RESEARCH ARTICLE **Open Access**

Gema Lingkungan Kesehatan
Vol. 24, No. 2 (2026), pp 277-286
e-ISSN 2407-8948 p-ISSN 16933761
doi: https://doi.org/10.36568/gelinkes.v24i2.525 *Journal Homepage: https://gelinkes.poltekkesdepkes-sby.ac.id/*

The Hepatoprotective Role of Ethanolic Mangosteen Peel Extract (Garcinia mangostana L.) on MDA, TNF-α, E-Selectin, and SGPT Levels in Isoniazid-Induced Liver Fibrosis Wistar Rats

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Isoniazid is a first-line anti-tuberculosis drug known to cause drug-induced liver injury (DILI) through oxidative stress and inflammatory mechanisms that contribute to the development of liver fibrosis. Mangosteen peel (*Garcinia mangostana* L.) contains xanthone compounds with antioxidant and anti-inflammatory properties, making it a potential hepatoprotective agent. This study aimed to determine the role of ethanol extract of mangosteen peel on malondialdehyde (MDA) levels, tumor necrosis factor-α (TNF-α) expression, E-selectin expression, and SGPT levels in the liver of isoniazid-induced fibrosis Wistar rats. This experimental study used a *post-test only control group design*. Twenty-eight male Wistar rats were randomly divided into four groups: negative control group, positive control group (isoniazid 50 mg/kgBW/day), treatment group 1 (isoniazid + mangosteen peel ethanol extract 250 mg/kgBW/day), and treatment group 2 (isoniazid + mangosteen peel ethanol extract 500 mg/kgBW/day) for 30 days. MDA and SGPT levels were measured using spectrophotometry, while TNF-α and E-selectin expression were assessed using immunohistochemistry. Administration of mangosteen peel ethanol extract significantly reduced MDA and SGPT levels and decreased TNF-α and E-selectin expression compared to the positive control group. The most significant reduction was observed in the group receiving the extract dose of 500 mg/kgBW. Mangosteen peel ethanol extract reduces MDA, TNF-α, E-selectin, and SGPT levels in isoniazid-induced Wistar rats. These findings demonstrate its hepatoprotective potential in a preclinical setting, further translational and clinical studies are warranted to evaluate its efficacy and safety in humans as potential hepatoprotective agent.

Keywords: E-selectin, Isoniazid, Mangosteen Peel, MDA, SGPT, TNF-α

INTRODUCTION

Tuberculosis remains a leading cause of global morbidity and mortality, particularly in high-burden countries like Indonesia (WHO, 2024). While Isoniazid is a cornerstone of first-line therapy, its clinical utility is often compromised by drug-induced liver injury (DILI) (Wang et al., 2022). This hepatotoxicity is primarily driven by oxidative stress, mitochondrial dysfunction, and inflammatory responses, which can progress to hepatic fibrosis if left uncontrolled. Biomarkers such as serum glutamate-pyruvate transaminase (SGPT), malondialdehyde (MDA), tumor necrosis factor-alpha (TNF-α), and E-selectin are critical indicators of hepatocellular damage, lipid peroxidation, inflammation, and endothelial activation in this process. In response to these challenges, natural products with potent antioxidant and anti-inflammatory properties have emerged as promising adjunctive strategies. The mangosteen peel (Garcinia mangostana L.) is particularly rich in bioactive xanthones and flavonoids known for their free radical scavenging and hepatoprotective effects (Abate et al., 2022). While previous research has highlighted the general benefits of mangosteen in reducing oxidative tissue injury, its specific role in mitigating the chronic progression of isoniazid-induced liver fibrosis remains insufficiently explored (Rusman et al., 2021). Therefore, this study aimed to evaluate the protective effects of ethanolic mangosteen peel extract on hepatic MDA, TNF-

α expression, E-selectin expression, and SGPT levels in a Wistar rat model of isoniazid-induced liver fibrosis. By analyzing these specific biochemical and inflammatory markers, this research seeks to clarify the underlying protective mechanisms, ranging from the suppression of oxidative stress to the modulation of vascular activation pathways that prevent structural liver damage.

