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# Sari Rapet Herbal Medicine Treatment and The Histological Effect on Kidney and Liver of Rats (*Rattus novergicus*)

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**Abstract**
Sari rapet herbal medicine is one of the medicines frequently consumed by the Madurese people, especially Sumenep Regency, for generations. The use of sari rapet herbal medicine aims to tighten female muscles and reduce vaginal discharge, however, the use of sari rapet herbal medicine has not yet gone through pre-clinical trials. This study aims to determine the effect of sari rapet essence herbal medicine on the histology of the kidney and liver organs of rats (*Rattus novergicus*). This type of research is True Experiment Research with a post-test-only control design method. The samples used were mice divided into four groups with different treatments, namely 0 g/200gBW, 0,54 g/200gBW, 1,08 g/200gBW, and 1,62 g/200gBW for 28 days a day. Histological changes data will be analyzed using the Shapiro-Wilk test and One-Way Annova. The research results showed that there was damage in all groups with the highest level of damage in group 3 (1.62 g/200gBW). The conclusion shows significant differences in kidney degeneration organ damage and inflammatory cell infiltration. Significant differences exist in bridging necrosis damage, degeneration focal necrosis, and inflammatory cell infiltration in the liver.

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**Keywords:** Kidney, Histology, Liver, Sari Rapet, Herbal Medicine

## 1. Introduction

A variety of plant resources have various benefits, one of which is used in traditional medicine. Traditional medicines based on BPOM Indonesia are categorized into phytopharmaca, standard herbal medicines, and herbal medicines. Traditional medicine that is often used by people to treat health problems is herbal medicine [1] and is believed to have fewer side effects than modern drugs [2] and it is believed that the benefits found in herbal medicine cannot be found in modern medicine [3, 4].

Herbal medicine generally has fewer side effects than modern medicine [2]. The use of herbal medicines in the health sector has become a recommendation from the World Health Organization (WHO) as a preventive medicine for chronic diseases of a generative nature [5], However, there are several views regarding traditional herbal medicines that are found illegally and do not have permits BPOM. Even though there is a law, it is still possible for herbal medicine that does not have BPOM permission to be distributed so that people make mistakes in the procedures for using it [6]. Public ignorance makes it possible to use herbal medicine that does not have BPOM permission or to use herbal medicine at the wrong dosage.

One of the herbal medicines that does not have a BPOM and is already used by the Madurese people is sari rapet herbal medicine. The packaging of sari rapet herbal medicine, production house X is still very simple, the composition is unclear, and the expiration date is not listed. People believe that consuming sari rapet herbal medicine aims to overcome itching, and unpleasant smells, and tighten the vaginal walls, however, people do not pay attention to the correct dosage of herbal medicine, which causes toxicity. Using an incorrect dose of sari rapet herbal medicine will cause negative impacts on the body, one of which is irreversible liver damage [7] and if used for a long period it will cause kidney failure and liver damage [8].

This is because the liver is susceptible to chemical compounds [9] and the kidneys which have the role of secreting chemical compounds will be susceptible to herbal medicine compounds [10].

The composition of sari rapet herbal medicine is still based on generations and has not gone through *in vivo* pre-clinical testing including toxicity and efficacy tests [11]. The pre-clinical test aims to determine the safety and true efficacy of sari rapet herbal medicine so that it is safe for use by the public [12]. Pre-clinical testing is an effort to provide safety assurance, as well as knowledge of the side effects of drugs after use.

Previous research shows that one of the ingredients of sari rapet herbal medicine, namely ginger, can be used as a traditional medicine for diabetes mellitus patients [13] and can prevent liver damage [14]. Areca nut seeds which can be found in sari rapet herbal medicine were tested on mice and did not cause changes or significant differences in the weight of the kidney organs [15]. Previous research on herbal medicine showed that kidney and liver damage was found in the treatment group [11].

In this research, uses rapet herbal medicine from the herbal medicine production house X district of Sumenep which has been distributed and is widely used by the public routinely without knowing the side effects. Therefore, it is necessary to carry out further testing to protect the public which may be detrimental and to see the damage that arises from the use of sari rapet herbal medicine for the kidney and liver organs so as to ensure the safety of its use. This research was conducted on research on kidney and liver histology specifically on sari rapet herbal medicine produced by herbal medicine houses in X district of Sumenep.

