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Histopathological Profile of Wistar Rat Kidney in High-Fat Diet Model Treated with a Combination of Tea and Mango Mistletoe Extracts

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Abstract

A high-fat diet (HFD) can cause kidney damage through oxidative stress and inflammation. This study aimed to analyze the histopathology of the kidneys in rats given HFD after administering a combination of tea mistletoe leaf extract *(Scurrula atropurpurea)* and mango mistletoe *(Dendrophthoe pentandra)* (MESA-DP). Using a randomized pretest-posttest control group design, the rats were divided into a negative control group (G1), an HFD control group (G2), and three treatment groups with combined doses of MESA-DP: 50, 100, and 200 mg/kg body weight (G3, G4, G5). During the 37-day treatment period, microscopic examinations were conducted. The results showed that (G2) experienced an increase in fat accumulation (12%) and glomerulus diameter (1783.1 μm), compared to G1 (6%; 1507.5 μm). G3 actually worsened the condition (22%; 2003.1 μm). G4 successfully reduced fat accumulation to 9% and glomerulus diameter to 1689.4 μm, while G5 approached normal levels (7%; 1674.4 μm). ANOVA tests on the kidney fat area and glomerulus diameter showed $p=0.018$ ($p<0.05$), indicating significant differences among the groups. These results demonstrate that the combination of MESA-DP at a dose of 100 mg/kg body weight (G4) can balance the side effects of HFD on kidney tissue and minimize inflammatory side effects in the glomerulus.

Keywords: High-fat diet; histopathology; kidney; mango mistletoe; tea mistletoe.

Abbreviations: MESA-DP: Methanolic Extract of *Scurrula atropurpurea* and *Dendrophthoe pentandra*, HFD: High-fat diet, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells

INTRODUCTION

A high-fat diet (HFD) is a dietary pattern characterized by a high proportion of fat in the total daily caloric intake, primarily saturated fat (Han et al., 2023). Prolonged consumption of HFD can lead to ectopic fat accumulation in non-adipose tissues such as the liver, muscles, and kidneys, which then triggers oxidative stress, inflammation, mitochondrial dysfunction, and cell death. The main mechanism involves increased β-oxidation in the mitochondria, leading to excessive production of reactive oxygen species (ROS). This condition is known as lipotoxicity, which is a cellular disorder caused by lipid accumulation exceeding the metabolic capacity of the tissue (Patil et al., 2025; Yang et al., 2021).

In the kidneys, lipotoxicity caused by a HFD can lead to serious damage because the accumulation of lipids in the proximal tubules and glomerular tissue can disrupt filtration function, trigger inflammation, and contribute to fibrosis (Gai et al., 2019). Additionally, HFD is also known to activate the renin-angiotensin-aldosterone system (RAAS), thereby increasing mechanical pressure on the glomeruli and renal tubules, which can ultimately accelerate the development of chronic kidney disease (Sofiani & Harun, 2025).

Previous research by Altunkaynak et al., (2008), showed that Sprague-Dawley rats fed an HFD for 3 months exhibited degenerative changes such as glomerular capillary dilation, mononuclear cell infiltration, glomerulosclerosis, segmental necrosis, tubular defects, and thickening of the glomerular and tubular basement membranes. Declèves et al., (2014) also demonstrated that HFD can trigger glomerulomegaly, interstitial fibrosis, and increased albuminuria excretion, which are early markers of kidney injury.

Various efforts have been made to find agents that can protect the kidneys from damage caused by HFD. One potential candidate is parasitic plants, particularly mistletoe *(Scurrula atropurpurea)* and mango mistletoe *(Dendropthoe pentandra)*, which have long been used in traditional medicine and are known to contain bioactive compounds such as flavonoids, saponins, tannins, and alkaloids (Athiroh et al., 2024). These compounds have high antioxidant activity capable of neutralizing reactive oxygen species (ROS), while also providing anti-inflammatory effects in inhibiting fibrosis progression

and improving cellular integrity in kidneys damaged by HFD (Roikhana et al., 2022)

Although previous studies have proven that tea mistletoe *(Scurrula atropurpurea*) and mango mistletoe *(Dendrophthoe pentandra)* each possess antioxidant, anti-inflammatory, and antihyperlipidemic activities that have the potential to protect the kidneys from damage caused by oxidative stress (Ma'ruf et al., 2025). There has been no research to date that evaluates the combined effects of these two extracts on the histopathological features of the kidney under HFD conditions. Earlier studies have focused more on the individual effects of each plant. Additionally, research on the optimal dosage of the combined extract of tea mistletoe and mango mistletoe that can quantitatively improve kidney histopathology is still limited, considering most previous studies only measured blood biochemical parameters without supporting objective histomorphometric analysis of the kidney. Therefore, this study aims to analyze the histopathology of the kidneys in HFD model rats after administration of a combination of tea and mango mistletoe leaf extracts and to determine the effective dose that provides the optimal nephroprotective effect.

