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Histopathology of the Liver of White Rats (Rattus Norvegicus) Given Binahong Leaf Extract (Anredera cordifolia)

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KATA KUNCI

Binahong Leaves, Drug-Induced Liver Injury, Diclofenac Sodium, Liver Damage

ABSTRACT

Drug-Induced Liver Injury (DILI) refers to hepatic damage caused by drug exposure, with established molecular mechanisms including mitochondrial dysfunction, elevated reactive oxygen species (ROS), increased apoptosis and necrosis, and bile duct injury via immune-mediated pathways. Binahong leaves (*Anredera cordifolia*) contain saponins, flavonoids, alkaloids, and tannins, which exhibit antioxidant properties. These compounds are known to neutralize free radicals in the liver. This study aimed to examine the effect of binahong leaf extract on the liver histopathology of white rats (*Rattus norvegicus*) induced by diclofenac sodium. A true experimental posttest-only design with a control group was employed. Thirty Wistar strain rats were divided into five groups: negative control, positive control (diclofenac sodium 10 mg/kgBW), and three treatment groups receiving diclofenac sodium plus binahong leaf extract at doses of 100, 150, and 200 mg/kgBW, respectively. Liver damage was assessed using the Roenigk histopathology scoring system. Data were analyzed using the Kruskal-Wallis test, followed by Post Hoc Tukey HSD. The results indicated a significant difference in liver histopathology among groups ($p=0.001$, $p<0.05$). Histopathological changes were observed as follows: negative control (4 normal, 1 parenchymatous), positive control (3 parenchymatous, 3 hydropic), P1 (3 parenchymatous, 2 hydropic), P2 (4 parenchymatous, 1 hydropic), and P3 (2 normal, 3 parenchymatous). In conclusion, binahong leaf extract significantly improved liver histopathology in diclofenac-induced rats, with the most effective dose being 200 mg/kgBW.

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INTRODUCTION

The global use of traditional medicine is expanding rapidly, with prevalence rates of 40–90% in Asia and 42–70% in Europe and America (Rollando et al., 2022; Ma et al., 2016). As a tropical country, Indonesia is rich in biodiversity, hosting approximately 30,000 plant species, of which about 7,000 possess medicinal properties (Lestari, 2016). According to Riskesdas (2018), 44.3% of Indonesians utilize traditional health services, underscoring the need to develop phytopharmaceutical products for future healthcare (Riskesdas, 2018).

Binahong (Anredera cordifolia) is a medicinal plant widely used in community-based healing practices. Previous studies have identified secondary metabolites in binahong leaves, including flavonoids, which exhibit antioxidant potential (Lestari et al., 2015; Yuziani, 2015). Additionally, binahong contains saponins, triterpenoids, and essential oils, with flavonoids demonstrating anti-inflammatory activity (Rachmawati, 2016). Recent research suggests that

herbal hepatoprotective agents, including antioxidants, may offer therapeutic benefits for liver diseases (Palawe et al., 2021).

The liver plays a vital role in metabolism, detoxification, protein synthesis, and immune function (Lal et al., 2016; Samuels, 2018). According to WHO data, liver diseases are commonly caused by viral infections and drug abuse. Hepatotoxic compounds from drugs, alcohol, and other toxins can lead to hepatocellular necrosis, cholestasis, and hepatic dysfunction. Among commonly used hepatotoxic agents are antibiotics, paracetamol, and nonsteroidal anti-inflammatory drugs (NSAIDs) (Sadiyah et al., 2019).

According to Wong (2019), OAINS are commonly used to treat headaches, fever, and pain in rheumatic diseases, cancer, neurological disorders and others. Lovell (2017) study, OAINS works by inhibiting cyclooxygenase enzymes 1 and 2 for the production of prostaglandins (PGE2) and prostasicline (PGI2), as inflammatory mediators. Data from the Model List of Essential Medicines of the World Health Organization (WHO), OAINS are commonly prescribed by doctors and sold freely in the community. The prescribing rate of OAINS in the United States and Western Europe is 4-7%.

