Biosaintifika 18 (1) (2026): 153-165 p-ISSN 2085-191X | e-ISSN 2338-7610
Journal of Biology & Biology Education https://journal.unnes.ac.id/nju/index.php/biosaintifika

Analysis of ellagic acid response in *Naphelium lappaceum* peel extract in the obesity rat model

Lisdiana Lisdiana[1]*, Djuna Lamondo[2], Annisaa Basar[3], Nugrahaningsih WH[1], Mirtaati Naimah[4], Yofi Ersyada Damayanti[1], Amalia Wilda Aulia[1], Fitria Salsabila[1]

[1]Faculty of Science and Mathematics, Universitas Negeri Semarang, Indonesia, 50229
[2] Faculty of Science and Mathematics, Department of Biology, Universitas Negeri, Gorontalo, Indonesia, 96128.
[3]Faculty of Education, Department of Educational and Foundations Humanities, Universiti Malaya, 50603
[4]Department of Biology Education, UIN Walisongo Semarang, Indonesia, 50185

*Corresponding Author: lisdiana@mail.unnes.ac.id

Submitted: 2025-12-13. Revised: 2026-02-17. Accepted: 2026-04-20.

Abstract. *Naphelium lappaceum L* or Rambutan in Indonesian, fruit peel has been identified as a potential source of polyphenolic compounds, including ellagic acid, geraniin, and corilagin. Ellagic acid has been reported to have strong antioxidant activity, inhibit adipogenesis, increase lipid oxidation, and reduce plasma lipid concentrations in obese animal models. This study aimed to analyze the response of ellagic acid contained in *N. lappaceum* peel extract on lipid profiles and liver histology in obese rat models. Twenty-five male *Sprague-Dawley* rats were divided into five groups: normal (P1), obese (P2), ellagic acid (P3), O-RPE (Obese rats treated with RPE) 15 mg/kgBW (P4), and O-RPE 30 mg/kgBW (P5). Treatment was administered for 30 days. The results showed that administration of ellagic acid and RPS (O-RPE) significantly improved metabolic parameters in obese rats. ANOVA analysis revealed lower LDL ($p < 0.05$), reduced triglycerides, and improved liver histology scores in treatment groups compared to the obese control, while other parameters showed favorable but non-significant trends. In conclusion, ellagic acid in RPE demonstrates potential as a herbal anti-obesity agent by improving lipid profiles and liver tissue structure. This research highlights the innovative use of *N. lappaceum* peel as a source of bioactive compounds for obesity management, an area that remains underexplored. This research supports SDGs 3 (Good Health and Well-being) by offering natural interventions for obesity, and SDGs 12 (Responsible Consumption and Production) by promoting sustainable use of agricultural waste.

Keywords: Elagic acid; obesity; *Naphelium lappaceum L* peel extract.

How to Cite: Lisdiana, L., Lamondo, D., Basar, A., Nugrahaningsih, W. H., Naimah, M., Damayanti, Y. E., Aulia, A. W., & Salsabila, F. (2026). Analysis of ellagic acid response in *Naphelium lappaceum* L peel extract in the obesity rat model. *Biosaintifika: Journal of Biology & Biology Education, 18(1)*, 153-165.

DOI: http://dx.doi.org/10.15294/biosaintifika.v18i1.37039

INTRODUCTION

Nephelium lappaceum L is a tropical fruit that grows widely in Indonesia. Of 1 g of *N. lappaceum* fruit, 0.4 g is edible, while the rest is peel and seeds, which are often discarded as waste. *N. lappaceum* peel has been identified as a potential source of polyphenolic compounds, including ellagic acid (EA) (Phuong et al., 2020), geranine, and corilagin. Among these compounds, ellagic acid has attracted attention due to its strong antioxidant capacity and regulatory effects on lipid metabolism. Previous studies have shown that ellagic acid can inhibit adipogenesis, increase lipid oxidation, and reduce plasma lipid concentrations in obese animal models (Amin & Arbid, 2017; Ghadimi et al., 2021; Karimi et al., 2020; Sharifi-Rad et al., 2022).

In *N. lappaceum* plants, secondary metabolites such as flavonoids, phenolics, tannins, and saponins have been identified as bioactive components with various biological activities (Chigurupati et al., 2019; Shahrajabian et al., 2020). Flavonoids and phenolic compounds are widely known to have strong antioxidant activities, capable of neutralizing free radicals and inhibiting lipid oxidation in the body. In *N. lappaceum* plants, the peel in particular has the most prominent phenolics, consisting of ellagic acid, geraniin, and corilagin (Mistriyani et al., 2020). All three are types of polyphenols that have important pharmacological effects in modulating lipid metabolism and controlling obesity.

Ellagic acid (EA) is a bioactive compound that is abundant in several fruits, including *N. lappaceum*. The EA content in *N. lappaceum* peel

is relatively high (176.99 mg/g) (Phuong et al., 2020) So it is known to have strong antioxidant and anti-inflammatory properties (Cerda-cejudo et al., 2024). EA has the ability to scavenge free radicals by donating hydrogen atoms or electrons from its hydroxyl group, thereby neutralizing free radicals into stable non-radical forms (Tiwari & Mishra, 2023; Tošovi & Bren, 2020). In addition, EA can inhibit the formation and accumulation of new fat cells through the regulation of adipogenesis factors through the regulation of cell cycle proteins, thus EA also plays a role in anti-obesity.

Obesity has become one of the major global health challenges, with its prevalence steadily increasing in both developed and developing countries. Currently, 2.5 billion adults worldwide are overweight, and at least 890 million of them are obese. The prevalence of overweight varies by region, from 31% in Southeast Asia and Africa to 67% in the Americas. Obesity is a complex chronic disease characterized by excess fat deposits that can interfere with health. Obesity can lead to an increased risk of type 2 diabetes and heart disease, affect bone and reproductive health, and increase the risk of certain cancers. Obesity affects quality of life, such as the quality of sleep or activity (WHO, 2025). Obesity is characterized by excessive accumulation of adipose tissue due to an imbalance between energy intake and expenditure, leading to hyperlipidemia. Hyperlipidemia is one of the main metabolic parameters associated with obesity. This condition is characterized by increased levels of cholesterol, triglycerides, and low-density lipoproteins (LDL), and decreased levels of high-density lipoproteins (HDL) (T. Zhang et al., 2019).

Maintaining good eating habits with healthy foods and foods rich in antioxidants can play a protective role against metabolic diseases. It is well known that the balance between oxidants and antioxidants is very important for the body. The advantage of antioxidant substances is one of the important factors to control the healthy lives of individuals, which has a protective effect at the population level (Jomova et al., 2024). Polyphenols are the most abundant antioxidants, with intake levels 10 times higher than those of vitamin C and 100 times higher than those of vitamin E or carotenoids. Polyphenols are the most abundant antioxidants, and their intake is 10 times higher than vitamin C intake and 100 times higher than vitamin E or carotenoids. Phenolic compounds act as electron catchers of reactive oxygen species and prevent their increased activity (Ling et al., 2010). Indirectly, polyphenols can interfere with cellular detoxification systems, such as superoxide dismutase, catalase, or glutathione peroxidase (Jomova et al., 2024)

Efforts to manage hyperlipidemia in obesity and its metabolic complications generally involve lifestyle changes and pharmacological interventions. Concerns about unwanted side effects in the use of synthetic drugs are driving interest in safer, plant-derived bioactive compounds with lipid-lowering and anti-obesity properties. Polyphenol-rich natural products have shown promising effects in regulating lipid metabolism through antioxidant and anti-inflammatory mechanisms (Su & Wang, 2024).

