

**HEPATIC HISTOPATHOLOGY OF WHITE RATS EXPOSED TO LEAD AND TREATED WITH *MORINGA OLEIFERA* LEAF SIMPLICIA****Histopatologi Hati Tikus yang Dipapar Logam Berat Timbal dan Diterapi dengan Simplisia Daun Kelor (*Moringa oleifera*)****Paula Bintang Wuriandari<sup>1\*</sup>, I Ketut Berata<sup>2</sup>, Ida Bagus Oka Winaya<sup>2</sup>, I Made Kardena<sup>2</sup>, Ni Luh Eka Setiasih<sup>3</sup>, Samsuri<sup>4</sup>, Ni Nyoman Werdi Susari<sup>5</sup>**<sup>1</sup>Undergraduate Student of Veterinary Medicine Education, Faculty of Veterinary Medicine, Udayana University, Jl. PB Sudirman, Denpasar, Bali, Indonesia 80234<sup>2</sup>Veterinary Pathology Laboratory, Faculty of Veterinary Medicine, Udayana University, Jl. PB Sudirman, Denpasar, Bali, Indonesia 80234<sup>3</sup>Veterinary Histology Laboratory, Faculty of Veterinary Medicine, Udayana University, Jl. PB Sudirman, Denpasar, Bali, Indonesia 80234<sup>4</sup>Laboratory of Veterinary Physiology, Pharmacology, and Pharmacy, Faculty of Veterinary Medicine, Udayana University, Jl. PB Sudirman, Denpasar, Bali, Indonesia 80234<sup>5</sup>Laboratory of Veterinary Anatomy and Embryology, Faculty of Veterinary Medicine, Udayana University, Jl. PB Sudirman, Denpasar, Bali, Indonesia 80234

\*Corresponding author email: wuriandari.2209511017@student.unud.ac.id

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**Abstract**

Lead (Pb) is a heavy metal that induces the formation of free radicals and causes hepatocellular damage, making the liver one of the primary target organs of lead toxicity. *Moringa oleifera* leaves contain natural antioxidants with the potential to counteract oxidative stress induced by lead exposure. This study aimed to evaluate the effect of *Moringa oleifera* leaf simplicia on liver histopathology in white rats (*Rattus norvegicus*) exposed to lead acetate. A total of 20 rats were randomly divided into four groups: P0 (negative control; standard feed and water), P1 (positive control; 0.5 mg/head/day of lead acetate for 3 days), P2 (0.5 mg/head/day of lead acetate plus 0.1 g/mL/day of *Moringa oleifera* leaf simplicia), and P3 (0.5 mg/head/day of lead acetate plus 0.6 g/mL/day of *Moringa oleifera* leaf simplicia). Treatments were administered for 14 days via intragastric gavage. On day 15, the rats were euthanized, and liver tissues were collected, processed histologically, and stained with hematoxylin-eosin. Histopathological lesions, including congestion, fatty degeneration, and necrosis, were scored on a scale from 0 to 3 based on severity. The Kruskal-Wallis test showed significant differences among groups for all lesions ( $P < 0.05$ ). The Mann-Whitney test revealed significant differences in hepatic congestion between P0 and P1, P0 and P2, as well as between P3 and P1-P2, while no significant difference was observed between P0 and P3. For fatty degeneration and necrosis, P0 differed significantly from P1, P2, and P3. In conclusion, *Moringa oleifera* leaf simplicia at

a dose of 0.6 g/mL/day reduced the severity of hepatic congestion caused by lead exposure; however, its effects on fatty degeneration and necrosis were not statistically significant.

