DENTINO
JURNAL KEDOKTERAN GIGI
Vol X. No 1. MARCH 2025

TOXICITY TEST OF *Eusideroxylon zwageri* BARK EXTRACT ON LIVER HISTOPATHOLOGY PARENCHYMATOUS DEGENERATION AND FATTY DEGENERATION

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ABSTRACT
Background: *Ironwood bark extract can be developed into an alternative herbal medicine for wound healing because it contains phenolics, flavonoids, and proanthocyanidins which can act as an antioxidant. Before being used as an herbal medicine, it is necessary to ensure its safety through an toxicity test.* ***Purpose:*** *To find out whether there is no toxic effect on the orally administration of ironwood bark extract (Eusideroxylon zwageri) at the doses of 1,250 mg/kgBW, 2,750 mg/kgBW, and 4,750 mg/kgBW to the livers of Wistar rats (Rattus norvegicus) based on histopathological appearance of parenchymatous degeneration and fatty degeneration.* ***Methods:*** *This research is purely experimental with a posttest only with control design. The sample in this study were 16 Wistar rats which were divided into* 4 groups, namely the control group which *was only* administered *distilled water and the treatment groups P1, P2, P3 which were administered ironwood bark extrac at the doses* of 1,250 mg/kg BW, 2,750 mg/*kg BW, and 4,750 mg/kgBW of 2x1 ml every 24 hours for 14 days.* ***Results:*** *The average percentages of histopathological appearance of parenchymatous degeneration and fatty degeneration in the K, P1, P2, and P3 groups showed a score of 0 which was categorized as normal. Data analysis showed that there were no significant differences between groups P1, P2, and P3 with the control group.* ***Conclusion:*** Ironwood bark extract doses of 1,250 mg/kg BW, 2,750 mg/kg *BW*, and *4,750 mg/kg BW had no toxic effect on the liver of Wistar rats based on histopathological appearance of parenchymatous degeneration and fatty degeneration.*

Keywords *: Fatty degeneration, Histopathology, Ironwood bark, Parenchymatous degeneration*

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INTRODUCTION

Tooth extraction is a common procedure performed by a dentist.[1] Based on the 2018 Basic Health Research (Riskesdas), the prevalence of tooth extraction in South Kalimantan province is around 8.46%.[2] The area around the removal scar will experience injury and complications may occur that hinder the wound healing process.[1,3] This can be prevented by the use of post-tooth extraction drugs.[4] However, the use of chemical drugs has unexpected side effects, so alternative drugs with minimal side effects are needed.[4] According to WHO data, 70-80% of the world's population uses alternative medicine in the form of herbal medicine because the price is affordable and the side effects are smaller.[5]

One alternative treatment that can be developed is herbal medicine derived from ironwood bark. Ulin (*Eusideroxylon zwageri)* is a typical plant from the island of Borneo.[6] According to phytochemical tests in previous studies, the phenolic, flavonoids, and proanthocyanidins in ironwood bark were 31.28 mg GAE/g, 30.48 mg CE/g, and 183.30 mg PE/g.[7] These compounds can act as antioxidants that help the wound healing process.[8–10] However, previously ironbark extract needed to be confirmed for safety through toxicity tests.[11]

Toxicity tests are carried out to determine whether there are toxic effects on medicinal plants before they can be used by humans.[11] Toxicity tests consist of in *vitro* and *in vivo* toxicity tests.[12] Research on the

toxicity test of ironbark extract in *vitro* against BHK-21 cells has been conducted by Salwa et al (2021).[6] The results of the study showed that at concentrations of 5%, 15%, 25%, 35%, 45%, 55%, 65%, 75%, 85%, and 95% ironbark extract had no toxic effect on BHK-21 fibroblast cells.[6] Meanwhile, *in vivo* toxicity test consists of acute toxicity test, subchronic toxicity, and chronic toxicity.[12] Acute oral toxicity test is a test intended to detect the toxic effects of a preparation that arises in a short time and is carried out for 14 days.[12] One of the parameters in the toxicity test can be seen from the histopathological appearance of the liver.[11]

