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Effect of *Premna serratifolia* Leaf Ethanol Extract on Pancreatic Histopathology in Hypercholesterolemic Diabetic Rats

Efek Ekstrak Etanol Daun *Premna serratifolia* terhadap Gambaran Histopatologi Pankreas Tikus Diabetes-Hiperkolesterolemia

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ABSTRACT

This study evaluated the protective effect of *Premna serratifolia* leaf ethanol extract on pancreatic histopathology in hypercholesterolemic diabetic rats. Thirty male rats (n = 5/group) were assigned to normal, negative, and positive (metformin) controls and extract-treated groups (200, 300, and 400 mg/kg BW). Phytochemical screening detected alkaloids, flavonoids, saponins, and tannins in the extract. Pancreatic damage scores differed significantly among groups (Kruskal–Wallis H(5) = 20.13, p = 0.001, ε^2 = 0.63). After correcting for multiple comparisons, damage scores at 300 and 400 mg/kg were significantly lower than the negative control, while 200 mg/kg was not. No extract dose differed significantly from the positive control or from each other, so a clear dose-response pattern was not established; 300 mg/kg gave the numerically lowest mean damage score. These findings indicate that *P. serratifolia* leaf ethanol extract has a protective, though only partly dose-related, effect against pancreatic damage in hypercholesterolemic diabetic rats.

Kata kunci:

Diabetes-hiperkolesterolemia;
Histopatologi;
Pankreas;
Premna serratifolia;
Streptozotosin

ABSTRAK

Penelitian ini mengevaluasi efek protektif ekstrak etanol daun *Premna serratifolia* terhadap gambaran histopatologi pankreas tikus diabetes-hiperkolesterolemia. Tiga puluh tikus jantan dibagi ke dalam kelompok kontrol normal, negatif, dan positif (metformin) serta kelompok perlakuan ekstrak (200, 300, dan 400 mg/kg BB); n = 5/kelompok. Penapisan fitokimia menunjukkan adanya alkaloid, flavonoid, saponin, dan tanin pada ekstrak. Skor kerusakan pankreas berbeda signifikan antarkelompok (Kruskal-Wallis H(5) = 20,13, p = 0,001, ε^2 = 0,63). Setelah koreksi perbandingan berganda, skor kerusakan pada dosis 300 dan 400 mg/kg secara signifikan lebih rendah dibandingkan kontrol negatif, sedangkan dosis 200 mg/kg tidak. Tidak satu pun dosis ekstrak berbeda signifikan dari kontrol positif maupun dari dosis lainnya, sehingga pola dosis-respons yang jelas belum dapat ditetapkan; dosis 300 mg/kg memberikan skor rerata terendah secara numerik. Temuan ini menunjukkan bahwa ekstrak etanol daun *P. serratifolia* memiliki efek protektif, meskipun hanya sebagian berkaitan dengan dosis, terhadap kerusakan pankreas pada tikus diabetes-hiperkolesterolemia.

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1. INTRODUCTION

Diabetes mellitus is a metabolic disorder marked by chronic hyperglycemia that arises from impaired insulin secretion, reduced insulin action, or both, and over time damages several organs, including the pancreas itself, the tissue responsible for maintaining glucose homeostasis through insulin secretion (Dinić et al., 2022). Hypercholesterolemia commonly co-occurs with diabetes mellitus and can intensify hyperglycemic conditions: impaired lipid metabolism promotes excessive accumulation of free fatty acids, and the resulting lipotoxicity shifts energy utilization toward fatty acid oxidation, limits cellular glucose uptake, and adds to the oxidative stress that damages pancreatic tissue (Plötz & Lenzen, 2024).

Within the pancreas, the endocrine islets of Langerhans regulate glucose homeostasis through insulin secretion by β-cells, and structural damage to these cells — degeneration, necrosis, or fibrosis — impairs insulin production and worsens hyperglycemia; histopathological evaluation of pancreatic tissue is therefore an established approach for assessing diabetes-related injury and the protective effects of candidate interventions in this type of model (Irwan et al., 2017).

