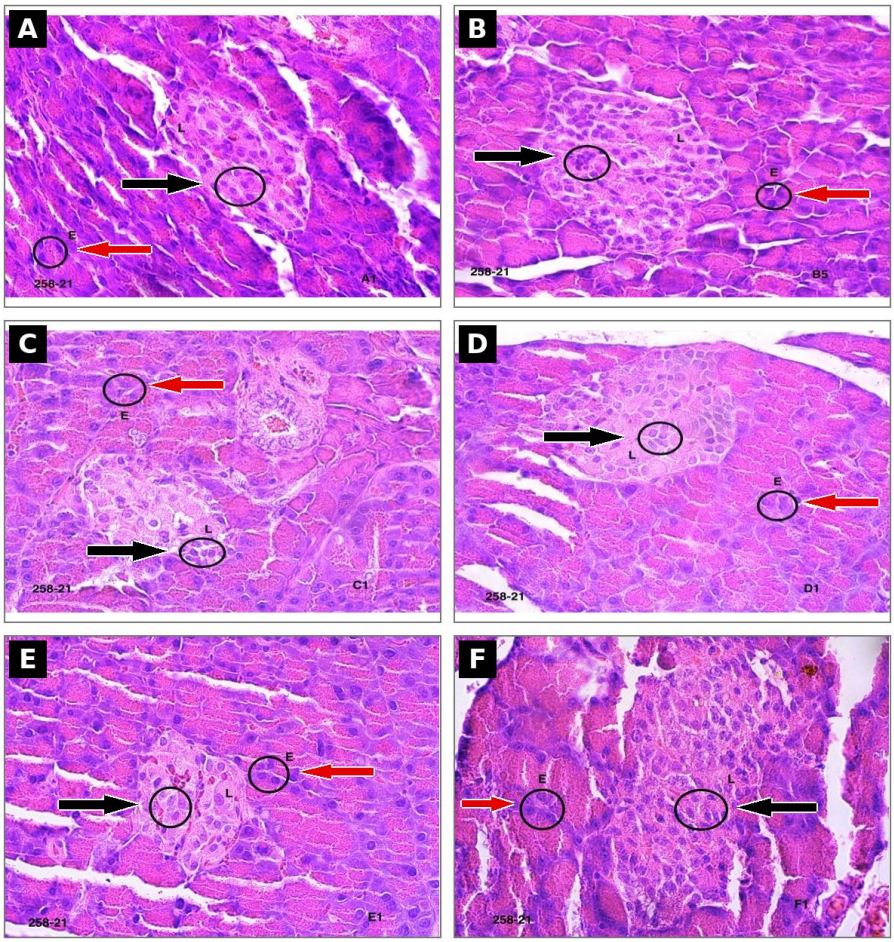



**Figure 2.** Representative photomicrographs of pancreatic tissue by experimental group in male rats (haematoxylin–eosin, 400× magnification): (A) normal control; (B) negative control (0.5% Na-CMC); (C) positive control (glibenclamide 0.45 mg/kg BW); (D–F) ethanolic leaf extract of *M. citrifolia* at 250, 500 and 750 mg/kg BW, respectively. Black arrows indicate islets of Langerhans (L); red arrows indicate exocrine acinar tissue (E).

