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Hepatoprotective Activity of Hibiscus Flowers (*Hibiscus rosa-sinensis*) and Soursop Leaves (*Annona muricata*) Mix Infusion in *Mus musculus* Post Hyperuricemia Induction

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Abstract

Background: *Liver has many functions in the metabolic system and detoxification of substances that are harmful to the body. Chemical intoxication due to drug use might induce liver damage. A histology examination can indicate liver damage induced by a chemical substance, as well as the condition of tissue structure and function associated with the disease. This study aims to investigate the hepatoprotective effect of mix infusion of hibiscus flowers and soursop leaves on the liver histological structure in mice induced by hyperuricemia using potassium oxonate.* **Methodology:** *This study used an experimental group design, involving 8-week-old mice. The groups were divided as follows: A1 (control), A2 (Potassium oxonate), A3 (allopurinol), A4 (infusion 25 %), A5 (infusion 35 %), and A6 (infusion 45 %). Histological image was examined using an optilab with five fields of view.* **Findings:** *The study's revealed that the control group had a normal liver histology structure, whereas the hyperuricemia treatment group experienced significant liver damage, including congestion and leukocyte infiltration, and the allopurinol treatment group experienced significant damage, including leukocyte infiltration and necrosis. Therapy with a combined infusion of hibiscus flowers and soursop leaves shown a hepatoprotective effect. Based on histological analysis, the 25 % concentration provided the greatest hepatoprotective impact when compared to other infusion concentration. Mix infusion of hibiscus flowers and soursop leaves demonstrates heproprotective activity in hyperuricemia mice induced by potassium oxonate.* **Contribution:** *This study demonstrates that the mix infusion of hibiscus flowers and soursop leaves has the potential to be a hepatoprotective agent, but further research is needed regarding long-term effects.*

Keywords: *Hepatoprotective; Hibiscus; Histology; Hyperuricemia; Infusion*

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INTRODUCTION

Hyperuricemia is a condition when the amount of uric acid in the blood exceeds normal levels. The prevalence of hyperuricemia in Indonesia has also increased in recent decades. According to data from Riset Kesehatan Dasar (2018) the percentage of people with hyperuricemia has increased, the hyperuricemia was documented at 11.9 % in 2013 and grew up to 18.9 % in 2018. Indonesia ranks fourth in the world for gout prevalence. According to Riset Kesehatan Dasar (2018) data, based on diagnosis and symptoms, the prevalence of hyperuricemia was 24.7 %. According to Wen et al., (2020), hyperuricemia is one of the risk factors for liver dysfunction, metabolic disorders, cardiovascular, and chronic kidney disease problems.

The liver produces the majority of uric acid in the human body. When uric acid production is excessive, uric acid levels in the blood rise, allowing it to accumulate in the joints and mesenchymal tissues (Burhan et al., 2018). The liver is an important organ in the body because it plays a role in metabolism and detoxification of harmful chemicals. The liver can be harmed if there is an infection or chemical poisoning caused by the use of harmful medicines. The liver's detoxifying function is impaired as a result of a hazardous chemical overload. If the drug surpasses the liver's physiological limits, it will respond pathologically. Exposure to chemicals will undoubtedly impact the structure and function of the liver, as well as produce oxidative stress in hepatocytes. According to Irtanto et al., (2017), this is due to an increase in the production of *Reactive Oxygen Species* (ROS) which is not accompanied by sufficient antioxidants. Oxidative stress has a significant impact on hepatocytes, causing liver cell death (Barnes et al., 2014).

Hibiscus flower infusion (*Hibiscus rosa-sinensis* L.) can reduce blood uric acid levels in mice (Fatimatuzzahra & Lestari, 2022). Soursop leaves (*Annona muricata* L.) have the ability to lower uric acid levels (Ilkafah, 2018). Plants containing flavonoid and phenolic chemicals can lower uric acid levels, making them possible anti-hyperuricemia agents. Ebenyi (2012) stated that flavonoids have antioxidant properties that may contribute to hepatoprotective protection (hepatoprotectors), because cells have a mechanism to protect against the effects of ROS and are associated with increased levels of liver glutathione. Histological examination, which examines the structure and function of tissue associated to the effects of exposure to a chemical on specific organs, is one method of detecting liver damage caused by the effects of exposure to a compound. The purpose of this study is to investigate the hepatoprotective activity of a combination of hibiscus flower and soursop leaf infusion on the histological structure of the liver in mice induced by hyperuricemia.