Our study addresses a critical research gap by evaluating E-selectin, a key adhesion molecule that recruits circulating leukocytes into the hepatic parenchyma, thereby perpetuating inflammation and early fibrogenesis. By mapping E-selectin alongside MDA and TNF-α, this research uniquely bridges the gap between oxidative triggers and the vascular response, establishing whether mangosteen xanthones mitigate drug-induced liver injury not only through direct hepatocyte protection but also by stabilizing the vascular endothelium. This investigation of the vascular activation pathway represents a unique scientific contribution, demonstrating how the extract attenuates endothelial dysfunction and leukocyte adhesion beyond general inflammation. Furthermore, by utilizing a chronic fibrosis model rather than an acute injury model, these findings provide a robust preclinical foundation and offer significant clinical potential for mangosteen extract as a complementary therapy to improve the safety profile and prognosis of patients undergoing long-term anti-tuberculosis treatment.

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METHODS

Research Type

This study was an experimental laboratory study using a post-test only control group design to analyze This study was an experimental laboratory study using a post-test only control group design to analyze The Hepatoprotective Role of Ethanolic Mangosteen Peel Extract (Garcinia mangostana L.) on MDA, TNF-α, E-Selectin, and SGPT Levels in Isoniazid-Induced Liver Fibrosis Wistar Rats.

Population and Study Subjects

Twenty-eight healthy male Wistar rats aged 3–4 months and weighing 170–200 g were randomly allocated into four groups (n = 7 per group). The minimum sample size for this study was determined using the Federer formula (t − 1) (n − 1) > 15. Where: t: represents the number of experimental groups (t = 4). n: represents the number of samples per group. Based on the formula above, the minimum sample size for each treatment group is 6 subjects. Thus, the total minimum sample required is 24 subjects. This study was conducted using 4 treatment groups, with each group consisting of 7 subjects, resulting in a total sample size of 28 subjects. Negative control group receiving distilled water while positive control group receiving isoniazid 50 mg/kg body weight/day, treatment group 1 receiving isoniazid plus ethanolic mangosteen peel extract 250 mg/kg body weight/day, and treatment group 2 receiving isoniazid plus ethanolic mangosteen peel extract 500 mg/kg body weight/day. All interventions were administered daily for 30 consecutive days under standardized housing and feeding conditions.

Research Variables

The variables in this study were classified into independent and dependent variables, which were analyzed to evaluate the hepatoprotective effects of the administered treatment. The independent variable utilized in this research was the ethanolic extract of *Garcinia mangostana* L. peel, which was orally administered to Wistar rat models of liver fibrosis induced by isoniazid. Meanwhile, the investigated dependent variables encompassed indicators of oxidative stress, inflammation, endothelial damage, and liver function impairment, each evaluated with specific parameters and units. The concentration of malondialdehyde (MDA), serving as a biomarker for lipid peroxidation and oxidative stress, was measured using a spectrophotometric method and expressed in nanomoles per milliliter (nmol/mL). To assess the degree of hepatocyte injury, SGPT levels were determined and reported in Units per Liter (U/L). Furthermore, the tissue expressions of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α) and the cell adhesion molecule E-selectin in the liver were evaluated via immunohistochemistry (IHC). The quantification of both protein expressions was evaluated using an ordinal scoring system (IHC score on a 0–4 scale), determined based on the percentage of hepatocytes or endothelial cells demonstrating positive staining.

Statistical Analysis

Data were analyzed using statistical software SPSS ver 25.0. Normality and Homogenity Test was assessed prior to comparative analysis. Parametric data were analyzed using One-Way Analysis of Variance (ANOVA) followed by Tukey's post hoc test, while non-parametric data were analyzed using the Kruskal–Wallis test followed by the Mann–Whitney post hoc test. A p-value of <0.05 was considered statistically significant.