Premna serratifolia L. is a medicinal plant traditionally used in Indonesia and reported to contain bioactive secondary metabolites, including alkaloids, flavonoids, tannins, and saponins, with described antihypercholesterolemic and antihyperglycemic activity (Hadiarti, 2017; Martina Restuati et al., 2017; Ariyanto et al., 2026). Prior work indicates that ethanol extracts of *P. serratifolia* and the closely related *P. pubescens* lower blood cholesterol and glucose in experimental animals, but evidence on their effect on pancreatic histopathology under combined hypercholesterolemic and diabetic conditions remains limited. This study therefore evaluated the effect of *P. serratifolia* leaf ethanol extract on pancreatic histopathology in hypercholesterolemic diabetic rats. We hypothesized that oral administration of the extract would reduce pancreatic histopathological damage in this combined hypercholesterolemic-diabetic model, consistent with the antioxidant and antihyperglycemic activity reported for its secondary metabolites, and tested this across three doses (200, 300, and 400 mg/kg BW) to characterize the dose-response relationship.

2. METHODS

2.1. Experimental Animals

This study received ethical approval from the Health and Medical Research Ethics Commission of the Faculty of Medicine, Tadulako University (Approval Number 364/UN28.10/KL/2024). Thirty healthy male white rats (*Rattus norvegicus*), aged 3–4 months and weighing 200–250 g, were used in this study. All animals underwent a 14-day acclimatization period in an environment maintained at room temperature with a 12-hour light/12-hour dark cycle. Throughout acclimatization and treatment, rats were housed in standard polypropylene cages with rice husk or wood-shaving bedding that was changed regularly; standard feed and drinking water were provided ad libitum. The 30 rats were randomly assigned to six groups of five animals each — normal control, negative control, positive control, and three extract-dosage groups — by assigning each rat an identification number and conducting a draw to determine group allocation. During the histopathological assessment of the pancreas, each pancreas was placed in an individual container specifically, one container per pancreas. These containers were labeled according to the group of the rat from which the organ was harvested, ensuring that the organs are not mixed up. Regarding the number of test animals, Federer's formula, which stipulates that the number of test animals must exceed four, was used; the calculation is as follows:

$$(t-1)(n-1) \geq 15$$

$$(6-1)(n-1) \geq 15$$

$$5(n-1) \geq 15$$

$$n-1 \geq 3$$

$$n \geq 4 \text{ rats}$$

2.2. Materials and Equipment

Blender, mortar–pestle, and 40-mesh sieve (local laboratory supplier, Indonesia); maceration vessel and glassware (Erlenmeyer flask, volumetric flask, measuring cylinder) (Pyrex, USA); rotary evaporator and water bath (Büchi, Switzerland; Memmert, Germany); analytical balance (Ohaus, USA); glucometer and glucose test strips (Accu-Chek®, Germany); digital cholesterol testing device and test strips (Accu-Chek®, Germany); animal cages and oral gavage needle (local manufacturer, Indonesia); injection syringes (Terumo, Japan); tissue processor, microtome knife, and light microscope (Leica, Germany; Olympus, Japan).

P. serratifolia leaves collected from Buyumpondoli Village, Poso Regency, Central Sulawesi, Indonesia. The botanical identity of the plant was confirmed by the Biological Resources Unit (Herbarium Celebes) under reference number 122/UN.28.UPT-SDHS/LK/2024; ethanol 96% and 70% (Merck, Germany); distilled water (laboratory grade, Indonesia); sodium carboxymethylcellulose (Na-CMC) (Sigma-Aldrich, USA); streptozotocin (Sigma-Aldrich, USA); metformin tablets (PT Hexpharm Jaya Laboratories, Indonesia); citrate-buffered saline (laboratory grade, Indonesia); standard rat feed (Comfeed, Indonesia); reagents for phytochemical screening (Dragendorff, Mayer, $FeCl_3$, Liebermann–Burchard) (Merck, Germany); hematoxylin and eosin solutions (Merck, Germany).

