Effect of *Annona muricata* Leaf Extract on Hepatic Histopathology and Hepatocyte Index in a Diabetic *Rattus norvegicus* Model

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ABSTRACT

***Background**: The oxidative stress caused by diabetes mellitus (DM) damages hepatocytes and reduces liver function. In this context, flavonoids and acetogenins found in soursop (Annona muricata L.) leaf have hepatoprotective and antioxidant qualities. Therefore, this study aimed to assess the effect of Annona muricata leaf extract on hepatocyte index and hepatic histopathology in diabetic Wistar rats.*

***Methods**: In a laboratory experiment, 16 male Wistar rats weighing 100–150 g and aged 2-3 months were given a high-fat diet and an injection of streptozotocin (27.5 mg/kg BW) to induce type 2 diabetes. Rats were placed in a randomized posttest-only control group. For 21 days, these experimental animals were split into two groups at random, namely control (n = 8) receiving aquadest, and treatment group (n = 8) receiving Annona muricata leaf extract at a dose of 100 mg/kg BW. Hematoxylin-eosin staining was used to analyze hepatic histopathology, and a quantitative evaluation of hepatocyte index was conducted. The independent t-test and Mann-Whitney U test were adopted to assess the data.*

***Results**: There was a significant difference (p=0.041) in hepatocyte index between treatment and control groups. Treatment group had less hepatocyte deterioration than the control, according to histopathological scoring (p=0.037).*

***Conclusion**: Diabetic Wistar rats treated with Annona muricata leaf extract showed better hepatocyte index and decreased hepatic degeneration, suggesting hepatoprotective potential.*

***Keywords**: Annona muricata, diabetes mellitus, hepatic histopathology, hepatocyte index, soursop leaf extract*

ABSTRAK

***Latar belakang**: Stres oksidatif akibat diabetes melitus (DM) merusak hepatosit dan menurunkan fungsi hati. Flavonoid dan asetogenin yang terkandung dalam daun sirsak (Annona muricata L.) memiliki sifat hepatoprotektif dan antioksidan. Tujuan penelitian ini adalah untuk mengkaji pengaruh ekstrak daun sirsak terhadap indeks hepatosit dan histopatologi hati pada tikus Wistar diabetes.*

***Metode**: Dalam sebuah percobaan laboratorium, 16 tikus Wistar jantan dengan berat 100–150 g dan berusia 2-3 bulan diberi diet tinggi lemak dan suntikan streptozotocin (27,5 mg/kg BB) untuk menginduksi diabetes tipe 2. Tikus-tikus tersebut ditempatkan dalam kelompok kontrol acak pasca-uji saja. Selama 21 hari, tikus dibagi menjadi dua kelompok secara acak: kelompok kontrol (n = 8) yang menerima akuades, dan kelompok perlakuan (n = 8) yang menerima ekstrak daun sirsak dengan dosis 100 mg/kg BB. Pewarnaan hematoksilin-eosin digunakan untuk menganalisis histopatologi hati, dan evaluasi kuantitatif indeks hepatosit dilakukan. Uji-t independen dan Uji Mann Whitney U digunakan untuk menilai data.*

***Hasil**: Terdapat perbedaan indeks hepatosit yang signifikan (p=0,041) antara kelompok perlakuan dan kelompok kontrol. Kelompok perlakuan mengalami degenerasi hepatosit yang lebih sedikit dibandingkan kelompok kontrol, berdasarkan skor histopatologi (p=0,037).*

***Kesimpulan**: Tikus Wistar penderita diabetes yang diobati dengan ekstrak daun sirsak menunjukkan indeks hepatosit yang lebih baik dan penurunan degenerasi hati, yang menunjukkan potensi hepatoprotektif.*

***Kata kunci**: Annona muricata, ekstrak daun sirsak, indeks hepatosit, histopatologi hepar, diabetes mellitus*

INTRODUCTION

Diabetes mellitus (DM) is a long-term metabolic disease marked by persistently high blood sugar levels due to deficiencies in the action or secretion of insulin. Increased production of reactive oxygen species (ROS) over time following high blood glucose causes oxidative stress, which affects several organs. Given the central role in the metabolism of fats and carbohydrates, the liver is particularly susceptible to damage in DM. Oxidative stress associated with DM contributes to hepatocyte degeneration, inflammatory cell infiltration, and impaired liver function. A previous study showed that diabetic rats given streptozotocin (STZ) exhibited significant hepatic histological alterations, including cytoplasmic vacuolization and disorganized hepatocyte organization.[1,2]