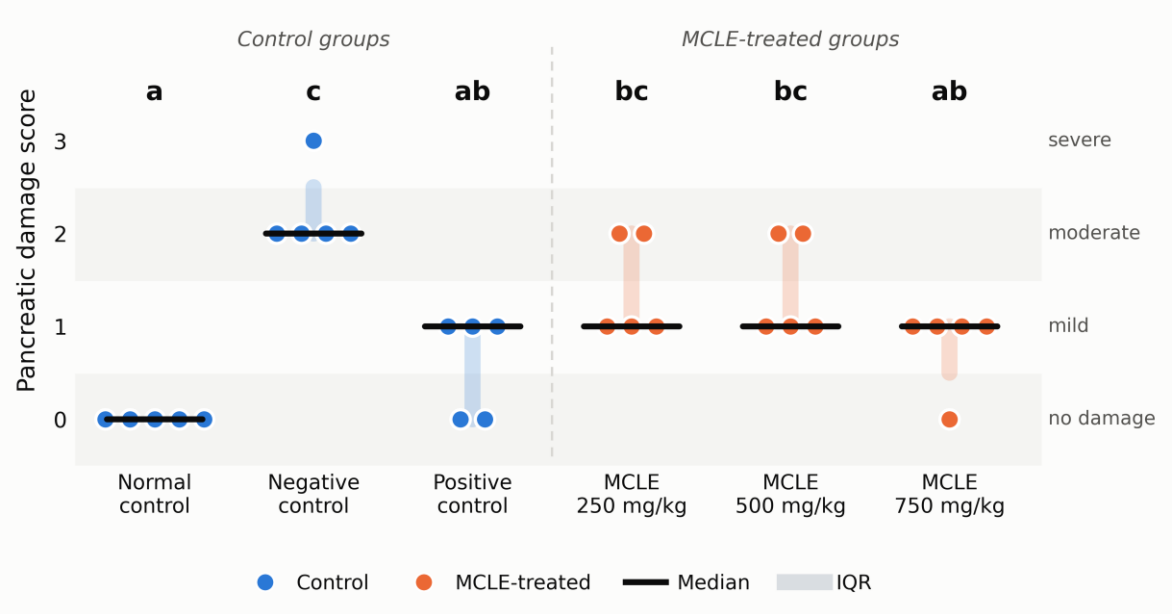



**Figure 3.** Individual pancreatic histopathological damage scores in male rats after 28 days of treatment. Each point represents one animal (n = 5 per group); the black bar indicates the group median and the shaded vertical band the interquartile range. Scores are ordinal: 0 = no damage; 1 = mild damage; 2 = moderate damage; 3 = severe damage, as defined in the Methods. Overall comparison by Kruskal–Wallis: $H = 21.66$, $df = 5$, $p < 0.001$, $\varepsilon^2 = 0.69$. Groups not sharing a common letter differ significantly (Dunn's test with Benjamini–Hochberg correction, $p < 0.05$). MCLE = ethanolic leaf extract of *M. citrifolia*; BW = body weight.

Two features of this pattern deserve emphasis. First, the protective effect demonstrable in this experiment is confined to the highest dose: at 750 mg/kg BW the pancreas was both significantly better preserved than in untreated diabetic animals and statistically indistinguishable from healthy animals. Second, the absence of a difference between any MCLE dose and glibenclamide should not be read as evidence of equivalence. With five animals per group the study has low power, and the two intermediate doses are compatible with both the negative and the positive control — the signature of an underpowered comparison rather than of therapeutic parity. The decline in mean score from 1.4 to 0.8 between 500 and 750 mg/kg BW is therefore best described as a threshold that becomes detectable only at the highest dose tested, rather than as a demonstrated dose–response relationship, since no two MCLE doses differed from one another ($p \geq 0.263$).

### 3.4. Interpretation and Plausible Mechanisms

The lesion seen in the negative control group — necrosis of a quarter to a half of the islet cell population with concurrent lysis of exocrine cells — is the expected consequence of STZ. STZ reaches the β-cell through GLUT2 and kills it through DNA alkylation, PARP-1 overactivation and $NAD^+$/ATP depletion, effects amplified by nitric oxide and ROS (Lenzen, 2008; Ved et al., 2022). Because β-cells hold unusually low reserves of antioxidant enzymes, this oxidative component is the step most amenable to pharmacological interruption (Mukai et al., 2022; Wei et al., 2023). The normal control confirmed that the vehicle was inert: Na-CMC is a suspending agent without pancreatic activity, and animals receiving it without STZ showed no lesion. The performance of glibenclamide as the positive control is consistent with reports in which glibenclamide preserved islet β-cell morphology on haematoxylin–eosin histology in STZ-based models (Jia et al., 2024), although chronic sulfonylurea exposure carries its own risk of β-cell dedifferentiation (Watanabe et al., 2024).

Because the present study measured histoarchitecture alone, the mechanisms discussed below are advanced as literature-based hypotheses consistent with the observed protection, not as pathways demonstrated here.