Keywords: antioxidant, histopathology, lead, liver, *Moringa oleifera*

### Abstrak

Timbal (Pb) merupakan logam berat yang bersifat memicu radikal bebas dan menyebabkan kerusakan sel hati sehingga hati menjadi salah satu organ target utama toksisitas. Daun kelor (*Moringa oleifera*) mengandung antioksidan alami yang berpotensi menangkal stres oksidatif akibat paparan timbal. Penelitian ini bertujuan mengevaluasi efek pemberian simplisia daun kelor terhadap gambaran histopatologi hati tikus putih (*Rattus norvegicus*) yang dipapar dengan Pb. Sebanyak 20 ekor tikus dibagi secara acak ke dalam empat kelompok, yaitu P0 (kontrol negatif, hanya diberi pakan dan minum), P1 (kontrol positif, diberi Pb asetat 0,5 mg/ekor/hari selama tiga hari), P2 (Pb asetat 0,5 mg/ekor/hari dan simplisia daun kelor 0,1 g/mL/hari), serta P3 (Pb asetat 0,5 mg/ekor/hari dan simplisia daun kelor 0,6 g/mL/hari) selama 14 hari melalui sonde atau secara intragastrik. Pada hari ke-15 tikus dieutanasia dan hati diambil untuk dibuat preparat histologis yang diwarnai dengan pewarnaan hematoksilin-eosin. Lesi histopatologi berupa kongesti, degenerasi melemak, dan nekrosis dinilai menggunakan skoring 0-3 berdasarkan tingkat keparahan. Uji Kruskal-Wallis menunjukkan perbedaan signifikan antar kelompok untuk semua jenis lesi ( $P < 0,05$ ). Uji Mann-Whitney menunjukkan perbedaan signifikan lesi kongesti antara P0 dengan P1 dan P2, serta antara P3 dengan P1 dan P2, sedangkan P0 dan P3 tidak berbeda signifikan. Untuk lesi degenerasi melemak dan nekrosis, kelompok P0 berbeda signifikan dengan P1, P2, dan P3. Disimpulkan bahwa pemberian simplisia daun kelor dosis 0,6 g/mL/hari mampu menurunkan tingkat keparahan lesi kongesti hati akibat paparan timbal, namun belum menunjukkan pengaruh yang signifikan terhadap lesi degenerasi melemak dan nekrosis.

Kata kunci: antioksidan, hati, histopatologi, *Moringa oleifera*, timbal

### INTRODUCTION

The use of the heavy metal lead (Pb) in industrial sectors has increased rapidly along with the growth of chemical manufacturing and economic development. Approximately 27,000 deaths in Indonesia were attributed to lead poisoning in 2019 (Seitz and Setiawan, 2021). This condition indicates that excessive exposure to lead has become a serious threat to the environment and to living organisms.

Lead is widely recognized as a common environmental contaminant and poses significant risks to human and animal health. This is supported by Pratiwi (2020), who reported that lead is a chemical substance distributed globally in large quantities while being highly hazardous. Its physical characteristics, such as malleability, softness, low thermal and electrical conductivity, and resistance to corrosion, make its use difficult to reduce. Animals may be exposed to lead from various sources, including metal smelting industries, ceramics, leaded gasoline, shipbuilding, weapons manufacturing, lead-containing pipes, battery recycling, printing industries, lead-based paints, pigments, and other related activities (Putra *et al.*, 2023).

Within the body, lead acts as an oxidant or free radical. It is a highly reactive molecule with one or more unpaired electrons that can attack essential macromolecules such as DNA, proteins, carbohydrates, and lipids, leading to cellular damage and disruption of homeostasis (Karina *et al.*, 2022). Lead is able to accumulate and deposit in various organs, particularly the liver, which functions as the central organ of metabolism.

Long-term exposure to lead acetate in rats may induce toxic effects on hepatocytes and liver tissue structure. This toxicity is characterized by reduced glycogen content in the cytoplasm,

resulting in vacuolization and the presence of pyknotic nuclei as indicators of necrosis (Hegazy and Fouad, 2016). Furthermore, Karina *et al.* (2022) reported that administration of lead acetate at doses of 0.5 ppm, 1.0 ppm, and 2.0 ppm for 30 days caused histopathological changes in rat livers, including congestion, fatty degeneration, and necrosis, compared with animals that were not exposed to lead acetate.