MATERIALS AND METHODS

Study Design

This study is an experimental research with a Randomized Pretest-Posttest Control Group Design aimed at assessing the effect of a combination of MESA-DP extract on the histopathology of wistar white rat kidneys induced by HFD. This research has received approval from the Ethical Review Committee of the Islamic Hospital of Malang (Ethical Clearance) with the number: 36/KEPK/RSI-U/VI/2025.

Tools and Materials

The tools and materials used in this study were categorized based on several stages, including animal maintenance, extraction, dose preparation, surgery, and slide preparation. For animal maintenance, cages measuring 40 x 30 x 25 cm, cage covers, digital scales, sondes, water bottles, and feed containers are used, while the materials include Wistar rats, high-fat diet (HFD) consisting of PARS (57.3%), wheat flour (31%), cholesterol powder (2%), and pork fat (8.9%), as well as supporting materials such as husk and tissue paper. Extraction processes utilized equipment such as blenders, ovens, freezers, and rotary evaporators, with materials including mistletoe tea leaves, mango mistletoe leaves, and 90% methanol. Dose preparation involved measuring glasses, micropipettes, distilled water, and extract solutions. During surgery, tools such as scissors, forceps, and syringes were used, along with materials like 75% alcohol, ketamine, xylazine, and neutral buffered formalin (NBF) 10%. Histology slide preparation employed equipment such as microtomes, tissue cassettes, water baths (40-45°C), staining jars, embedding centers, ovens, glass slides, cover slips, and microscopes. The required materials included kidney tissue, 10% NBF, alcohol, xylene, paraffin, hematoxylin-eosin, and neutral gum (adhesive).

Procedures

Test Animal Care

The maintenance of test animals was carried out at the FKG Universitas Brawijaya Lab Animal House, starting with a 10-day acclimatization period. During maintenance, wistar rats were placed in cages and given feed. For the negative control treatment (G1), standard feed was used, which is pars; for the positive control treatment (G2), a high-fat diet (HFD) was used with a composition of 310 grams of PARS, 171 grams of wheat flour, 11 grams of cholesterol powder, 49 grams of lard, and water, with the proportions based on the total of all these components (Susanti et al., 2012).

Preparation of Mistletoe Tea Leaf Extract and Mango Mistletoe

The sorted tea and mango mistletoe leaves were selected for good physical condition and then taken to the Batu East Java Medicinal Plant Center laboratory for extraction. Extraction was carried out using maceration with 90% methanol. The herbal material is soaked in the solvent, shaken for 60 minutes, then left for 24 hours to allow the active compounds to dissolve optimally into the solvent. After that, the supernatant was separated and evaporated using a rotary evaporator at 35°C until a thick extract is obtained. (Athiroh et al., 2014, 2024)

Preparation of Doses

The combination extract was prepared in a ratio of 3:1 between mistletoe tea and mango mistletoe. The treatment doses used were 50 mg/KgBW, 100 mg/KgBW, and 200 mg/KgBW. The extract solution was prepared in a specific volume using distilled water, then adjusted according to each rat's body weight before being administered orally.

Administration of Extract Dose

The extract was administered daily for 37 days via oral gavage using a gastric tube. During the treatment period, the rats' body weight was measured periodically to adjust the extract dose to remain consistent with the animals' body weight.

Surgery

After the treatment period was completed, the rats were anesthetized using ketamine and xylazine until unresponsive. The animals were then dissected through an incision in the abdominal area to the thorax using sterile surgical tools. The kidneys were removed, weighed, and then immediately placed into 10% neutral

buffered formalin (NBF) for fixation (Sulistyowati et al., 2020; Ugwu et al., 2026).