The constituent with the most direct supporting evidence is scopoletin, a coumarin characteristic of *M. citrifolia* (Hou et al., 2025; Sam-Ang et al., 2023). In pancreatic INS-1 β-cells, scopoletin increases viability and insulin secretion under glucotoxic stress while lowering ROS and lipid peroxidation, restoring antioxidant enzyme activity, raising Bcl-2 and suppressing the JNK/Bax/cytochrome c/caspase-9 axis (Park & Han, 2023). The flavonoid fraction offers a second, convergent route. Flavonoid-rich extracts limit β-cell loss in rodent models by restoring superoxide dismutase, catalase and glutathione peroxidase activity, lowering malondialdehyde and suppressing apoptosis (Amjadi et al., 2021; Gallardo-Villanueva et al., 2024; Khoirunnisa & Sumiwi, 2019); these effects converge on Nrf2/HO-1 activation with parallel NF-κB inhibition (Al-Hussan et al., 2023; Wei et al., 2023). Fermented noni preparations have been shown to engage precisely this Nrf2/ARE axis *in vivo* (Zhang et al., 2022).

The remaining classes detected here plausibly contribute through complementary routes. Alkaloids and polyphenols have been proposed as agents capable of preserving β-cell mass and function (Lodato et al., 2023), and alkaloid administration over a 28-day schedule comparable to ours raised superoxide dismutase and catalase activity in STZ-diabetic rats (Alamzeb et al., 2024). Saponins act on pancreas and liver through IRS-1/PI3K/Akt,

AMPK and Nrf2/ARE signalling (Zhou & Xu, 2023) and have been reported to reduce degenerative change in islet β-cells on histology in diabetic mice (Deng et al., 2023). Tannins, flavonoids and saponins together restrict carbohydrate digestion and absorption and lower oxidative and inflammatory load (Shehadeh et al., 2021), and noni constituents including ursolic acid, quercetin, rutin and scopoletin bind human pancreatic α-amylase *in silico* (Lolok et al., 2022). Anthraquinones, abundant in *Morinda* species, additionally improve insulin signalling (Xia et al., 2023). A crude extract is therefore a multi-constituent intervention, and the effect observed at 750 mg/kg BW is more plausibly additive across these classes than attributable to any single compound.

These findings sit consistently within the comparable literature. Ethanolic plant extracts have repeatedly been shown to preserve islet architecture in STZ rats against a glibenclamide comparator (Duman et al., 2022; Mansouri et al., 2023), including designs that score endocrine and exocrine compartments separately as we did (Mansouri et al., 2023). Graded histopathological assessment has likewise demonstrated restoration of islet cells under plant treatment (Deora et al., 2024). Within this journal, ethanolic leaf extracts of *Coleus atropurpureus* (Handayani et al., 2026) and *Morus alba* (Salampe et al., 2026) have likewise improved pancreatic histology in diabetic rats; notably, the *Morus alba* study identified a dose optimum rather than a linear dose–response, paralleling the threshold pattern observed here.

The relationship to our own earlier work merits comment. Using the same plant part, the same 96% ethanol maceration, the same STZ dose and the same three dose levels, Tandi et al. (2023) identified 250 mg/kg BW as effective for creatinine and urea in diabetic nephropathy. That the pancreatic endpoint here required 750 mg/kg BW suggests the protective dose is organ-dependent, plausibly reflecting differences in tissue exposure and in the sensitivity of the two endpoints, and argues against extrapolating an effective dose across target organs. Comparison with fruit-based preparations is similarly indirect: most *in vivo* noni work uses fruit or fermented juice (de Oliveira Fernandes et al., 2023; Zhang et al., 2022), and leaf and fruit differ measurably in phenolic composition (Anwar & Triyasmono, 2016; Lima et al., 2022; Wigati & Pratoko, 2016).

One safety signal in the literature warrants explicit mention: chronic noni supplementation in STZ rats improved glycaemia but was accompanied by renal changes, including increased Bowman's space (de Oliveira Fernandes et al., 2023). Renal and hepatic histology were not examined in the present study, and the favourable pancreatic finding at 750 mg/kg BW should not be interpreted as evidence of systemic safety at that dose.