Hepatocyte index is a quantitative histological parameter used to assess liver tissue integrity by estimating the proportion of structurally intact, normal hepatocytes relative to damaged or altered cells. This parameter represents the overall functional status of hepatocytes and is commonly used to evaluate liver injury in experimental studies. Hepatocyte index, also known as hepatocyte integrity, is a crucial indicator of the health of liver tissue since the variable shows the number and state of functional hepatocytes. Hyperglycemia, weakened antioxidant defenses, and elevated lipid peroxidation are correlated with decreased hepatocyte index and histological deterioration in diabetic animals.[3,4] Antioxidant treatments have been investigated to lessen liver damage brought on by DM. According to review studies, oxidative stress and inflammation play a major role in the processes that cause hepatic lesions in people with diabetes, and substances altering redox balance have the potential to preserve the structure and function of the liver.[5,6]

Traditional medicine recognizes soursop (*Annona muricata* L.) for hepatoprotective and antidiabetic properties. Bioactive substances found in leaf, seed, and fruit have been shown in a variety of animal models to have anti-inflammatory, antioxidant, and glucose-lowering properties. For instance, "Ameliorative Effect of *Annona muricata* Extract" reduced liver damage in diabetic rats by having protective histological effects.[7,8] The methanol extract of *Annona muricata* seed decreased hyperglycemia and reported hepatoprotective effects in Wistar rats with diabetes caused by alloxan.[9] However, limited studies provide thorough evaluations of histology and the quantitative hepatocyte index using a standardized experimental design.

Based on the description above, this study aims to examine the effect of *Annona muricata* leaf extract on hepatic histopathology and hepatocyte index in a diabetic Wistar rat (*Rattus norvegicus*) model. A randomized post-test-only control group design was used to strengthen the evidence concerning the hepatoprotective effects of *Annona muricata* against DM-induced hepatic alterations.

METHODS

Study Design

This study used a randomized posttest-only control group design and was conducted entirely in a laboratory. The investigation was carried out at Udayana University's Faculty of Medicine's Integrated Biomedical Laboratory.

Experimental Animals

Sample sizes were estimated based on minimum requirements for experimental animal studies and adjusted for potential withdrawal. A 10% adjustment was applied to account for potential mortality. After diabetes induction, 4 rats from each group were removed due to mortality related to diabetes induction, leading to a final sample size of 8 rats per group for analysis.

A total of 16 healthy male Wistar rats weighing between 100 and 150 g and 2 to 3 months of age were used. Healthy appearance, age between 2 and 3 months, and body weight within the specified range were the inclusion criteria for admission. The exclusion criteria include rats that fell ill or passed away during the trial. The animals were kept in wire-topped plastic cages of 30 by 40 by 40 cm, with a 12-hour light/dark cycle and a temperature of 30 ± 1°C with unlimited access to food and drink. Rats were given a week to acclimate before the trial. Subsequently, the animals were randomly assigned to the control and treatment groups using a simple random sample procedure.

Induction of Diabetes Mellitus

Rats were given a high-fat diet followed by a single intraperitoneal injection of streptozotocin (STZ) at a dose of 27.5 mg/kg body weight, dissolved in 0.1 M citrate buffer (pH 4.5), to induce a type 2 DM-like condition. Fasting blood glucose levels were measured using a glucometer to confirm hyperglycemia. In this study, a fasting blood glucose level ≥135 mg/dL was used as the operational cutoff to define diabetic status in line with previously reported experimental models.

Grouping and Treatment

Rats were divided into two groups of eight at random:

1. Control (K) was given aquadest orally at a volume adjusted to body weight similar to the treatment group (placebo) for 21 days.
2. Treatment group (P) received *Annona muricata* leaf extract orally at a dose of 100 mg/kg body weight for 21 days.

