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Research Article

Nephelium lappaceum Peel Extract Alleviates High Fat-High Fructose Diet-Induced Fatty Liver in Mice

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Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) occurs due to excessive fat accumulation in the liver, triggered by high fat and sugar intake. This study aims to investigate the effect of Nephelium lappaceum peel extract (NLE) on hepatic profile in mice induced with a High Fat High Fructose Diet (HFHFD). The study involved 25 male mice divided into five groups: (1) normal group, (2) HFHFD group, (3) NLE 125 mg/kg bw, (4) NLE 250 mg/kg bw, and (5) NLE 500 mg/kg. HFHFD and NLE administration were carried out for 14 days. On the 15th day, mice were sacrificed and liver was harvested for further analysis. Descriptive analysis was performed for macroscopic and microscopic (histological) liver observations. ANOVA was used to analyze liver index. The results showed that NLE improved the fatty liver both macroscopically and microscopically. The liver index also improved significantly in group treated by NLE 250 ($p<0,05$) and NLE 500 ($p<0,0001$). The study suggests that NLE exhibits a promising therapeutic potential against fatty liver disease.

Keywords: Non-alcoholic fatty liver disease (NAFLD), *Nephelium lappacium*, hepatic profile.

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1 Introduction

Non-alcoholic fatty liver disease (NAFLD) has emerged as a growing public health concern in Indonesia. This condition is characterized by excessive fat accumulation within hepatocytes in the absence of alcohol consumption [1]. The prevalence of NAFLD in Indonesia reaches 30.6%, which is higher compared to India and China (24.6% and 20%, respectively) [2]. NAFLD can be triggered in part by a high intake of dietary fat with atherogenic properties [3]. In addition to high-fat diets, excessive sugar consumption also contributes to hepatic fat accumulation through de novo lipogenesis [4]. These pathogenic mechanisms highlight the pivotal roles of lipid metabolism dysregulation and oxidative stress in the development of hepatic steatosis.

Pharmacological therapy for NAFLD currently relies on antidiabetic agents such as metformin and antihyperlipidemic drugs such as simvastatin. These medications act through mechanisms that do not directly target hepatic steatosis, thereby increasing the potential for significant side effects [5]. Consequently, the search for and development of novel therapeutic strategies for NAFLD remains an important area of investigation. Accordingly, natural products with antioxidant and lipid-modulating properties have emerged as potential therapeutic options for NAFLD.

Rambutan peel (*Nephelium lappaceum* L.) is an agricultural waste product and one of Indonesia's natural resources traditionally used for medicinal purposes. Previous studies have shown that the ethanol extract of rambutan peel contains several secondary metabolites, including flavonoids, polyphenols, saponins, steroids, terpenoids, and alkaloids. Earlier research reported that the ethanol extract exhibits antioxidant activity [6]. Compounds such as ellagic acid and other polyphenols, including quercetin, that present in rambutan peel are considered to play a crucial role in mediating its hepatoprotective effects [7], [8]. Furthermore, in vivo studies using rambutan peel ethanol extract at doses of 125 mg/kg BW, 250 mg/kg BW, and 500 mg/kg BW demonstrated antidiabetic and antihypercholesterolemic effects [9]. Diabetes and hypercholesterolemia are closely associated with NAFLD [10]. Although doses ranging from 125 to 500 mg/kg BW have shown efficacy in diabetes and lipid profile improvement, information regarding its potential effect on fatty liver conditions remains limited. Accordingly, this dose range was selected to assess the potential dose-dependent effects of rambutan peel ethanol extract on hepatic steatosis based on previous in vivo evidence.

Therefore, this study was conducted to explore the potential of rambutan peel ethanol extract in mice with HFHFD-induced hepatic steatosis. The HFHFD model used in this study consisted of a high-fat diet formulated with beef fat as the primary lipid source, combined with other ingredients, along with the administration of 60% fructose [11].

2 Method

2.1 Animals

All animals were housed under controlled environmental conditions temperature 25 ± 2°C, humidity 60 ± 10%, 12-hour light/dark cycle) with free access to food and water. All procedures were conducted in accordance with institutional ethical guidelines and were approved by the Animal Ethics Committee of Faculty of Pharmacy Mulawarman University (Approval No. 148/KEPK-FFUNMUL/EC/EXE/10/2024).