The liver is the largest organ of the body, which is 2.5% of body weight weighing about 1-2.3 kg.[13] The liver is a detoxification organ that plays a role in protecting the body from the entry of foreign materials or toxins into the body.[13] A damaged liver is characterized by cellular changes in its histological appearance.[13] The cellular changes that occur can be cell degeneration such as parenchymatous degeneration and fatty degeneration or steatosis.[13]

Cell degeneration is cell damage in the early stages caused by toxins and is reversible.[13] Parenchymatous degeneration is the mildest degeneration with a description of cell swelling and granulated cytoplasm caused by cell failure to eliminate water.[13] Meanwhile, fatty degeneration is the accumulation of fatty in the cell characterized by the formation of vacuoles in the cytoplasm.[13] The occurrence of fatty degeneration is caused by disruption of lipid transport which results in the accumulation of lipids in hepatocytes.[13]

METHODS

This research was carried out after obtaining ethical approval from the Health Ethics Commission of the Faculty of Dentistry, Lambung Mangkurat University No. 025/KEPKG-FKGULM/EC/II/2023. This research is purely experimental (true experimental designs) with posttest-only designs with control designs.

The total number of Wistar rat samples in this study was 16 rats with sampling techniques using simple random sampling techniques.

Table 1. Test Animal Group

Group	Treatment	Samples
K	Aquades	4
P1	Ironwood bark extract 1,250 mg/kgBB	4
P2	Ironwood bark extract 2,750 mg/kgBB	4
P3	Ironwood bark extract 4,750 mg/kgBB	4

The inner ironwood bark is brownish-red at a height above 50 cm and the diameters above 60 cm are taken as much as 14 kg. The ironwood bark is cleaned of dirt or moss then potted using wood crabs and dried in an oven temperature 40ºC for 4 hours. Ironwood bark is mashed using a blender to produce 2,100 grams of simplisia. The maceration process is carried out using ironwood bark powder soaked for 3 x 24 hours in 96% ethanol solvent. Next, the extract is filtered with WH 40 filter paper. Maserat is evaporated with a rotary vacuum evaporator for 4-6 hours at a temperature of 60ºC, then heated using a waterbath until the solvent evaporates and a thick extract of 102 grams is obtained. The ethanol-free test is done using a sample of ironwood bark ethanol extract added with a few drops of Potassium dichromate ($K_2C_2O_7$). Preparation of concentrations of 25%, 55%, 95% ironbark extract by dilution using aquades. Then the conversion was carried out into doses of 1,250 mg/kgBW, 2,750 mg/kgBW, and 4,750 mg/kgBW.

Wistar rats were satisfied ±6 hours before treatment. Each group was given 2 x 1 ml every 24 hours for 14 days. All mice were sacrificed with a 0.6 ml dose *of ketamine-xylazine* intraperitoneally on day 15. Before being sacrificed, rats are satisfied first for 8-12 hours. Rats that have been sacrificed and taken tissue are then buried at a depth of 75 cm. The rat liver that had been taken was then soaked in 10% Neutral Buffered Formalin (NBF), then made preparations and stained Hematoxylin Eosin (HE).

Histopathological preparations were observed using a microscope in 5 fields of view with a magnification of 400x in each field of view. The percentage of cell damage in one field of view were calculated by dividing the number of cells in a field of view divided by the total number of cells in a field of view and multiplied by 100%. Then calculated the average percentage of damage was from 5 fields of view. Scoring is based on the average percentage of histopathological appearance of each group.