## 2. Method

### 2.1. Material

The material used in this research was sari rapet herbal medicine obtained from the district of Sumenep, Madura, East Java with a powder texture. Sari rapet herbal medicine the ones used comes from several herbal ingredients that are clove (*Syzigium aromaticum*), betel leaf (*Piper betle*), curcuma (*Curcuma xanthorrhiza Roxb*), areca nut (*Areca catechu L.*), reeds (*Imperata cylindrica*), waru porcupine (*Hibiscus tiliaceus*), elephant foot (*Elephantopus scaber*), around-rooted galangal (*Kaempferia rotunda*). There were 12 Female rats (*Rattus novergicus*), 2-3 months old with a weight of ±200 grams and physically healthy. Materials used in making histology preparations chloroform, paraffin, HE (Hematoksilin eosin), FAA solution, alcohol 50%, 70%, 80%, 100%, xylol, entellen, dan formalin 10%.

The equipment used in this research includes a light microscope (Nikon Eclipse type Ei) with the help of Optilab Microscope. Cameras connected to a computer. Tools for making histology include microtomes, glass objects, and incubators, Meanwhile, the equipment used in experimental animal laboratories includes animal cages (units), syringes, drinking bottles, surgical tools, and other supporting equipment.

### 2.2. Methods

This research has ethical clearance from Komite Etik Penelitian Kesehatan (KEPK) Medical School Muhammadiyah University of Malang, on ethical certificate no. E.5.a/197/KEPK-UMM/XI/2022. This research used a completely randomized design method. This study had 3 rat treatments and 1 control group (n=3).

#### 2.2.1. Adaptation and Caring for Experimental Animals

To prevent stress in rats which would impact research, the rats adapted for 7 days at the Muhammadiyah University of Malang on Campus 2. Maintenance is performed at room temperature 20-25°C in plastic cages covered with woven wire measuring 30 cm x 45 cm x 15 cm and equipped with husk bedding replaced twice a week.

#### 2.2.2. Division of Experimental Animal Groups

The experimental animals were divided into 4 groups, namely control group (no treatment), experiment 1 (dose 1), experiment 2 (dose 2), and experiment 3 (dose 3). After dividing the groups, weighing was carried out using a digital balance with an accuracy of 0.1 kg.

#### 2.2.3. Making Doses of Sari Rapet Herbal Medicine

In making the dose of Sari Rapet herbal medicine, a human-to-rat dose conversion factor is used, namely the human dose multiplied by 0.018 [16]. Then, a multilevel dose calculation was carried out using multiples of 2 from the dose conversion [17], thus obtaining dose 1 (0.54 g/200gBW/rat/day), dose 2 (1.08 g/200gBW/rat/day), and dose 3 (1.62 g/200gBW/rat/day).

#### 2.2.4. Giving of Sari Rapet Herbal Medicine

The Sari Rapet herbal medicine used is an extract that is then brewed with 3 ml of hot water and filtered because the stomach capacity of a 200-gram rat is 5 ml to avoid inflammation caused by exceeding the maximum capacity [18]. Giving a Sari Rapet herbal medicine using the sonde method using a syringe that has been modified essentially aims to make it easier for the herbal medicine to enter the rat's body.

#### 2.2.5. Dissection and Preparation of Organ Samples for Experimental Animals

On the 29th day, the rats underwent surgery to remove the kidneys and liver according to the surgical procedure. Histology preparations were made using the paraffin block method with HE (Hematoxylin eosin) staining. First, the kidney and liver tissues were soaked in 10% formalin for one hour and the samples were cut into 2-4 mm pieces. The sample pieces were fixed in FAA solution for 24 hours and dehydrated in 50%, 70%, 80%, and 100% alcohol solutions for 30 minutes. The next stage is purification which aims to withdraw the alcohol content after dehydration using alcohol: xylol solutions in a ratio of 3:1, 1:1, and 1:3 for 30 minutes and continued with xylol 1 and 2 for 30 minutes.

Samples were immersed in a liquid mixture of xylol: paraffin in a ratio of 9:1 for 24 hours in an incubator at 60°C, then blown by inserting the sample into a mold containing paraffin and left at room temperature until hardened. The cuts were made using a microtome with a thickness of 4-5 microns, the incisions were placed on a glass slide, then immersed into xylol 1 and 2 solutions for 5 minutes and alcohol: xylol in a ratio of 1:3, 3:1, 1:1, and 3:1 for 3 minutes each.

Samples were hydrated with graded alcohol (100%, 95%, 70%, 50%, and 30%) for 3 minutes, followed by HE (Hematoxylin Eosin) staining for 6-7 minutes, and washed with distilled water for 3 minutes. The stained samples were soaked with graded alcohols (30%, 50%, 70%, 95%, and 100%) for 3 minutes, then treated with alcohol: xylol in the

ratio of 3:1, 1:1, and 1:3 for 2 minutes each. The samples were placed on a glass slide and soaked with xylol 1 and 2 solutions for 5 minutes each, then the samples were placed on a glass prepared dripped with ethylene, and slowly covered using a glass cover.