METHOD

Preparation of Hibiscus Flower and Soursop Leaf Mix Infusion

Fresh *Hibiscus rosa-sinensis* flowers are picked and selected. *Annona muricata* leaves are also harvested from the third through sixth leaf shoots. The hibiscus flowers and soursop leaves are then rinsed with running water. Each of these components is weighed according on the concentration to be evaluated. Then, add 100 ml of distilled water and boil for around 15 minutes (90 °C). The following step is to remove and

filter while still hot. Boiling water can be added through the dregs to obtain a capacity of 100ml.

Preparation of Potassium Oxonate Solution

1 gram of potassium oxonate is weighed and added to 0.5 % Na-CMC solution in a beaker glass, then added to 30 mL. Potassium oxonate induction of 250 mg/kgBW intraperitoneally.

Experimental design

Thirty mice approximately 8 weeks old were acclimatized for 7 days and then weighed (body weight ranging from 25-30 grams). The mice were treated for 14 days before being terminated via cervical dislocation on the 15th day. The administration of potassium oxonate and chicken liver juice in the first week aims to increase uric acid levels in the mice."The test animals were separated into six groups of five repetitions each, as shown below.

Table 1. Treatment of experimental mice

No	Group	Week-1	Week-2
1	A1 (Control)	-	-
2	A2	Potassium oxonate + chicken liver juice	Potassium oxonate + chicken liver juice
3	A3		Allopurinol
4	A4		25% mix infusion*
5	A5		35% mix infusion*
6	A6		45% mix infusion*

Symbol * = mix infusion of hibiscus flower and soursop leaves

Histology Preparation

The mice were dissected with a dissecting kit, and the liver was extracted. Histology preparation according to (Lestari et al., 2022), the liver organs were rinsed with 0.9% NaCl before being fixed with 10% *Neutral Buffer Formalin* (NBF) in a flacon bottle for 24 hours. The organs were then cleaned with 70% alcohol before being dehydrated in graded and absolute alcohol for 30 minutes each. The following step is to clean the organs by immersing them in toluol for 2 hours, followed by infiltration, which involves immersing the organs in liquid paraffin four times for 60 minutes each. The organs are then embedded by placing them in liquid paraffin and allowed to harden in the embedding cassette. Furthermore, the organs are sectioned using a Leica histocore biocut rotary microtome, and affixed to a glass object to which Meyer albumin has been previously applied. The next stage is deparaffinization using xylol for 15 minutes. Before staining with hematoxylin eosin, the rehydration step was carried out by inserting into graded alcohol. Additionally, soaking in xylol for half an hour repeats the dehydration process in graded alcohol and continues the cleansing process. The final stage is mounting using a cover glass that is given entellan and labeled on the preparation.

Data Analysis

The histology preparation data was assessed qualitatively based on the condition of the liver tissue in 5 fields of view per preparation.

RESULT AND DISCUSSION

Histological research findings reveal the development of histological alterations in the liver of mice following the production of hyperuricemia. Based on the study's findings, Figure 1, the negative control group, which did not induce hyperuricemia, shows a normal hepatocyte structure, a central vein free of congestion, and sinusoids free of congestion. Figures 1 (a and b) demonstrate that the liver tissue is undamaged, however there is cell degradation in certain hepatocytes, or liver cells. In some quantities, this is typical under normal circumstances. Based on various research results, it also shows that in the control group in the histological image of the liver, hepatocytes experience some damage such as degeneration, pyknosis, and karyolysis. This is normal in a cell because each cell in a tissue will go through a physiological process that will experience aging which can end with the cell dying, then being replaced with new cells (regeneration process) (Zakiah et al., 2017; Putri et al., 2021).