Although several studies have highlighted the antioxidant potential of *N. lappeceum* peel, comprehensive studies evaluating its lipid-lowering activity and underlying mechanisms in obesity models are still limited. The findings from this study suggest that ellagic acid in *N. lappaceum* peel extract can provide lipid-lowering effects by inhibiting lipogenesis and increasing FA oxidation through antioxidant mechanisms. RPE containing ellagic acid has potential as a natural lipid-lowering agent, capable of improving lipid profiles and protecting tissues from damage associated with obesity. Research on natural antioxidants has reported improvements in liver histology and enzyme function (AST-ALT), suggesting that hepatoprotective effects are an important mechanism underlying lipid-lowering activity. The study results suggest that RPE has potential as a natural ingredient that can help address obesity and metabolic disorders. These findings are also expected to contribute to the development of natural plant-based therapeutic strategies for obesity management.

This study aims to analyze the potential of ellagic acid from RPE as a lipid-lowering agent in obese rats. The focus is on its effects on body weight, lipid profile, and liver function (including histological structure and enzyme activities), as well as the possible mechanisms involved in lipid metabolism regulation. Exploring RPE as a natural lipid-lowering agent also can provide important contributions. It adds knowledge about the role of plant-derived compounds in managing obesity and metabolic disorders, while also offering practical value by reducing agricultural waste and presenting a safer alternative to synthetic drugs with potential application in controlling hyperlipidemia linked to obesity.

METHODS

Experimental Design and Research Variables

The study was conducted using a Completely Randomized Design (CRD) comprising five treatment groups, each replicated five times, for a total of 25 mice. The treatment groups were as follows: Normal group, standard feed (P0); Obesity feed group (P1); Obesity feed supplemented with ellagic acid (EA) (P2); Obesity feed supplemented with RPE at a dose of 15 mg/BB (P3); and Obesity feed supplemented with RPE at a dose of 30 mg/BB (P4).

The independent variables consisted of the type of feed (normal or obesity feed), ellagic acid (EA), and RPE at two dosage levels (15 mg/BB and 30 mg/BB). The dependent variables included body weight, visceral fat, lipid profile (total cholesterol, LDL, HDL, and triglycerides), as well as liver structure and function, assessed through ALT, AST, and hepatic histology.

Test Animal Preparation

This study used *Sprague-Dawley* mice obtained from the laboratory of Averroes Unisula Semarang, as well as 25 male rats, normal, aged 6-8 weeks, with an average weight ranging from 150 -200 grams. Upon arrival at the cage, the rats were rested and acclimatized for 7 days, with standard feeding and drinking water ad libitum. Next, the mice were weighed to find out their initial weight.

The research material includes Elagic Acid obtained from Biotech Nutritions, and RPE. *N. lappaceum* was obtained from Sekaran Village, Gunungpari, Semarang, *N. lappaceum* peel was extracted with ethanol and dried with a rotary evaporator, rats were divided into 2 groups, control, namely normal control (P0) and obesity control (P1), and three treatment groups, namely the group with ellagic acid (P2), the group with RPE 15 mg/BB (P3) and RPE 30 mg/BB (P4) The ellagic acid used in this study was obtained from Biotech Nutritinons.

N. lappaceum Peel Extract Preparation

N. lappaceum fruits were collected from Sekaran Village, Gunungpati, Semarang. *N. lappaceum* peels were thoroughly washed with distilled water to remove residual pulp and contaminants, then shade-dried until a constant weight was achieved. A total of 0.5 g of dried *N. lappaceum* peel was homogenized with 10 mL of distilled water. The homogenate was centrifuged at 10,000 rpm for 5 minutes, and the resulting supernatant was collected. The supernatant was then filtered through a 0.45 µm Millipore membrane filter to ensure clarity and sterility. The filtrate obtained was designated as RPE and stored at 4 °C until use in animal experiments.

Animal Experiments

This research protocol has been approved by the Ethics Committee of the Faculty of Medicine, State University of Semarang (Approval Letter No. 1011/KEPK/FK/KLE/2025). Animal acclimatization is attempted during the first 7 days in controlled room conditions with a temperature of 22°C and a humidity of 50%. and Fed standard feed and drinking water ad libitum, conditioning obesity by feeding 15% sugar solution and 3 ml of coconut oil containing 136,336 calories per teak. Induction of obesity is carried out for 7 weeks. Obesity confirmed by the Index Lee (Bast & Serra, 2020). Daily weight weighing during treatment. Treatment was given for 30 days orally; on the 31st day, blood samples were taken through the orbital sinuses.

Organ Isolation and Sample Analysis

The isolated liver organs were cleaned with a 0.9% physiological saline solution and fixed in a sample bottle containing 10% BNF solution to keep the tissue fresh and not damaged. Histological preparations of hepatic tissue were carried out at BBVT Wates, Yogyakarta, using Hematoxylin-Eosin (HE) staining. Hepatocyte morphology was examined under a light microscope at 400× magnification. For each slide, five random fields of view were observed to ensure representative sampling. Histopathological changes, including cellular degeneration, pyknosis, and necrosis, were evaluated. Semi-quantitative scoring was performed by two independent pathologists to minimize observer bias, and the scoring criteria followed established guidelines for liver histopathology assessment.

Lipid profile analysis and liver function biomarkers (ALT and AST) were carried out at the Central Java Province health laboratory. Cholesterol level analysis was carried out using the enzymatic calorimetric method *CHOD-PAP* (*Cholesterol Oxidase Method).* Triglyceride analysis was carried out using the enzymatic calorimetric method GPO-PAP (*Glycerol Peroxidase Phosphat Acid*). LDL and HDL were measured by enzymatic methods with a spectrophotometer. ALT and AST levels were measured using the International Federation of

Statistical Analysis.

Data were analyzed to determine distribution patterns and homogeneity using the Shapiro-Wilk normality test. The results of the data analysis showed a normal and homogeneous distribution, followed by Variance Analysis (ANOVA) with a significance level of 5 percent. Further test with the Duncan Multi Range Test at a significance level of 5%. For variables that did not meet the assumptions of normality and homogeneity, the Kruskal-Wallis test was performed using the Kruskal–Wallis test at a 5% significance level and followed by the Mann–Whitney U test for post hoc comparisons.

RESULTS AND DISCUSSION

The administration of ellagic acid (EA) and RPE in obese rats for 31 days produced distinct effects across measured parameters. Visceral fat levels remained comparable among groups, indicating that neither EA nor RPE reduced fat accumulation. Total cholesterol concentrations also showed no meaningful differences, and LDL levels remained similar across treatments, with only a slight downward trend in the intervention groups. HDL concentrations did not differ significantly among groups, confirming that supplementation did not alter this parameter. In contrast, triglyceride levels were significantly affected. The normal control group (P0) exhibited higher triglyceride values compared to P3, while groups P1, P2, and P4 showed intermediate values that did not differ significantly from either P0 or P3.

Liver enzymes (ALT and AST) varied widely but showed no significant differences among groups, suggesting that EA and RPE did not markedly influence hepatocellular enzyme leakage. Histological evaluation of the liver revealed clear differences. The obese group (P1) displayed the most severe damage, characterized by higher histological scores, steatosis, and hepatocyte degeneration. In contrast, the normal control (P0) had the lowest score. Treatment groups (P2, P3, and P4) exhibited intermediate scores, indicating partial protection against liver injury compared to untreated obese rats.