### 3.5. Limitations

This study has several limitations. First, with five animals per group, statistical power was sufficient only for large effects; the failure of the 250 and 500 mg/kg BW doses to separate from the negative control is therefore an absence of evidence rather than evidence of absence, and equivalence between MCLE and glibenclamide cannot be asserted. Second, the outcome was a single ordinal score per animal at one time point; islet number, islet area, β-cell mass and immunohistochemical markers were not quantified, and no inter- or intra-observer reliability statistic was computed for the scoring. Third, blood glucose was used only to confirm the diabetic state at entry, so end-of-study glycaemia, insulin, HbA1c and pancreatic oxidative-stress markers (malondialdehyde, superoxide dismutase, catalase, glutathione) are unavailable and the proposed antioxidant mechanism remains inferential. Fourth, the extract was characterised qualitatively: total phenolic and flavonoid contents were not determined and individual markers such as scopoletin, rutin and quercetin were not quantified chromatographically, so the effect cannot be attributed to defined constituents or reproduced from the description given. Fifth, only male rats within a single age range were studied and organs other than the pancreas were not examined. Future work should combine a larger group size with chromatographic standardisation of the extract, biochemical and immunohistochemical endpoints, a wider and more finely spaced dose range to define the threshold identified here, and multi-organ safety assessment.

## 4. CONCLUSION

The ethanolic leaf extract of *M. citrifolia* contains alkaloids, flavonoids, saponins, tannins and steroids, and 96% ethanol maceration of dried leaf powder gave a yield of 9.0% (w/w). In streptozotocin-induced male rats treated for 28 days, pancreatic histopathological damage differed significantly among groups ($p < 0.001$; $\varepsilon^2 = 0.69$). A significant reduction relative to untreated diabetic animals was obtained only at 750 mg/kg BW, a dose at which the pancreas was statistically indistinguishable from that of healthy animals, whereas 250 and 500 mg/kg BW did not differ from the untreated diabetic control. The extract therefore exerts a pancreatoprotective effect at 750 mg/kg BW under these conditions, with no dose–response relationship demonstrable among the doses tested. Given the small group size and the exclusively histological endpoint, these findings should be regarded as preliminary and confirmed in an adequately powered study incorporating biochemical and immunohistochemical measures.

## AUTHOR CONTRIBUTIONS

Conceptualization, Y.S.K.; methodology, Y.S.K.; formal analysis, N.P.D.; investigation, Y.S.K.; resources, I.K.U.; data curation, N.P.D.; writing—original draft preparation, Y.S.K.; writing—review and editing, N.R. and N.A.P.; supervision, I.K.U.; project administration, N.A.P. All authors have read and agreed to the published version of the manuscript.

## INSTITUTIONAL REVIEW BOARD STATEMENT

All experimental procedures involving animals were approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Tadulako (approval number 5115/UN28.1.30/KL/2021). The study was conducted in accordance with ethical guidelines for the use of

laboratory animals and is reported in accordance with the ARRIVE 2.0 guidelines (Percie du Sert et al., 2020).

## INFORMED CONSENT STATEMENT

Not applicable. This study did not involve human participants; all experiments were conducted exclusively in animal models.

## DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

## FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. No funder had any role in the design of the study; in the collection, analysis or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

## ACKNOWLEDGMENT

The authors thank the laboratory staff and animal-house technicians who assisted with the preparation, maintenance and handling of the experimental animals, and gratefully acknowledge the support and facilities provided by the Technical Implementation Unit for Biological Resources, Universitas Tadulako.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

## DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) as a language-support tool to improve the clarity, organization, grammar, and overall readability of the text. Following its use, the authors carefully reviewed, revised, and verified the manuscript to ensure that all content accurately reflects their own ideas, data, analyses, and interpretations. The authors remain fully responsible for the accuracy, integrity, and originality of the work presented in this manuscript.

## REFERENCES

Alamzeb, M., Shah, S. W. A., Hussain, H., Zahoor, M., Ahmad, S., Mughal, E. U., Ahmad, S., Ullah, I., Khan, S., Ullah, A., Ghias, M., Ullah, R., & Ali, E. A. (2024). Beneficial effects of natural alkaloids from *Berberis glaucocarpa* as antidiabetic agents: An in vitro, in silico, and in vivo approach. *ACS Omega, 9*(8), 9813–9822. https://doi.org/10.1021/acsomega.3c10232

Al-Hussan, R., Albadr, N. A., Alshammari, G. M., Almasri, S. A., & Yahya, M. A. (2023). Phloretamide prevent hepatic and pancreatic damage in diabetic male rats by modulating Nrf2 and NF-κB. *Nutrients, 15*(6), 1456. https://doi.org/10.3390/nu15061456

Amjadi, S., Shahnaz, F., Shokouhi, B., Azarmi, Y., Siahi-Shadbad, M., Ghanbarzadeh, S., Kouhsoltani, M., Ebrahimi, A., & Hamishehkar, H. (2021). Nanophytosomes for enhancement of rutin efficacy in oral administration for diabetes treatment in streptozotocin-induced diabetic rats. *International Journal of Pharmaceutics, 610*, 121208. https://doi.org/10.1016/j.ijpharm.2021.121208