In the last three decades, there has been an increase in the use of OAINS without a doctor's prescription in both developed and developing countries by 67% of patients (Bindu et al., 2020). In Indonesia, as many as 19.8% of total households store OAINS and the highest number of indications of use is 65.17% (Asiri et al., 2020). The Essential Medicines List (EML) data has contained 100 countries of which 74 countries use OAINS in the form of diclofenac. Diclofenac is the most widely prescribed drug and has the highest adverse drug reaction at 73% (Fokunang, 2018; Soleha et al., 2018). Data from PAPDI (2014), the therapeutic dose of diclofenac sodium is 25 mg-50 mg in 2 or 3 times a day, while the maximum dose is 150 mg-200 mg in a day.

Mechanism of liver injury by multifactorial diclofenac drugs (Gettigan & Henry, 2014). Injury to hepatocytes causes the release of intracellular hepatic enzymes from the cytoplasm and organelles to the sinuses, resulting in increased levels of Serum Glutamic Pyruvic Transaminase (SGPT) and Serum Glutamic Oxaloacetic Transaminase (SGOT) in the blood which are indicators of liver damage (Gor & Saksena, 2011). Rohmani's (2016) study, stated that hepatic histopathology found that hepatocyte cells underwent parenchymatose, hydropic, and necrotic degeneration. Solomon's study (2019), regarding the administration of sodium diclofenac at a dose of 10 mg/kgBB orally for 7 days and hepatotoxicity occurred in rats (Lazarska et al., 2018).

Based on the background that has been described, the content of binahong leaves can provide benefits for people with liver disorders, so research is needed to determine the histopathology of the liver of white rats given diclofenac sodium to the administration of binahong leaf extract.

RESEARCH METHOD

This study employed a laboratory-based true experimental design, specifically a posttest-only approach with a control group. The sample comprised 30 Wistar strain white

rats, divided into five groups of six animals each, calculated using Federer's formula with an additional sample to account for potential dropouts. The research was conducted across three locations: the Integrated Laboratory of the Medical Education Study Program (animal maintenance and treatment), the Laboratory of Mathematics and Natural Sciences at Widya Mandira University (extract preparation and testing), and the Anatomical Pathology Laboratory at Prof. Dr. W.Z. Yohanes Hospital (tissue processing and staining).

In the negative control group, only standard BR-1 and aquades feeds were given. The positive control group was given standard BR-1 and aquades feeds, and given sodium diclofenac at a dose of 10 mg/kgBB. Treatment group 1 was given standard BR-1 and aquades feed, given sodium dilfenak at a dose of 10 mg/kgBB and given binahong leaf extract at a dose of 100 mg/kgBB. Treatment group 2 was given standard BR-1 and aquades feed, given diclofenac sodium at a dose of 10 mg/kgBB and given binahong leaf extract at a dose of 150 mg/kgBB. Treatment group 3 was given standard feed BR-1 and aquades, given sodium diclofenac at a dose of 10 mg/kgBB and given binahong leaf extract at a dose of 200 mg/kgBB.

The test animals were adapted for 7 days and given standard BR-1 and aquades feed, as well as weight weighing before being treated. Days 8 to 14 (7 days) sodium diclofenac dose of 10 mg/kgBB was administered orally in the positive control group and 3 treatment groups (P1, P2, P3). On the 15th to the 21st day (7 days), binahong leaf extract was given to 3 groups of oral treatment with different doses, namely P1 100 mg/kgBB, P2 150 mg/kgBB, P3 200 mg/kgBB. On day 015, test animal surgery was also carried out for the positive control group.

Test animal surgery was carried out on the 22nd day, for the negative control group and 3 treatment groups (P1, P2, P3) that had been anesthetized using inhalation using ether before surgery. The liver organs are then taken and stored in formalin before being used as a preparation using the Hematoxylin-Eosin (HE) staining method.

The preparation aims to find out whether there are changes in hepatocyte cells after the administration of binahong leaf extract and diclofenac sodium. The assessment on the preparation of liver cells in 5 fields of view, the components assessed were normal hepatocyte cells with a value of 1, parenchymatous degeneration with a value of 2, hydroic degeneration with a value of 3, and necrosis with a value of 4. The scoring used for the liver organ is Histopathology Manja Roenigk.

The data were analyzed using the Kruskall-Wallis test because the data was distributed abnormally, followed by a post hoc test. The post hoc test used is the HSD (Honestly Significance Different) Test to find out whether or not there is a significant difference between groups from one group to another.