To neutralize free radicals, the body requires antioxidants. According to Rabeta and Faraniza (2013), antioxidants are compounds that donate hydrogen atoms or single electrons to stabilize unpaired electrons in free radicals. Natural antioxidants can be found in *Moringa oleifera*. Indahsari (2017) reported that administration of *Moringa oleifera* leaf extract for seven days showed antioxidant potential, as indicated by a decrease in malondialdehyde (MDA) levels in rats induced with toxic doses of paracetamol. The effects of three different doses of *Moringa oleifera* leaf extract on MDA levels showed that low (0.25 g per 200 g body weight), medium (0.50 g per 200 g body weight), and high doses (1 g per 200 g body weight) significantly reduced MDA levels, with P values of 0.05, 0.01, and 0.001, respectively. In Indonesia, *Moringa oleifera* is known by various local names, including kelor, kele, moltong, muronggih, barunggai, murong, and ongge (Marhaeni, 2021).

Based on the background described above, this study was conducted to evaluate the protective effect of *Moringa oleifera* leaf simplicia against lead-induced liver damage in rats. Specifically, this study aimed to assess histopathological changes in the liver of rats exposed to lead acetate, including congestion, fatty degeneration, and necrosis, following administration of *Moringa oleifera* leaf simplicia at different doses.

## RESEARCH METHODS

### Ethical Approval

The use of animals in this study was approved by the Animal Ethics Committee of the Faculty of Veterinary Medicine, Udayana University, under approval number B/208/UN14.2.9/PT.01.04/2025.

### Research Subjects

The research subjects consisted of 20 healthy male white rats (*Rattus norvegicus*) of the Wistar strain, with an average body weight of approximately 160 g and an age of 2 months. The liver was used as the target organ for histopathological evaluation.

### Experimental Design

This study employed an experimental design consisting of four treatment groups, each containing five rats. The groups were P0 (negative control), P1 (positive control with lead exposure), P2 (lead exposure plus *Moringa oleifera* leaf simplicia at a dose of 0.1 g/mL/day), and P3 (lead exposure plus *Moringa oleifera* leaf simplicia at a dose of 0.6 g/mL/day).

The *Moringa oleifera* leaf simplicia used in this study was obtained in a 150 g packaged product (brand: Daribumi) manufactured by PT. Solusi Pangan Kita. Because the use of leaf simplicia requires relatively higher doses, the simplicia was weighed and prepared prior to administration. A total of 60 g of simplicia was dissolved in 100 mL of distilled water to obtain a concentration of 0.6 g/mL, which represented the dose with antitoxic potential. To prepare the 0.1 g/mL solution, 10 g of simplicia was dissolved in 100 mL of distilled water. These dose variations were used to evaluate differences in liver histopathological features among the treatment groups.

Lead acetate was administered at a dose of 0.5 mg per rat per day for three consecutive days. *Moringa oleifera* leaf simplicia was administered orally via gavage for 14 days according to

the respective group doses. On day 15, the rats were euthanized by intramuscular injection of a xylazine-ketamine combination at a volume of 0.2 mL. Necropsy was then performed, and liver samples were collected for histopathological examination.

### **Histopathological Preparation**

Liver samples from all treatment groups were collected after 14 days of treatment and processed at the Veterinary Center using the method described by Kiernan (1990). The liver tissues were cut into approximately  $1 \times 1 \times 1$  cm sections and fixed in 10% neutral buffered formalin. The samples were then trimmed into thinner sections, placed in tissue cassettes, and refixed in neutral buffered formalin.

Subsequently, the samples underwent gradual dehydration and clearing using 70%, 80%, and 90% ethanol, absolute alcohol, toluene, and paraffin in a single processing sequence lasting one day. The tissues were embedded in paraffin using an embedding set and allowed to solidify. Paraffin blocks were sectioned using a microtome at a thickness of 4 to 5  $\mu\text{m}$ . The final step involved staining with hematoxylin and eosin, followed by mounting with an adhesive medium. Hematoxylin and eosin staining serves two main purposes. First, it allows differential staining of tissue components, enabling their identification. Second, it produces varying color intensities that enhance tissue contrast (Peckham, 2014).

