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Collagen-1 Suppression and Fibrosis Prevention by Garcinia Mangostana L. Rind Extract: A Study on NF-κB and TGF-β1 Pathway Inhibition

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ABSTRACT

Background: Liver fibrosis is a progressive disease characterized by excessive deposition of extracellular matrix components, such as collagen-1, resulting in tissue scarring and impaired liver function. Activation of the NF-κB and TGF-β1 pathways plays a central role in fibrogenesis. Garcinia mangostana L. rind extract (GMREE) has demonstrated potential anti-fibrotic and anti-inflammatory effects in previous studies. This research investigates the ability of GMREE to suppress collagen-1 production and prevent liver fibrosis by inhibiting the NF-κB and TGF-β1 pathways in an isoniazid-induced fibrosis model in Wistar rats.

Methods: Thirty-two male Wistar rats were divided into four groups: a control group, a positive control group treated with isoniazid, and two treatment groups receiving GMREE at doses of 250 mg/kg/day and 500 mg/kg/day alongside isoniazid. Serum levels of SGPT were measured as a marker of liver injury. Liver tissues were analyzed for collagen-1 deposition, and immunohistochemical assays were performed to assess NF-κB and TGF-β1 expression.

Results: GMREE treatment significantly reduced serum SGPT levels ($p < 0.001$) and suppressed liver fibrosis, as evidenced by decreased collagen-1 deposition in the liver tissues. Immunohistochemical analysis revealed a significant reduction in NF-κB and TGF-β1 expression in the treatment groups compared to the positive control group ($p < 0.05$), with the 500 mg/kg/day dose showing the greatest inhibitory effects on these key fibrotic markers.

Conclusion: Garcinia mangostana L. rind extract demonstrates strong anti-fibrotic properties by downregulating collagen-1 production and inhibiting the NF-κB and TGF-β1 pathways. These findings highlight GMREE as a potential therapeutic agent for the prevention and management of liver fibrosis, particularly in cases of drug-induced liver injury.

Keywords: Garcinia mangostana L., liver fibrosis, collagen-1, NF-κB, TGF-β1, isoniazid, hepatoprotection

1. INTRODUCTION

Liver fibrosis is a critical health issue that arises from chronic liver injury due to viral infections, toxins, alcohol, or drug-induced hepatotoxicity(Barinda et al., 2022). Fibrosis occurs when excessive deposition of extracellular matrix proteins, particularly collagen-1, leads to the distortion of normal liver architecture, eventually progressing to cirrhosis or liver failure if untreated(Pramana et al., 2019). The pathogenesis of liver fibrosis is primarily driven by the activation of hepatic stellate cells (HSCs), which produce large amounts of collagen in response to inflammatory and oxidative stress signals.

Two key molecular pathways involved in the activation of HSCs are the nuclear factor-kappa B (NF-κB) and transforming growth factor-beta 1 (TGF-β1) pathways(Chiu et al., 2020). NF-κB, a transcription factor, is

activated by pro-inflammatory stimuli, while TGF-β1 is a potent fibrogenic cytokine that promotes extracellular matrix production, including collagen-1(Siriwattanasatorn et al., 2020). Inhibition of these pathways is critical for preventing the progression of liver fibrosis.

Garcinia mangostana L., commonly known as mangosteen, is a tropical fruit rich in xanthones, which have antioxidant and anti-inflammatory properties(Anam et al., 2023). Previous studies have indicated that extracts from the rind of mangosteen exhibit protective effects in various models of tissue injury(Swastini et al., 2021). However, limited research has been conducted to explore the role of Garcinia mangostana L. rind extract (GMREE) in modulating the NF-κB and TGF-β1 pathways, particularly in the context of liver fibrosis(Ansori et al., 2020).

This study aims to investigate the anti-fibrotic potential of GMREE by evaluating its effects on collagen-1 production and the NF-κB and TGF-β1 pathways in a model of isoniazid-induced liver fibrosis in Wistar rats.

2. MATERIALS AND METHODS

2.1. Animal Model

Thirty-two male Wistar rats, weighing between 170-200 grams, were obtained from the Veterinary Faculty of Gadjah Mada University. The rats were housed under standard laboratory conditions with a 12-hour light/dark cycle and free access to food and water. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret (Approval No.: [insert number]).

2.2. Experimental Design

The rats were randomly divided into four groups (n = 8 per group):

- **Control Group (KN)**: Received normal saline (NaCl 0.9%) intraperitoneally for 35 days.
- **Positive Control Group (KP)**: Received isoniazid (80 mg/kg/day) intraperitoneally for 35 days.
- **Treatment Group 1 (P1)**: Received isoniazid (80 mg/kg/day) and GMREE at 250 mg/kg/day intraperitoneally for 35 days.
- **Treatment Group 2 (P2)**: Received isoniazid (80 mg/kg/day) and GMREE at 500 mg/kg/day intraperitoneally for 35 days.