Histological preparation

Histological preparation of the kidney was carried out through several stages. First, the organ is fixed with 70% formalin. Next, the kidney is dehydrated using graded alcohol. Then, the clearing process was performed by immersing the sample in xylene three times, each for 1 hour. After clearing, wax infiltration was done by immersing the sample in wax, then embedding it in paraffin. The next step was embedding in molds; after wax infiltration, the sample was embedded in a mold partially filled with liquid paraffin. The kidney was then sectioned using a microtome, cutting slices approximately 5 µm thick. Finally, the tissue sections were stained using the hematoxylin and eosin method (Roeslan et al., 2026).

Observation

Observation of kidney preparations using an Olympus BX53 microscope at 200x magnification for tissue fat analysis and 400x for glomerulus observation. Analysis was performed using QuPath software. The fat area was identified in five fields of view by marking the fat deposition area using annotation features. The obtained area was calculated in µm² and expressed as a percentage of the total field of view area. Meanwhile, the diameter of the glomerulus was measured by selecting the intact and clear glomerulus structure in the histological preparation. Measurements were made using the line measurement feature in QuPath by drawing a line along the longest part of the glomerulus. Each preparation was observed in two fields of view, and then the average glomerulus diameter was calculated for each group.

Data analysis

Fat adipose area and glomerular diameter data are presented as mean ± standard deviation. Prior to further analysis, data normality was assessed using the Shapiro–Wilk test. If the data were normally distributed, comparisons were performed using one-way ANOVA. If the normality assumption was not met, the nonparametric Kruskal–Wallis test was used. Post hoc analyses were conducted to determine pairwise differences between groups. All statistical analyses were performed using SPSS, and significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

Results

Based on the results of microscopic observation of kidneys from obesity-induced rats treated with tea mistletoe leaf extract and mango mistletoe leaf extract for 37 days, the high-fat diet group exhibited significant changes in kidney histopathological structure compared to the normal group. Administration of the combination of tea and mango mistletoe leaf extracts in the treatment group showed potential improvement in kidney structure, as indicated by changes in fat accumulation parameters and glomerular diameter.

Histopathological Image of Kidney Adipose Tissue

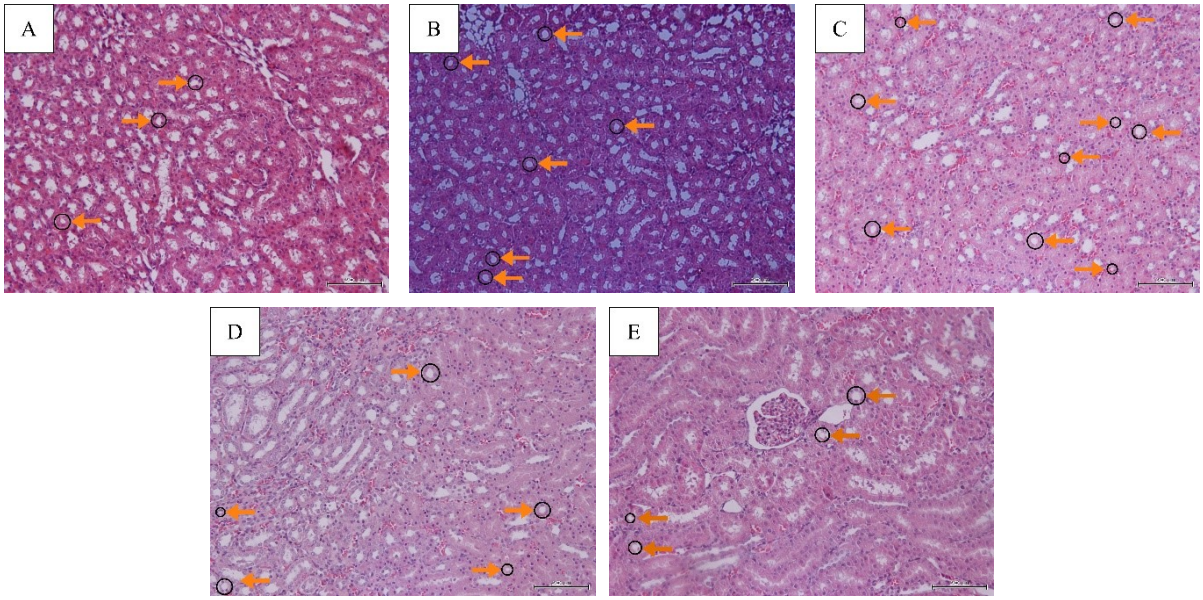

Figure 1. Renal adipose tissue. A. Negative control group (G1); B. Positive control group HFD (G2); C. HFD+MESA-DP dose 50 mg/KgBW (G3); D. HFD+MESA-DP dose 100 mg/KgBW (G4); E. HFD+MESA-DP dose 200 mg/KgBW(G5). (Olympus BX53,20x10). Orange arrow: renal adipose tissue.