2.2 Extract Preparation

Rambutan peels (*Nephelium lappaceum* L.) were collected from Samarinda, Kalimantan Timur and authenticated by Herbarium Mulawarman, Faculty of Forestry, Universitas Mulawarman (No.193/UN17.4.08/LL/2024). The dried peels were powdered and subjected to extraction using maceration technique with 70% ethanol as solvent for 3 x 24 hours at room temperature (25 ± 2°C).

The filtrate was concentrated using a rotary evaporator and dried to obtain a crude extract of N. lappaceum (NLE).

2.3 HFHFD Preparation

The HFHFD was formulated by combining beef tallow, regular chow (BR II), duck egg,wheat flour and liquid fructose (Table 1). The preparation procedure refers to previous studies [12]. Beef tallow served as the primary lipid component owing to its substantial proportion of saturated fatty acids, including palmitic and stearic acids, along with monounsaturated fatty acids like oleic acid [13]. The diet mixture was homogenized, pelletized, and stored frozen at -20°C. The HFHFD diet was administered in combination with 60% oral fructose (a mixture of liquid fructose and tap water) throughout the experimental period.

Table 1.Composition of HFHFD

Ingredients	Mass
Standard chow	100 g
What flour	q.s
Beef tallow	100 g
Egg yolk	25 g
Egg white	8 g
Palm oil	7 mL
Liquid fructose	25 g

2.4 Experimental Design

After one week of acclimatization, the animals were randomly divided into 5 groups (n = 25):

1. Normal group
2. HFHFD group
3. HFHFD group treated with NLE at dose 125 mg/kg BW
4. HFHFD group treated with NLE at dose 250 mg/kg BW
5. HFHFD group treated with NLE at dose 500 mg/kg BW

The number of animals per group was determined using Federer's formula. The minimum required sample size was $n \geq 4.75$. Therefore, five animals were included in each group to ensure adequate statistical reliability.

All groups, except the normal group, were fed with HFHFD and 60% fructose (p.o.) from day 1 to day 14. NLE interventions were provided concurrently over the same 14-day period. The 14-day HFHFD induction period was selected based on previous studies demonstrating that HFHFD administration for this duration was sufficient to significantly increase serum triglyceride levels, which serve as an early indicator of lipid metabolism dysregulation [11]. On day 15th, mice were sacrificed using servical dislocation method. Liver was harvested for further analysis.

2.5 Liver Index

The liver was removed, washed in cold saline, and weighed. The liver index was calculated as:

$$\text{Liver Index (\%)} = \frac{Liver\ weight\ (g)}{Body\ weight\ (g)} \text{ x } 100$$

2.6 Macroscopic and Microscopic Assessement

Macroscopic and microscopic analyses were conducted according to the procedures described in previous studies.The liver was observed for color, texture, and the presence of visible lesions. Representative images were recorded for macroscopic evaluation. For microscopic evaluation, liver tissues were fixed in 10% neutral-buffered formalin for at least 24 hours, embedded in paraffin,

sectioned at 4-5 μm, and stained with Hematoxylin and Eosin. Microscopic evaluation focused on assessing steatosis degree, hepatocellular ballooning, necrosis, and overall tissue architecture.

2.7 Data Analysis

Macroscopic and microscopic data were analyzed descriptively, whereas liver was subjected to statistical analysis. All quantitative data are presented as mean ± standard deviation (SD). Statistical analysis was performed using GraphPad Prism. Differences among groups were evaluated using one-way ANOVA followed by post-hoc test (Tukey's test) for multiple comparisons. A p-value of < 0.05 was considered statistically significant.

3 Result and Discussion

The liver is a vital organ that plays an essential role in metabolism, detoxification, and the regulation of the body's energy balance. Therefore, dietary patterns have a substantial impact on liver function and can alter hepatic tissue structure when nutritional imbalance occurs [14]. A high-fat diet combined with fructose, as in the High-Fat High-Fructose Diet (HFHFD) model, can accelerate hepatic lipogenesis and promote excessive fat accumulation, thereby increasing the risk of developing non-alcoholic fatty liver disease (NAFLD) [15]. In this study, HFHFD was formulated using beef tallow as the primary fat source and fructose as an inducer of *de novo* lipogenesis. This research aimed to evaluate the hepatoprotective potential of *Nephelium lappaceum* peel extract (NLE) against HFHFD-induced liver damage.