Ethics

This study was conducted in accordance with the ethical guidelines for animal experimentation and received formal approval from the Research Ethics Committee of Dr. Moewardi General Hospital under reference number: 1.725/VIII/HREC/2025. All efforts were made to minimize animal suffering and to reduce the number of animals used. The procedures followed institutional and national guidelines for the care and use of laboratory animals

RESULT AND DISCUSSION

Result

Administration of isoniazid significantly increased hepatic MDA levels, TNF-α expression, Eselectin expression, and SGPT levels in the positive control group compared with the negative control group, indicating marked oxidative stress, endothelial dysfunction, and hepatocellular injury. Histopathological examination also demonstrated fibrotic changes in liver tissue following isoniazid exposure. These findings confirm the hepatotoxic potential of isoniazid and support previous evidence that prolonged exposure to this drug induces reactive oxygen species formation, mitochondrial dysfunction, and inflammatory cascades that contribute to liver fibrosis.

Treatment with ethanolic mangosteen peel extract significantly reduced all measured biomarkers compared with the positive control group. Both treatment doses showed protective effects; however, the 500 mg/kg body weight dose produced the greatest reduction in MDA, TNF-α, E-selectin, and SGPT levels, suggesting a dose-dependent response. Histological findings also showed attenuation of hepatic fibrosis and improved liver architecture in treated groups. These results indicate that mangosteen peel extract effectively mitigates oxidative and inflammatory liver damage induced by isoniazid.

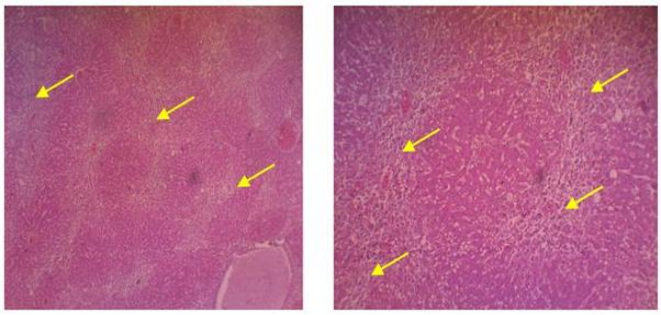

Figure 1.
Fibrosis in Rat Liver Tissue with INH Dose of 50 mg/kg BW/day (40x and 100x Magnification)
Description: The rat liver tissue shows severe fibrosis (presence of numerous bridges and fibrous tissue septa indicated by arrows).

We have clarified that the Shapiro-Wilk test was used to confirm normality given our sample size (n=7 per group). For data that followed a normal distribution and met the homogeneity of variance assumption, One-Way ANOVA followed by Tukey's post-hoc test was applied. For any non-normally distributed data, the Kruskal-Wallis test followed by Mann-Whitney U tests was utilized. Differences in MDA levels across treatment groups receiving the Ethanolic Extract of Mangosteen Peel (Garcinia mangostana L.) at week 5 were analyzed using One-Way ANOVA, followed by Post-Hoc tests, as the research utilized ratio-scale data. Since MDA levels constitute numerical data, they must fulfill parametric test assumptions, specifically normality and homogeneity. Consequently, Normality and Homogeneity tests were performed. The results are as follows:

Table 1
Liver Tissue MDA Levels Across Experimental Groups (nmol/ml)

Group	Mean MDA Level (nmol/ml)
Negative Control (NC)	1,42
Positive Control (PC)	9,96
Treatment 1 (P1)	5,11
Treatment 2 (P2)	3,13

Table 2.
Normality Test for MDA Levels

Variable	Groups	Shapiro-Wilk			Description
		Statistic	df	p-value	
MDA	NC	.945	7	.752	Normal
	PC	.987	7	.985	Normal
	P1	.988	8	.991	Normal
	P2	.898	7	.316	Normal

Statistical analysis indicated that the MDA variable met the assumptions for parametric testing. Based on the normality test (Shapiro-Wilk) for all variables in each treatment group yielded $p > 0.05$, signifying a normal data distribution. The homogeneity test (Levene's test) results shown in Table 3 also yielded $p > 0.05$, indicating that the variance across treatment groups was homogeneous. With these criteria satisfied, further statistical analysis proceeded with parametric tests.