Histopathological observation of the kidney in the negative control group showed almost no accumulation of excess fat tissue. In the positive HFD group (B) and the treatment group with a dose of 50 mg/KgBW (C), there was an increase in fat tissue accumulation (indicated by the orange arrow), while in the doses of 100 and 200 mg/KgBW groups (D, E), there was a decrease in fat tissue accumulation respectively.

Accumulation of Adipose Tissue in Kidney

Table 1. Percentage and average fat content.

Treatment	%	$(\bar{x}) \pm SD$	Notation
G1 (Control)	**6%**	2,4 ± 1,2	a
G2 (HFD)	**12%**	5,2 ± 2,3	b
G3 (HFD+50 mg/KgBW)	**22%**	8 ± 1,6	c
G4 (HFD+100 mg/KgBW)	**9%**	4,4 ± 1,9	a
G5 (HFD+200 mg/KgBW)	**7%**	3,8 ± 1,7	a

Key: G1: Treatment rats without HFD + MESA-DP, G2: HFD treatment rats, G3: HFD + MESA-DP dose 50 mg/KgBW treatment rats, G4: HFD + MESA-DP dose 100 mg/KgBW treatment rats, G5: HFD + MESA-DP dose 200 mg/KgBW treatment rats. %: Percentage, ($\bar{x}$): Average, SD: Standard deviation

The data in Table 1 shows that the G3 group has the highest percentage of fat area (22%) with larger and more extensive fat vacuoles, followed by G2 at 12%, while G4 and G5 each have 9% and 7%, respectively, approaching the control group G1 at 6%, which shows a significant reduction in the number and size of fat tissue, even approaching the histological appearance of the control group G1, which almost shows no fat tissue accumulation.

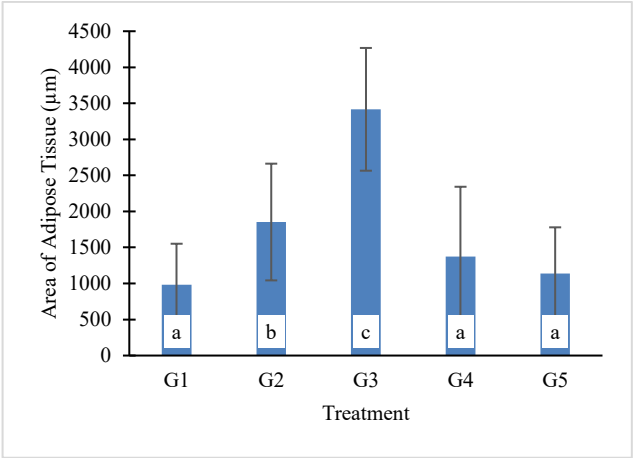

Figure 2. Histogram data of kidney adipose tissue.

The data on fat area width are not normally distributed, so they were analyzed using the Kruskal-Wallis test. The test results showed a significant difference between groups with a p-value of 0.018. The follow-up test results indicated that groups G4 and G5 did not differ significantly from the negative control group, while group G3 was significantly different from the other groups.