Histopathology and Hepatocyte Index Examination

Animals were put to sleep with ketamine (60 mg/kg BW, intramuscular) on day 59 and decapitated. After being removed, the liver was embedded in paraffin, fixed in 10% buffered formalin, sectioned at a thickness of 4-5 μm, and stained with hematoxylin-eosin. Hepatocyte index, assessed by the proportion of morphologically intact hepatocytes in relation to the total number of hepatocytes, was quantitatively determined per field of view using a light microscope at standard magnification. For each sample, 5 randomly selected, non-overlapping fields were evaluated. Furthermore, the mean value was calculated to represent the hepatocyte index for each sample. Histopathological evaluation was performed independently by two experienced pathologists in a blinded manner to minimize observer bias. Hepatocyte degeneration was scored histopathologically as 4 (very severe, >75%), 3 (severe, 51–75%), 2 (moderate, 26–50%), 1 (mild, ≤25%), and 0 (none or normal).

Statistical Analysis

Shapiro-Wilk test was used to check the data for normality. An independent t-test was used to compare control and treatment groups based on normally distributed data (hepatocyte index). Non-normally distributed data or histopathological scores were analyzed using the Mann–Whitney U test. Meanwhile, P-values less than 0.05 were regarded as statistically significant. Statistical analysis was conducted using IBM SPSS Statistics version 18.0 (IBM Corp., Armonk, NY, USA).

Ethical Approval

The Research Ethics Committee of Universitas Warmadewa's Faculty of Medicine approved this study (Approval No. 548/Unwar/FKIK/EC-KEPK/XII/2024). Every procedure was carried out in compliance with the ethical guidelines for using animals in experimental analysis.

RESULTS

Hepatocyte Index

In comparison to the control group, the treatment group's mean hepatocyte index was greater. An independent t-test statistical analysis reported a significant difference between the groups ($p = 0.041$), suggesting that the administration of diabetic rats' leaf extract from *Annona muricata* enhanced the integrity of the liver.

Histopathological Findings

Histopathological readings were performed by blinded observers to minimize assessment bias. Histological analysis showed that the control group had significant degenerative abnormalities, including disordered hepatic cords, nuclear modifications, and cytoplasmic vacuolization **(Figure 1A).** The treatment group showed less hepatocyte degradation, more normal hepatocyte shape, and comparatively intact hepatic architecture **(Figure 1B).**

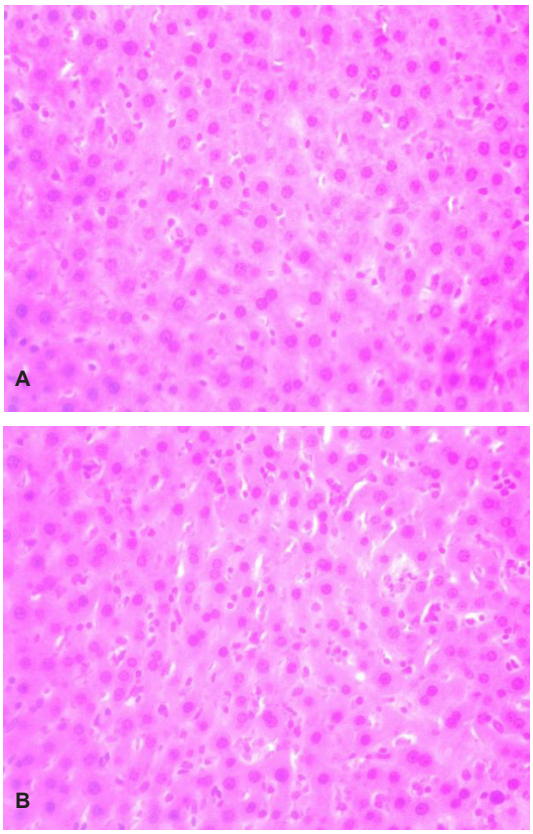

Figure 1. Histopathological features of liver (H&E staining, 40×).

(A) Control group: This histological appearance is consistent with moderate hepatocyte degeneration in the diabetic condition without therapeutic protection. The observed changes, including cloudy swelling, cytoplasmic vacuolization, and lobular disorganization, indicate the presence of significant oxidative stress.