Table 2. Parenchymatous Degeneration and Fatty Degeneration Scoring

Parenchymatous Degeneration	Score	Information
<25% of the liver has parenchymatous degeneration around the centrolobulary (central vein).	0	Normal
25-50% of the liver has parenchymatous degeneration that extends to the central region (midzona	1	Mild
50-75% of the liver has parenchymatous degeneration that extends to the periporta (perilobule).	2	Moderate
>75% of the liver has parenchymatous degeneration that extends to the periportal (perilobulary) zone.	3	Severe
Fatty Degeneration	**Score**	**Information**
Fatty degeneration <5% of all hepatocytes	0	Normal
Fatty degeneration 5%-33% of all hepatocytes	1	Mild
Fatty degeneration 34%-66% of all hepatocytes	2	Moderate
Fatty degeneration >66% of all hepatocytes	3	Severe

RESULTS

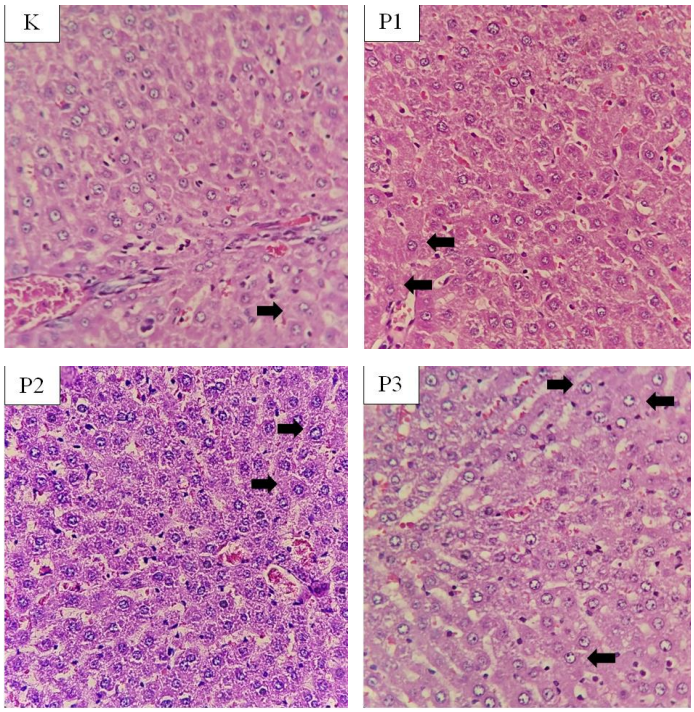

Figure 1. Histopathological Appearance of Parenchymatous Degeneration of Wistar Rat Liver Tissue Group (K) Control, (P1) Ironbark Extract Dose 1,250 mg/kgBB, (P2) Ironstem Bark Extract Dose 2,750 mg/kgBB, and (P3) Ironwood Bark Extract Dose 4,750 mg/kgBB. Using Olympus CX43 Microscope (400x, HE)

Figure 1 shows the histopathological appearance of parenchymatous degeneration in the liver of Wistar rats shown by black arrows. The histopathological appearance of parenchymatous degeneration is characterized by a larger size of the cell because the cell swells due to water accumulation in the cell and the presence of granules in the cytoplasm due to protein deposits. In groups K, P1, P2, and P3, some cells experienced parenchymatous degeneration, but more pictures of normal hepatocyte cells were found.

Table 3. The results of data analysis mean percentage of histopathological picture of parenchymatous degeneration and its standard deviation

Group	Mean±Standard Deviation Parenchymatous Degeneration	Score
K	0.95±0.191	0
P1	1.1±0.258	0
P2	1.2±0.163	0
P3	1.4±0.432	0

Table 3 shows the results of data analysis of the average percentage of histopathological appearance of parenchymatous degeneration along with the standard deviation of each group. The average percentage of histopathological appearance of parenchymatous degeneration in groups K, P1, P2, and P3 received a score of 0 with the normal category, namely there was a picture of parenchymatous degeneration around the centrilobular (central vein) of <25% of the 5 fields of view observed. Based on data analysis using the One Way ANOVA test, there was no significant difference in the average percentage of histopathological appearance of parenchymatous degeneration.