### 2.2.6. Histology Observation

Kidney and liver organ preparate were observed using a light microscope at 400x magnification, then, microscopic changes were averaged in five fields of view. The following table reads the histology preparation of kidney and liver organs based on damage scoring.

**Table 1:** Kidney Damage Scoring [19]

| Type of Damage | Damage Level | Score |
|---|---|---|
| Degeneration | There was no degeneration of renal tubular epithelial cells | 0 |
| | <25% degeneration of renal tubular epithelial cells | 1 |
| | 26%-50% degeneration of renal tubular epithelial cells | 2 |
| | 51%-75% degeneration of renal tubular epithelial cells | 3 |
| | >76% degeneration of renal tubular epithelial cells | 4 |
| Necrosis | There was no necrosis of tubular epithelial cells | 0 |
| | <25% necrosis of renal tubular epithelial cells | 2 |
| | 26%-50% necrosis of renal tubular epithelial cells | 4 |
| | 51%-75% necrosis of renal tubular epithelial cells | 6 |
| | >76% necrosis of renal tubular epithelial cells l | 8 |
| inflammatory cell infiltration | No inflammatory cell infiltration was found | 0 |
| | Inflammatory cell infiltration <25% in the interstitial lumen | 1 |
| | Inflammatory cell infiltration 26-50% in the interstitial lumen | 2 |
| | Inflammatory cell infiltration 51-75% in the interstitial lumen | 3 |
| | Inflammatory cell infiltration >76% in the interstitial lumen | 4 |

**Table 2:** Liver Damage Scoring [20]

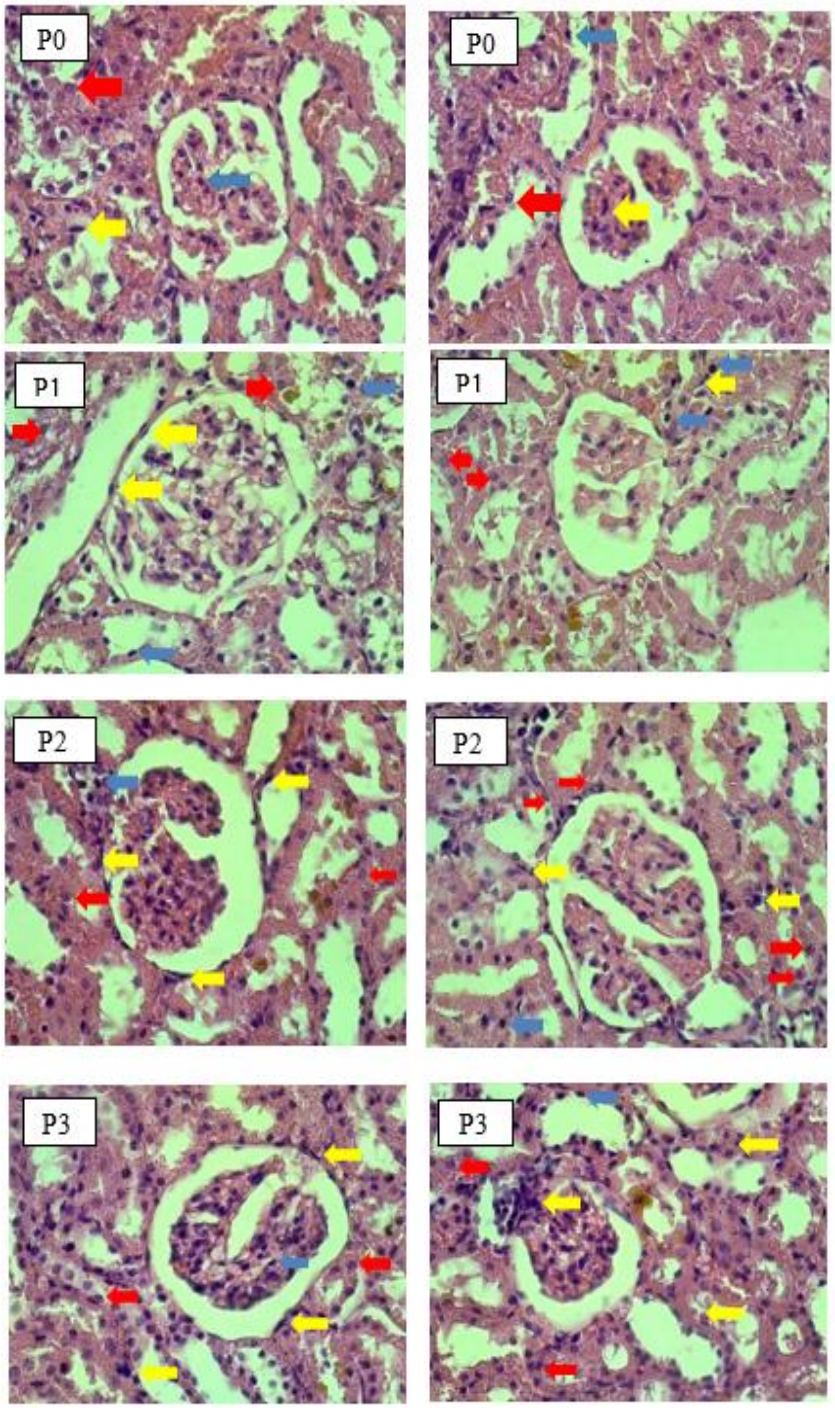
| Lesion Form | Description | Score |
|---|---|---|
| Bridging Necrosis | No necrosis | 0 |
| | Mild piecemeal necrosis | 1 |
| | Moderate piecemeal necrosis (involves less than 50% of the circumference of most portal tracts) | 3 |
| | Moderate piecemeal necrosis (involves more than 50% of the circumference of most portal tracts) | 4 |
| | Moderate piecemeal necrosis plus bridging necrosis | 5 |
| | Marked piecemeal necrosis plus bridging necrosis | 6 |
| | Multilobular necrosis | 10 |
| Degeneration and Focal Necrosis | No degeneration | 0 |
| | Mild (*acidophilic bodies*, *ballooning* degeneration, and/or scattered foci of hepatocellular necrosis in < 1/3 lobules or nodules) | 1 |
| | Moderate (involvement of 1/3-2/3 of lobules or nodules) | 3 |
| | Market (involvement of >2/3 of lobules or nodules | 4 |
| inflammatory cell infiltration (inflammation) | No portal inflamation | 0 |
| | Mild (sprinkling of inflammatory cells in <1/3 of portal tracts) (light) | 1 |
| | Moderate (increased inflammatory cells in 1/3-2/3 of portal tracts) (currently) | 3 |
| | Marked (dense packing of inflammatory cells in >2/3 of portal tracts) (heavy) | 4 |
| Cholangitis | No Fibrosis | 0 |
| | Fibrous portal expansion | 1 |
| | Bridging fibrosis (portal-portal or portal-central linkage) | 3 |
| | Cirrhosis | 4 |