Overall, EA and RPE supplementation did not significantly alter visceral fat, cholesterol, LDL, HDL, ALT, or AST, but significantly reduced the severity of hepatic damage and modulated triglyceride levels. The detailed results are presented in Table 1.

Statistical analyses supported these findings. Variables that did not meet the assumptions of normality or homogeneity (visceral fat, total cholesterol, HDL, ALT, and AST) were analyzed using the Kruskal–Wallis test, which revealed no significant differences except for liver histology. Post-hoc analysis identified a specific difference between groups P0 and P1 for histological scores. For variables that met the assumptions of normality and homogeneity (LDL and triglycerides), analysis was performed using ANOVA. LDL showed no significant differences among groups, while triglycerides differed significantly. Further analysis with Duncan's Multiple Range Test demonstrated that group P0 differed significantly from P3, with groups P1, P2, and P4 showing intermediate values.

Table 1. Average visceral fat, cholesterol, LDL, HDL, AST-ALT content after the addition of ellagic acid and RPE in an obese rat model for 31 days

Variabel	Treatment				
	P0 ($\bar{x}$ ± SD)	P1 ($\bar{x}$ ± SD)	P2 ($\bar{x}$ ± SD)	P3 ($\bar{x}$ ± SD)	P4 ($\bar{x}$ ± SD)
Lemak visceral (g)	4.26 ± 3.23[a]	1.59 ± 0.21 [a]	4.03 ± 1.46 [a]	2.92 ± 1.34 [a]	2.79 ± 1.38 [a]
Cholesterol (mg/dL)	81.80 ± 15.95 [a]	66.04 ± 6.24 [a]	68.53 ± 9.52 [a]	79.38 ± 26.21 [a]	54.10 ± 6.66 [a]
LDL (mg/dL)	54.4 ± 3.64 [a]	37.8 ± 4.76 [a]	42.0 ± 12.0[a]	49.8 ± 14.92 [a]	28.8 ± 2.49[a]
HDL (mg/dL)	11.17 ± 7.784 [a]	11.25 ± 2.761 [a]	9.43 ± 2.191 [a]	16.24 ± 8.745 [a]	7.05 ± 3.410 [a]
Trigliseride (mg/dL)	119.02 ± 24.25[b]	87.86 ± 15.30[ab]	87.98 ± 15.20[ab]	66.62 ± 26[a]	91.24 ± 21.88[ab]
ALT (u/L)	50.82 ± 111.49 [a]	59.94 ± 299.48 [a]	75.76 ± 271.14 [a]	56.82 ± 74.41 [a]	61.78 ± 96.21 [a]
AST (u/L)	125.64 ± 264.9[a]	127.94± 549.46 [a]	145.5 ± 350.89 [a]	127.4 ± 157.31 [a]	182.8 ± 346.42 [a]
Liver histology	1.40 ± 0.55 [a]	3.20 ± 0.45 [b]	2.00 ± 0.00 [ab]	2.00 ± 0.00 [ab]	2.60 ± 0.55 [ab]

Descriptions: Data are presented as mean ± standard deviation (SD). Superscripts with identical letters indicate no statistically significant difference, whereas superscripts with different letters denote significant differences. P0 (control group, standard feed without elagic acid and RPE); P1 (obesity end, obesity feed), P2, P3, and P4 are obesity feeds with elagic acid and RPE 15 and 30 mg/Kg BB, respectively.

Visceral fat amounts and cholesterol levels did not differ significantly between the control and treatment groups ($P > 0.05$). This is due to the low Bioavailability of EA. Ellagic acid has poor oral absorption and is quickly metabolized into urolithin in the intestine, so only a small number of active compounds reach the blood and target tissues (M. Zhang et al., 2023). Moreover, RPE contains various phenolic compounds other than ellagic acid, such as geraniin, corilagin, and quercetin. The interaction between these compounds can reduce the effectiveness of ellagic acid. This can also be caused because the bioactive compounds contained in *N. lappaceum* peel, such as flavonoids, polyphenols, and tannins, play a greater role in inhibiting fat absorption and helping to speed up triglyceride metabolism than slowing down cholesterol synthesis in the liver directly. Cholesterol in the body is mostly produced through the endogenous pathway by the liver through the activity of the enzyme HMG-CoA reductase. If the mechanism of action of the compounds in *N. lappaceum* peel extract is not strong enough to suppress this pathway, then total cholesterol levels are unlikely to undergo significant changes.

The absence of cholesterol-lowering effects may be attributed to the relatively low dosage administered. In research Susanti & Bramantio, (2018) regarding the effect of *N. lappaceum* peel extract on cholesterol reduction, it gave the result that at doses of 125, 250, and 500 mg/kgBB, there was an antihypercholesterolemic effect, which means that the higher the dose given, the greater the percentage of decreased cholesterol levels in the blood. In addition, another underlying factor is that at a dose of 15 mg/kgBB the rat body is still in the phase of adjustment to lipid metabolism, where the activation of PPARα receptors and the increase in fatty acid β-oxidation have not occurred optimally. The cause of a significant increase or absence of blood cholesterol levels can be caused by rats in a state of stress, as well as differences in metabolic rate between individual rats. Some of these factors affect the lipid metabolism process, potentially causing increased cholesterol levels in the blood (Djajanti & Shafira, 2024).

In the process of lowering cholesterol by active compounds, it takes time to work optimally in the body, related to the mechanism of inhibition of the enzyme HMG-CoA reductase or increased excretion of bile acids. The process of cholesterol formation takes place through a series of enzymatic reactions on the mevalonate pathway. In this pathway, the enzyme HMG-CoA reductase has an important role as a catalyst in converting HMG-CoA into mevalonate, which is further used in cholesterol synthesis. If the enzyme HMG-CoA reductase is inhibited, then cholesterol production can be significantly suppressed. This mechanism occurs through the activation of sterol-binding proteins, which then affect the regulation of HMG-CoA reductase and LDL receptors, thus ultimately having an impact on reducing cholesterol levels in the body (Oktavelia & Kusuma, 2022).

The increase in LDL levels and significant decrease in HDL levels in the group with an RPE of 30 mg/Kg BB is due to the polyphenol properties of *N. lappaceum* peel, which at low doses tend to be moderately pro-oxidant, thus triggering mild oxidative stress in the liver. This condition interferes with the activity of LCAT enzymes as well as the expression of ApoA-I and lipid transporters ABCA1/ABCG1, which play a role in the formation of HDL. As a result, the HDL that is formed becomes dysfunctional and degrades faster (Farhan et al., 2022; Laguna-Maldonado et al., 2025). Although high doses of RPE (≥1250 mg/kgBB) are reported to cause histopathological changes in the liver (Li et al., 2020), the dose of 30 mg/kgBB is still far below the toxic threshold. Therefore, the decrease in HDL in P3 is more due to disruption of lipid metabolism due to modulation of polyphenols to liver function than direct toxicity (Rostiani, 2023).