The first finding of this study concerns the effect of the ethanolic extract of *Naphelium lappaceum* peel (NLE) on the liver index of mice induced with HFHFD (Figure 1). The results showed that the liver index in the HFHFD group increased significantly compared with the normal group ($p = 0.001$), indicating enhanced fat accumulation. This observation is consistent with previous studies reporting that HFHFD can trigger alterations in hepatic histology accompanied by increased liver weight (hepatomegaly) due to lipid accumulation [16]. Furthermore, a significant reduction in liver index percentage was observed in the groups treated with NLE at doses of 250 mg/kg BW ($p = 0.05$) and 500 mg/kg BW ($p = 0.0003$). These findings suggest that NLE at these doses effectively attenuates HFHFD-induced an elevated liver index. Although a decrease in liver index was also observed in the NLE 125 mg/kg BW group, the reduction was not statistically significant. Previous studies reported that this extract is rich in phenolic compounds with strong antioxidant properties, which may protect hepatocytes from damage [17]. By mitigating cellular injury, rambutan peel extract may contribute to overall improvements in liver health.

The second finding of this study examines the effect of NLE on the macroscopic appearance of the liver in HFHFD-induced mice (Figure 2). In the normal group, the liver appeared smooth and reddish-brown, consistent with normal physiological morphology [18]. This color is associated with hemoglobin-rich blood flow within hepatic tissues [19]. In contrast, the HFHFD group showed pale discoloration and whitish granules on the liver surface, indicating steatosis. Continuous HFHFD feeding promotes excessive lipid accumulation, leading to hepatocyte damage, reduced blood perfusion, and changes in liver coloration [18], [20]. These findings are consistent with previous reports showing granular surface changes and pale coloration in high-fat diet–induced fatty liver [21]. HFHFD also increases ROS and lipid peroxidation, contributing to hepatomegaly and visible macroscopic alterations [22]. In the NLE 125 group, the liver remained slightly pale with some white granules, indicating partial improvement. More notable recovery was seen in the NLE 250 and 500 groups, where the liver exhibited a darker reddish color. The NLE 500 group showed the most normal-like appearance, with a smooth surface and reddish-brown coloration. These improvements are likely due to the phenolic and flavonoid compounds in *N. lappaceum* peel, such as apigenin-7-neohesperidoside and eriocitrin, which possess antioxidant activity capable of reducing ROS and protecting hepatocytes [9], [23]

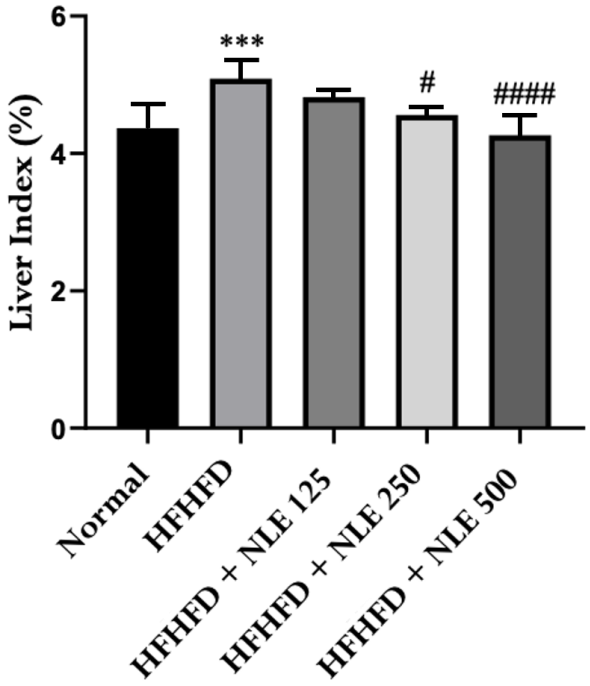

Figure 1 Effect NLE on Liver Index. Liver index was calculated as the ratio of liver weight to body weight and expressed as a percentage and analyzed using one-way Anova based on the mean ± SD (n = 5 mice). ***p <0.001 vs normal group, #p <0.05, ####p <0.0003 vs HFHFD group