Anwar, K., & Triyasmono, L. (2016). Kandungan total fenolik, total flavonoid, dan aktivitas antioksidan ekstrak etanol buah mengkudu (*Morinda citrifolia* L.) [Total phenolic content, total flavonoid content and antioxidant activity of noni fruit ethanolic extract]. *Jurnal Pharmascience, 3*(1), 83–92. https://pharmascience.ulm.ac.id/index.php/pharmascience/article/view/5838

Deng, Y., Zhang, Y., Liu, G., Zhou, P., Li, P., Zhao, Z., Zhang, R., Tang, X., Wang, Z., Wei, Z., & Zhang, M. (2023). Saponins from *Momordica charantia* exert hypoglycemic effect in diabetic mice by multiple pathways. *Food Science & Nutrition, 11*(12), 7626–7637. https://doi.org/10.1002/fsn3.3682

de Oliveira Fernandes, D., César, F. G., Melo, B. P., Brandão, J. S. F., dos Santos, K. J., de Andrade, M. T., da Fonseca Casteluber, M. C., de Carvalho, M. V., de Barcellos, L. A. M., Soares, D. D., & Bohnen Guimarães, J. (2023). Chronic supplementation of noni in diabetic type 1-STZ rats: Effects on glycemic levels, kidney toxicity and exercise performance. *Diabetology & Metabolic Syndrome, 15*(1), 191. https://doi.org/10.1186/s13098-023-01171-1

Deora, N., Harishankar, N., Satyavani, M., Sunitha, M. M., Venkataraman, K., & Venkateshan, V. (2024). Deciphering the ameliorative effect of *Aloe vera* (L.) Burm. f. extract on histopathological alterations in streptozotocin-induced WNIN/GR-ob rats. *Journal of Ethnopharmacology, 337*(Pt 1), 118849. https://doi.org/10.1016/j.jep.2024.118849

Dewi, N. P., Afifah, A. S., Tandi, J., & Yusriadi, Y. (2018). Efek ekstrak etanol daun jambu air (*Syzygium aqueum* (Burm.f.) Alston) terhadap histopatologi pankreas tikus putih [Effect of water apple leaf ethanolic extract on the pancreatic histopathology of white rats]. *Farmakologika: Jurnal Farmasi, 15*(1), 18–26. https://jfarma.org/index.php/farmakologika/article/view/26

Dinić, S., Arambašić Jovanović, J., Uskoković, A., Mihailović, M., Grdović, N., Tolić, A., Rajić, J., Đorđević, M., & Vidaković, M. (2022). Oxidative stress-mediated beta cell death and dysfunction as a target for diabetes management. *Frontiers in Endocrinology, 13*, 1006376. https://doi.org/10.3389/fendo.2022.1006376

Dludla, P. V., Mabhida, S. E., Ziqubu, K., Nkambule, B. B., Mazibuko-Mbeje, S. E., Hanser, S., Basson, A. K., Pheiffer, C., & Kengne, A. P. (2023). Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress. *World Journal of Diabetes, 14*(3), 130–146. https://doi.org/10.4239/wjd.v14.i3.130

Duman, K. E., Doğan, A., & Kaptaner, B. (2022). Ameliorative role of *Cyanus depressus* (M.Bieb.) Soják plant extract against diabetes-associated oxidative-stress-induced liver, kidney, and pancreas damage in rats. *Journal of Food Biochemistry, 46*(10), e14314. https://doi.org/10.1111/jfbc.14314

Eelager, M. P., Masti, S. P., Chougale, R. B., Dalbanjan, N. P., & Praveen Kumar, S. K. (2024). Noni (*Morinda citrifolia*) leaf

extract incorporated methylcellulose active films: A sustainable strategy for browning inhibition in apple slice packaging. *International Journal of Biological Macromolecules, 269*(Pt 2), 132270. https://doi.org/10.1016/j.ijbiomac.2024.132270

Furman, B. L. (2021). Streptozotocin-induced diabetic models in mice and rats. *Current Protocols, 1*(4), e78. https://doi.org/10.1002/cpz1.78