Histopathological Image of Glomerular Diameter

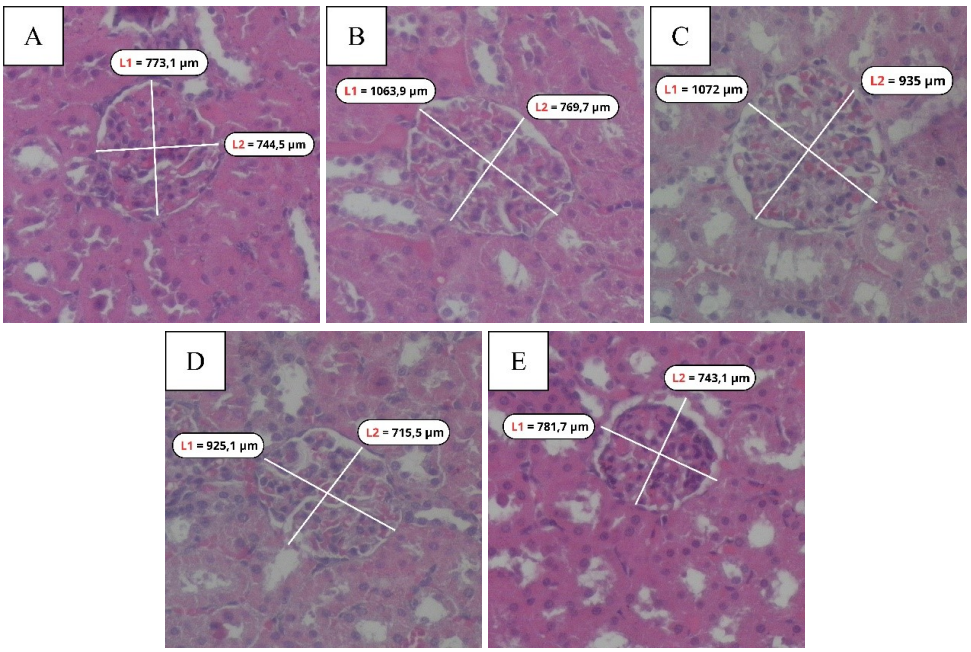

Figure 3. glomerular diameter length. A. Negative control group (G1), B. Positive control group HFD (G2), C. HFD+MESA-DP dose 50 mg/KgBW, D. HFD+MESA-DP dose 100 mg/KgBW, E. HFD+MESA-DP dose 200 mg/KgBW (Olympus BX53,40x10). L : Length.

Measurement of glomerulus diameter showed an increase in the HFD group compared to the negative control group. The group with a dose of 50 mg/KgBW (G3) showed the largest diameter. Meanwhile, the groups with doses of 100 mg/KgBW (G4) and 200 mg/KgBW (G5) showed a decrease in glomerulus diameter with values more similar to the negative control group.

Glomerulus Diameter Results

Table 2. Average glomerulus diameter value.

Treatment	$(\bar{x})$ ± SD	Notation
G1 (Control)	1507,5±10,05	a
G2 (HFD)	1783,1±50,45	b
G3 (HFD+50 mg/KgBW)	2003,1±3,85	c
G4 (HFD+100 mg/KgBW)	1689,4±48,8	a
G5 (HFD+200 mg/KgBW)	1674,4±15,1	a

Key: G1: Treatment rats without HFD + MESA-DP, G2: HFD treatment rats, G3: HFD + MESA-DP dose 50 mg/KgBW treatment rats, G4: HFD + MESA-DP dose 100 mg/KgBW treatment rats, G5: HFD + MESA-DP dose 200 mg/KgBW treatment rats. $(\bar{x})$: Average, SD : Standard deviation.

The data in Table 2 shows that the HFD group (G2) experienced a significant increase in the average glomerulus diameter (1783.1 ± 50.45) compared to the control group (G1) which was fed a standard diet (1507.5 ± 10.05). In the treatment groups given MESA-DP, there was a decrease in glomerulus diameter compared to the HFD group, even approaching normal values. The G3 group (HFD + 50 mg/KgBW) showed an average diameter of 2003.1 ± 3.85, slightly higher than the positive control. Meanwhile, groups G4 (HFD + 100 mg/KgBW) (1689.4 ± 48.8) and G5(HFD + 200 mg/KgBW) (1689.4 ± 48.8) showed smaller diameters than G3 and progressively approached the control values.

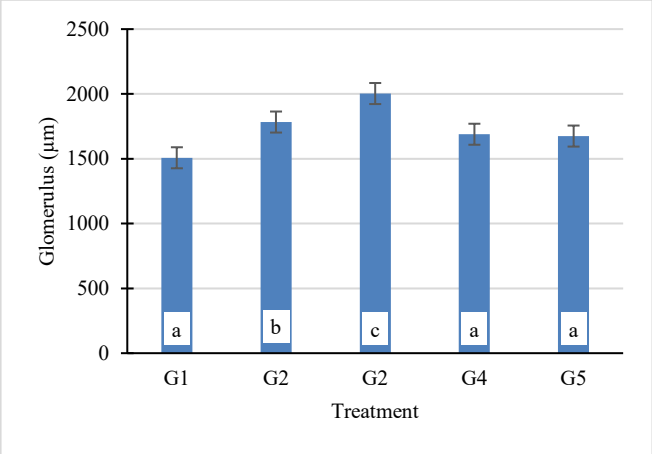

Figure 4. Average glomerular diameter.