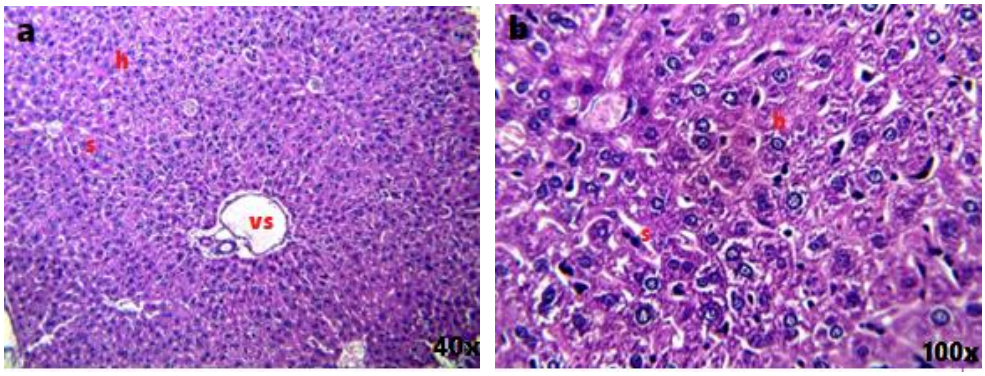

Figure 1. Histological structure of the liver in negative control showing normal histological structure. vs: central vein, h: hepatocyte, s: sinusoid

Figure 2 shows the histological image of the 14-day induction of chicken liver juice and potassium oxonate for the treatment of hyperuricemia and there is a changes in liver structure. There appears to be hemorrhage, a significant leukocyte infiltration, and congestion in the liver's primary veins. Additionally, hepatocytes undergoing sinusoidal dilatation, binuclear, and necrosis are depicted in Figure b. Potassium oxonate is one of the compounds used to induce hyperuricemia because it inhibits uricase, which increases uric acid release (Tang et al., 2017). Chicken liver is preferred over chicken brain because it contains more purines. Elevated blood uric acid levels can result from purine exposure-induced liver tissue damage. Research has shown that mice on a high-protein diet exhibited abnormal structural changes in their liver mitochondria (Ulusoy & Eren, 2006). Sinusoidal dilatation and hydropic degeneration can result from an imbalanced diet. Leukocyte infiltration in a tissue indicates

inflammation in the liver tissue, which serves as non-specific immunity and phagocytoses pathogens. Furthermore, bleeding from injury to the vascular wall that causes blood to depart the vascular system has been recognized as a sort of hemorrhage (Abasa & Ishak, 2022).

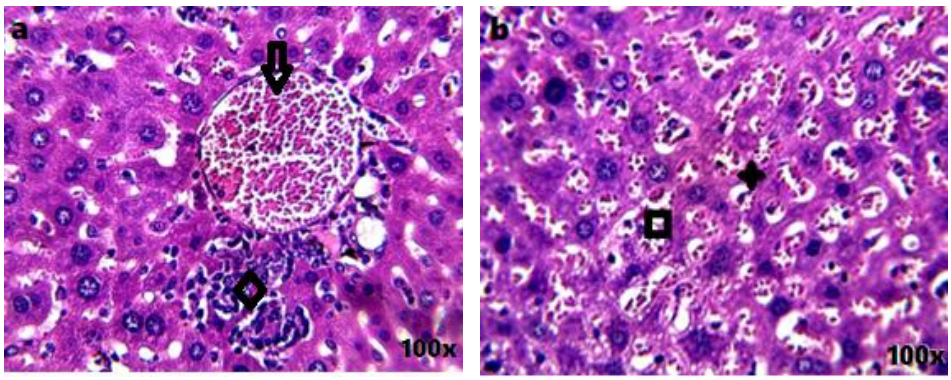

Figure 2. The histological structure of the liver in the hyperuricemia treatment group showed damage to the liver structure. Symbol ⇩ : hemorrhage, ◇ : leukocyte infiltration, ☐ : necrosis, ✦: hydropic degeneration

Potassium oxonate, a competitive uricase inhibitor, is administered intraperitoneally to cause hyperuricemia in animals such as mice and rats. It particularly inhibits uricase in the liver, causing uric acid to be generated (Tang et al., 2017). The liver plays a vital role in detoxification, intermediate metabolism, and the elimination of toxic substances. A range of medications and environmental toxins regularly have an affect on the liver, putting strain on this vital organ and weakening and damaging it, eventually leading to illness.