RESULTS AND DISCUSSION

Binahong Leaf Extract *(Anredera cordifolia)* used in this study is expected to provide changes in the histopathology of white rats *(Rattus norvegicus)* who are given sodium diclofenac at a dose of 10 mg/kgBB. The results of non-parametric analysis, namely testing to assess the significance of a hypothesis, found that the value $p = 0.001$ ($p < 0.05$) showed significant results so that binahong leaf extract had an effect on the histopathology of the liver of white rats of *the Wistar* strain who were given sodium diclofenac.

In the negative control group, white rats were not treated with only BR-1 and *aquades* feed during the study period. The results of the hepatic histopathology sample showed normal hepatocyte cells with a round to oval shape and a dense nucleus and chromatin substances that still appeared thick, the presence of sinusoids shown in the images of capillary plates (Leliqia et al., 2017). However, the results of the readings in the test preparation showed that hepatocyte cells experienced parenchymatous degeneration or cell swelling.

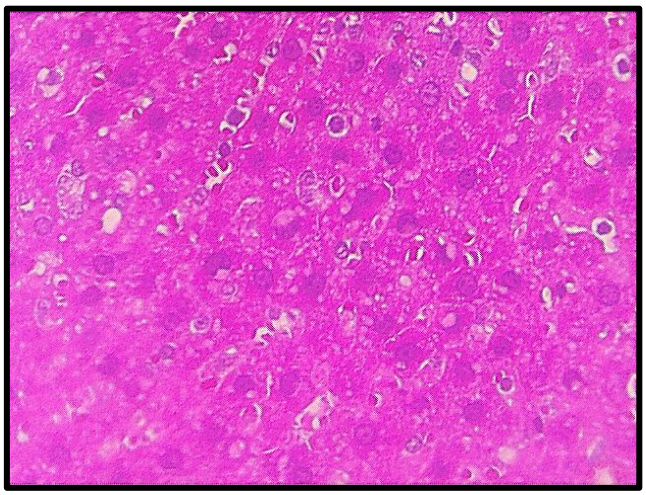

Figure 1. Hepatic histopathology of the negative control group
Description, SH: Normal hepatocyte cells; S: Sinusoid

The positive control group was given sodium diclofenac at a dose of 10 mg/kgBB for 7 days and underwent surgery and microscopic observation to obtain hepatic histopathology in the form of hydropic degeneration and necrosis. This hepatic histopathology also showed a significant difference between other sample groups with a result of $p = 0.001$ ($p < 0.05$), proving that the most cell damage occurred in the positive control group. The appearance of hydronic degeneration is described as hepatocyte damage characterized by small clear vacuoles in the cytoplasm that pale and swelling of hepatocyte cells occurs (Maulina, 2018).

Histopathological results found necrosis as a result of progressive degradation by enzymes in affected cells. Necrosis or cell death occurs when tissue undergoes hypoxia and the entry of foreign bodies that are considered toxins. The presence of this toxin, forms *a reactive oxygen species* (ROS) reaction and causes oxidative stress (Maulina, 2018; Kumar et al., 2017). Positive control also in one of the fields of view shows an inflammatory or inflammatory reaction due to the defensive response of the incoming foreign body.

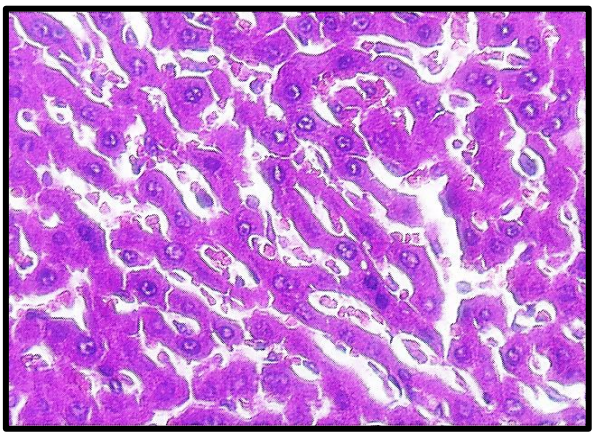

Figure 2. Hepatic histopathology of the positive control group
Description, DP: Parenchymatous degeneration; DH: Hydrocephalus degeneration; N: Necrosis