### **Data Analysis**

Histopathological liver sections were examined under a light microscope to assess the presence of congestion, fatty degeneration, and necrosis using a scoring system ranging from 0 to 3, where 0 indicates no lesion, 1 indicates mild or focal lesions, 2 indicates moderate or multifocal lesions, and 3 indicates severe or diffuse lesions. The scoring data were analyzed using the Kruskal-Wallis test to determine differences among groups, followed by the Mann-Whitney test to identify pairwise differences between groups, with statistical significance set at  $P < 0.05$ .

## **RESULTS AND DISCUSSION**

### **Results**

Based on the histopathological examination of the liver, varied histopathological findings were observed among the treatment groups. The mean scores of histopathological changes are presented in Table 1, while the results of the nonparametric Kruskal-Wallis test and the subsequent Mann-Whitney test are presented in Table 2.

The Kruskal-Wallis test showed significant differences ( $P < 0.05$ ) among the negative control and treatment groups for all three lesions evaluated. Therefore, further analysis was performed using the Mann-Whitney test to determine differences between individual groups. The Mann-Whitney test results for hepatic congestion showed significant differences ( $P < 0.05$ ) between P0 and groups P1 and P2, as well as between P3 and groups P1 and P2. However, no significant difference ( $P > 0.05$ ) was observed between P0 and P3.

For fatty degeneration, the Mann-Whitney test revealed significant differences ( $P < 0.05$ ) between P0 and groups P1, P2, and P3. No significant differences ( $P > 0.05$ ) were found between P1 and groups P2 and P3. Regarding necrosis, the Mann-Whitney test showed significant differences ( $P < 0.05$ ) between P0 and groups P1, P2, and P3. No significant difference ( $P > 0.05$ ) was observed between groups P1 and P2. Representative histopathological images from each treatment group are presented in Figure 1.

## Discussion

The results of this study demonstrate that administration of lead acetate at a dose of 0.5 mg per rat per day for three consecutive days, followed by treatment with *Moringa oleifera* leaf simplicia for 14 days, affected the histopathological appearance of the liver in white rats. In the negative control group, mild or focal histopathological changes in the form of congestion and fatty degeneration were observed. The presence of histopathological alterations in the negative control group may be related to the health status of the experimental animals prior to treatment. The use of conventional laboratory animals that are not specific pathogen free (SPF) often results in unexpected histopathological findings in control animals. Such changes may be influenced by non-hygienic feed or environmental factors that compromise the health status of the rats (Karina *et al.*, 2022).

The severity of hepatic congestion varied among the treatment groups. In groups P1 and P2, mild to moderate congestion was observed in hepatocytes, whereas group P3, which received *Moringa oleifera* leaf simplicia therapy, showed mild congestion comparable to that of the negative control group (P0). Congestion is defined as the accumulation of erythrocytes within blood vessels resulting from pathophysiological disturbances originating either within or outside the vasculature (Berata *et al.*, 2022). This lesion may be induced by several factors, including inflammatory responses triggered by trauma, toxins, or microorganisms (Salbahaga *et al.*, 2012).

In the present study, hepatic congestion was likely induced by exposure to the toxic compound lead acetate administered for three consecutive days. Congestion is characterized by the accumulation of erythrocytes within venous blood vessels as a consequence of pathological disturbances in the tissue. According to Royan *et al.* (2014), congestion arises as a result of inflammatory reactions and organ damage and is associated with changes in tissue coloration corresponding to the degree of blood oxygenation. Congestion is also considered an early pathological sign of tissue injury and is marked by increased blood volume within vessels, resulting in dilated capillaries and sinusoids filled with erythrocytes. Additionally, the presence of congestion may reflect active angiogenesis during the tissue repair process (Humaira *et al.*, 2020).