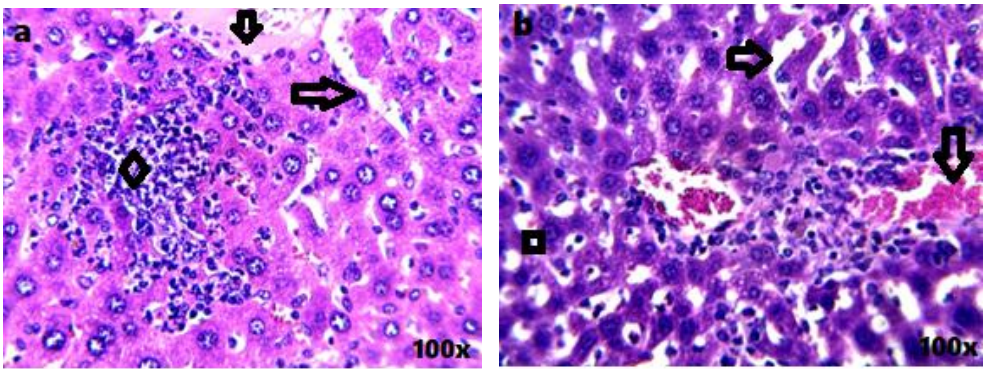

Figure 3. Histological structure of the liver in the treatment group using allopurinol after induction of hyperuricemia. Symbol ⇩ : hemorrhage, ◇ : leukocyte infiltration, ☐ : necrosis, ⇨: sinusoidal dilatation

Positive control group (Figure 3) received hyperuricemia induction for 7 days before receiving hyperuricemia drugs orally using allopurinol. Based on the figure, it shows moderate liver damage. The positive control group (Figure 3) received hyperuricemia induction for 7 days before receiving hyperuricemia therapy orally via allopurinol. The scan indicates moderate liver damage. There is extensive leukocyte infiltration, bleeding, hepatocyte necrosis, and sinusoid dilatation. Several

investigations have demonstrated that the use of allopurinol might produce acute or mixed cholestatic hepatitis, characterized by histological alterations in the form of leukocyte infiltration (eosinophils) and acute granulomatosis (Fontana et al., 2021). Hepatotoxicity caused by chemicals is a common problem due to the liver's position as a metabolic center for all medicines and xenobiotics introduced to the body. In addition to inflammation, liver cells undergo a significant amount of necrosis, which is an aberrant process of cell death induced by the interaction of specific substances such as harmful chemicals. Toxic chemicals can cause necrosis in hepatocytes (Abasa & Ishak, 2022). Liver damage might develop instantly, weeks, or months following treatment. Several factors influence liver damage caused by toxic compounds, including the dose administered, the type of chemical used, and the duration of exposure. Typically, the higher the concentration of a certain molecule. Typically, the higher the dosage of a substance administered, the greater the hazardous response.

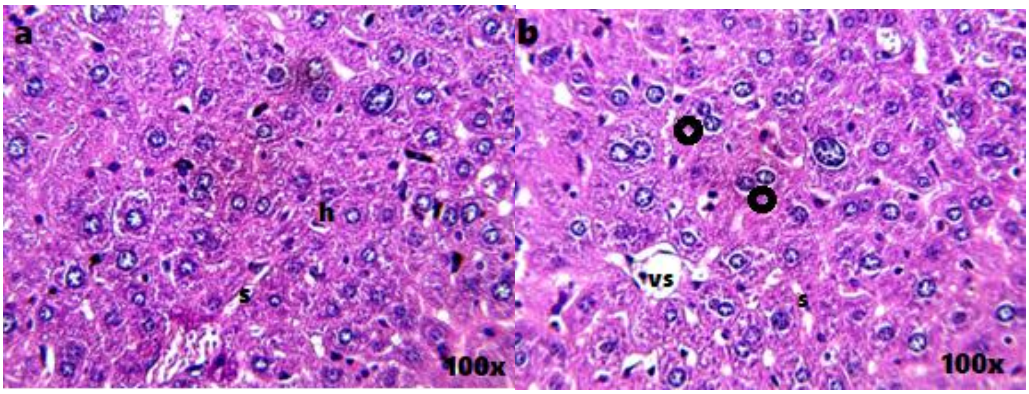

Figure 4. Histological structure of the liver in the treatment group using mix infusion with a concentration of 25 % after induction of hyperuricemia. vs: central vein, h: hepatocyte, s: sinusoid, ○: binuclear.