Gallardo-Villanueva, P., Fernández-Marcelo, T., Villamayor, L., Valverde, A. M., Ramos, S., Fernández-Millán, E., & Martín, M. Á. (2024). Synergistic effect of a flavonoid-rich cocoa–carob blend and metformin in preserving pancreatic beta cells in Zucker diabetic fatty rats. *Nutrients, 16*(2), 273. https://doi.org/10.3390/nu16020273

GBD 2021 Diabetes Collaborators. (2023). Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: A systematic analysis for the Global Burden of Disease Study 2021. *The Lancet, 402*(10397), 203–234. https://doi.org/10.1016/S0140-6736(23)01301-6

Ghasemi, A., & Jeddi, S. (2023). Streptozotocin as a tool for induction of rat models of diabetes: A practical guide. *EXCLI Journal, 22*, 274–294. https://doi.org/10.17179/excli2022-5720

Gibson-Corley, K. N., Olivier, A. K., & Meyerholz, D. K. (2013). Principles for valid histopathologic scoring in research. *Veterinary Pathology, 50*(6), 1007–1015. https://doi.org/10.1177/0300985813485099

Halimah, H., Suci, D. M., & Wijayanti, I. (2019). Studi potensi penggunaan daun mengkudu (*Morinda citrifolia* L.) sebagai bahan antibakteri *Escherichia coli* dan *Salmonella typhimurium* [Study of the potential use of noni leaves as an antibacterial agent against *Escherichia coli* and *Salmonella typhimurium*]. *Jurnal Ilmu Pertanian Indonesia, 24*(1), 58–64. https://doi.org/10.18343/jipi.24.1.58

Handayani, T. W., Mariyani, M., Tandi, J., Caroline, C., & Magfirah, M. (2026). Antidiabetic effects of miana (*Coleus atropurpureus*) leaf ethanol extract on blood glucose and pancreatic-renal histopathology in diabetic rats. *Jurnal Jamu Indonesia, 11*(3), 192–201. https://doi.org/10.29244/jji.v11i3.445

Hou, S., Ma, D., Wu, S., Hui, Q., & Hao, Z. (2025). *Morinda citrifolia* L.: A comprehensive review on phytochemistry, pharmacological effects, and antioxidant potential. *Antioxidants, 14*(3), 295. https://doi.org/10.3390/antiox14030295

Jia, R., Liang, L., Yin, Y., Niu, C., Zhao, X., Shuwen, X., Zhang, M., & Yan, X. (2024). Vitamin D supplementation could enhance the effectiveness of glibenclamide in treating type 2 diabetes by improving the function of pancreatic β-cells through the NF-κB pathway. *Biochemical and Biophysical Research Communications, 733*, 150596. https://doi.org/10.1016/j.bbrc.2024.150596

Khoirunnisa, I., & Sumiwi, S. A. (2019). Peran flavonoid pada berbagai aktivitas farmakologi [The role of flavonoids in various pharmacological activities]. *Farmaka, 17*(2), 131–142. https://jurnal.unpad.ac.id/farmaka/article/view/21922

Lenzen, S. (2008). The mechanisms of alloxan- and streptozotocin-induced diabetes. *Diabetologia, 51*(2), 216–226. https://doi.org/10.1007/s00125-007-0886-7

Lima, D. B. M., dos Santos, A. L., Cardoso, C. A. L., Krause, L. C., & Caramão, E. B. (2022). Studies related to the chemical composition, biological activities and toxicity of methanolic extracts of noni (*Morinda citrifolia*) fruits and leaves. *Natural Product Research, 36*(22), 5868–5871. https://doi.org/10.1080/14786419.2021.2021199

Lodato, M., Plaisance, V., Pawlowski, V., Kwapich, M., Barras, A., Buissart, E., Dalle, S., Szunerits, S., Vicogne, J., Boukherroub, R., & Abderrahmani, A. (2023). Venom peptides, polyphenols and alkaloids: Are they the next antidiabetics that will preserve β-cell mass and function in type 2 diabetes? *Cells, 12*(6), 940. https://doi.org/10.3390/cells12060940

Lolok, N., Sumiwi, S. A., Muhtadi, A., Susilawati, Y., Hendriani, R., Ramadhan, D. S. F., Levita, J., & Sahidin, I. (2022). Molecular docking and molecular dynamics studies of bioactive compounds contained in noni fruit (*Morinda citrifolia* L.) against human pancreatic α-amylase. *Journal of Biomolecular Structure and Dynamics, 40*(15), 7091–7098. https://doi.org/10.1080/07391102.2021.1894981