The administration of binahong leaf extract in treatment group 1 with a dose of 100 mg/kgBB proved that there was a change in the degree of liver cell damage caused by binahong leaf extract. There was a difference in hepatocyte cell damage in treatment 1 that underwent parenchymatous degeneration and hydroceptic degerennation, but the number was less in each field of view than in the positive control. Treatment group 1 also showed an inflammatory or inflammatory reaction due to the defensive response from the entry of objects considered foreign. A study conducted on rats given binahong leaf extract by Estowo (2014), the treatment group induced a significant change in necrosis in the histopathology of the hepa, this concludes that at a dose of 100 mg/kgBB binahong leaf extract provides a fairly good improvement in the histopathology of heparous cell necrosis. Another study conducted by Dwiyiyanti (2021), stated that binahong leaf extract used at a dose of 100 mg/kgBB in rats can reduce blood glucose levels in the metabolic organs of test animals.

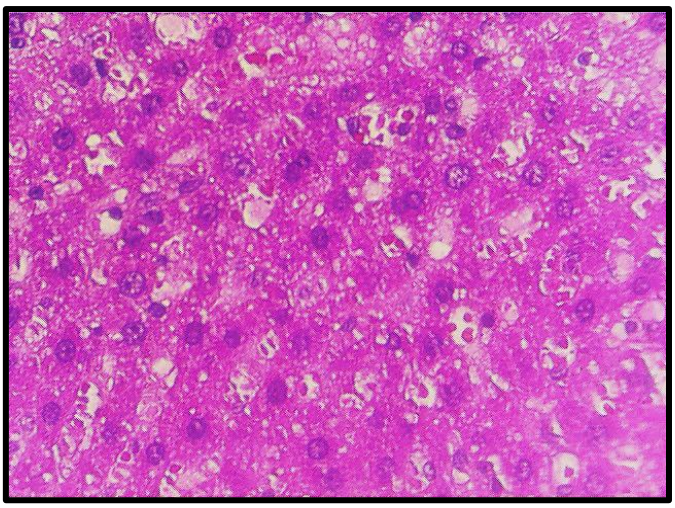

Figure 3. Hepatic Histopathology Treatment Group 1

Description, DP: Parenchymatous degeneration; DH: Hydrophic degeneration

In treatment group 2 who were given binahong leaf extract 150 mg/kgBB, they obtained a significantly different hepatic histopathology from the negative control group. The histopathological differences in treatment group 2 when compared with treatment group 1 did not show any significant difference. The histopathological results of the difference in hepatocyte cell damage with treatment 2 that experienced parenchymatous degeneration and hydroceptic degeneration were less in each field of view in treatment group 1. Treatment group 2 also showed an inflammatory or inflammatory reaction due to the defensive response from the entry of objects considered foreign in one of the fields. It was concluded that the dose of binahong leaf extract of 150 mg/kgBB provided a significant picture of the repair of necrosis cells and hydropic degeneration of liver cells.

Research conducted on rats given bianhong leaf extract by Leliqia (2017) and Santi (2022), showed relatively similar results at a dose of binahong leaf extract of 150 mg/kgBB to improve damage to the liver and kidney nephrons as well as other organs. This histopathological improvement is based on the flavonoid content in binahong leaves, which occurs a hepatoprotective mechanism of ROS that can result in inflammatory damage to the liver organs (Rachmawati, 2016; Palawe et al., 2021).

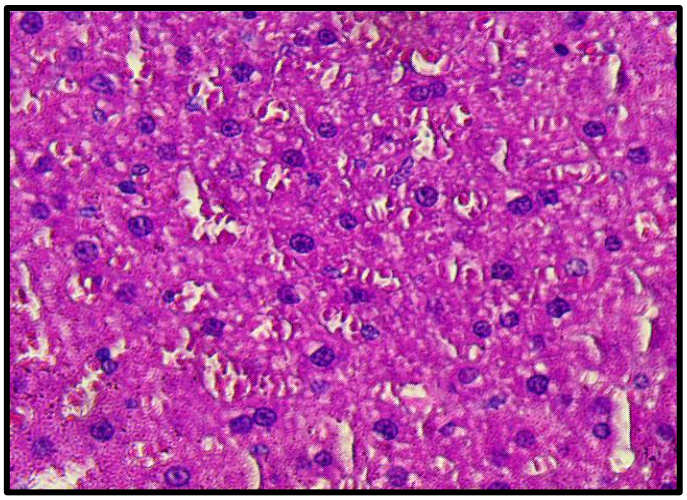

Figure 4. Hepatic Histopathology Treatment Group 2
Description, SH: Normal hepatocyte cells; DP: Parenchymatous degeneration