2.3. Preparation of Extract, Vehicle, and Treatment Suspensions

The ethanolic extract of *P. serratifolia* leaves was prepared by maceration, following standard phytochemical extraction procedures: 1,500 g of dried leaf powder was macerated in 96% ethanol at a powder-to-solvent ratio of 1:2 (6 L of 96% ethanol) for 72 hours at room temperature, with occasional stirring and protection from light; the filtrate was concentrated under reduced pressure using a rotary evaporator and then further concentrated in a water bath until a viscous extract was obtained, with a yield of 130 g (8.7% w/w of the dried powder). A 0.5% sodium carboxymethylcellulose (Na-CMC) suspension was prepared in distilled water and used as the vehicle for oral administration of both the extract and the reference drug; metformin was suspended in 0.5% Na-CMC at a human-equivalent rat dose of 9 mg/kg BW and administered once daily for 28 consecutive days, starting after confirmation of the diabetic condition.

2.4. Induction, Confirmation, and Treatment of the Hypercholesterolemic-Diabetic Model

A high-cholesterol diet consisting of lard and quail egg yolk (1:1) was administered orally for 14 consecutive days during the acclimatization period to induce hypercholesterolemia. Following acclimatization, the rats were fasted for 16 hours, and their baseline blood glucose and cholesterol levels were measured. Subsequently, streptozotocin (dissolved in citrate-buffered saline, pH 4.5) was administered intraperitoneally at a dose of 40 mg/kg body weight to all groups except the normal control group; blood glucose and total cholesterol levels were measured in all groups 7 days after streptozotocin induction.

Diabetes was confirmed by measuring blood glucose with a glucometer (Accu-Chek®) from fasting tail-vein blood samples; rats with blood glucose ≥ 200 mg/dL were considered diabetic and retained in the study. Hypercholesterolemia was confirmed by measuring total cholesterol with a cholesterol test strip/analyzer from fasting tail-vein blood samples collected after the induction period; rats with total cholesterol ≥ 240 mg/dL were considered hypercholesterolemic and retained in the study. After confirmation of the hypercholesterolemic-diabetic condition, rats in the treatment groups received the ethanolic extract of *P. serratifolia* leaves at 200, 300, or 400 mg/kg BW, administered orally once daily for 28 days; the positive control group received metformin suspension (9 mg/kg BW) on the same schedule, and the negative control group received only 0.5% Na-CMC suspension.

2.5. Histopathological Assessment

Histopathological testing of the pancreas was performed on day 28 of treatment. Before euthanasia, rats were anesthetized by inhalation using ether in a closed container containing cotton wool impregnated with the anesthetic agent, following an approved ethical protocol; loss of consciousness was confirmed by the absence of a paw-withdrawal reflex to stimulation of the paw pad. Once unresponsive, rats were euthanized by cervical dislocation under the same approved protocol, then placed on a fixation board in a supine position. The pancreas was removed and immediately placed in 10% buffered neutral formalin (BNF) at a fixative volume of at least 10 times the tissue volume, for 48 hours.

After fixation, pancreatic tissue was processed using standard paraffin-embedding techniques, sectioned at 5–6 μm (microtome), and stained with hematoxylin-eosin (H&E). For each animal, five microscopic fields were examined at 400× magnification using an Olympus CX-21 light microscope and scored using the following semi-quantitative system: score 0, normal Langerhans cells and normal exocrine cells; score 1, swollen and degenerative Langerhans cells with normal exocrine cells; score 2, 25–50% necrotic Langerhans cells with 25–50% lysed exocrine cells; score 3, >50% necrotic Langerhans cells with >50% lysed exocrine cells. Each animal's score is the mean across its scored fields (n = 5 animals per group); these per-animal scores were then summarized at the group level as described below.