Fatty degeneration was observed in groups P1, P2, and P3 with varying severity ranging from mild to moderate. Moderate fatty degeneration predominated in groups P1 and P2. Fatty degeneration occurs as a result of lipid accumulation within hepatocytes and is histologically characterized by the presence of vacuoles of varying sizes (Adikara *et al.*, 2013). This lesion may be induced by toxic substances, nutritional dysfunction, or advanced age (Fahmi *et al.*, 2012). Excessive free radicals promote oxidative stress, leading to lipid peroxidation through increased malondialdehyde (MDA) levels. Accumulation of free radicals is one of the key mechanisms involved in liver injury, contributing to the development of fatty degeneration and progression to necrosis (Yoon *et al.*, 2016).

Necrosis represents abnormal cell death resulting from exposure to harmful agents such as toxins or chemical substances, including drugs, insecticides, strong acids, alkalis, and industrial chemicals such as lead (Berata *et al.*, 2022). Necrotic changes begin with morphological alterations including pyknosis, characterized by nuclear condensation, followed by karyorrhexis, in which the nucleus fragments, and karyolysis, marked by nuclear dissolution (Adikara *et al.*, 2013). In this study, severe necrosis with a score of 3 was observed in groups P2 and P3. In necrotic areas, infiltration of inflammatory cells, particularly lymphocytes and monocytes, was evident.

Hepatic necrosis may occur as a result of oxidative stress induced by exposure to toxic substances (Muselin *et al.*, 2010). Oxidative stress develops when the production of free radicals exceeds the capacity of endogenous antioxidant defense systems (Jaishankar *et al.*, 2014). Necrosis may also result from free radicals extracting electrons from lipid molecules within hepatocyte membranes, leading to lipid peroxidation. High concentrations of free radicals can damage erythrocyte

composition, membrane proteins, and lipids, inhibit hemoglobin synthesis (Sharma *et al.*, 2014), and ultimately lead to cell death (Abdou and Hassan, 2014).

The histopathological liver alterations observed in rats exposed to lead acetate in this study are consistent with previous findings reported by Karina *et al.* (2022), who demonstrated that lead exposure adversely affects liver tissue structure, resulting in congestion, fatty degeneration, and necrosis. These findings are also in agreement with Berata *et al.* (2017), who reported that the liver is the primary organ for lead accumulation in cattle and exhibits more pronounced lesions compared with other organs.

The effect of *Moringa oleifera* leaf simplicia was reflected by the lower lesion scores observed in group P3, which received a dose of 0.6 g/mL/day. This therapeutic dose was intended to provide maximal hepatoprotective effects and thereby reduce liver tissue damage caused by lead exposure (Nurhayati *et al.*, 2024). Fattah *et al.* (2020) reported that administration of aqueous *Moringa oleifera* leaf extract at a dose of 200 mg/kg body weight concurrently with lead acetate at 100 mg/kg body weight for several weeks significantly reduced liver enzyme activities, including alanine aminotransferase and aspartate aminotransferase, and improved liver histopathological features compared with animals exposed to lead alone. Based on these findings, group P3 in the present study represents a dose level sufficient to mitigate hepatic damage induced by lead acetate (Fattah *et al.*, 2020; Nurhayati *et al.*, 2024).

*Moringa oleifera* leaves are rich in antioxidant compounds such as flavonoids, vitamin C, and phenolic compounds, which play an important role in neutralizing free radicals and reducing oxidative stress in hepatocytes (Nurhayati *et al.*, 2024). In cases of lead intoxication, excessive production of reactive oxygen species damages hepatocyte membranes and sinusoidal endothelial cells, resulting in congestion, degeneration, and necrosis. Administration of *Moringa oleifera* leaves at a therapeutic dose in group P3 likely enhanced endogenous antioxidant activity, such as superoxide dismutase, and reduced MDA levels as a marker of lipid peroxidation (Fattah *et al.*, 2020).