2.3. Preparation of Garcinia Mangostana L. Rind Extract

The rind of Garcinia mangostana L. was collected, dried, and ground into a fine powder. The powdered rind was subjected to ethanol extraction using a Soxhlet apparatus. The ethanol extract was concentrated using a rotary evaporator and stored at 4°C. The extract was dissolved in saline to the appropriate concentrations for administration to the treatment groups.

2.4. Biochemical and Histopathological Analysis

- **Serum SGPT Measurement**: Blood samples were collected on day 35, and serum SGPT levels were measured using an automated biochemical analyzer to assess liver damage.
- **Histopathological Analysis**: Liver tissues were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with Hematoxylin and Eosin (H&E) and Masson's Trichrome to evaluate liver fibrosis and collagen-1 deposition.
- **Immunohistochemistry**: Liver sections were stained for NF-κB, TGF-β1, and collagen-1 using specific antibodies, and staining was visualized under a light microscope.

2.5. Statistical Analysis

Statistical analysis was performed using SPSS version 25.0. Data were expressed as mean ± standard deviation (SD). Group differences were analyzed using one-way ANOVA followed by Tukey's post-hoc test for multiple comparisons. A p-value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Serum SGPT Levels

The positive control group (KP) showed significantly elevated serum SGPT levels compared to the control group (KN), confirming liver injury induced by isoniazid ($p < 0.001$). Both GMREE-treated groups (P1 and P2) exhibited significantly lower SGPT levels compared to the KP group, with the greatest reduction observed in the P2 group (500 mg/kg/day) ($p < 0.001$).

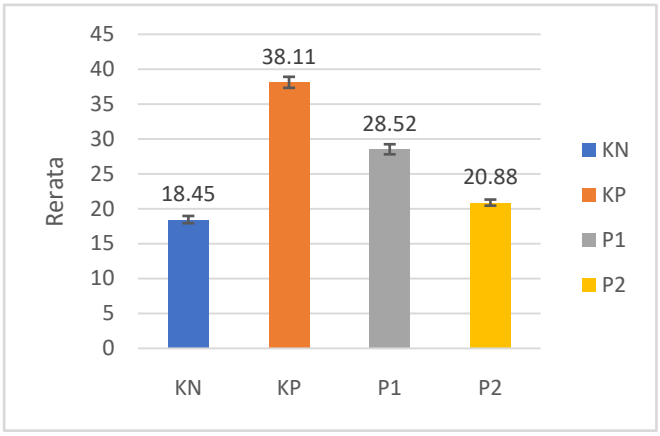

Fig 3.1. Bar Chart Comparison of SGPT 'Mean Rank' Between Treatment Groups

3.2. Collagen-1 Expression

Histopathological analysis showed marked collagen-1 deposition in the liver tissues of the positive control group (KP), indicating significant fibrosis. The GMREE-treated groups showed a substantial reduction in collagen-1 expression, with the highest dose (P2) demonstrating the greatest reduction in collagen-1 levels ($p = 0.020$). This suggests that GMREE effectively suppresses collagen-1 production in a dose-dependent manner, preventing the excessive accumulation of extracellular matrix in the liver.

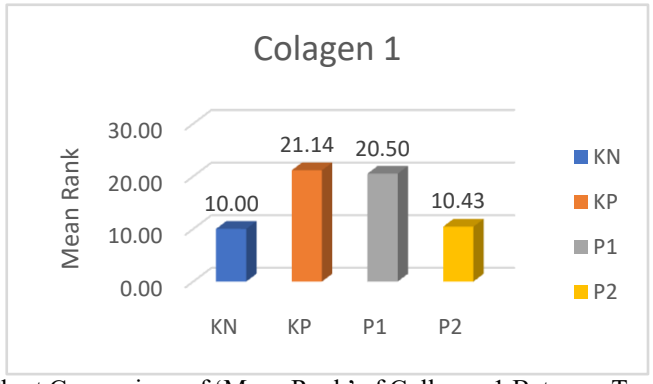

Fig 3. 2 Bar Chart Comparison of 'Mean Rank' of Collagen 1 Between Treatment Groups

3.3. NF-κB Expression

Immunohistochemical staining revealed increased NF-κB expression in the positive control group (KP) compared to the control group (KN) ($p < 0.001$). Treatment with GMREE significantly reduced NF-κB expression in both treatment groups, with the greatest reduction observed in the P2 group ($p = 0.030$), suggesting that GMREE inhibits NF-κB-mediated inflammatory responses that contribute to fibrogenesis.