Mansouri, R. A., Ahmad, A., Roushdy, M. M., Alshaibi, H. F., & Ragab, M. (2023). Pharmacological studies on the antidiabetic, antioxidant, and antimicrobial efficacies of *Commiphora myrrha* resin in streptozotocin-induced diabetes in rats: A preclinical study. *Journal of Diabetes Research, 2023*, 5478267. https://doi.org/10.1155/2023/5478267

Mata, D. A., & Milner, D. A. (2021). Statistical methods in experimental pathology: A review and primer. *The American Journal of Pathology, 191*(5), 784–794. https://doi.org/10.1016/j.ajpath.2021.02.009

Miao, M., Chen, X., Wu, Z., Liu, J., Xu, C., Zhang, Z., & Wang, J. (2023). Extraction, composition, and antioxidant activity of flavonoids from *Xanthoceras sorbifolium* Bunge leaves. *Journal of AOAC International, 106*(3), 769–777. https://doi.org/10.1093/jaoacint/qsac148

Muharram, F. R., Swannjo, J. B., Melbiarta, R. R., & Martini, S. (2025). Trends of diabetes and pre-diabetes in Indonesia 2013–2023: A serial analysis of national health surveys. *BMJ Open, 15*(9), e098575. https://doi.org/10.1136/bmjopen-2024-098575

Mukai, E., Fujimoto, S., & Inagaki, N. (2022). Role of reactive oxygen species in glucose metabolism disorder in diabetic pancreatic β-cells. *Biomolecules, 12*(9), 1228. https://doi.org/10.3390/biom12091228

Nascimento Júnior, J. A. C., Santos, A. M., Oliveira, A. M. S., Santana Júnior, C. C., Serafini, M. R., Quintans, J. S. S., Picot, L., de Menezes, I. R. A., & Quintans-Júnior, L. J. (2025). Botany, ethnomedicinal uses, biological activities, phytochemistry, and technological applications of *Morinda*

*citrifolia* plants. *Molecules, 30*(18), 3831. https://doi.org/10.3390/molecules30183831

Park, J. E., & Han, J. S. (2023). Scopoletin protects INS-1 pancreatic β cells from glucotoxicity by reducing oxidative stress and apoptosis. *Toxicology in Vitro, 93*, 105665. https://doi.org/10.1016/j.tiv.2023.105665

Percie du Sert, N., Hurst, V., Ahluwalia, A., Alam, S., Avey, M. T., Baker, M., Browne, W. J., Clark, A., Cuthill, I. C., Dirnagl, U., Emerson, M., Garner, P., Holgate, S. T., Howells, D. W., Karp, N. A., Lazic, S. E., Lidster, K., MacCallum, C. J., Macleod, M., … Würbel, H. (2020). The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. *PLoS Biology, 18*(7), e3000410. https://doi.org/10.1371/journal.pbio.3000410

Pradipta, I. S., Aprilio, K., Febriyanti, R. M., Ningsih, Y. F., Pratama, M. A. A., Indradi, R. B., Gatera, V. A., Alfian, S. D., Iskandarsyah, A., & Abdulah, R. (2023). Traditional medicine users in a treated chronic disease population: A cross-sectional study in Indonesia. *BMC Complementary Medicine and Therapies, 23*(1), 120. https://doi.org/10.1186/s12906-023-03947-4

Salampe, M., Widiasri, D. A. D., Wahyuddin, N., Agus, R. R., Imrawati, I., Awaluddin, A., & Wahyuni, W. (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

Salleh, S. Z., Hamid, A. A., Jaafar, A. H., Abdul Majid, N. D., Saari, N., Halim, H. H., Ismail, A., Abdul Razis, A. F., Ramli, N. S., & Pak Dek, M. S. (2022). Ergogenic property of *Morinda citrifolia* L. leaf extract affects energy metabolism in obese Sprague Dawley rats. *Journal of Food Biochemistry, 46*(1), e14027. https://doi.org/10.1111/jfbc.14027