LDL levels did not differ significantly among groups ($p > 0.05$). This indicates that the administration of EA and RPE does not have a noticeable effect on LDL levels. The lack of response may be related to the dosage, which was insufficient to elicit changes compared to other treatments. Although the differences were not statistically significant, a downward trend in LDL levels observed in the P3 group suggests that bioactive compounds in RPE may begin to exert hypolipidemic effects at this dose. Additionally, stress factors in experimental animals could have contributed to unexpected increases in LDL levels. Stress can trigger increased secretion of the hormones corticosterone and cortisol (Xu et al., 2025) which play a role in increased lipolysis and the release of free fatty acids (FFA) into the blood, so LDL levels tend to increase (Mushumba et al., 2025)

Triglyceride levels differed significantly between the control group and the groups treated with ellagic acid (EA) and RPE. Differences in triglyceride levels between control and treatment

groups showed that ellagic acid and RPE had significant biological effects on lipid metabolism in obese rats. These effects are likely mediated through multiple mechanisms. EA and polyphenols in RPE can modulate the activity of key lipogenic enzymes such as fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), and lipoprotein lipase (LPL), thereby reducing triglyceride synthesis and enhancing lipid clearance. In addition, activation of the AMPK–PPARα signaling pathway promotes fatty acid oxidation and suppresses lipogenesis, contributing to lower circulating triglyceride levels. Improvement of insulin sensitivity further reduces hepatic triglyceride production and enhances peripheral lipid utilization (Wulandari, 2024).

ALT and AST levels remained comparable between the control and treatment groups ($P > 0.05$). In the liver, glucose will be converted into glycogen through the process of glycogenesis as an energy reserve. However, when the glycogen storage capacity in the liver and muscles is full, excess glucose will be converted into fatty acids through lipogenesis (Zhao et al., 2021). Fatty acids will be synthesized into triglycerides and stored in hepatocytes. High-fat intake from food also increases levels of FFA (Free Fatty Acid) in the blood to be transported to the liver. When the amount of FFA is excessive, the metabolism of these fats produces ROS in large quantities (Ye et al., 2022). The accumulation of ROS triggers oxidative stress that causes lipid peroxidation, protein damage, and DNA damage, thereby interfering with the physiological function of hepatocytes.

Liver tissue from rats exposed to a diet high in fat and carbohydrates shows changes in the form of fat droplet accumulation in the cytoplasm of hepatocytes (steatosis), cell swelling (ballooning degeneration), and infiltration of inflammatory cells (Kim et al., 2021). This condition also causes stress on the endoplasmic reticulum, which results in cell defense mechanisms such as unfolded protein response (UPR) becoming ineffective, thus activating apoptosis pathways through CHOP and caspase-12 proteins. As a result, intracellular enzymes such as AST-ALT leaks into the blood circulation, which is an indicator of hepatocyte damage. Therefore, elevated levels of ALT and AST are often used as biochemical parameters to assess liver damage due to obesity and metabolic stress (Jalili et al., 2022).

Obesity can cause severe metabolic stress on the liver through intracellular lipid accumulation, insulin resistance, and increased ROS that triggers lipotoxicity and lipid peroxidation (Cavaliere et al., 2023). This process disrupts the integrity of key organelles such as the mitochondria and endoplasmic reticulum, ultimately triggering pathways of apoptosis and leading to hepatocyte necrosis. Consistent with these mechanisms, the obesity group exhibited the highest histological damage score (score 3). In this group, hepatocytes commonly showed hydropic degeneration and fatty degeneration, reflecting severe cellular injury. These alterations indicate that the level of histological damage in obese rats was markedly greater than that observed in the normal control group.

The administration of RPE at a dose of 15 mg/kg BB was able to reduce the levels of ALT and AST in the serum. The decrease in these enzymes indicates restoration of hepatocyte membrane stability, thereby preventing the leakage of intracellular enzymes into the bloodstream. Thus, RPE serves not only as a natural source of antioxidants but also as a potential therapeutic candidate for preventing and treating liver damage associated with obesity and metabolic disorders.

Elevated ALT and AST levels in obese mice serve as biochemical indicators of hepatocellular injury resulting from chronic disturbances in lipid and glucose metabolism. In obese conditions, excessive energy intake from foods high in fat and carbohydrates leads to the accumulation of intracellular lipids within the hepatocytes (Ye et al., 2022). This accumulation causes lipotoxicity, which is a toxic condition due to an excess of free fatty acids that disrupts the stability of the liver cell membrane. Excess free fatty acids undergo incomplete oxidation, resulting in ROS. Increased ROS triggers oxidative stress, which damages membrane phospholipids, proteins, and DNA in hepatocytes (Jalili et al., 2022). When the integrity of the cell membrane is disturbed, intracellular enzymes such as ALT and AST enter the bloodstream, so their concentration in the serum increases significantly.

Administration of ellagic acid and RPE reduced the degree of liver histological damage caused by obesity, demonstrating a protective effect on hepatocytes. An illustration of obesity-induced liver injury is presented in Fig. 1.

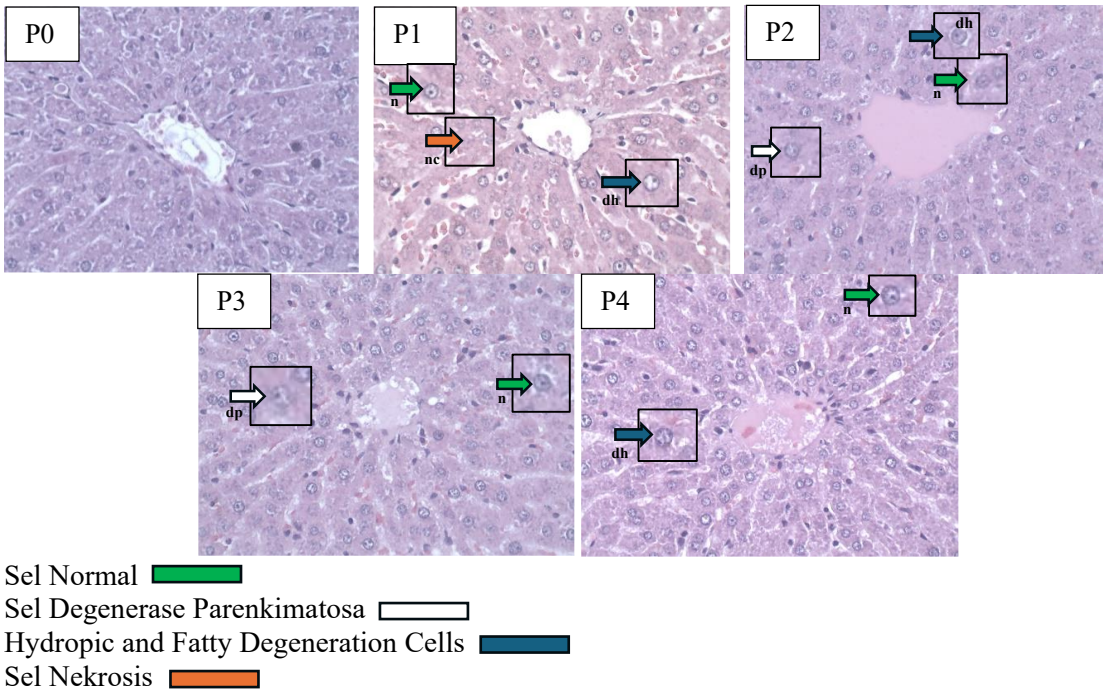

Figure 1. Normal hepatocytes (n), hepatocytes with parenchymatous degeneration (dp), hepatocytes with hydropic and fatty degeneration (dh), hepatocytes with necrosis (nc). (Hematoxilin-Eosin staining, 400x magnification). P0 = standard feed, P1 + Obesity feed (sugar water 15% = coconut oil), P2 = Obesity feed + Elagic acid, P3 = obesity feed + RPE 15 mg/KgBB, P4 = Obesity feed + RPE 30 mg Kg/BB.