Table 3.
Homogeneity Test for MDA Levels

Variable	Group	*Levene's Test*	
		P-value	Description
MDA	NC	.356	Homogen
	PC		
	P1		
	P2		

ANOVA was utilized to evaluate the influence of Ethanolic Mangosteen Peel Extract administration on MDA levels relative to the control group and to assess its specific therapeutic impact. These results are presented in Table 4.

Table 4.
One-Way ANOVA Results for MDA Levels

	Sum of Squares	df	Mean Square	F	p-value
Between Groups	296.789	3	98.930	478.585	.000
Within Groups	5.375	26	.207		
Total	302.164	29			

The statistical test yielded p = 0.00 (p < 0.05), indicating a significant difference in MDA levels among the various Ethanolic Mangosteen Peel Extract treatment groups at week 5 simultaneously. To determine specific group differences, data were analyzed using the Tukey HSD Post-Hoc test.

Table 5.
Tukey HSD Post-Hoc Test Results for MDA Levels

MDA		P-value
Group	Group	
NC	PC	.000
NC	P1	.000
NC	P2	.000
PC	NC	.000
PC	P1	.000
PC	P2	.000
P1	NC	.000
P1	PC	.000
P1	P2	.000
P2	NC	.000
P2	PC	.000
P2	P1	.000

Based on Table 5, mean MDA level comparisons in each group showed significant differences (p < 0.05). There was a significant difference between the 250 mg/kgBW and 500 mg/kgBW dose groups, with means of 5.11 nmol/ml and 3.13 nmol/ml, respectively. This demonstrates that the 500 mg/kgBW dose reduces MDA levels more effectively. However, the 250 mg/kgBW dose remained effective, as it still showed significant differences compared to the positive control (mean: 9.96 nmol/ml vs 5.11 nmol/ml).

The reduction in MDA levels suggests inhibition of lipid peroxidation and improved antioxidant defense. Mangosteen peel is rich in xanthones, particularly alpha-mangostin and gamma-mangostin, which have been reported to possess strong free radical scavenging properties. The decrease in TNF-α expression further indicates suppression of pro-inflammatory cytokine signaling, while lower E-selectin expression reflects reduced endothelial activation and leukocyte adhesion, both important processes in hepatic inflammation and fibrogenesis. These mechanisms are consistent with previous studies demonstrating the antioxidant, anti-inflammatory, and hepatoprotective properties of mangosteen-derived compounds.

Differences in TNF-α expression across Ethanolic Mangosteen Peel Extract treatment groups at week 5 were analyzed using the Kruskal-Wallis test due to the ordinal nature of the data. Since TNF-α expression data are ordinal, normality and homogeneity tests were not required. The Kruskal-Wallis results are shown in Table 7 below.

Table 6.
Mean Liver Tissue TNF-α Across Experimental Groups

Group	Mean TNF-α Score ± SD
Negative Control (NC)	1,0 ± 0,0
Positive Control (PC)	3,1429 ± 0,69007
Treatment 1 (P1)	2,875 ± 0,35355
Treatment 2 (P2)	1,7143 ± 0,48795

Table 7.
Kruskal-Wallis Test Results for TNF-α Expression

Treatment Group	Mean Rank	*P-value*
Negative Control (NC)	5.00	.000
Positive Control (PC)	22.57	
250 mg/kgBW Dose (P1)	20.88	
500 mg/kgBW Dose (P2)	10.71	

The statistical test yielded p = 0.00 (p < 0.05), indicating significant simultaneous differences in TNF-α expression among the Ethanolic Mangosteen Peel Extract treatment groups at week 5. To identify specific group differences, the Mann-Whitney Post-Hoc test was applied.