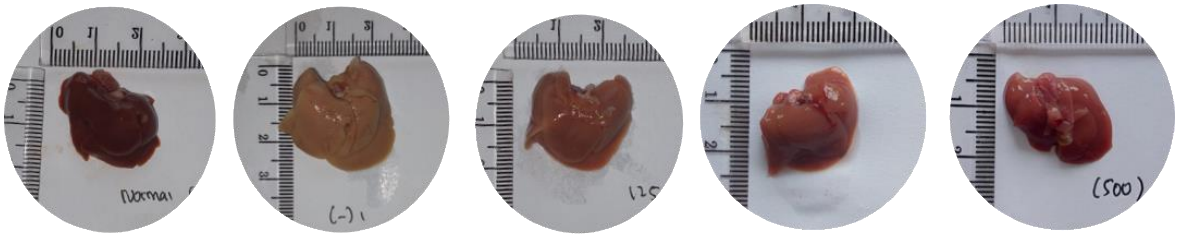

Figure 2 Effect of NLE on liver macroscopic appearance. Representative images of liver tissue from the normal froup (A), HFHFD group (B), HFHFD treated with NLE 125 mg/kg bw (C), HFHFD treated with NLE 250 mg/kg bw (D), HFHFD treated with NEL 500 mg/kg bw (E).

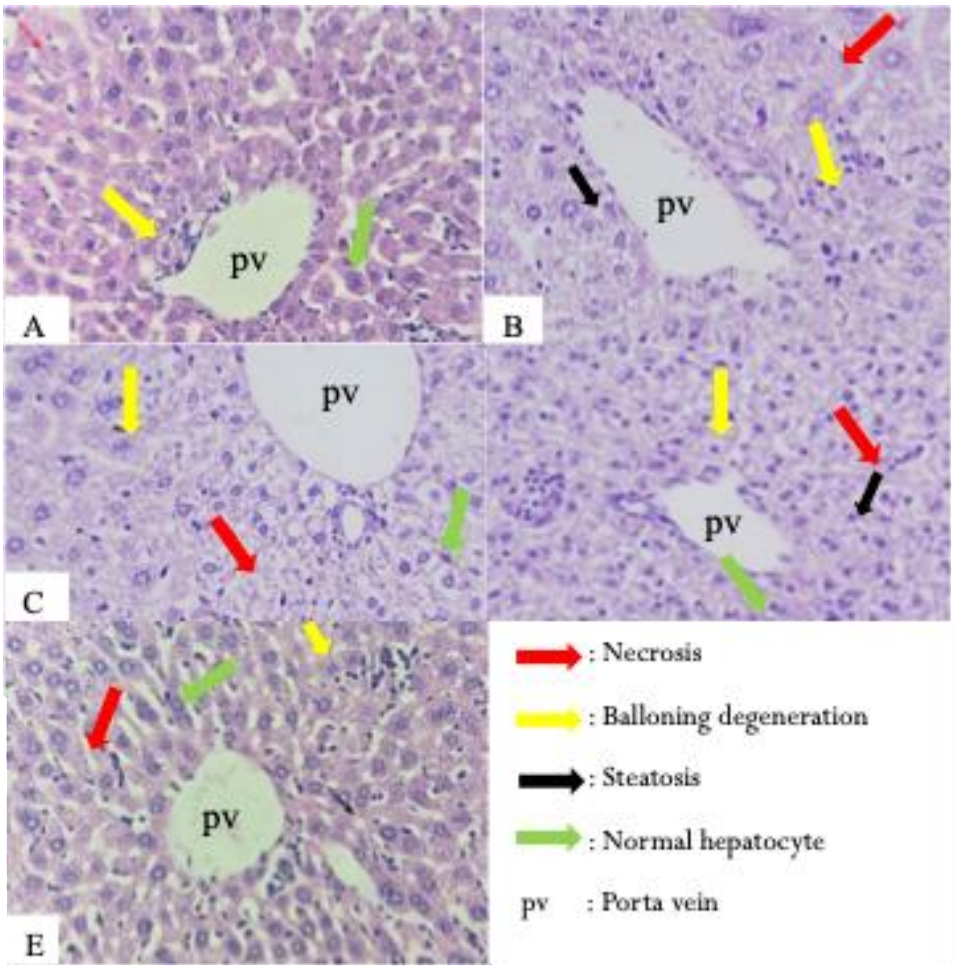

Figure 3 Effect of NLE on liver histopathology. Representative hematoxylin and eosin (H&E) stained liver sections from the normal group (A), HFHFD group (B), HFHFD treated with NLE at 125 mg/kg BW (C), HFHFD treated with NLE at 250 mg/kg BW (D), and HFHFD treated with NLE at 500 mg/kg BW (E). Original magnification ×400.