2.6. Statistical Analysis

Pancreatic damage scores are ordinal and are presented as median (interquartile range, IQR), with mean ± SD reported as supplementary descriptive information. Differences among the six groups were analyzed using the Kruskal–Wallis test; where this indicated an overall difference, pairwise comparisons were made with Dunn's post hoc test, with the Benjamini–Hochberg procedure used to control the false discovery rate across the fifteen pairwise comparisons. Statistical significance was set at $\alpha = 0.05$. Analyses were performed using SPSS 25.

3. RESULTS AND DISCUSSION

3.1. Phytochemical Screening

To identify secondary metabolites that may contribute to the biological activity of the extract, a qualitative phytochemical screening was performed on the ethanol extract of *P. serratifolia* leaves using group-specific reagents; the results are shown in Table 1. The screening confirmed that the ethanol extract of *P. serratifolia* leaves contains flavonoids, alkaloids, saponins, and tannins (Table 1), compound classes repeatedly linked to antioxidant and antidiabetic activity.

Table 1. Phytochemical Screening of the Ethanol Extract of *P. serratifolia* Leaves

No.	Chemical Compound	Reagent	Observation	Result
1	Alkaloids	Dragendorff	Formation of an orange-red precipitate	+
2	Flavonoids	Concentrated HCl and Mg metal	Formation of a yellow precipitate	+
3	Saponins	Shaken with 2 N HCl	Formation of foam	+
4	Tannins	$FeCl_3$	Formation of a dark bluish color	+

Description: (+) indicates a positive reaction for the compound class tested.

Antioxidant constituents can offset the oxidative stress that drives streptozotocin-induced β-cell injury (Dinić et al., 2022; Mihailović et al., 2021), and the ethanol extract of *P. serratifolia* leaves has itself been shown to scavenge free radicals effectively across several assay methods (Muhaimin et al., 2024). These four compound classes provide the basis for the mechanistic interpretation of the histological findings below.

3.2. Pancreatic Histopathology

Representative photomicrographs of pancreatic tissue from all six experimental groups are shown in Figure 1. Sections were stained with hematoxylin-eosin and examined at 400× magnification; circled regions (L) indicate the islets of Langerhans and arrows (E) indicate exocrine acinar tissue.

These photomicrographs illustrate the histological features underlying the semi-quantitative scoring system applied in Figure 2: intact islets of Langerhans with clearly demarcated β-cells indicate minimal injury, whereas swelling and necrosis of Langerhans-cell nuclei together with lysis of the surrounding exocrine acinar tissue indicate progressively greater damage. The group-level damage scores derived from this scoring system are presented next.

3.3. Pancreatic Damage Scores and Statistical Analysis

Pancreatic damage was scored for each animal using the semi-quantitative system described in Methods. The distribution of individual and group-level damage scores, together with the results of the corrected post hoc comparisons, is illustrated in Figure 2.