Table 8.
Mann-Whitney Post-Hoc Test Results for TNF-α Expression

TNF-α		*P-value*
Group	Group	
NC	PC	0.001
NC	P1	0.000
NC	P2	0.026
PC	NC	0.001
PC	P1	0.463
PC	P2	0.002
P1	NC	0.000
P1	PC	0.463
P1	P2	0.001
P2	NC	0.026
P2	PC	0.002
P2	P1	0.001

Based on Table 8, comparison of mean TNF-α expression across groups showed significant differences (p < 0.05). The 500 mg/kgBW dose significantly reduced TNF-α expression more effectively than the 250 mg/kgBW

dose. The 250 mg/kgBW dose was not sufficiently effective, as it failed to show a significant difference compared to the positive control (p = 0.463).

The Kruskal-Wallis test was used to evaluate E-Selectin expression differences across groups at week 5 due to the use of ordinal data.

Table 9.
Mean Liver Tissue E-Selectin Expression Scores Across Experimental Groups

Group	Mean E-Selectin Score ± SD
Negative Control (NC)	1,5714 ± 0,51716
Positive Control (PC)	1,8571 ± 0,59045
Treatment 1 (P1)	2,00 ± 0,72435
Treatment 2 (P2)	1,00 ± 0,43611

Tabel 10.
Kruskal-Wallis Test Results for E-Selectin Expression

Group	Mean Rank	*P-value*
Negative Control (NC)	14.00	.001
Positive Control (PC)	19.36	
Treatment 1 (P1)	21.50	
Treatment 2 (P2)	6.50	

The statistical result (p = 0.01) indicates significant simultaneous differences across groups. Mann-Whitney Post-Hoc test results are displayed in Table 10.

Table 11.
Mann-Whitney Post-Hoc Test Results for E-Selectin Expression

E-Selectin		*P-value*
Groups	Groups	
NC	PC	0.281
NC	P1	0.105
NC	P2	0.121
PC	NC	0.281
PC	P1	0.694
PC	P2	0.004
P1	NC	0.105
P1	PC	0.694
P1	P2	0.000
P2	NC	0.121
P2	PC	0.004
P2	P1	0.000

Administration of Ethanolic Mangosteen Peel Extract at 500 mg/kgBW (P2) reduced E-selectin expression more effectively than both P1 (250 mg/kgBW) and the positive control. P1 was found to be less effective, as it showed no significant difference compared to the positive control.

We acknowledge that while the higher dose of Ethanolic Mangosteen Peel Extract (500 mg/kgBW) showed a clear protective effect, the lower dose of 250 mg/kgBW (P1) was not sufficient to significantly reduce E-selectin expression. This observation aligns with our statistical analysis, which showed no significant difference (p = 0.694) between the P1 group and the positive control. This suggest that the anti-inflammatory mechanism of Ethanolic Mangosteen Peel Extract on E-selectin may be dose-dependent, with a specific threshold required to modulate this adhesion molecule.

Increased expression of E-selectin facilitates the attachment and migration of leukocytes to the endothelium, marking the initial stage of the vascular inflammatory process. Therefore, the reduction of TNF-α levels due to xanthone administration has the potential to suppress E-selectin expression in endothelial cells, thereby reducing monocyte adhesion and improving endothelial function. This mechanism demonstrates that xanthone plays a role in inhibiting endothelial inflammation through the downregulation of inflammatory mediators and adhesion molecules.

Differences in SGPT levels at week 5 were evaluated using One-Way ANOVA, followed by Post-Hoc analysis.