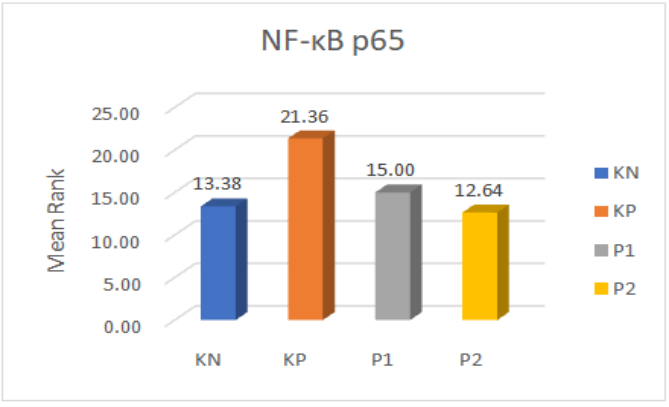

Fig 3.3. Bar Chart Comparison of 'Mean Rank' of NF-κBBetween Treatment Groups

3.4. TGF-β1 Expression

TGF-β1 expression was significantly elevated in the positive control group (KP), consistent with its role as a key fibrogenic cytokine. The GMREE-treated groups (P1 and P2) demonstrated a dose-dependent reduction in TGF-β1 expression, with the P2 group showing the most significant reduction ($p = 0.012$). This indicates that GMREE disrupts TGF-β1 signaling, thereby preventing the activation of hepatic stellate cells and the subsequent production of collagen.

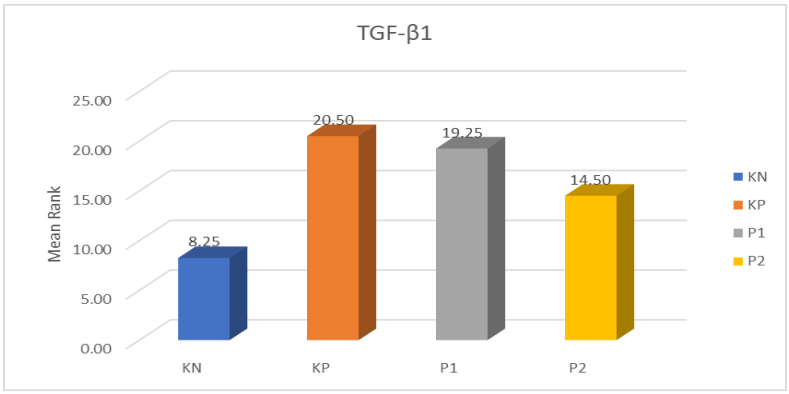

Fig 3.4. Bar Chart Comparison of 'Mean Rank' TGF-β1 Between Treatment Groups.

4. DISCUSSION

4.1. Collagen-1 Suppression

Collagen-1 is the most abundant extracellular matrix protein in fibrotic liver tissue and serves as a key indicator of fibrosis progression(Pramana, Wasita, Widyaningsih, et al., 2021). The overproduction of collagen-1 by activated hepatic stellate cells (HSCs) contributes to the thickening and scarring of liver tissue, ultimately impairing normal liver function and leading to cirrhosis(Ansori et al., 2021). In liver fibrosis, collagen-1 deposition results in excessive extracellular matrix accumulation, disrupting the liver's structural integrity and function.

In this study, we observed significant collagen-1 overexpression in the positive control group (KP) that was treated with isoniazid alone(El-Agamy et al., 2020). This increase confirms that isoniazid-induced liver injury drives the fibrotic response through the stimulation of collagen production(Pramana, Wasita, Vitri, et al., 2021). However, treatment with Garcinia mangostana L. rind extract (GMREE) resulted in a notable reduction in collagen-1 expression in a dose-dependent manner(Kharaeva et al., 2022). The group treated with 500 mg/kg/day of GMREE (P2) exhibited the most substantial reduction in collagen-1 levels, with the results approaching those observed in the negative control group (KN).

This reduction in collagen-1 highlights GMREE's potential to directly inhibit the activation of HSCs, thereby suppressing fibrotic matrix formation(Kharisma et al., 2023). It also suggests that GMREE may promote the resolution of fibrosis by enhancing matrix degradation or limiting collagen production(Nishanthi et al., 2019). These findings are significant, as they demonstrate that GMREE can prevent or mitigate the fibrotic process at the molecular level by reducing collagen-1 synthesis.

4.2. NF-κB Pathway Inhibition

The nuclear factor-kappa B (NF-κB) pathway plays a critical role in regulating inflammation and is closely associated with liver fibrosis(El-Agamy et al., 2020). Inflammatory stimuli, such as oxidative stress and pro-inflammatory cytokines, activate NF-κB, which translocates to the nucleus and promotes the transcription of genes responsible for inflammation and immune cell recruitment(Fu et al., 2014). In the liver, chronic activation of NF-κB leads to persistent inflammation, which activates HSCs and promotes fibrogenesis.