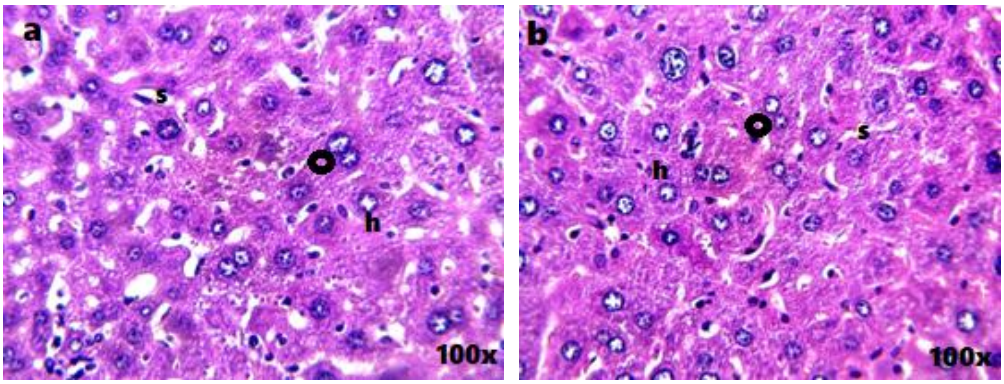

Figure 5. Histological structure of the liver in the treatment group using a mix infusion with a concentration of 35% after induction of hyperuricemia. vs: central vein, h: hepatocyte, s: sinusoid, ○: binuclear.

The histological structure with a 7-day induction of hyperuricemia and mix infusion of hibiscus flower and soursop leaves was shown in Figures 4, 5, and 6. The combined infusion was subsequently given for seven days at gradually increasing doses of 25 % (Fig.4), 35 % (Fig.5), and 45 % (Fig.6). According to the histological

structure's, the number of cells experiencing binuclear indicates that the liver cells regenerated. Liver cell proliferation, binuclear hepatocytes are always utilized to show liver regeneration (Zulkawi et al., 2017). Treatment with a combined infusion of hibiscus and soursop leaves shows greater liver cell regeneration activity than other treatment groups. Additionally, normal hepatocytes are observed during the infusion treatment, albeit some areas still exhibit mild hemorrhage.

Figure 6 shows liver cells experiencing binuclear at a dose of 45 %, but not as effectively as the 25 % mix infusion. Furthermore, at this dosage, leukocyte infiltration was detected, indicating inflammation, as well as necrosis of liver cells. This demonstrates that increasing the infusion concentration does not necessarily improve liver cell regeneration. The liver is one of the organs that metabolizes many drugs/substances, making it vulnerable to injury from xenobiotic compounds (Yuliawati et al., 2018). If the liver does not function effectively during the metabolic process, it can cause a range of changes and damage.