In addition to its antioxidant properties, *Moringa oleifera* leaf extract exhibits anti-inflammatory activity by inhibiting the nuclear factor kappa B signaling pathway and reducing the expression of proinflammatory cytokines such as tumor necrosis factor alpha (Karthivashan *et al.*, 2015). Suppression of inflammatory responses that exacerbate tissue injury, combined with antioxidant effects, contributes to the preservation of hepatocyte membrane integrity, reduced sinusoidal congestion, and decreased severity of fatty degeneration and necrosis in group P3. These effects are reflected in the lower histopathological lesion scores observed in this group compared with other treatment groups (Fattah *et al.*, 2020).

Group P2, which received *Moringa oleifera* leaf simplicia at a dose of 0.1 g/mL/day following lead exposure, did not demonstrate adequate protection against lead-induced hepatotoxicity. At doses below the therapeutic range, several studies have shown that hepatoprotective effects tend to be minimal and not significantly different from those observed in the positive control group (P1). This limitation is associated with insufficient concentrations of active compounds to effectively neutralize reactive oxygen species and suppress inflammatory pathways activated by lead exposure (Nurhayati *et al.*, 2024). These findings are supported by the study of Meles *et al.* (2024), which evaluated multiple doses of *Moringa oleifera* leaf extract in lead-exposed rats and demonstrated a dose-dependent pattern, whereby higher doses were associated with greater reductions in hepatic congestion, fatty degeneration, and necrosis scores.

## CONCLUSION AND SUGGESTIONS

### Conclusion

Based on the results of this study, it can be concluded that administration of *Moringa oleifera* leaf simplicia in white rats (*Rattus norvegicus*) exposed to lead acetate at a dose of 0.5 mg per rat per day affected liver histopathological features. A dose of 0.6 g/mL/day administered for 14 days was more effective than a dose of 0.1 g/mL/day as a therapeutic agent, as it reduced the severity of hepatic congestion and necrosis to levels approaching those of the negative control group. However, this dose did not result in a significant improvement in fatty degeneration.

### Suggestions

Given the therapeutic potential of *Moringa oleifera* leaf simplicia in mitigating lead-induced liver toxicity in white rats (*Rattus norvegicus*), further studies are recommended to elucidate the mechanisms underlying the interaction between *Moringa oleifera* and lead in hepatic tissue. Additional histopathological evaluations over longer observation periods are also suggested to assess more pronounced and progressive tissue changes.

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### Tables

Table 1. Scoring results of hepatic congestion, fatty degeneration, and necrosis lesions

Treatment	Replication	Mean histopathological lesion scores of the liver		
		Congestion	Fatty degeneration	Necrosis
P0	1	0	0	0
	2	1	1	0
	3	1	0	0
	4	0	0	0
	5	1	1	0
Mean		0.6	0.4	0
P1	1	2	2	3
	2	1	1	2
	3	2	2	3
	4	1	2	2
	5	2	2	3
Mean		1.6	1.8	2.6
P2	1	2	2	3
	2	1	1	2
	3	2	2	2
	4	1	1	2
	5	2	2	3
Mean		1.6	1.6	2.4
P3	1	0	1	1
	2	1	1	2
	3	1	2	1
	4	0	1	2
	5	1	1	1
Rerata		0.6	1.2	1.4

Note: P0=Negative control; P1= Lead acetate administration at 0.5 mg/rat/day; P2= Lead acetate administration at 0.5 mg/rat/day plus *Moringa oleifera* leaf simplicia at 0.1 g/rat/day; P3= Lead acetate administration at 0.5 mg/rat/day plus *Moringa oleifera* leaf simplicia at 0.6 g/rat/day.