Table 12.
Liver Tissue SGPT Levels Across Experimental Groups (U/L)

Group	Mean SGPT Score ± SD
Negative Control (NC)	18,44 ± 0,0
Positive Control (PC)	32,28 ± 0,69007
Treatment 1 (P1)	28,52 ± 0,35355
Treatment 2 (P2)	20,94 ± 0,48795

Table 13.
Normality Test for SGPT Levels

Variable	Groups	*Shapiro-Wilk*			Description
		Statistic	*df*	*P-value*	
SGPT	NC	.859	8	0.118	Normal
	PC	.859	7	0.149	Normal
	P1	.920	8	0.434	Normal
	P2	.818	7	0.061	Normal

Analysis confirmed that SGPT variables satisfied parametric testing assumptions. Table 10 shows the homogeneity test yielded p = 0.285, indicating the variance is homogeneous.

Table 14.
Homogeneity Test for SGPT Levels

Variable	Groups	*Levene's Test*	
		P-value	Description
SGPT	NC	0.285	Homogen
	NP		
	P1		
	P2		

Table 15.
One-Way ANOVA Results for SGPT Levels

	Sum of Squares	df	Mean Square	F	p-value

Between Groups	1738.788	3	579.596	1716.765	.000
Within Groups	8.778	26	.338		
Total	1747.566	29			

The results yielded p = 0.00 (p < 0.05), indicating significant differences in SGPT levels across groups simultaneously. Tukey HSD post-Hoc analysis determined specific group differences.

Table 16.
Tukey HSD Post-Hoc Test Results for SGPT Levels

SGPT		*P-value*
Group	Group	
NC	PC	.000
NC	P1	.000
NC	P2	.000
PC	NC	.000
PC	P1	.000
PC	P2	.000
P1	NC	.000
P1	PC	.000
P1	P2	.000
P2	NC	.000
P2	PC	.000
P2	P1	.000

Significant differences were observed between the 250 mg/kgBW and 500 mg/kgBW dose groups, with means of 28.52 U/L and 20.94 U/L, respectively. This suggests that the 500 mg/kgBW dose is more effective in lowering SGPT levels. However, the 250 mg/kgBW dose remained effective, as it differed significantly from the positive control (38.28 U/L vs 20.94 U/L).

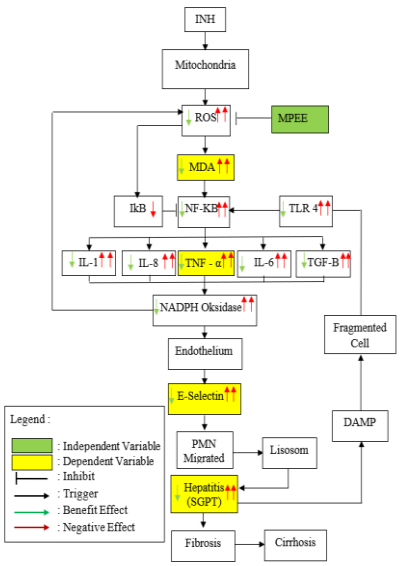

Figure 2: Pathophysiological Pathway

The reduction in SGPT levels in treatment groups suggests preservation of hepatocyte membrane integrity and decreased cellular injury. Since SGPT is a sensitive marker of hepatocellular damage, its improvement strengthens the evidence that ethanolic mangosteen peel extract has clinically relevant hepatoprotective potential. Similar findings have been reported in experimental models of toxin-induced liver injury, where mangosteen extract reduced transaminase elevation and improved tissue histology. Furthermore, we have clarified our terminology throughout the text. Instead of describing the P1 group as improved in terms of E-selectin, we now more accurately state that it showed no statistically significant reduction compared to the positive control. This adjustment ensures that our conclusions regarding the protective role of Ethanolic Mangosteen Peel Extract are precisely attributed to the effective dose (500 mg/kgBW) while acknowledging the limitations of the lower dosage in this specific pathway. We believe this more transparent interpretation strengthens the scientific integrity of our report