The third finding concerns the effect of NLE on the microscopic (histological) structure of the liver in HFHFD-induced mice (Figure 3). In the normal group, liver tissue generally showed preserved architecture with hepatocytes displaying relatively organized cytoplasm. However, occasional mild ballooning-like changes and limited focal necrosis were observed sporadically and are considered incidental background findings that have been reported in normal untreated laboratory mice [24]. These minimal histological alterations did not indicate pathological liver injury and were not associated with functional impairment. In the HFHFD group, marked histological alterations were evident. Numerous hepatocytes exhibited ballooning degeneration, characterized by enlarged, dispersed cytoplasm with loss of uniform eosinophilic staining. Pronounced lipid accumulation was also present, indicating steatosis, seen as clear intracellular vacuoles [15], [22]. Additionally, hepatocyte necrosis was prominent, identified by nuclear disappearance or indistinct nuclei, reflecting oxidative stress– and inflammation-induced cell death [25]. These features are typical of hepatic injury caused by high-fat diets [11]. In the NLE 125 mg/kg BW group, ballooning degeneration remained high, and steatosis and necrosis were still evident, suggesting that this dose did not provide sufficient hepatoprotection. In the NLE 250 mg/kg BW group, hepatocyte ballooning persisted, but steatosis was reduced and necrosis appeared less extensive compared to the HFHFD group, indicating partial improvement. The most notable recovery was observed in the NLE 500 mg/kg BW group, where hepatocytes appeared more organized with a higher proportion of normal cells. Ballooning

degeneration was reduced, steatosis was minimal, and necrosis was markedly lower than in the HFHFD group. Overall, the histopathological findings confirm that HFHFD causes significant hepatic injury, including ballooning degeneration, steatosis, and necrosis. Treatment with *Nephelium lappaceum* extract attenuated these alterations by reducing lipid accumulation and cellular damage. The hepatoprotective effects of rambutan peel extract are likely attributable to its antioxidant constituents, as previously reported [25]. Nevertheless, histopathological evaluation in this study was performed qualitatively, and quantitative scoring systems such as the NAFLD Activity Score (NAS) were not applied. This represents a limitation of the present study and should be addressed in future investigations to provide a more objective assessment of histological changes.

4 Conclusion

Our study demonstrate that HFHFD administration induces physiological and structural alterations in the liver, including increased liver index and notable macroscopic and microscopic changes in hepatic tissue. Treatment with *Nephelium lappaceum* peel extract (NLE) was able to ameliorate these alterations, with the highest dose (500 mg/kg BW) showing the most pronounced improvement in liver morphology and cellular integrity. These results indicate that NLE possesses promising hepatoprotective potential. However, a more comprehensive evaluation of liver injury would benefit from incorporating the NAFLD Activity Score (NAS) to quantitatively assess steatosis, inflammation, and ballooning. Therefore, further studies are needed to include this scoring system and to explore the molecular mechanisms underlying the protective effects of NLE, as well as its potential development as an adjunct therapeutic agent for NAFLD.

5 Declarations

5.1 Acknowledgements

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5.2 Author contributions

First author was responsible for conceptualization, methodology development, investigation, data curation, and preparation of the original draft. Second author contributed to the formal analysis, validation, and served as the primary executor of the research, as well as assisting in the review and editing of the manuscript. Thrid author performed data visualization, and laboratory analysis, and also served as the coordinator for the extraction process. Fourth author performed and coordinated the preparation of the HFHFD diet and contributed to editing of the manuscript.

5.3 Ethics

All procedures were approved by the Animal Ethics Committee of Faculty of Pharmacy Mulawarman University (Approval No. 148/KEPK-FFUNMUL/EC/EXE/10/2024).

5.4 Conflict of Interest

The authors declare no conflict of interest

5.5 Funding Statement

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