Table 2. Mean  $\pm$  standard deviation of liver histopathological lesion scores in white rats and the results of the Mann-Whitney test among treatment groups

Treatment	Mean $\pm$ standard deviation of histopathological lesion scores		
	Congestion	Fatty degeneration	Necrosis
P0	0,60 $\pm$ 0,548 <sup>a</sup>	0,40 $\pm$ 0,548 <sup>a</sup>	0,00 $\pm$ 0,000 <sup>a</sup>
P1	1,60 $\pm$ 0,548 <sup>b</sup>	1,80 $\pm$ 0,447 <sup>b</sup>	2,60 $\pm$ 0,548 <sup>b</sup>
P2	1,60 $\pm$ 0,548 <sup>b</sup>	1,60 $\pm$ 0,548 <sup>b</sup>	2,40 $\pm$ 0,548 <sup>b</sup>
P3	0,60 $\pm$ 0,548 <sup>a</sup>	1,20 $\pm$ 0,447 <sup>b</sup>	1,40 $\pm$ 0,548 <sup>c</sup>
Asymp. Sig	0,020	0,014	0,002

Note: P0=Negative control; P1= Lead acetate administration at 0.5 mg/rat/day; P2= Lead acetate administration at 0.5 mg/rat/day plus *Moringa oleifera* leaf simplicia at 0.1 g/rat/day; P3= Lead acetate administration at 0.5 mg/rat/day plus *Moringa oleifera* leaf simplicia at 0.6 g/rat/day.

Figure

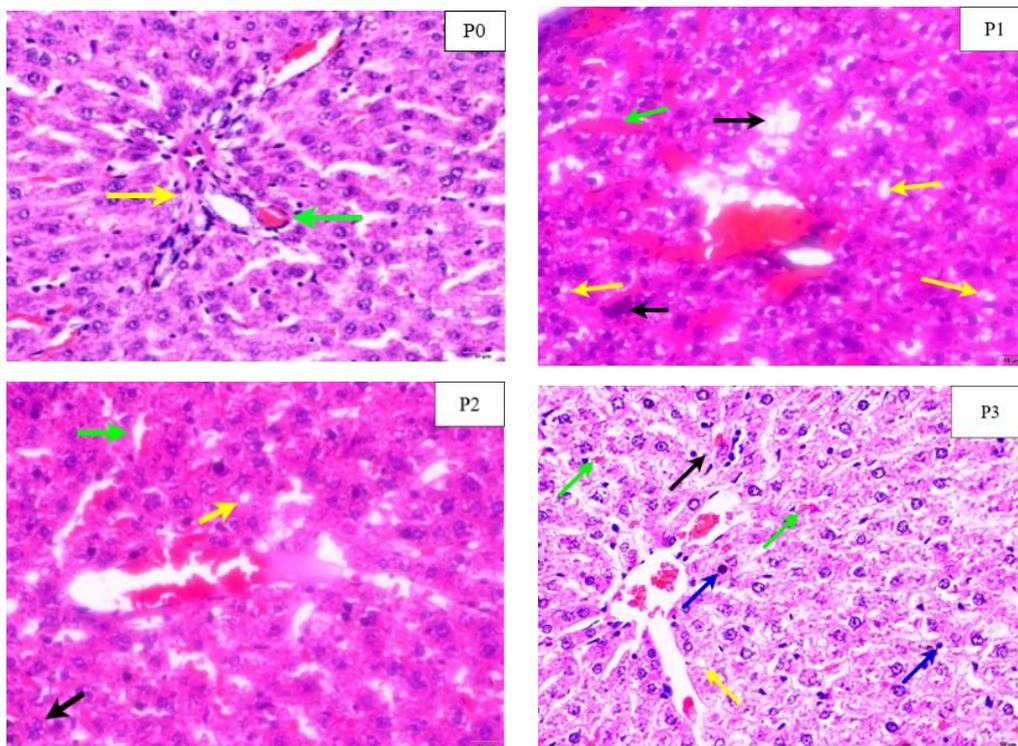


Figure 1. Liver histopathology of white rats (*Rattus norvegicus*) in each treatment group (Hematoxylin-eosin staining, 400 $\times$ ). Congestion (green arrows), fatty degeneration (yellow arrows), necrosis (black arrows), and inflammatory cells consisting of lymphocytes (blue arrows) are observed.