### 2.2.7. Data Analysis

All data were analyzed using statistical analysis tests through SPSS (Statistical Product of Service Solution) software. Normality testing uses Shapiro-Wilk to assess whether the data is distributed or not, if it is not normally distributed, it is continued with Krustal-Wallis. If the distribution is normal, it is continued with the One-Way ANOVA test to determine whether there is an effect of treatment and continued with the Duncan test.

## 3. Results and Discussion

Identification of Damage Scoring in the Kidney Organ. The following are the results of cell damage scoring in the kidney organs of rats (*Rattus novergicus*) given a sari rapet herbal medicine:




**Description:** (P0) Control, (P1) Dose 0.54 g/200gBW, (P2) Dose 1.08 g/200gBW, (P3) Dose 1.62 g/200gBW

**Fig 1:** Liver histology magnification 400x, hematoxylin-eosin staining (red arrow:degeneration, yellow arrow: necrosis, blue arrow: inflammatory cell infiltration)

The results of histology reading of rat kidney organs given a sari rapet herbal medicine showed the discovery of cell damage in both the control group and the experimental group. Damage can be found in the form of degeneration, necrosis, and inflammatory cell infiltration. Based on Figure 1, it shows that the more doses given, the more damage scoring is caused. From the histology readings, the damage score for each treatment can be determined. The level of cell damage that can be found in kidney histology can be seen in (Figure 2) as follows:

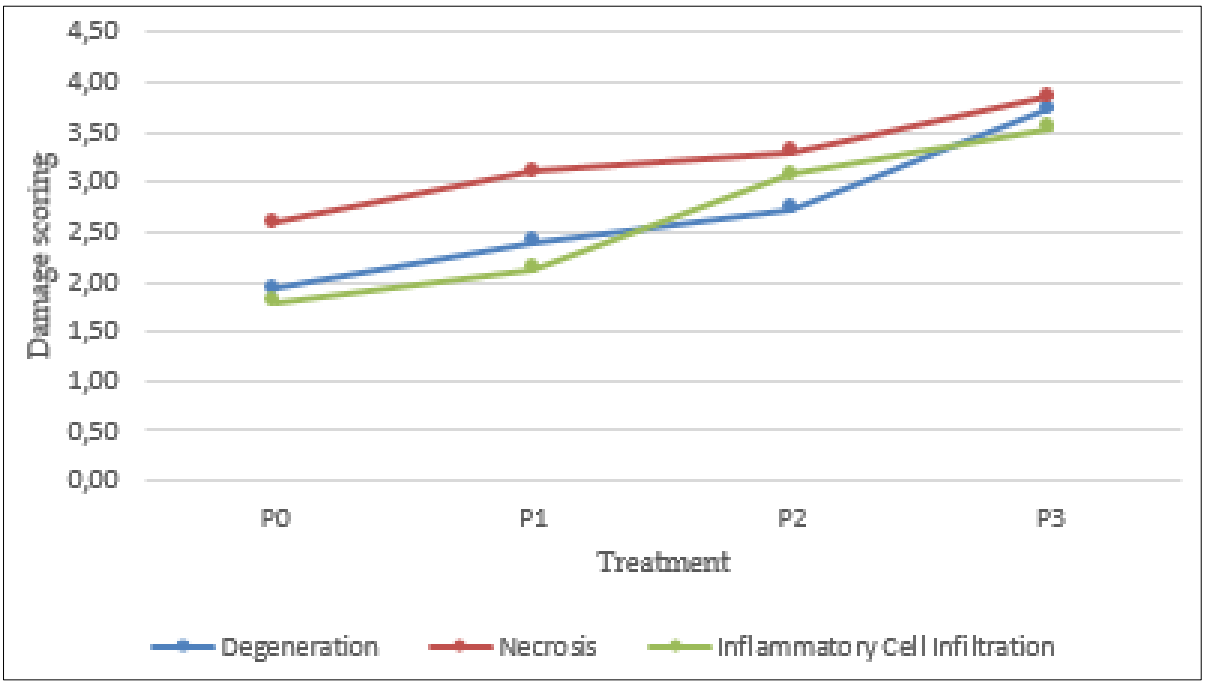



**Fig 2:** Line graph of the average cell damage scoring of kidney and liver organs of rats (*Rattus novergicus*). The P3 group showed the highest damage scoring.

The results of the average scoring of renal cell damage based on (Figure 2.) show that the more doses given, the more damage caused. The average results will be followed by static calculations (Table 3):