(B) Treatment group: This histological appearance shows hepatocytes in a relatively better condition, with only mild degeneration and minimal cloudy swelling. The result is interpreted as a more evident protective effect of the extract therapy.

Table 1 summarizes the distribution of hepatocyte degeneration scores. Even though the treatment group showed a shift toward milder degeneration (scores 1–3), the majority of rats in the control group reported very severe degeneration (score 4). A significant difference between the groups was confirmed by the Mann-Whitney U test ($p = 0.037$).

Table 1. Hepatocyte degeneration score distribution between treatment (P) and control (K) groups

Degeneration score	Control (K), n (%)	Treatment (P), n (%)
0 (none, normal)	0 (0%)	0 (0%)
1 (mild, ≤25%)	0 (0%)	1 (12,5%)
2 (moderate, 26–50%)	0 (0%)	1 (12,5%)
3 (severe, 51–75%)	2 (25%)	4 (50%)
4 (very severe, >75%)	6 (75%)	2 (25%)
Total	**8 (100%)**	**8 (100%)**

Mann–Whitney U test showed a significant difference in hepatocyte degeneration scores between groups ($p = 0.037$). K = control; P = treatment.

Figure 2 presents the comparison of hepatocyte degeneration scores as a bar chart to better visualize the differences between groups. In line with the preventive effect of *Annona muricata* leaf extract, the treatment group showed a greater distribution in mild to severe categories, while the control group primarily reported extremely severe deterioration.

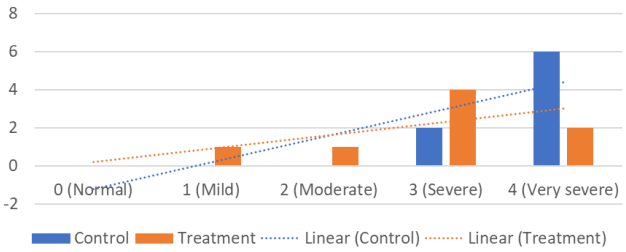

Figure 2. Comparison of hepatocyte degeneration scores between groups.

The bar chart suggests that most rats in the control and treatment groups exhibit very severe degeneration (score 4) and milder scores (1–3), respectively.

DISCUSSION

An improvement in hepatocyte index and a decrease in the degeneration scores show that leaf extract of *Annona muricata* considerably reduced hepatic damage in diabetic rats. These results support and add to earlier studies on *Annona muricata* hepatoprotective properties in both diabetic and non-diabetic rats.

Significant improvements in metabolic and hepatic parameters were observed in diabetic rats fed a high-fat diet and STZ after receiving 50 or 100 mg/kg BW of *Annona muricata* extract for nine weeks. The extract decreased oxidative stress indicators, including 4-HNE and protein carbonyls, while enhancing insulin signaling pathways, as reported by elevated IRS-1 and GLUT2 expression. Improved hepatic architecture was suggested by morphological evaluation,

which showed fewer lipid droplets and autophagic process activation, including induction of p-AMPK and LC3 conversion. In line with biochemical and histological alterations, fasting blood glucose and HbA1c decreased. Therefore, *Annona muricata* has a dual function in glycemic management and hepatoprotection.[8] These results point to the function of *Annona muricata* in maintaining the integrity of hepatocytes by regulating oxidative stress, metabolic control, and structural preservation.

Another pertinent study showed that chronic hyperglycemia causes inflammatory reactions and oxidative stress, which leads to liver damage. Increased lipid peroxidation, as reported by raised levels of MDA and TBARS, excessive formation of ROS, and activation of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, were connected to the disease. These changes promoted hepatocyte deterioration and apoptosis, which led to compromised liver function.[10]

An experimental investigation in which rats with STZ-induced diabetes were given an aqueous extract of *Annona muricata* leaf showed biochemical and structural hepatoprotective effects. The extract improved endogenous antioxidant defenses by raising SOD, CAT, and GSH activities and lowering ROS and TBARS levels. Improvements in lipid metabolism were also reported, with lower serum insulin levels and lower levels of LDL and triglycerides. Histological examination showed a greater hepatocyte index and less degeneration, suggesting better liver structure preservation due to metabolic management and reduced oxidative stress.[11] Mechanistically, the effects seen in this study could be explained by multiple pathways as follows.