Histopathology of liver cells in treatment group 3 given binahong leaf extract of 200 mg/kgBB is the most optimal picture to repair damaged liver cells. In the histopathology of the liver organs, it was found that there were more normal hepatocyte cells while less parenchymatous degeneration was found in each field of view of the test preparation. Treatment group 3 also showed an inflammatory or inflammatory reaction due to a defensive response from the entry of objects considered foreign. The results of a study conducted on rats given binahong leaf extract by Estowo (2014), the induced treatment group experienced a

significant change in necrosis in liver histopathology and the study conducted, this concludes that at a dose of 200 mg/kgBB binahong leaf extract provides a good improvement in the picture of liver cell necrosis.

Another study conducted by Siswanto (2018), showed that the increase in SGOT and SGPT levels in rats could be inhibited by the administration of binahong leaf extract at a dose of 200 mg/kgBB. In addition, in the proof of Post Hoc analysis, $p = 0.001$ ($p < 0.05$) was obtained for the comparison of the negative control group and the treatment group 3, where when the conclusion was drawn, only treatment group 3 had the same significant difference as the negative control group.

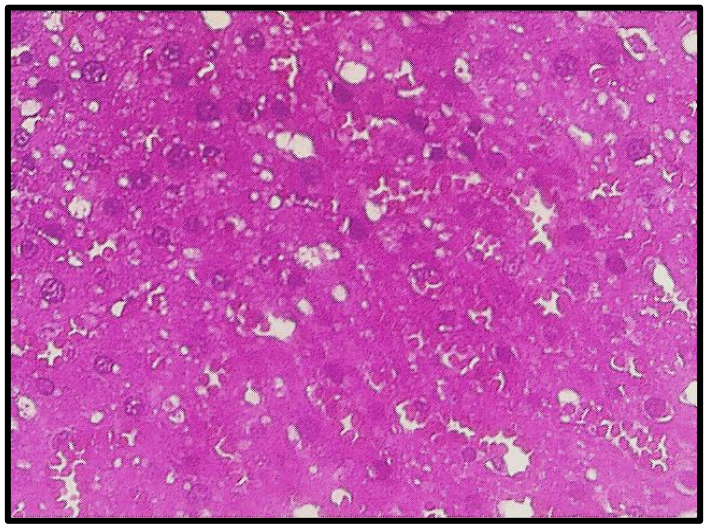

Figure 5. Hepatic Histopathology Treatment Group 3
Description, SH: Normal hepatocyte cells; S: Sinusoid

This proves that the dose of binahong leaf extract of 200 mg/kgBB provides a more effective healing effect on histopathological damage to liver cells (Estowo et al., 2014). The content in binahong leaf extract acts as an antioxidant to ward off free radicals that can damage liver tissue. The damage caused by sodium diclofenac, as a toxic compound, results in damage to the gastric epithelial lining which can lead to complications in liver tissue and result in inflammation and damage to hepatocyte cells (Loka et al., 2020; Yunarto et al., 2019).

CONCLUSION

This study found that binahong leaf extract (*Anredera cordifolia*) significantly improved liver histopathology in white rats (*Rattus norvegicus*) exposed to sodium diclofenac, with notable differences between the positive control group (diclofenac only) and the treatment groups receiving both diclofenac and the extract. While lower doses (100 and 150 mg/kgBW) did not show significant improvement compared to the positive control, the highest dose of 200 mg/kgBW demonstrated a significant protective effect, comparable to the negative control. Future research could explore the underlying molecular mechanisms of this protective effect

and evaluate the long-term safety and efficacy of binahong leaf extract in different liver injury models.

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