**Table 3:** The Effect of Giving Sari Rapet Herbal Medicine on the Histology of Rat (*Rattus novergicus*)

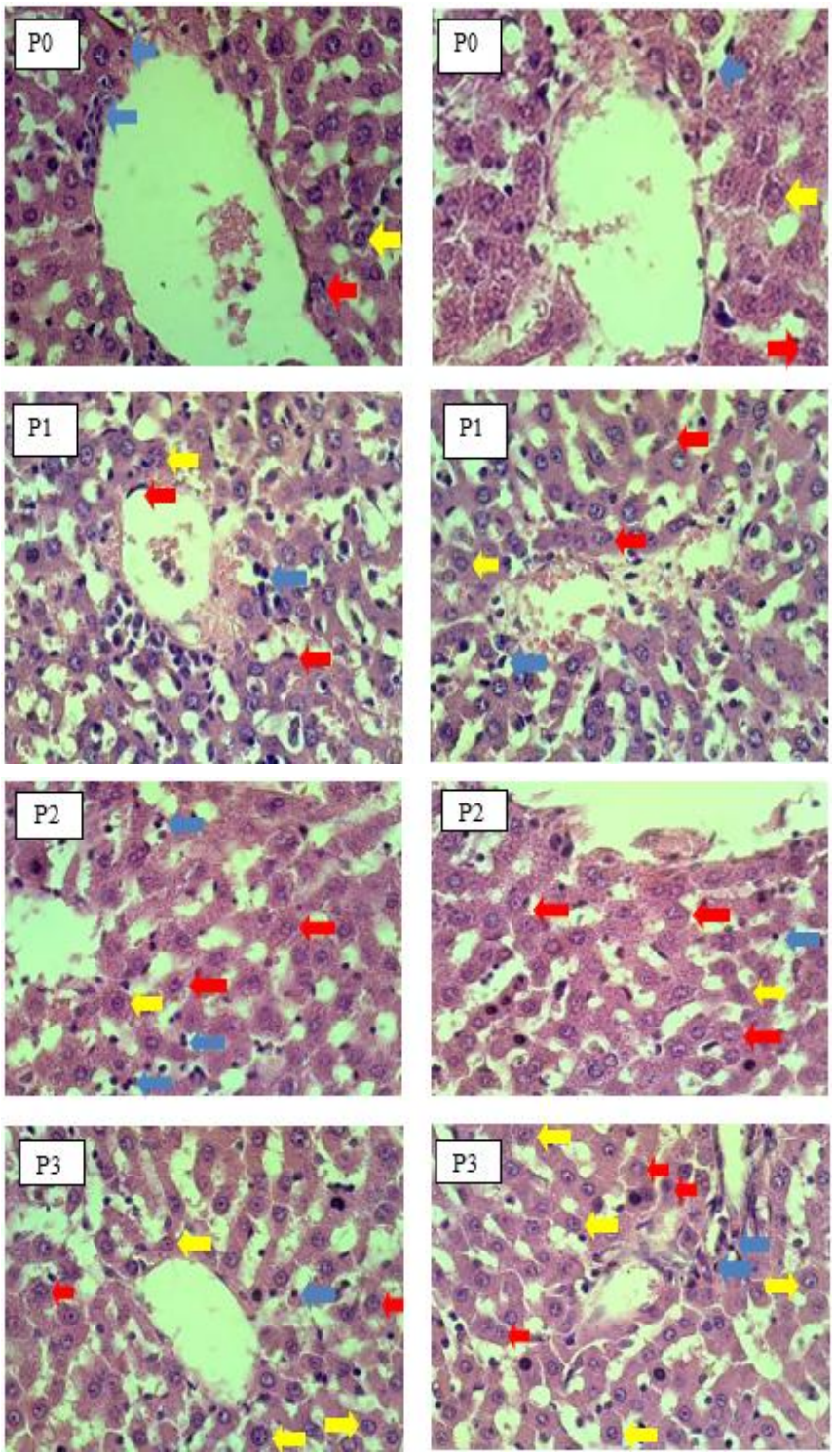
| Groups | Degeneration | Necrosis | Inflammatory Cell Infiltration |
|---|---|---|---|
| P0 | 1,93[a] | 2,60 | 1,80[a] |
| P1 | 2,40[b] | 3,10 | 2,13[b] |
| P2 | 2,73[c] | 3,33 | 3,07[b] |
| P3 | 3,73[c] | 3,86 | 3,53[b] |

**Description:** The average values in the same column and followed by different superscript letters show a significant difference in the Duncun post hoc test (p=0.05). P0 (control without treatment), P1 (dose 1; 0.54 g/200gBW), P2 (dose 2; 1.08 g/200gBW), P3 (dose 3; 1.62 g/200gBW).

Based on (Table 3.) show that there are significant differences in damage types of degeneration and inflammatory cell infiltration ($P < 0.05$). In degeneration damage, the P0 group has a significant difference with P1, and the P1 group has a significant difference with P2 and P3. In damage to inflammation cell infiltration, P0 has a significant difference with P1, P2, and P3. The P1, P2, and P3 groups had no significant difference. In necrosis damage, the statistical results show that there is no significant difference ($P>0.05$). Kidney cell damage in the form of degeneration was found to have the highest average in the P3 group with a score of 3.73 which is included in the 51-71% (moderate) category. In the type of necrosis damage, the highest average was in the P3 group with a score of 3.86, which was included in the <25% (low) category, while in the type of damage, inflammatory cell infiltration of kidney cells, the highest score was in the P3 group with a value of 3.53, which indicated >76. % (tall).

### 4. Identification of Damage Scoring in Liver Histology

The following are the results of scoring cell damage in the kidney organs of rats (*Rattus novergicus*) given the sari rapet herbal medicine:




**Description:** (P0) Control, (P1) Dose 0.54 g/200gBW, (P2) Dose 1.08 g/200gBW, (P3) Dose 1.62 g/200gBW

**Fig 3:** Liver histology with 400x magnification, hematoxylin-eosin staining (yellow arrow: degeneration, red arrow: necrosis, blue arrow: inflammatory cell infiltration).

The results of histology readings of the kidney organs of rats given the sari rapet herbal medicine showed that cell damage was found in both the control and experimental groups. Damage can be found in bridging necrosis, degeneration and focal necrosis, inflammatory cell infiltration, and cholangitis. based on (Figure 3) shows that liver cell damage bridging necrosis, inflammatory cell infiltration, degeneration and focal necrosis, and cholangitis increase as the dose administered increases.