Histological observations in the normal group showed intact structure with rounded hepatocytes, clear nuclei, and homogeneous cytoplasm without signs of degeneration or necrosis. In P1, parenchymatous degeneration was evident, characterized by hepatocyte swelling and cytoplasmic changes. P2 exhibited more severe alterations, including hydropic degeneration, fat accumulation in the cytoplasm, and the presence of necrotic cells, indicating advanced hepatocellular damage. In contrast, P3 and P4 still displayed parenchymatous degeneration, but the severity was lower than in P2, and necrotic cells were absent. These findings suggest that RPE administration at both 15 mg/kg BW and 30 mg/kg BW provides a protective effect against obesity-induced liver injury, although histological conditions were not fully restored to normal.

Liver damage in the form of parenchymal degeneration and hydropic degeneration is seen in obese and obese-EA groups. This is because in obesity, oxidative stress increases and triggers insulin resistance, which can increase lipolysis in adipose tissue and free fatty acid levels in the blood. This excess fatty acid enters the liver and causes hepatic steatosis, which triggers the activation of inflammatory pathways and increases the production of proinflammatory cytokines (Zhang et al., 2023). Cytokines can exacerbate hepatocyte damage through the recruitment of immune cells and increased activity of proapoptotic enzymes, which cause liver cell death (apoptosis). The combination of oxidative stress, inflammation, and apoptosis is the main cause of increased ALT and AST levels in obese mice and exacerbates liver cell damage, leading to necrosis. Increased ALT reflects direct hepatocellular damage, while increased AST indicates mitochondrial dysfunction or more extensive tissue damage (Kim et al., 2021).

In addition to oxidative stress, obesity also triggers insulin resistance, which increases lipolysis in adipose tissue and free fatty acid levels in the blood. This excess fatty acid enters the liver and causes hepatic steatosis, which triggers the activation of inflammatory pathways such as nuclear factor-kappa B (NF-κB) and increases the production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (Zhang et al., 2023). These cytokines exacerbate hepatocyte damage through immune cell recruitment and increased activity of proapoptotic enzymes such as caspase-3, ultimately leading to liver cell death (apoptosis).

The combination of oxidative stress, inflammation, and apoptosis is the main cause of elevated ALT and AST levels in obese mice. ALT is more specific to the liver, while AST is also found in other tissues such as the heart and muscles; therefore, elevated ALT reflects direct hepatocellular damage, while elevated AST indicates mitochondrial dysfunction or more widespread tissue damage (Kim et al., 2021).

In the obese + RPE group, a protective effect on the liver was observed. This is because ellagic acid, flavonoids, and polyphenols act as powerful antioxidants that neutralize ROS and reduce lipid peroxidation levels (X Zhang et al., 2024). With reduced ROS, the integrity of the hepatocyte membrane is maintained, thereby reducing liver cell damage. In addition, ellagic acid is able to activate the Nrf2/ARE antioxidant signaling pathway, which increases the expression of endogenous defense enzymes such as glutathione peroxidase (GPx) and heme oxygenase-1 (HO-1) (Xiao et al., 2022). This pathway plays a crucial role in maintaining redox balance, protecting mitochondria, and preventing the activation of the apoptosis pathway due to oxidative stress. Thus, the decrease in ALT and AST levels reflects the recovery of hepatocyte function and a reduction in the level of liver damage due to decreased oxidative stress and inflammation. In addition to their antioxidant effects, the polyphenolic compounds in RPE also exhibit anti-inflammatory activity by inhibiting NF-κB activation, which reduces the expression of proinflammatory cytokines such as TNF-α and IL-6 (Li et al., 2020).

This study provides new insights into the biological effects of ellagic acid and RPE at relatively low doses (15–30 mg/kg BW) in an obese rat model. Unlike previous studies that focused on high-dose administration, our findings highlight that even low concentrations can partially protect hepatocytes and modulate triglyceride metabolism, despite not significantly altering cholesterol, LDL, or HDL levels. The novelty lies in demonstrating the histological protection of liver tissue and the specific reduction in triglycerides at doses far below those commonly tested, thereby opening opportunities for safer, more practical applications of RPE as a functional food ingredient or herbal supplement.

This research contributes to scientific knowledge by clarifying the mechanisms through which ellagic acid and polyphenols in *N. lappaceum* peel act on lipid metabolism and hepatocyte integrity. The results strengthen evidence that agricultural by-products such as *N. lappaceum* peel can be repurposed into valuable bioactive sources, reducing waste while providing health benefits. For society, this study supports the development of natural, accessible, and sustainable interventions for obesity related liver damage, which is a growing public health concern. By demonstrating hepatoprotective and triglyceride-lowering effects, the findings encourage further exploration of RPE as a cheaper nutraceutical that can complement existing therapies.

This research supports SDGs 3 (Good Health and Well-being) by offering a natural intervention to reduce obesity-related metabolic and liver disorders, thereby promoting healthier lives and reducing the burden of non-communicable diseases. It also supports SDGs 12 (Responsible Consumption and Production) by utilizing *N. lappaceum* peel, an agricultural waste product, as a sustainable source of bioactive compounds. This approach not only reduces environmental waste but also creates added value from local resources, aligning with global efforts toward sustainable food systems and circular economy practices.

CONCLUSION

The administration of ellagic acid in RPE in obese model rats produced biological responses that improved metabolic conditions. RPE lowered several metabolic parameters, including triglycerides and partially ALT–AST levels, and improved the histological profile of liver tissue. These findings demonstrate that ellagic acid and RPE can modulate lipid metabolism and provide hepatoprotective effects in obese rats, thereby fulfilling the objectives of this study. Further research is needed to determine the optimal dose and duration of administration, as well as to clarify the specific molecular mechanisms involved. Future research should also explore comparative efficacy with other natural antioxidants and assess translational potential in preclinical or clinical settings, aspects that were not examined in this study.

ACKNOWLEDGEMENT

We would like to thank the Institute for Research and Community Service (LPPM), Universitas Negeri Semarang, for funding this research and publication through the DPA LPPM UNNES Fiscal Year 2025, in accordance with the Research Assignment Agreement for Fundamental-Regular Research, Contract

Number: 139.032.693449/2025.01, dated June 2, 2025.

AUTHOR CONTRIBUTION STATEMENT

All authors contributed significantly to the work reported in this manuscript. Lisdiana, Mirtaati Naimah, and Nugrahaningsih WH conceived and designed the study, and conducted the data analysis. Amalia Wilda Aulia and Fitria Salsabila were responsible for data collection. Djuna Lamondo, Annisaa Basar, and Yofi Ersyada Damayanti assisted in the literature review, supported data visualization, and provided substantial feedback during the manuscript drafting process. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study, referring to Ethical Clearance (EC) Number 1011/KEPK/FK/KLE/2025 issued by the Ethics Committee of the Faculty of Medicine, Universitas Negeri Semarang. Prior to participation, each subject was provided with a detailed explanation of the study's objectives, procedures, potential risks, and benefits.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this paper

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that no artificial intelligence (AI)-based tools were used in the preparation, analysis, or writing of this manuscript. All aspects of the study, including data collection, interpretation, and manuscript preparation, were carried out entirely by the authors without the assistance of AI-based technologies

REFERENCES

Amin, M. M., & Arbid, M. S. (2017). Estimation of ellagic acid and/or repaglinide effects on insulin signaling, oxidative stress, and inflammatory mediators of liver, pancreas, adipose tissue, and brain in insulin resistant/type 2 diabetic rats. *Applied Physiology, Nutrition and Metabolism*, *42*(2), 181–192. https://doi.org/10.1139/apnm-2016-0429

Bast, M., & Serra, D. (2020). Dietary Options for Rodents in the Study of Obesity. *Nutrients*, *12*(3234), 1–19.