Oxidative stress reduction: Hyperglycemia increases the production of free radicals through glucose auto-oxidation, mitochondrial failure, NADPH oxidase activation, advanced glycation end products (AGEs) binding to RAGE, and other mechanisms. The imbalance is increased by decreased antioxidant defenses, such as GSH, SOD, and CAT. *Annona muricata* upregulates the antioxidant systems to reduce lipid peroxidation (TBARS, MDA) and ROS, preventing damage to cellular membranes and organelles in hepatocytes.[12,13]

Control of inflammation: Increased ROS frequently sets off inflammatory reactions with cytokines (TNF-α, IL-6, and IL-1β), which directly or indirectly cause hepatocyte damage by attracting immune infiltrates. Studies on the Effect of Graviola and Ginger extract show that *Annona muricata* alters the production of apoptotic proteins (Bax, Bcl-2, and p53) and inflammatory markers in the liver.[14]

Better insulin signaling (IRS-1, GLUT2), decreased insulin resistance, decreased HbA1c, and enhanced lipid metabolism contribute to better metabolic regulation, which lessens lipotoxic stress in hepatocytes. A 2021 study suggested that *Annona muricata* also improved energy balance through AMPK to shield hepatic cells, and the expression of autophagy markers (lipophagy).[8,15]

Hyperglycemia-induced ischemia–reperfusion injury activated NLRP3 inflammasome-mediated hepatocyte pyroptosis and suppressed cytoprotective pathways, including Nrf2 signaling and mitophagy, in diabetic liver, even though apoptosis- and pyroptosis-related markers were not evaluated in the present study. Therefore, the potential contribution of cell survival and death pathways to the observed hepatic alterations requires further investigation.[16,17] These could be pertinent to additional investigations on *Annona muricata*.

CONCLUSION

In conclusion, *Annona muricata* leaf extract has hepatoprotective benefits in streptozotocin-induced diabetic rats by significantly improving hepatocyte index and reducing histological degeneration in comparison to controls. These results imply that anti-inflammatory and antioxidant qualities may protect hepatocyte integrity in the face of oxidative stress and hyperglycemia. The therapeutic potential of the extract as a supplemental method in protecting the liver against diabetes-induced harm requires more studies with longer treatment durations, dose-response evaluations, and molecular analysis.

Limitations and Suggestions

Limitations of this study should be acknowledged. First, dose-response effects were not investigated because only a dosage of *Annona muricata* leaf extract (100 mg/kg BW) was administered. Second, hematoxylin–eosin staining was used for histological examination. This method was sufficient for identifying hepatocyte degeneration, but did not offer molecular-level information. Biochemical markers such as ALT, AST, and oxidative stress parameters were not measured, limiting the mechanistic interpretation. Furthermore, the diabetes model used an operational fasting blood glucose threshold (≥135 mg/dL) without direct confirmation of insulin resistance (insulin

levels or HOMA-IR). This limited the model's characterization as a fully representative model of type 2 DM. Therefore, the model did not fully reflect the complex pathophysiology of type 2 DM in humans.

Future studies can clarify the mechanisms behind the hepatoprotective benefits of *Annona muricata* by evaluating various dosages and using supplementary methods such as immunohistochemistry (caspase-3, TGF-β). Longer observation times can provide more details about the capacity of the extract to stave off chronic liver damage.

Implications

The results indicate that *Annona muricata* leaf extract has potential as a hepatoprotective agent. Antioxidant, anti-inflammatory, and metabolic modulating properties may help stop or slow diabetes-induced liver damage. However, further study is needed regarding safety, pharmacokinetics, human trials, and standardization of the extract.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

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AUTHOR CONTRIBUTIONS

D.A.A.A.S.A. contributed to the concept, methodology, analysis, writing and drafting of the original draft, and supervision. D.P.O.L. contributed to the methodology, investigation, and analysis. L.G.E., N.P.D.W., and K.T.S. contributed to the investigation. N.P.D.W. and N.M.G.K.D. contributed to data curation. F.F.A.K. and I.A.L.A.D.M. contributed to the writing, review, and editing. The authors have read and approved the published version of the manuscript.

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DATA AVAILABILITY

The data in this study are available upon reasonable request from the corresponding author.

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