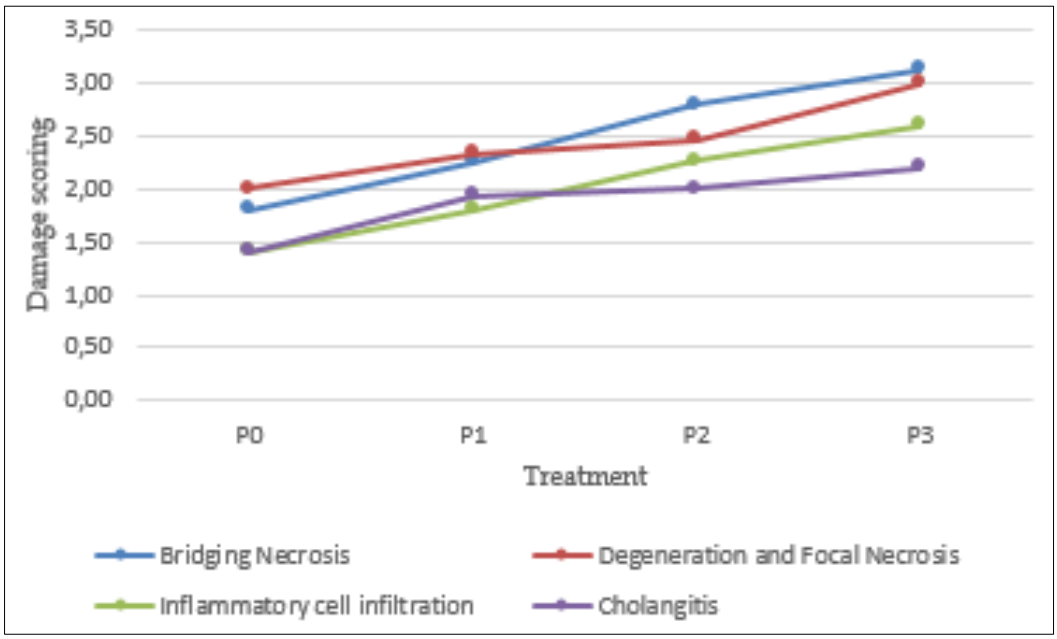



**Fig 4:** Line graph of the mean scoring of kidney and liver cell damage in rats (*Rattus novergicus*). The P3 group showed the highest damage scoring.

The results of the average scoring of kidney cell damage based on (Figure 4.) show that the more doses given, the more damage is caused. The average results will be continued with static calculations (Table 4):

**Table 4:** The Effect of Giving Sari Rapet Herbal Medicine on the Histology of Rat (*Rattus novergicus*) Livers.

| Group | Bridging Necrosis | Degeneration and Focal Necrosis | Inflammatory cell infiltration | Cholangitis |
|---|---|---|---|---|
| P0 | 1,80[a] | 2,00[a] | 1,40[a] | 1,40 |
| P1 | 2,26[a] | 2,33[a] | 1,80[a] | 1,93 |
| P2 | 2,80[b] | 2,47[a] | 2,27[b] | 2,00 |
| P3 | 3,13[b] | 3,00[b] | 2,60[b] | 2,20 |

**Descriptive:** The average value in the same column followed by a different superscript letter shows a significant difference in the post huc duncan test (P=0,05). P0 (control without treatment), P1 (dose 1; 0,54 d/200gBW), P2 (dose 2; 1,08 g/200gBW), P3 (dose 3; 1,62 g/200gBW).

Based on (Table 4.) show that there are significant differences in the types of damage such as bridging necrosis, degeneration and focal necrosis, and inflammatory cell infiltration (P<0.05).

In bridging necrosis damage, P0 did not have a significant difference with P1, the P1 group had a significant difference with P2 and P3, and the P2 group had no significant difference with P3. In terms of degeneration and focal necrosis damage, it shows that groups P0, P1, P2 do not have significant differences, and groups P0, P1, P2 have significant differences with P3.

The damage to inflammatory cell infiltration showed that groups P1 and P2 did not have significant differences, groups P1 and P2 had significant differences, and groups P2 and P3 did not have significant differences. In terms of cholangitis damage, the statistical results show that there is no significant difference (P>0.05).

Based on (Table 4), it shows that the highest risk of bridging necrosis type liver cell damage occurs in the P3 group which has a score of 3.13 (moderate), in degeneration and focal necrosis type liver cell damage with the highest mean is P3 with a score of 3. 00 (moderate), in inflammatory cell infiltration type liver cell damage, the highest mean occurred at P3 with a score of 2.60 (low), and the highest mean for cholangitis damage occurred at P3 with a score of 2.20 (low).