Cavaliere, G., Cimmino, F., Trinchese, G., Catapano, A., Petrella, L., Angelo, M. D., Lucchin, L., & Mollica, M. P. (2023). From Obesity-Induced Low-Grade Inflammation to Lipotoxicity and Mitochondrial Dysfunction : Altered Multi-Crosstalk between Adipose Tissue and Metabolically Active Organs. *Antioxidants*, *12*(1172), 1–23.

Cerda-cejudo, N. D., Buenrostro-figueroa, J. J., Sep, L., Torres-le, C., Ch, L., Aguilar, N., & Ascacio-vald, J. A. (2024). Enhancing the Release of Ellagic Acid from Mexican Rambutan Peel Using Solid-State Fermentation. *Biomass*, *4*, 1005–1016.

Chigurupati, S., Vijayabalan, S., Selvarajan, K. K., & Hashish, N. E. (2019). Identification of nephelium lappaceum leaves phenolic and flavonoid component with radical scavenging , antidiabetic and antibacterial potential Identification of Nephelium lappaceum leaves phenolic and flavonoid component with radical scavenging , antidi. *Indian Journal of Traditional Knowledge*, *18*(2), 360–365.

Djajanti, A. D. D., & Ade Shafira. (2024). Aktivitas Sirup Ekstrak Kulit Buah Rambutan (Nephelium lappaceum L.) Terhadap Kadar Kolesterol Total Darah Mencit (Mus musculus). *Jurnal Kesehatan Yamasi Makassar*, *8*(1), 35–43. https://doi.org/10.59060/jurkes.v8i1.317

Farhan, M., Rizvi, A., & Giordano, M. E. (2022). Understanding the Prooxidant Action of Plant Polyphenols in the Cellular Microenvironment of Malignant Cells : Role of Copper and Therapeutic Implications. *Frontiers in Pharmacology*, *13*(June), 1–11. https://doi.org/10.3389/fphar.2022.929853

Ghadimi, M., Foroughi, F., Hashemipour, S., Rashidi Nooshabadi, M., Ahmadi, M. H., Ahadi Nezhad, B., & Khadem Haghighian, H. (2021). Randomized double-blind clinical trial examining the Ellagic acid effects on glycemic status, insulin resistance, antioxidant, and inflammatory factors in patients with type 2 diabetes. *Phytotherapy Research*, *35*(2), 1023–1032. https://doi.org/10.1002/ptr.6867

Jalili, V., Poorahmadi, Z., Hasanpour Ardekanizadeh, N., Gholamalizadeh, M., Ajami, M., Houshiarrad, A., Hajipour, A., Shafie, F., Alizadeh, A., Mokhtari, Z., Shafaei,

H., Esmaeili, M., & Doaei, S. (2022). The association between obesity with serum levels of liver enzymes, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transferase in adult women. *Endocrinology, Diabetes & Metabolism*, *5*(6), e367.

Jomova, K., Alomar, S. Y., Alwasel, S. H., Nepovimova, E., Kuca, K., & Valko, M. (2024). Several lines of antioxidant defense against oxidative stress : antioxidant enzymes, nanomaterials with multiple enzyme - mimicking activities , and low - molecular - weight antioxidants. In *Archives of Toxicology* (Vol. 98, Issue 5). Springer Berlin Heidelberg. https://doi.org/10.1007/s00204-024-03696-4

Karimi, M. Y., Fatemi, I., Kalantari, H., Mombeini, M. A., Mehrzadi, S., & Goudarzi, M. (2020). Ellagic Acid Prevents Oxidative Stress, Inflammation, and Histopathological Alterations in Acrylamide-Induced Hepatotoxicity in Wistar Rats. *Journal of Dietary Supplements*, *17*(6), 651–662. https://doi.org/10.1080/19390211.2019.1634175

Kim, D., Konyn, P., Sandhu, K. K., Dennis, B. B., Cheung, A. C., & Ahmed, A. (2021). Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. *J Hepatol*, *75*(6), 1284–1291. https://doi.org/10.1016/j.jhep.2021.07.035

Laguna-maldonado, K. D., Uribe-ramírez, D., Vázquez-carrada, M., Matuz-mares, D., & Vilchis-landeros, M. M. (2025). Dysfunction of the ABCA1 and ABCG1 Transporters and Their Impact on HDL Metabolism. *Antioxidants*, *14*(1362), 1–17.

Li, Y., Zhuang, Y., Tian, W., & Sun, L. (2020). In vivo acute and subacute toxicities of phenolic extract from rambutan (Nephelium lappaceum) peels by oral administration. *Food Chemistry*, *320*, 126618. https://doi.org/10.1016/j.foodchem.2020.126618

Ling, L. T., Radhakrishnan, A. K., Subramaniam, T., Cheng, H. M., & Palanisamy, U. D. (2010). Assessment of Antioxidant Capacity and Cytotoxicity of Selected Malaysian Plants. *Molecules*, *15*, 2139–2151. https://doi.org/10.3390/molecules15042139

Mistriyani, M., Riyanto, S., Windarsih, A., & Rohman, A. (2020). Antioxidant Activities and Identification of an Active Compound from Rambutan (Nephelium lappaceum L.) Peel. *Indonesian Journal of Chemistry*, *21*(2), 259. https://doi.org/10.22146/ijc.50421

Mushumba, P., Uwineza, D. N., Nsanzimana, V., Mapira, H. T., Gori, E., & Musarurwa, C. (2025). Stress, Cortisol, and Lipid Profiles Among Rwandan Undergraduate Students : A Cross-Sectional Study. *Risk Management and Healthcare Policy*, *18*(June), 1869–1880.

Oktavelia, W., & Kusuma, S. A. F. (2022). Therapy for Dyslipidemia: Plant Inhibitors of HMG-CoA Reductase. *Indonesian Journal of Biological Pharmacy*, *2*(3), 159–170.

Phuong, N. N. M., Le, T. T., Dang, M. Q., Camp, J. Van, & Raes, K. (2020). Selection of extraction conditions of phenolic compounds from rambutan (Nephelium lappaceum L.) peel. *Food and Bioproducts Processing*, *122*, 222–229. https://doi.org/10.1016/j.fbp.2020.05.008

Shahrajabian, M. H., Sun, W., & Khoshkharam, M. (2020). Rambutan, A Tropical Plant with Ethno-Pharmaceutical Properties. *Agrociencia*, *54*(1), 1–9.