Ethanolic Mangosteen Peel Extract, particularly its xanthone compounds such as α-mangostin and γ-mangostin, demonstrates hepatoprotective effects through anti-inflammatory and antioxidant mechanisms. These effects are reflected by reductions in TNF-α, MDA, E-selectin, and SGPT levels in various models of liver injury. Fu et al. reported that α-mangostin exerted hepatoprotective activity in a paracetamol-induced acute liver injury model by suppressing the expression of TNF-α, IL-6, IL-1β, and inhibiting the activation of IκBα and NF-κBp65 signaling pathways (Fu et al., 2018).

TNF-α is recognized as a major inflammatory biomarker in both acute and chronic liver diseases and plays a central role in hepatic injury and tissue repair processes (Zolfaghari et al., 2023). Persistent TNF-α stimulation promotes inflammatory responses and increases reactive oxygen species (ROS) production, thereby aggravating oxidative stress and cellular damage. The α-mangostin, γ-mangostin, and flavonoid compounds contained in Ethanolic Mangosteen Peel Extract exhibit anti-inflammatory activity by inhibiting the COX-2 pathway and reducing prostaglandin E_2 (PGE_2) production. These compounds also modulate immune responses through T-cell activation, IFN-γ production, and regulation of monocyte and macrophage activity, ultimately suppressing TNF-α expression and other pro-inflammatory mediators (Herdiani et al., 2023).

In the present study, administration of Ethanolic Mangosteen Peel Extract at a dose of 500 mg/kgBW/day significantly reduced TNF-α expression and MDA levels. These findings are consistent with the study by Tatiya-Aphiradee et al., which demonstrated that Garcinia mangostana ethanolic extract improved inflammatory conditions in ulcerative colitis models by reducing TNF-α levels (Tatiya-aphiradee, Chatuphonprasert and Jarukamjorn, 2021). Similarly, Majdalawieh et al. reported that α-mangostin inhibited the release of IL-8, IL-1β, IL-6, and TNF-α through suppression of the Toll-like receptor 4-mediated TAK1–NF-κB signaling pathway (Majdalawieh, Khatib and Terro, 2025).

Previous studies also showed that α- and γ-mangostin reduced the expression of inflammatory genes

induced by lipopolysaccharide, including TNF-α, IL-1, IL-6, IL-8, monocyte chemoattractant protein-1, and Toll-like receptor-2 (Kresnoadi, Hadisoesanto and Prabowo, 2016). Herdiani et al. further demonstrated that mangosteen peel extract effectively reduced TNF-α expression in streptozotocin-induced rats at a dose of 600 mg/kgBW (Herdiani et al., 2023).

Isoniazid-induced hepatotoxicity is known to cause mitochondrial injury, resulting in increased MDA production as a marker of oxidative stress (Shrestha et al., 2020).

Elevated MDA levels activate NF-κBp65 through dissociation from IκB, subsequently enhancing the expression of inflammatory cytokines such as IL-6, TNF-α, and TGF-β1 (Arsana and Ayu Juliasih, 2023). TNF-α further contributes to endothelial dysfunction through ROS generation mediated by NADPH oxidase activation (Abdolvand et al., 2023). Pramana et al. demonstrated that mangosteen peel ethanolic extract attenuated isoniazid-induced liver injury by reducing fibrosis, decreasing TGF-β1 expression, and improving liver function parameters (Pramana et al., 2021).

Ethanolic Mangosteen Peel Extract administration in this study also significantly decreased E-selectin expression at a dose of 500 mg/kgBW/day. This effect is likely associated with inhibition of the NF-κB signaling pathway, which regulates the transcription of inflammatory mediators, including E-selectin. Jiang et al. reported that xanthones reduced TNF-α levels and inhibited monocyte adhesion to oxidized LDL-induced endothelial cells, thereby suppressing E-selectin expression and improving endothelial function (Jiang et al., 2003). Consistently, Bai et al. demonstrated that α-mangostin reduced ROS and MDA levels, inhibited apoptosis, improved endothelial integrity, and attenuated fibrosis in diabetic cardiomyopathy models (Bai et al., 2025).