The Effect of Giving Sari Rapet Herbal Medicine on the Histology of Kidney Organs. The results of the kidney damage scoring measurements are presented in Table 4. The control group experienced degeneration, necrosis, and inflammatory cell infiltration which was in the low category. Giving sari rapet herbal medicine has the effect of increasing damage to kidney cells, the higher the dose given, the greater the damage to kidney cells caused. The type of kidney cell damage, degeneration, and inflammatory cell infiltration in the control group had significant differences (p<0,05) from the experimental group, different from the type of necrosis damage which did not have a significant difference (p>0,05) between all groups.

Degeneration damage to the cells found is hydropic degeneration caused by the entry of toxic compounds resulting in increased accumulation of water in the cytoplasm and is reversible [21, 22]. The hydropic degeneration found increased with increasing dose. This is caused by giving sari rapet herbal medicine which can have toxic consequences in excessive amounts. The concentration of chemical compounds that can be found in herbal medicine with the wrong composition can be toxic if the amount is large [23]. Reviewed from the results of histological observations, no fatty degeneration was found, which shows that sari rapet herbal medicine does not cause fat accumulation so there is no more severe disturbance in cell function. The discovery of fatty degeneration shows that there is a biochemical disturbance in cells caused by toxic chemical compounds [24]. The next stage of damage after degeneration is necrosis which is caused by too many toxic substances entering the kidneys and the inability of cells to maintain a balanced

physiological state resulting in cell death [25, 26]. The necrotic damage found can be caused by several factors including toxic compounds, metabolic disorders, and infections caused by viruses [27]. Inflammatory cell infiltration is found as a form of the body's defense against toxic compounds [28].

One of the factors causing necrosis and infiltration of inflammatory cells is the discovery of metabolite compounds in erratic doses and large quantities. Chemical compounds are no exception, metabolites with uncertain doses and large amounts can be toxic [29]. One of the metabolite compounds found is curcumin, which can be found in ginger in inappropriate amounts, causing damage to kidney cells [30]. Not only that, the ethanol compound which has an antihypertensive effect can cause blood pressure in the kidneys to decrease and trigger hypoxia in the epithelial cells of the renal tubules which, if it lasts for a long period, can cause cell necrosis which responds to inflammation [31, 32].

Not only that, the ethanol compound which has an antihypertensive effect can cause blood pressure in the kidneys to decrease and trigger hypoxia in the epithelial cells of the renal tubules which, if it lasts for a long period of time, can cause cell necrosis which responds to inflammation. Kidney cell damage caused by administering P3 (dose 3) is still in the normal category because acute tubular necrosis has not been found, which is a sign of kidney damage caused by large amounts of toxic substances [33].

The Effect of Giving Sari Rapet Herbal Medicine on Liver Histology. The results of liver cell damage scoring are presented in Table 4. The control group experienced the lowest cell damage and the experimental group experienced increased damage as the dose given increased. The control group and treatment groups experienced cell damage in the form of bridging necrosis, degeneration, and inflammatory cell infiltration which had significant differences ($p<0,05$), while cholangitis did not have a significant difference ($p>0,05$).

The damage that occurs to liver cells is caused by the presence of chemical compounds from the plant composition of sari rapet herbal medicine. The cause of liver damage is because the liver is susceptible to chemical compounds [34]. The compound that can be found in sari rapet herbal medicine, namely ethanol, which can be found in betel leaves and around-rooted galangal, can be toxic if given in high doses and can reduce liver function [35]. Toxic compounds will enter the body and be metabolized by cytochrome P450 enzymes in the liver and become free radicals so that they covalently bond with cell membrane components so that the cell membrane becomes damaged. Herbal medicines with varying compositions and uncertain dosages can enable the discovery of chemical components in herbal formulas that are hepatotoxic, causing liver damage [36].

Another possibility that influences the results of this research is the compound content contained in sari rapet herbal medicine, namely metabolite, compounds such as eugenol, phenol, cavinol, curcumin, flavonoids, alkaloids, tannins, saponins and polyphenols which have different benefits and activities that can mutually cancel out the effects of other compounds. and can be mutually contradictory or contradictory [37]. Metabolite compounds with erratic doses will have detrimental effects and can cause cell damage [38]. Flavonoid secondary metabolite compounds can produce prooxidant phenoxyl radicals which can have toxic effects on mitochondria, causing cell membrane damage [39, 40]. Metabolite compounds with incorrect dosage will inhibit the work of enzymes involved in intracellular lipid metabolism, resulting in cell damage [38].

## 5. Conclusion

Sari rapet herbal medicine production house X district of Sumenep has an effect on kidney cell damage namely degeneration and inflammatory cell infiltration, while necrosis has no influence. Sari rapet herbal medicine has an effect on liver cell damage, namely bridging necrosis, degeneration and focal necrosis, and inflammatory cell infiltration, while cholangitis has no effect.

## 6. Thank-You Note

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