Sharifi-Rad, J., Quispe, C., Castillo, C. M. S., Caroca, R., Lazo-Vélez, M. A., Antonyak, H., Polishchuk, A., Lysiuk, R., Oliinyk, P., De Masi, L., Bontempo, P., Martorell, M., Daştan, S. D., Rigano, D., Wink, M., & Cho, W. C. (2022). Ellagic Acid: A Review on Its Natural Sources, Chemical Stability, and Therapeutic Potential. *Oxidative Medicine and Cellular Longevity*, 1–24. https://doi.org/10.1155/2022/3848084

Su, Z., & Wang, S. (2024). The anti-obesity effects of polyphenols : a comprehensive review of molecular mechanisms and signal pathways in regulating adipocytes. *Frontiers in Nutrition*, *30*(October), 1–20. https://doi.org/10.3389/fnut.2024.1393575

susanti, G., & Bramantio, S. (2018). Pengaruh Pemberian Ekstrak Etanol Kulit Buah Rambutan (Nephelium lappaceum L.) terhadap Kadar Kolesterol Total Darah Tikus Putih Jantan Galur Sprague-Dawley. *Jurnal Kesehatan : Jurnal Ilmiah Multi Sciences*, *8*(2), 84–88. https://doi.org/10.52395/jkjims.v8i02.134

Tiwari, M. K., & Mishra, P. C. (2023). Modeling the scavenging activity of ellagic acid and its methyl derivatives towards hydroxyl , methoxy , and nitrogen dioxide radicals. *J Mol Model*, *19*, 2445–5456. https://doi.org/10.1007/s00894-013-2023-5

Tošovi, J., & Bren, U. (2020). Antioxidative Action of Ellagic Acid — A Kinetic DFT Study. *Antioxidants*, *9*(587), 1–13.

WHO. (2025). *World health statistics 2025. World Health Organization*.

Wulandari, P. S. (2024). Review Artikel: Daun Jati

Belanda dengan Potensi Penurunan Kadar Lipid dalam Darah. *Kunir: Jurnal Farmasi Indonesia*, *2*(1), 74–79. https://doi.org/10.36308/kjfi.v2i1.685

Xiao, Y., Huang, R., Wang, N., Deng, Y., Tan, B., Yin, Y., Qi, M., & Wang, J. (2022). Ellagic Acid Alleviates Oxidative Stress by Mediating Nrf2 Signaling Pathways and Protects against Paraquat-Induced Intestinal Injury in Piglets. *Antioxidants*, *11*(252), 1–15.

Xu, J., Wang, B., & Ao, H. (2025). Corticosterone effects induced by stress and immunity and in fl ammation: mechanisms of communication. *Frontiers in Endocrinology*, *16*(March), 1–34. https://doi.org/10.3389/fendo.2025.1448750

Ye, J., Zheng, J., Tian, X., Xu, B., Yuan, F., & Wang, B. (2022). Fucoxanthin Attenuates Free Fatty Acid-Induced Nonalcoholic Fatty Liver Disease by Regulating Lipid Metabolism / Oxidative. *Marine Drugs*, *20*(225), 1–14.

Zhang, M., Cui, S., Mao, B., Zhang, Q., & Zhao, J. (2023). Ellagic acid and intestinal microflora metabolite urolithin A : A review on its sources , metabolic distribution , health benefits , and biotransformation. *Critical Reviews in Food Science and Nutrition*, *63*(24), 6900–6922. https://doi.org/10.1080/10408398.2022.2036693

Zhang, T., Chen, J., Tang, X., Luo, Q., Xu, D., & Yu, B. (2019). Interaction between adipocytes and high-density lipoprotein : new insights into the mechanism of obesity-induced dyslipidemia and atherosclerosis. *Lipids in Health and Disease*, *9*(18), 1–11.

Zhang, X., Liu, Y., Liu, M., Ma, Q., Hao, Z., & Tang, S. (2024). Ellagic acid supplementation ameliorates cisplatin-induced liver injury in mice by inhibiting the NF-κB pathway and activating the Nrf2 / HO-1 pathway. *One Health Advances*, *2*(20). https://doi.org/10.1186/s44280-024-00056-w

Zhao, S., Zhong, J., Sun, C., & Zhang, J. (2021). Effects of aerobic exercise on TC, HDL-C, LDL-C and TG in patients with hyperlipidemia: A protocol of systematic review and meta-analysis. *Medicine (United States)*, *100*(10), E25103. https://doi.org/10.1097/MD.0000000000025103

Amin, M. M., & Arbid, M. S. (2017). Estimation of ellagic acid and/or repaglinide effects on insulin signaling, oxidative stress, and inflammatory mediators of liver, pancreas, adipose tissue, and brain in insulin resistant/type 2 diabetic rats. *Applied Physiology, Nutrition and Metabolism*, *42*(2), 181–192. https://doi.org/10.1139/apnm-2016-0429

Bast, M., & Serra, D. (2020). Dietary Options for Rodents in the Study of Obesity. *Nutrients*, *12*(3234), 1–19.

Cavaliere, G., Cimmino, F., Trinchese, G., Catapano, A., Petrella, L., Angelo, M. D., Lucchin, L., & Mollica, M. P. (2023). From Obesity-Induced Low-Grade Inflammation to Lipotoxicity and Mitochondrial Dysfunction : Altered Multi-Crosstalk between Adipose Tissue and Metabolically Active Organs. *Antioxidants*, *12*(1172), 1–23.

Cerda-cejudo, N. D., Buenrostro-figueroa, J. J., Sep, L., Torres-le, C., Ch, L., Aguilar, N., & Ascacio-vald, J. A. (2024). Enhancing the Release of Ellagic Acid from Mexican Rambutan Peel Using Solid-State Fermentation. *Biomass*, *4*, 1005–1016.

Chigurupati, S., Vijayabalan, S., Selvarajan, K. K., & Hashish, N. E. (2019). Identification of nephelium lappaceum leaves phenolic and flavonoid component with radical scavenging , antidiabetic and antibacterial potential Identification of Nephelium lappaceum leaves phenolic and flavonoid component with radical scavenging , antidi. *Indian Journal of Traditional Knowledge*, *18*(2), 360–365.

Djajanti, A. D. D., & Ade Shafira. (2024). Aktivitas Sirup Ekstrak Kulit Buah Rambutan (Nephelium lappaceum L.) Terhadap Kadar Kolesterol Total Darah Mencit (Mus musculus). *Jurnal Kesehatan Yamasi Makassar*, *8*(1), 35–43. https://doi.org/10.59060/jurkes.v8i1.317

Farhan, M., Rizvi, A., & Giordano, M. E. (2022). Understanding the Prooxidant Action of Plant Polyphenols in the Cellular Microenvironment of Malignant Cells : Role of Copper and Therapeutic Implications. *Frontiers in Pharmacology*, *13*(June), 1–11. https://doi.org/10.3389/fphar.2022.929853

Ghadimi, M., Foroughi, F., Hashemipour, S., Rashidi Nooshabadi, M., Ahmadi, M. H., Ahadi Nezhad, B., & Khadem Haghighian, H. (2021). Randomized double-blind clinical trial examining the Ellagic acid effects on glycemic status, insulin resistance, antioxidant, and inflammatory factors in patients with type 2 diabetes. *Phytotherapy Research*, *35*(2), 1023–1032. https://doi.org/10.1002/ptr.6867

Jalili, V., Poorahmadi, Z., Hasanpour Ardekanizadeh, N., Gholamalizadeh, M., Ajami, M., Houshiarrad, A., Hajipour, A., Shafie, F., Alizadeh, A., Mokhtari, Z., Shafaei, H., Esmaeili, M., & Doaei, S. (2022). The association between obesity with serum levels

of liver enzymes, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma-glutamyl transferase in adult women. *Endocrinology, Diabetes & Metabolism*, *5*(6), e367.