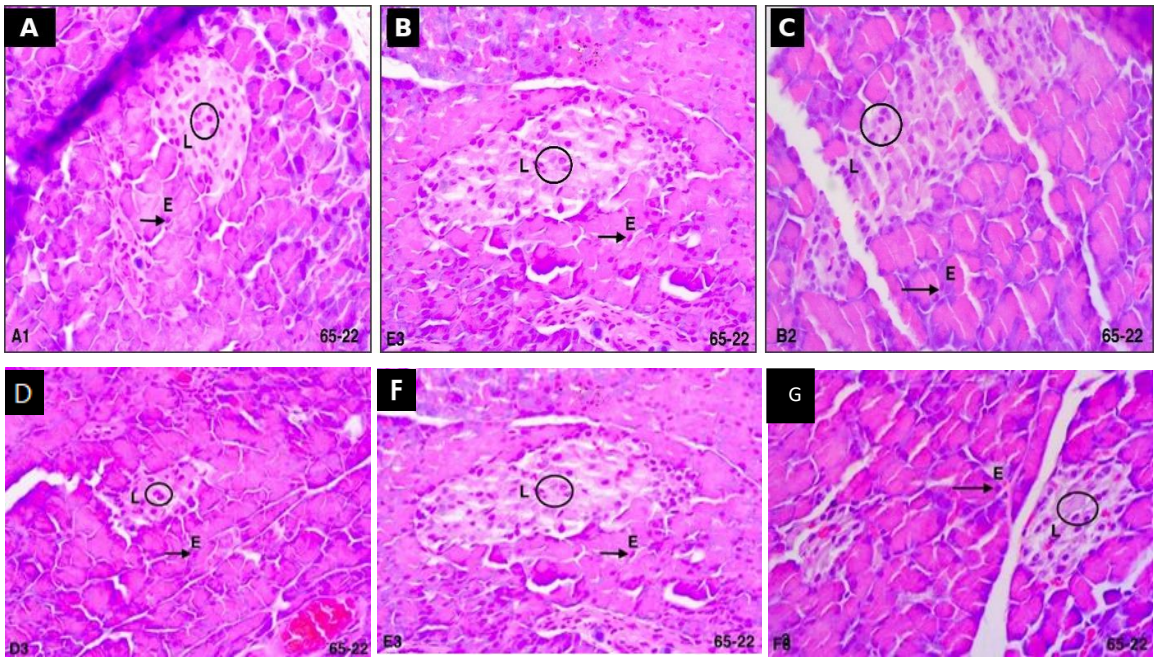

Figure 1. Representative photomicrographs of pancreatic tissue (hematoxylin-eosin staining, 400× magnification). L = islets of Langerhans; E = exocrine cells. Panels are labelled as in the original slide records (A = Normal control, B = Negative control, C = Positive control, D = 200 mg/kg BW, F = 300 mg/kg BW, G = 400 mg/kg BW).

Mean damage scores rose from 0.40 ± 0.47 [median 0.20 (0.90)] in the normal control to 2.20 ± 0.47 [2.00 (0.70)] in the negative control, the highest of all six groups; the positive control (metformin) was intermediate at 1.36 ± 0.38 [1.40 (0.70)], and the three extract doses were lower than the negative control without a monotonic dose-response — 1.12 ± 0.11 [1.20 (0.20)] at 200 mg/kg BW, 0.88 ± 0.30 [1.00 (0.50)] at 300 mg/kg BW, and 0.96 ± 0.26 [0.80 (0.40)] at 400 mg/kg BW (Figure 2). The overall Kruskal–Wallis test confirmed a significant difference among groups ($H(5) = 20.13$, $p = 0.001$, $\varepsilon^2 = 0.63$, a large effect), and Dunn's post hoc test with Benjamini–Hochberg correction across the fifteen pairwise comparisons identified four significant differences, each with a medium-to-large rank-biserial effect size ($r = |z|/\sqrt{N}$): normal versus negative control ($p = 0.0007$, $r = 0.75$), normal versus positive control ($p = 0.035$, $r = 0.47$), negative versus 300 mg/kg BW ($p = 0.016$, $r = 0.54$), and negative versus 400 mg/kg BW ($p = 0.016$, $r = 0.54$); every comparison between an extract dose and the positive control (adjusted $p = 0.24$–0.64) and every comparison among the three doses (adjusted $p = 0.41$–0.97) remained non-significant. This pattern fits established mechanisms of injury and protection in this model: the elevated damage in the negative control reflects the cytotoxic action of streptozotocin, which destroys pancreatic β-cells largely through oxidative stress and DNA damage (Yavuz et al., 2024), compounded by diet-induced lipotoxicity that further impairs β-cell function (Plötz & Lenzen, 2024); Na-CMC in this group served only as a suspending vehicle. Metformin's numerically lower but not statistically confirmed reduction relative to the negative control, together with its persistent significant difference from the normal control, is consistent with its understood mechanism of lowering hyperglycemia-associated oxidative stress and inflammation rather than directly protecting β-cells (Koroglu et al., 2025). The extract's significant protection at 300 and 400 mg/kg BW, without a significant difference from

the positive control or a confirmed dose-response relationship, is broadly consistent with reports that flavonoid-rich extracts limit streptozotocin-induced pancreatic damage and preserve islet architecture in other *in vivo* models (Arora et al., 2021); the 200 mg/kg BW dose's failure to reach significance against the negative control ($p = 0.110$) suggests this lowest dose was insufficient at this sample size.