The ANOVA test results showed a significant difference between groups (p = 0.018). The post hoc test indicated that P3 has the highest glomerulus diameter and is significantly different from the other groups, while G4 and G5 show values closer to the control.

Overall, the administration of a combination of MESA-DP showed an effect on the histopathological changes in the kidneys of rats induced by HFD. The doses of 100 mg/KgBW and 200 mg/KgBW tended to improve fat accumulation and glomerular diameter, while the 50 mg/KgBW dose showed worse results compared to the HFD group. Based on the data, the 100 mg/KgBW dose (G4) appears to provide the most stable effect on kidney histopathological parameters.

Discussion

The research results indicate that the administration of HFD causes an increase in fat tissue accumulation in the kidneys and an enlargement of the glomerulus diameter compared to the normal control group. These findings are consistent with the concept that HFD can trigger lipotoxicity through increased free fatty acids, oxidative stress, and chronic inflammation in the kidneys (Sun et al., 2020). Excess lipid accumulation in kidney tissue can disrupt cellular homeostasis, increase the production of reactive oxygen species (ROS), and stimulate the release of pro-inflammatory cytokines that contribute to kidney structural damage. Ultimately, this condition can impair filtration function and accelerate histopathological changes in the kidney (Rico-Fontalvo et al., 2026).

Extract of the combination of mistletoe tea and mango mistletoe is suspected to provide a protective effect through the content of bioactive compounds such as flavonoids, saponins, alkaloids, and phenolic compounds (Anjani et al., 2021). Flavonoid compounds act as antioxidants by capturing free radicals and inhibiting lipid peroxidation, while other bioactive components can help reduce inflammation and maintain the integrity of kidney cells. Theoretically, this mechanism can decrease oxidative stress caused by HFD, thereby improving the histopathological appearance of the kidneys (Mabruroh et al., 2025).

Based on histological observations in Figure 1, there is an accumulation of fat tissue in the kidneys of rats across different treatment groups. The negative control group (G1), with an average of 2.4 ± 1.2, shows normal amounts of fat tissue without fat accumulation, while the positive control group with a HFD (G2) shows an increased accumulation of fat tissue at 5.2 ± 2.2. This indicates that a high-fat diet causes lipid accumulation in the kidneys, which can trigger oxidative stress, inflammation, and kidney cell damage. (Abdullah et al., 2025). The treatment group with a dose of MESA-DP 50 mg/KgBW (G3) showed less effective results, with an average increase higher than the HFD group by (8 ± 1.6). This indicates that this dose is not yet sufficient to produce an optimal protective effect. Biologically, it is likely that the active compound at this low dose is not able to counteract the oxidative and inflammatory burdens caused by HFD, so the expected protective effects have not yet manifested clearly. Therefore, the

low dose cannot yet suppress the lipotoxicity process in the kidney tissue (Sun dkk., 2020).

Meanwhile, in the treatment groups of 100 and 200 mg/KgBW (G4 & G5), fat tissue accumulation began to gradually decrease from 4.4 in G4 to 3.8 in G5, approaching normal conditions. Histological images in these groups showed improved kidney cell structure, with minimal fat droplets and more intact cell membranes. This improvement proves that the combination of MESA-DP extract provides a more stable effect, thereby reducing kidney cell membrane damage. Additionally, bioactive compounds in MESA-DP also have the potential to suppress inflammatory pathways such as NF-κB and enhance endogenous antioxidant defenses through Nrf2 activation. As a result, oxidative stress initially triggered by HFD can be suppressed, leading to less severe histological damage to the kidneys. (Anjani dkk., 2021).

Table 2 showed that the measurement results of the glomerulus diameter in group HFD (G2) (1783.1 ± 50.45) illustrate an increase compared to the control group (G1) (1507.5 ± 10.05). This indicates glomerular enlargement (glomerulomegaly). Glomerular enlargement is an adaptive response of the kidney to obesity conditions and increased filtration load (Wei et al., 2021). In HFD conditions, increased renal plasma flow and intraglomerular pressure can trigger glomerular hypertrophy as an initial compensation for metabolic stress. (D'Agati et al., 2016). The G3 (HFD + 50 mg/KgBW) showed a diameter of (2003.1 ± 3.85), which was higher than the positive control HFD, indicating that this dose was not yet able to provide a protective effect on the glomerulus structure due to HFD.