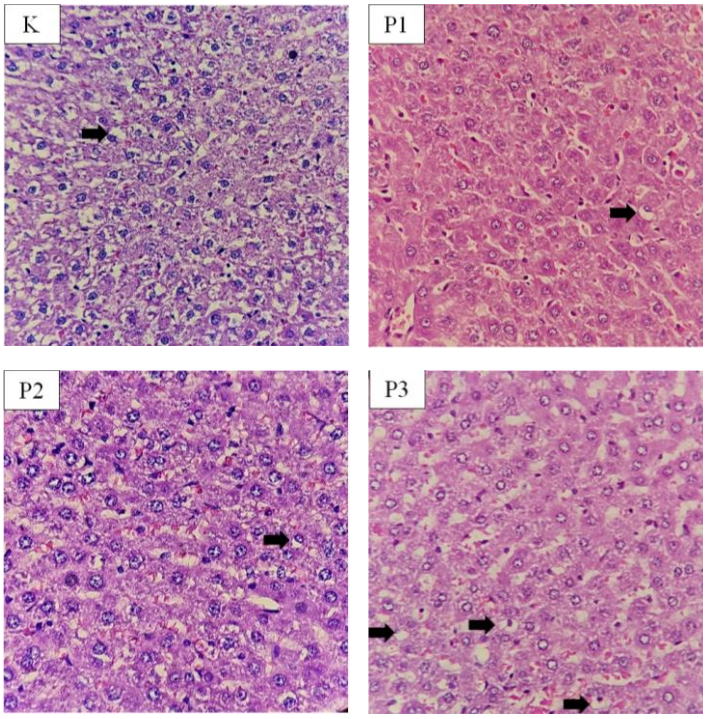

Figure 2. Histopathological Appearance of Fatty Degeneration of Wistar Rat Liver Tissue Group (K) Control, (P1) Extract of Ulin Stem Dosis 1,250 mg/kgBB, (P2) Ulin Bark Extract of Ulin Stem Dosis 2,750 mg/kgBB, and (P3) Bark Extract Ulin Stem Dosis 4,750 mg/kgBB. Muse Microscope *Olympus CX43* (400x, HE)

Figure 2 shows the histopathological appearance of fatty degeneration in the liver of Wistar rats shown by black arrows. The histopathological appearance of fatty degeneration is empty vacuoles in the cytoplasm that push the cell nucleus to the edge. In groups K, P1, P2, and P3, some cells experienced fatty degeneration, but more pictures of normal hepatocyte cells were found.

Table 4. The results of data analysis mean percentage of histop atology picture of fatty degeneration and its standard deviation

Group	Mean±Standard Deviation Fatty Degeneration	Score
K	0.15±0.191	0
P1	0.2±0.163	0
P2	0.25±0.251	0
P3	0.4±0.163	0

Table 4 shows the results of data analysis of the average percentage histopathological appearance of fatty degeneration along with the standard deviation of each group. The average percentage of histopathological appearance of fatty degeneration in groups K, P1, P2, and P3 received a score of 0 with the normal category, namely there was a picture of fatty degeneration of <5% of all hepatocytes in the 5 fields of view observed. Based on data analysis using the One Way ANOVA test, there was no significant difference in the average percentage of histopathological appearance of fatty degeneration.

DISCUSSION

The results of this study showed that the lowest average percentage of histopathological appearance of parenchymatous degeneration occurred in group K, which was 0.95±0.191. Based on the level of histopathological appearance of parenchymatous degeneration, group K has a score of 0 with the normal category, namely there is an appearance of parenchymatous degeneration around the centrilobular (central vein) of <25% of the 5 fields of view observed. This is in line with research conducted by Januar et al (2014) which obtained the percentage of cell damage in the control group given aquades was only 0.47% and the percentage of normal hepatocyte cells was higher than in other groups.[14] According to Alhamdy et al (2018), hepatocytes under normal conditions experience periodic cycle and some cell can experience a degeneration process caused by cell aging.[15]

The results of this study showed that the average percentage of histopathological appearance of parenchymatous degeneration in the treatment group increased. The average percentage of histopathological appearance of parenchymatous degeneration in the P1 group was 1.1±0.258, in the P2 group was 1.2±0.163, and in the P3 group was 1.4±0.432. Based on the level of histopathological appearance of parenchymatous degeneration, groups P1, P2, and P3 have a score of 0 with the normal category, namely there is an appearance of parenchymatous degeneration around the centrilobular (central vein) of <25% of the 5 fields of view observed. The results of the data analysis stated that there was no significant difference between groups P1, P2, and P3 against group K. This shows that damage caused in groups P1, P2, and P3 is still tolerable and non-toxic. This is supported by the results of research by Makiyah et al (2021) which showed that the *piperine* treatment group dose of 17.5 mg/kgBW did not have significant differences in the control group so it was declared not toxic to the liver.[16]