3.3. Mechanistic Synthesis and Study Limitations

The protection associated with the *P. serratifolia* extract is plausibly explained by the combined action of the secondary metabolites identified in Table 1. Alkaloids have been reported to reduce oxidative stress, modulate glucose-metabolism enzymes, and improve insulin sensitivity, helping to preserve β-cell structure under diabetic conditions (Shehadeh et al., 2021). Flavonoids act largely through free-radical scavenging and by suppressing lipid peroxidation and DNA damage in pancreatic cells (Arifin & Ibrahim, 2018): flavonoid-rich extracts have been shown to lower malondialdehyde levels while raising superoxide dismutase and catalase activity, improving islet morphology in the process (Liu et al., 2021). Saponins can delay carbohydrate digestion through α-glucosidase inhibition and reduce postprandial glucose excursions; saponin-containing extracts have been reported to attenuate pancreatic inflammation and limit β-cell degeneration in diabetic animal models (Deng et al., 2023). Tannins, as phenolic compounds, are further implicated in glucose homeostasis through modulation of intestinal glucose absorption and peripheral glucose utilization, creating conditions more favorable to tissue preservation even though their effects alone do not fully restore pancreatic architecture (Sahakyan et al., 2022; V & M, 2020).

Taken together, the ethanol extract of *P. serratifolia* leaves produced a measurable, statistically confirmed reduction in pancreatic damage scores at the two higher doses tested, without fully replicating the normal control's histological profile and without a confirmed dose-response relationship across the three doses used. Several design features temper how far these findings can be generalized. The sample size ($n = 5$ per group) is modest for a six-group comparison, and the absence of a significant difference between the extract-treated groups and the positive control should be read cautiously against this background; only male rats were used, so sex-dependent differences in response remain untested. Histological damage was scored with a single semi-quantitative 0–3 scale rather than an independent quantitative morphometric measure, and whether the scorer was blinded to group allocation is not yet stated (see Methods). The extract itself was characterized only by qualitative phytochemical screening (Table 1), without quantifying individual compound classes or identifying marker constituents, which limits reproducibility and mechanistic attribution. Finally, protection was inferred from histology alone: glucose and cholesterol were measured only to confirm successful model induction and were not re-measured after 28 days of treatment, so it remains untested whether the histological improvement seen here is accompanied by a corresponding biochemical improvement. Addressing these points — larger group sizes, blinded and quantitative histological scoring, standardized and quantified extract composition, and post-treatment biochemical endpoints such as glucose, cholesterol, insulin, and oxidative-stress markers — would help establish whether *P. serratifolia* leaf extract offers protection comparable to metformin in this model.