Sam-Ang, P., Phanumartwiwath, A., Liana, D., Sureram, S., Hongmanee, P., & Kittakoop, P. (2023). UHPLC-QQQ-MS and RP-HPLC detection of bioactive alizarin and scopoletin metabolites from *Morinda citrifolia* root extracts and their antitubercular, antibacterial, and antioxidant activities. *ACS Omega, 8*(32), 29615–29624. https://doi.org/10.1021/acsomega.3c03656

Shehadeh, M. B., Suaifan, G. A. R. Y., & Abu-Odeh, A. M. (2021). Plants secondary metabolites as blood glucose-lowering molecules. *Molecules, 26*(14), 4333. https://doi.org/10.3390/molecules26144333

Tandi, J., Yana Novika R., Lakiu, D. R., Magfira, M., & Dewi, N. P. (2023). Uji ekstrak alkohol daun mengkudu (*Morinda citrifolia* L.) terhadap konsentrasi kreatinin dan ureum tikus putih jantan (*Rattus norvegicus*) nefropati diabetes [Assay of noni leaf alcoholic extract on creatinine and urea concentrations in male white rats with diabetic nephropathy]. *Jurnal Jamu Indonesia, 8*(1), 23–28. https://doi.org/10.29244/jji.v8i1.241

Ved, A., Rais, N., Ahmad, R., Parveen, K., Gautam, G. K., Bari, D. G., Shukla, K. S., Gaur, R., & Singh, A. P. (2022). Model of streptozotocin-nicotinamide induced type 2 diabetes: A comparative review. *Current Diabetes Reviews, 18*(8), e171121198001. https://doi.org/10.2174/1573399818666211117123358

Watanabe, H., Asahara, S. I., Son, J., McKimpson, W. M., de Cabo, R., & Accili, D. (2024). Cyb5r3 activation rescues secondary failure to sulfonylurea but not β-cell dedifferentiation. *PLoS ONE, 19*(2), e0297555. https://doi.org/10.1371/journal.pone.0297555

Wei, B., Zhang, X., Qian, J., Tang, Z., & Zhang, B. (2023). Nrf2: Therapeutic target of islet function protection in diabetes and islet transplantation. *Biomedicine & Pharmacotherapy, 167*, 115463. https://doi.org/10.1016/j.biopha.2023.115463

Wigati, D., & Pratoko, D. K. (2016). Total flavonoid dan aktivitas penangkapan radikal bebas dari ekstrak etanolik daun dan buah mengkudu [Total flavonoid content and free radical scavenging activity of ethanolic extracts of noni leaves and fruits]. *Jurnal Farmasi (Journal of Pharmacy), 5*(1), 7–11. https://doi.org/10.37013/jf.v5i1.36

Xia, W., Li, S., Li, L., Zhang, S., Wang, X., Ding, W., Ding, L., Zhang, X., & Wang, Z. (2023). Role of anthraquinones in combating insulin resistance. *Frontiers in Pharmacology, 14*, 1275430. https://doi.org/10.3389/fphar.2023.1275430

Yeasmen, N., & Orsat, V. (2023). Green extraction and characterization of leaves phenolic compounds: A comprehensive review. *Critical Reviews in Food Science and Nutrition, 63*(21), 5155–5193. https://doi.org/10.1080/10408398.2021.2013771

Zhang, X., Zhang, B., Li, L., Li, X., Zhang, J., & Chen, G. (2022). Fermented noni (*Morinda citrifolia* L.) fruit juice improved oxidative stress and insulin resistance under the synergistic effect of Nrf2/ARE pathway and gut flora in db/db mice and HepG2 cells. *Food & Function, 13*(15), 8254–8273. https://doi.org/10.1039/d2fo00595f

Zhou, Y., & Xu, B. (2023). New insights into anti-diabetes effects and molecular mechanisms of dietary saponins. *Critical Reviews in Food Science and Nutrition, 63*(33), 12372–12397. https://doi.org/10.1080/10408398.2022.2101425

**Publisher's Note & Disclaimer**

All statements, opinions, and data in this publication were solely the responsibility of the individual authors or contributors and did not necessarily reflect the views of the publisher or editors. The publisher and editors did not guarantee the accuracy, completeness, or reliability of the content, and were not legally responsible for any errors, omissions, or consequences arising from its use. The publisher and editors also disclaimed any liability for injury, damage, or loss to persons or property resulting from the application of ideas, methods, or products mentioned herein. Readers were advised to independently verify all information before relying on it. The publisher accepted no responsibility for any consequences arising from the use of this publication's materials.