Furthermore, Ethanolic Mangosteen Peel Extract administration at doses of 250 mg/kgBW/day and 500 mg/kgBW/day significantly reduced SGPT levels compared with the positive control group. These findings are in accordance with the study by Zonouz et al., which demonstrated that Ethanolic Mangosteen Peel Extract at a dose of 500 mg/kgBW/day for 35 days reduced SGPT levels, TGF-β1 expression, and hepatic fibrosis in isoniazid-induced hepatotoxicity models (Zonouz, Rahbardar and Hosseinzadeh, 2023).

Overall, this study demonstrates that Ethanolic Mangosteen Peel Extract exerts protective effects against isoniazid-induced liver fibrosis through modulation of oxidative stress, inflammatory pathways, and endothelial responses. These findings are important because hepatotoxicity remains a major challenge during anti-tuberculosis treatment. Therefore, mangosteen peel extract may serve as a promising adjunctive therapy to reduce liver injury during isoniazid use. Nevertheless, further studies in humans are required to determine optimal dosing, long-term safety, bioavailability, and clinical efficacy before routine therapeutic application can be recommended.

Despite the promising findings, several limitations of this study should be acknowledged. First, the mangosteen peel extract used was not standardized for specific active compounds, such as alpha-mangostin, which may affect the reproducibility of the results. Second, although general liver architecture was observed, the absence of fibrosis-specific staining (e.g., Sirius Red or Masson's Trichrome) and detailed histopathological scoring limits the depth of the structural validation. Third, the relatively small sample size and short-term observation period may not fully capture the long-term effects or rare adverse outcomes associated with the extract. Furthermore, this study did not include a formal toxicity evaluation or an in-depth analysis of molecular signaling pathways, leaving the precise mechanistic actions and safety profile partially speculative. Future research incorporating larger cohorts, standardized extracts, and clinical pharmacokinetic drug-interaction studies is required to bridge these translational gaps.

ACKNOWLEDGMENTS

The authors would like to express their sincere gratitude to the supervisors and academic staff of the Internal Medicine Residency Program, Faculty of Medicine, Universitas Sebelas Maret, for their invaluable guidance, support, and constructive feedback throughout this study. Special appreciation is extended to the Department of Anatomical Pathology and all laboratory personnel who assisted in specimen processing, immunohistochemical analysis, and data collection. The authors also gratefully acknowledge the staff of the Animal Research Facility, Faculty of Medicine, Universitas Gadjah Mada, for their assistance in animal care, maintenance, and experimental procedures. Their technical support was essential to the successful completion of this research.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this study. The authors have no financial, personal, or professional relationships that could have inappropriately influenced the design, conduct, analysis, or interpretation of the findings.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All research activities were supported institutionally through facilities and resources provided by Universitas Sebelas Maret and collaborating laboratories involved in the study.

CONCLUSIONS

Ethanolic mangosteen peel extract (*Garcinia mangostana* L.) demonstrated significant hepatoprotective effects in a Wistar rat model of isoniazid-induced liver fibrosis. Administration of the extract significantly reduced

hepatic malondialdehyde (MDA) levels, TNF-α expression, E-selectin expression, and SGPT levels, with the strongest effects observed at the dose of 500 mg/kg body weight. These findings indicate that mangosteen peel extract attenuates oxidative stress, inflammatory responses, endothelial activation, and hepatocellular injury associated with isoniazid exposure.

The study suggests that mangosteen peel extract has potential as a complementary hepatoprotective agent during anti-tuberculosis therapy. Future studies should focus on identifying active compounds, clarifying molecular mechanisms, evaluating long-term safety, and conducting clinical trials to determine its therapeutic applicability in humans.

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