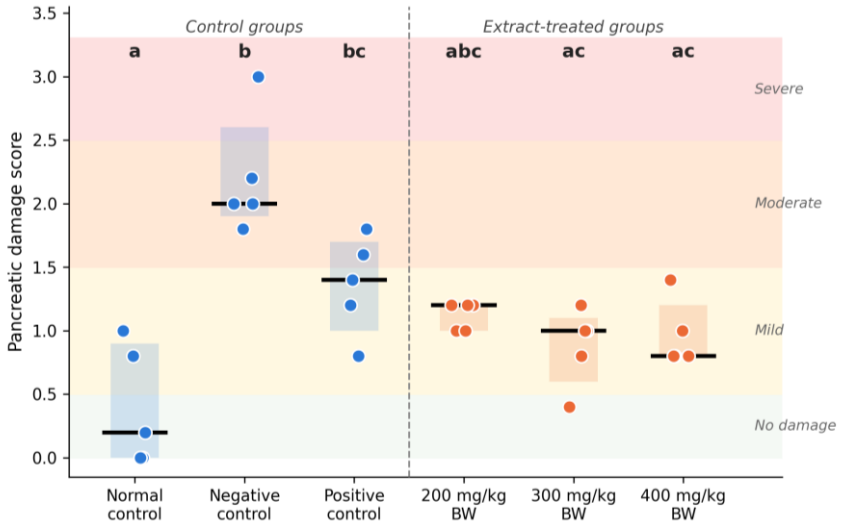

Figure 2. Individual pancreatic damage scores by experimental group (Kruskal–Wallis $H(5) = 20.13$, $p = 0.001$, $\varepsilon^2 = 0.63$). Points show scores for individual animals ($n = 5$ per group); black bars show the group median; shaded bands show the interquartile range. Background shading marks the qualitative severity band for each score. Letters above each group are from Dunn's post hoc test with Benjamini–Hochberg FDR correction ($\alpha = 0.05$); groups sharing a letter did not differ significantly. Median (IQR) damage scores: normal control, 0.20 (0.90); negative control, 2.00 (0.70); positive control, 1.40 (0.70); 200 mg/kg BW, 1.20 (0.20); 300 mg/kg BW, 1.00 (0.50); 400 mg/kg BW, 0.80 (0.40). Damage-score criteria: 0 = normal Langerhans cells, normal exocrine cells; 1 = swollen and degenerative Langerhans cells, normal exocrine cells; 2 = 25–50% necrotic Langerhans cells, 25–50% lysed exocrine cells; 3 = >50% necrotic Langerhans cells, >50% lysed exocrine cells.

4. CONCLUSION

The ethanol extract of *P. serratifolia* leaves contains alkaloids, flavonoids, saponins, and tannins. In hypercholesterolemic diabetic rats, the 300 and 400 mg/kg BW doses significantly reduced pancreatic damage scores relative to the untreated diabetic (negative control) group, while the 200 mg/kg BW dose did not reach statistical significance. The 300 mg/kg BW dose produced the numerically lowest mean damage score, though it did not differ significantly from the other two doses or from the metformin-treated positive control. These findings support a protective, though only partially dose-related, effect of *P. serratifolia* leaf extract on pancreatic histopathology under combined hypercholesterolemic-diabetic conditions.

AUTHOR CONTRIBUTIONS

Author 1: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Visualization. Author 2: Corresponding author, Validation, Resources, Writing – review & editing. Author 3: Project administration, Supervision. Author 4: Methodology & Investigation. Author 5: Formal analysis, Writing – review & editing. Author 6: Resources, Investigation (technical/laboratory and sample preparation). Author 7: Writing – review & editing. 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, Tadulako University (Approval Number: 364/UN28.10/KL/2024). The study was conducted in accordance with ethical guidelines for the use of laboratory animals to ensure their welfare and humane treatment, consistent with the ARRIVE 2.0 guidelines for reporting animal research (Percie du Sert et al., 2020).

INFORMED CONSENT STATEMENT

Not applicable. This study did not involve human participants; all experiments were conducted exclusively using animal models, so informed consent from human subjects was not required.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to ethical restrictions.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ROLE OF FUNDERS

Not applicable. This research received no external funding, so 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.

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

During the preparation of this manuscript, the authors used Grammarly, ChatGPT (OpenAI), and Claude (Anthropic) to assist in improving the clarity, structure, language, and readability of the text. Claude was specifically used to assist in paraphrasing and composing certain sections of the manuscript, including the methods and discussion. Following the use of these tools, the authors thoroughly reviewed, edited, and verified the entire manuscript to ensure that it accurately represented their data, ideas, and interpretations. The authors take full responsibility for the integrity, accuracy, and originality of the published work.

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