In this study, the positive control group (KP) demonstrated significant upregulation of NF-κB expression, consistent with the known pro-inflammatory effects of isoniazid-induced liver injury(Hafeez et al., 2014). However, treatment with GMREE significantly downregulated NF-κB expression in a dose-dependent manner(Ibrahim et al., 2018). The group treated with 500 mg/kg/day (P2) showed the greatest reduction in NF-κB expression, suggesting that GMREE effectively inhibits NF-κB activation and reduces inflammation.

The inhibition of NF-κB by GMREE likely disrupts the inflammatory-fibrotic cycle that drives liver fibrosis(Mohamed et al., 2023). By reducing the transcription of pro-inflammatory cytokines, GMREE limits the recruitment of immune cells to the liver and prevents the activation of HSCs. This reduction in inflammation is crucial for preventing the initiation and progression of fibrogenesis, as it halts the signaling cascade that leads to collagen-1 deposition. The dose-dependent effect observed in this study further supports the hypothesis that

GMREE's anti-inflammatory properties are mediated through the suppression of NF-κB activation(Pan et al., 2017).

4.3. TGF-β1 Pathway Inhibition

Transforming growth factor-beta 1 (TGF-β1) is a key pro-fibrotic cytokine involved in the pathogenesis of liver fibrosis(Tangphokhanon et al., 2021). TGF-β1 promotes the activation of HSCs, leading to their differentiation into myofibroblast-like cells that produce large amounts of collagen and other extracellular matrix proteins(Oetari et al., 2019). In addition, TGF-β1 inhibits the degradation of extracellular matrix components, further contributing to the accumulation of fibrotic tissue.

In the positive control group (KP), TGF-β1 expression was significantly elevated, confirming the role of TGF-β1 in promoting fibrosis in isoniazid-induced liver injury(Parekh et al., 2022). However, GMREE treatment resulted in a marked reduction in TGF-β1 expression, particularly in the group receiving 500 mg/kg/day (P2)(Pramana, Wasita, Widyaningsih, et al., 2021). This finding indicates that GMREE effectively interferes with TGF-β1 signaling, preventing the activation of HSCs and reducing collagen-1 production.

The ability of GMREE to downregulate TGF-β1 suggests that it not only inhibits the initiation of the fibrotic process but also promotes the resolution of fibrosis by reducing the accumulation of extracellular matrix components(Pratiwi, 2019). By disrupting the TGF-β1 signaling pathway, GMREE prevents the excessive deposition of collagen-1, thus maintaining the liver's structural integrity(Pratiwi, 2021). This dual inhibition of NF-κB and TGF-β1 by GMREE highlights its potential as a therapeutic agent that targets both the inflammatory and fibrotic components of liver disease.

4.4. Clinical Implications

The findings of this study suggest that Garcinia mangostana L. rind extract could be developed as a novel therapeutic agent for preventing and managing liver fibrosis, particularly in cases of drug-induced liver injury(R. Parijadi et al., 2019). Isoniazid is a commonly used anti-tuberculosis drug, but its hepatotoxic effects limit its long-term use in certain patients(Rivero & Garibay, 2019). The ability of GMREE to inhibit key fibrotic pathways and reduce collagen-1 production makes it a promising candidate for adjunct therapy in patients at risk of liver fibrosis due to prolonged isoniazid use.

Moreover, GMREE's natural antioxidant and anti-inflammatory properties make it a potentially safe and well-tolerated treatment option for chronic liver diseases(Rohman et al., 2020). The dual inhibition of NF-κB and TGF-β1 pathways by GMREE suggests that it could be effective in a range of fibrotic liver diseases, including non-alcoholic steatohepatitis (NASH) and hepatitis-related fibrosis(Rohman et al., 2019). Further research is needed to evaluate the safety and efficacy of GMREE in human populations and to explore its potential applications in other fibrotic conditions.

5. CONCLUSION

In conclusion, Garcinia mangostana L. rind extract demonstrates significant anti-fibrotic properties by suppressing collagen-1 production and inhibiting the NF-κB and TGF-β1 pathways. This study shows that GMREE can effectively reduce inflammation and fibrogenesis in a dose-dependent manner, with the 500 mg/kg/day dose showing the greatest efficacy. These findings highlight GMREE as a promising therapeutic agent for preventing and treating liver fibrosis, particularly in the context of drug-induced liver injury, such as isoniazid hepatotoxicity.

Future studies should focus on clinical trials to validate the efficacy of GMREE in human patients and to further explore its mechanism of action. Given its potent anti-fibrotic effects and its potential for safe use, GMREE may offer a novel treatment strategy for patients at risk of developing liver fibrosis.

Conflicts of Interest

The authors declare no conflict of interest.

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