Jomova, K., Alomar, S. Y., Alwasel, S. H., Nepovimova, E., Kuca, K., & Valko, M. (2024). Several lines of antioxidant defense against oxidative stress : antioxidant enzymes, nanomaterials with multiple enzyme - mimicking activities , and low - molecular - weight antioxidants. In *Archives of Toxicology* (Vol. 98, Issue 5). Springer Berlin Heidelberg. https://doi.org/10.1007/s00204-024-03696-4

Karimi, M. Y., Fatemi, I., Kalantari, H., Mombeini, M. A., Mehrzadi, S., & Goudarzi, M. (2020). Ellagic Acid Prevents Oxidative Stress, Inflammation, and Histopathological Alterations in Acrylamide-Induced Hepatotoxicity in Wistar Rats. *Journal of Dietary Supplements*, *17*(6), 651–662. https://doi.org/10.1080/19390211.2019.1634175

Kim, D., Konyn, P., Sandhu, K. K., Dennis, B. B., Cheung, A. C., & Ahmed, A. (2021). Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. *J Hepatol*, *75*(6), 1284–1291. https://doi.org/10.1016/j.jhep.2021.07.035

Laguna-maldonado, K. D., Uribe-ramírez, D., Vázquez-carrada, M., Matuz-mares, D., & Vilchis-landeros, M. M. (2025). Dysfunction of the ABCA1 and ABCG1 Transporters and Their Impact on HDL Metabolism. *Antioxidants*, *14*(1362), 1–17.

Li, Y., Zhuang, Y., Tian, W., & Sun, L. (2020). In vivo acute and subacute toxicities of phenolic extract from rambutan (Nephelium lappaceum) peels by oral administration. *Food Chemistry*, *320*, 126618. https://doi.org/10.1016/j.foodchem.2020.126618

Ling, L. T., Radhakrishnan, A. K., Subramaniam, T., Cheng, H. M., & Palanisamy, U. D. (2010). Assessment of Antioxidant Capacity and Cytotoxicity of Selected Malaysian Plants. *Molecules*, *15*, 2139–2151. https://doi.org/10.3390/molecules15042139

Mistriyani, M., Riyanto, S., Windarsih, A., & Rohman, A. (2020). Antioxidant Activities and Identification of an Active Compound from Rambutan (Nephelium lappaceum L.) Peel. *Indonesian Journal of Chemistry*, *21*(2), 259. https://doi.org/10.22146/ijc.50421

Mushumba, P., Uwineza, D. N., Nsanzimana, V., Mapira, H. T., Gori, E., & Musarurwa, C. (2025). Stress, Cortisol, and Lipid Profiles Among Rwandan Undergraduate Students : A Cross-Sectional Study. *Risk Management and Healthcare Policy*, *18*(June), 1869–1880.

Oktavelia, W., & Kusuma, S. A. F. (2022). Therapy for Dyslipidemia: Plant Inhibitors of HMG-CoA Reductase. *Indonesian Journal of Biological Pharmacy*, *2*(3), 159–170.

Phuong, N. N. M., Le, T. T., Dang, M. Q., Camp, J. Van, & Raes, K. (2020). Selection of extraction conditions of phenolic compounds from rambutan (Nephelium lappaceum L.) peel. *Food and Bioproducts Processing*, *122*, 222–229. https://doi.org/10.1016/j.fbp.2020.05.008

Shahrajabian, M. H., Sun, W., & Khoshkharam, M. (2020). Rambutan, A Tropical Plant with Ethno-Pharmaceutical Properties. *Agrociencia*, *54*(1), 1–9.

Sharifi-Rad, J., Quispe, C., Castillo, C. M. S., Caroca, R., Lazo-Vélez, M. A., Antonyak, H., Polishchuk, A., Lysiuk, R., Oliinyk, P., De Masi, L., Bontempo, P., Martorell, M., Daştan, S. D., Rigano, D., Wink, M., & Cho, W. C. (2022). Ellagic Acid: A Review on Its Natural Sources, Chemical Stability, and Therapeutic Potential. *Oxidative Medicine and Cellular Longevity*, 1–24. https://doi.org/10.1155/2022/3848084

Su, Z., & Wang, S. (2024). The anti-obesity effects of polyphenols : a comprehensive review of molecular mechanisms and signal pathways in regulating adipocytes. *Frontiers in Nutrition*, *30*(October), 1–20. https://doi.org/10.3389/fnut.2024.1393575

susanti, G., & Bramantio, S. (2018). Pengaruh Pemberian Ekstrak Etanol Kulit Buah Rambutan (Nephelium lappaceum L.) terhadap Kadar Kolesterol Total Darah Tikus Putih Jantan Galur Sprague-Dawley. *Jurnal Kesehatan : Jurnal Ilmiah Multi Sciences*, *8*(2), 84–88. https://doi.org/10.52395/jkjims.v8i02.134

Tiwari, M. K., & Mishra, P. C. (2023). Modeling the scavenging activity of ellagic acid and its methyl derivatives towards hydroxyl , methoxy , and nitrogen dioxide radicals. *J Mol Model*, *19*, 2445–5456. https://doi.org/10.1007/s00894-013-2023-5

Tošovi, J., & Bren, U. (2020). Antioxidative Action of Ellagic Acid — A Kinetic DFT Study. *Antioxidants*, *9*(587), 1–13.

WHO. (2025). *World health statistics 2025. World Health Organization*.

Wulandari, P. S. (2024). Review Artikel: Daun Jati Belanda dengan Potensi Penurunan Kadar Lipid dalam Darah. *Kunir: Jurnal Farmasi Indonesia*,

2(1), 74–79. https://doi.org/10.36308/kjfi.v2i1.685

Xiao, Y., Huang, R., Wang, N., Deng, Y., Tan, B., Yin, Y., Qi, M., & Wang, J. (2022). Ellagic Acid Alleviates Oxidative Stress by Mediating Nrf2 Signaling Pathways and Protects against Paraquat-Induced Intestinal Injury in Piglets. *Antioxidants*, *11*(252), 1–15.

Xu, J., Wang, B., & Ao, H. (2025). Corticosterone effects induced by stress and immunity and in fl ammation: mechanisms of communication. *Frontiers in Endocrinology*, *16*(March), 1–34. https://doi.org/10.3389/fendo.2025.1448750

Ye, J., Zheng, J., Tian, X., Xu, B., Yuan, F., & Wang, B. (2022). Fucoxanthin Attenuates Free Fatty Acid-Induced Nonalcoholic Fatty Liver Disease by Regulating Lipid Metabolism / Oxidative. *Marine Drugs*, *20*(225), 1–14.

Zhang, M., Cui, S., Mao, B., Zhang, Q., & Zhao, J. (2023). Ellagic acid and intestinal microflora metabolite urolithin A : A review on its sources , metabolic distribution , health benefits , and biotransformation. *Critical Reviews in Food Science and Nutrition*, *63*(24), 6900–6922. https://doi.org/10.1080/10408398.2022.2036693

Zhang, T., Chen, J., Tang, X., Luo, Q., Xu, D., & Yu, B. (2019). Interaction between adipocytes and high-density lipoprotein : new insights into the mechanism of obesity-induced dyslipidemia and atherosclerosis. *Lipids in Health and Disease*, *9*(18), 1–11.

Zhang, X., Liu, Y., Liu, M., Ma, Q., Hao, Z., & Tang, S. (2024). Ellagic acid supplementation ameliorates cisplatin-induced liver injury in mice by inhibiting the NF-κB pathway and activating the Nrf2 / HO-1 pathway. *One Health Advances*, *2*(20). https://doi.org/10.1186/s44280-024-00056-w

Zhao, S., Zhong, J., Sun, C., & Zhang, J. (2021). Effects of aerobic exercise on TC, HDL-C, LDL-C and TG in patients with hyperlipidemia: A protocol of systematic review and meta-analysis. *Medicine (United States)*, *100*(10), E25103. https://doi.org/10.1097/MD.0000000000025103