In treatment dose 100 mg/KgBW (G4) (1689.4 ± 48.8) and dose 200 mg/KgBW (G5) (1689.4 ± 48.8), there was a decrease in glomerulus diameter, even approaching normal values. These results indicate an improvement in glomerular structure after administration of the extract, which works by reducing the metabolic burden on the kidneys, thereby suppressing the need for harmful compensatory mechanisms. The combined extract of MESA-DP leaves works through mechanisms that reduce oxidative stress and inflammation to decrease the metabolic load on the kidneys, eliminating the stimulus for glomerular enlargement. (Priambudi et al., 2025). Overall, these results support the nephroprotective effect of the combination of mistletoe tea extract and mango mistletoe.

Based on the statistical results, there was a significant effect on both parameters, indicated by ($p<0.05$). The results state that the administration of a combination of mistletoe leaf extract and mango mistletoe extract has a real influence on the histopathological profile of Wistar rat kidneys, particularly in reducing fat tissue accumulation and glomerulus diameter enlargement compared to the control group. In other words, both types of mistletoe extracts together are effective in modifying the histological structure of the kidney under high-fat diet conditions.

Research evaluating the combined effects of MESA-DP leaf extract on kidney histopathology in the HFD model is still limited. Most previous studies primarily assessed the individual effects of each plant or focused only on biochemical parameters, thus not providing a sufficient picture of morphometric changes in the kidney, particularly fat tissue accumulation and glomerular diameter. Therefore, this study fills that gap by evaluating the effects of combined extracts at various doses to determine the most effective dose in repairing kidney damage caused by HFD.

The potential of mistletoe tea is known to have a stronger antioxidant activity through its ability to increase nitric oxide (NO) levels and decrease malondialdehyde (MDA) as markers of oxidative stress. (Athiroh et al., 2014), Conversely, mango mistletoe has been reported to have a more dominant antihyperlipidemic effect (Priambudi et al., 2025). Research by Athiroh et al., (2024) shows that administering a combination of methanol extracts of both mistletoe species significantly affects HDL and LDL levels, indicating a role in lipid metabolism. The combination of the two extracts provides a dual attack effect: the tea mistletoe reduces oxidative stress and inflammation through inhibition of the NF-κB pathway and activation of Nrf2, while the mango mistletoe decreases systemic and ectopic lipid accumulation through regulation of fat metabolism. Mabruroh et al., (2025) emphasize that flavonoids in both mistletoe species synergistically maintain kidney function through antioxidant, anti-inflammatory, diuretic mechanisms, and regulation of electrolyte transport.

The improvements observed in the groups with doses of 100 mg/kgBW (G4) and 200 mg/kgBB (G5) indicate that the combination of both types of mistletoe has a potential synergistic effect in improving both parameters. The dose from the 100 mg/KgBW (G4) was chosen as the effective dose because it was able to reduce the percentage of fat while also restoring the glomerulus diameter to normal size without causing side effects, making it more efficient and potentially having a lower risk of toxicity compared to the dose 200 mg/KgBW (G5).

This indicates that the administration of a combination of tea mistletoe leaf extract and mango mistletoe extract at a dose of 100 mg/KgBW (G4) significantly provides nephroprotective protection to the kidneys of high-fat diet (HFD) rat models. The dose successfully reduced the percentage of kidney fat tissue area and normalized the hypertrophied glomerulus diameter to nearly the same as the control group (G1). Based on the overall results, the combination of tea mistletoe extract and mango mistletoe extract at a dose of 100 mg/KgBW is the most consistent dose in improving kidney histopathology in this study.

CONCLUSIONS

Based on the research results, it can be concluded that the combination of tea mistletoe leaf extract *(Scurrula atropurpurea)* and mango mistletoe *(Dendrophthoe pentandra)* effectively improves the histopathological profile of rat kidneys in a high-fat diet (HFD) induced model at a dose of 100 mg/KgBW. This dose reduces intracellular fat accumulation by 9% (4.4 ± 1.9), approaching normal levels. It also normalizes the glomerulus diameter to (1689.4 ± 48.8), approaching normal. This nephroprotective effect is caused by the synergistic mechanism of both mistletoes in reducing oxidative stress and inflammation.

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Authors' Contributions: Rianda Siwi Cholida wrote the article, conducted data searches, and performed data analysis. Nour Athiroh AS designed the research and revised the article's writing based on the research. Ari Hayati helped with data analysis. All authors read and approved the final version of the manuscript.

Competing Interests: The authors declare there are no competing interests

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