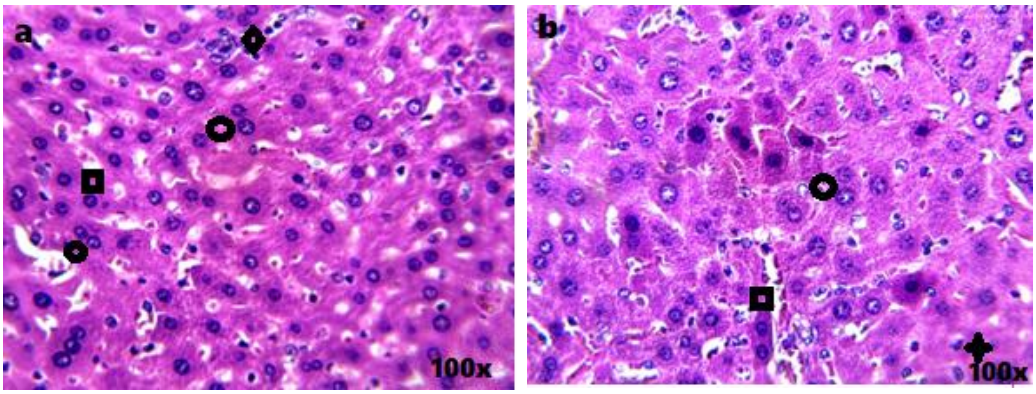

Figure 6. Histological structure of the liver in the treatment group using a mix infusion with a concentration of 45% after induction of hyperuricemia. vs: central vein, h: hepatocyte, s: sinusoid, ◇ : leukocyte infiltration, □ : necrosis, ○: binuclear.

Treatment group of a mix of hibiscus flower and soursop leaf infusion showed regeneration, and better liver conditions than the treatment group using medicines for hyperuricemia (allopurinol), indicating that mix infusion has hepatoprotective activity and potential to be a hepatoprotector. This is assumed to be due to secondary metabolites in the mix infusion, which can act as hepatoprotectors. According to the phytochemical analyses, secondary metabolites such as flavonoids, phenols, alkaloids, and tannins are present in the mix infusion of *H. sinensis* L. flower and *A. muricata* L. leaves (Lestari et al., 2024). Terpenoids, steroids, tannins, and alkaloids are examples of phytochemical composition that has long drawn a lot of attention because of its diverse pharmacological properties, including hepatoprotective and antioxidant effects. Several studies have demonstrated that plants help protect the liver because contains flavonoid chemicals that serve as antioxidants. Flavonoids are commonly found in natural medications and have high activity. They mostly contain flavones, favonols, dihydrofavonoids, and other similar chemicals. Most flavonoids have anti-inflammatory, antioxidant, and hepatoprotective effects (Zhou et al., 2021). Panche et al., (2016) also stated the antioxidant activity of secondary metabolites, such

as flavonoids and phenolics, can help shield tissues and cells from oxidative stress which can harm cells.

According to Hardiningtyas et al., (2014), flavonoids are free radical scavengers due to their high concentration of polyphenol compounds, which are particularly effective at reducing free radical levels. Their methods of action include inhibiting lipid peroxidation, promoting liver cell membrane repair, eliminating free radicals, preventing mitochondrial malfunction, treating cholestasis, and inhibiting the secretion of inflammatory agents (Zhou et al., 2021). Hepatoprotectors have therapeutic actions and are effective in the process of recovering, maintaining, and treating liver function deterioration and good efects on drug-induced liver injury (Farghali et al., 2015). This molecule will act to protect the liver from harm caused by medicines, toxic substances, and other conditions. The liver's enzymes detoxify xenobiotic chemicals and metabolic waste, converting them into inactive molecules. Alternative therapeutic alternatives for liver problems can include medicinal plants that contain antioxidants, because, in addition to their proven and useful effects, medicinal plants are also readily available in the environment (Ali et al., 2018). However, not every medicinal plant has the same hepatoprotective effect due to the different chemicals present (Oktavia et al., 2017). So, if we examine the findings of study on various types of antioxidant-containing plants, we can see that each plant's ability to hepatoprotective activity varies depending on the number and type of active molecules (secondary metabolites) included in the plant.

According to the histological image of all treatment groups, the combined infusion group had a hepatoprotective effect when compared to the positive control group given allopurinol. This is demonstrated by the presence of hepatocyte regeneration, which results in improved liver cells following hyperuricemia induction. In this study investigation, the optimal infusion concentration as a hepatoprotector was 25%, as evidenced by the histological structure of the mice' liver.

CONCLUSION

The negative control group showed normal histological liver structure, while the hyperuricemia treatment group had liver damage involving congestion and leukocyte infiltration, and the allopurinol treatment group showed damage with leukocyte infiltration and necrosis. Meanwhile, the treatment group that received a combination of hibiscus flower and soursop leaf infusion had a hepatoprotective effect. Based on the histological structure of this study, it was determined that the 25 % concentration had the optimum hepatoprotective effect. This study demonstrates that the mix infusion of hibiscus flowers and soursop leaves has the potential to be a hepatoprotective agent, but further research is needed regarding long-term effects.

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