The increase in the average appearance of parenchymatous degeneration that occurred in the treatment group showed that the higher the dose of ironbark extract given could cause more damage. This result is in line with research by Fitmawati et al (2018) which shows that at dose 1 (0.09 ml/200g BW) there is the least damage and at dose 4 (0.36 ml/200g BB) there is the most damage.[17] This can be due to the effects of phytochemical compounds contained in ironbark extract. According to Januar et al (2014) every active substance that has pharmacological abilities can potentially cause toxic effects.[14]

Based on research by Kusuma et al (2018), it is known that there are phenolic compounds, flavonoids, and proanthocyanidins in ironwood bark extract, each of which has levels of 31.28 mg GAE/g and 30.48 CE/g, and 183.30 mg PE/g.[7] These compounds can act as natural antioxidants that can inhibit the occurrence of oxidation processes and help overcome oxidative damage.[8–10] However, according to Hidayat et al (2014) antioxidant compounds at concentrations that are too high can act as prooxidants causing damage to cells.[18] Natural antioxidant mechanisms in reducing superoxide, peroxyl, alkoxyl, and hydroxyl radicals through H+ atomic donors produce aroxyl radicals that can react with oxygen to produce quinones and superoxide anions ($O2^-$).[19] Superoxide anions can react with hydrogen peroxide (H_2O_2) with Fe^{2+} metal ion catalysts to produce highly reactive hydroxyl radicals (*OH), increasing the amount of ROS resulting in lipid peroxidation.[20]

Parenchymatous degeneration is caused by lipid peroxidation which results in mitochondrial disruption resulting in a decrease in the amount of ATP and reduced plasma membrane activity of sodium-potassium pumps.[21,22] This causes an imbalance in fluid and ion levels in the cell, resulting in water accumulation and disrupted transport of proteins that have been produced by ribosomes.[14,22] Januar et al (2014) said parenchymatous degeneration in hepatocyte cells is characterized by enlargement of cell size beyond normal cells and granular cytoplasm due to protein deposits.[14]

The results of this study showed that the lowest average percentage of histopathological appearance of fatty degeneration occurred in group K, which was 0.15±0.191. Based on the level of histopathological appearance of fatty degeneration, group K has a score of 0 with the normal category, namely there is a picture of fatty degeneration of <5% of all hepatocytes in the 5 fields of view observed. This is supported by the results of research by Kurniawan et al (2014) which showed a picture of fatty degeneration in all groups including the control group.[23] In the research of Alhamdy et al (2018) also mentioned that hepatocytes under normal conditions experience periodic changes and some experience a degeneration process caused by cell aging.[15]

The results of this study showed that the average percentage of histopathological appearance of fatty degeneration in the treatment group increased. The average percentage of histopathological appearance of fatty degeneration in the P1 group was 0.2±0.163, in the P2 group was 0.25±0.251, and in the P3 group was 0.4±0.163. Based on the level of histopathological appearance of fatty degeneration, groups P1, P2, and P3 have a score of 0 with normal categories, namely there is a picture of fatty degeneration of <5% of all hepatocytes in 5 fields of view observed. The results of data analysis stated that there was no significant difference between groups P1, P2, and P3 against group K. This shows that damage to groups P1, P2, and P3 is still tolerable and non-toxic. This result is supported by the results of research by Makiyah et al (2021) which showed that the *piperine* treatment group dose of 17.5 mg/kgBW did not have significant differences with the control group so that it was declared not toxic to the liver.[16]

In the treatment group there was an increase in the average percentage of fatty degeneration appearance. This is in line with research by Fitmawati et al (2018) which shows more damage that occurs with increasing doses with the type of damage in the form of fatty degeneration. [17] This is related to the function of the liver as a detoxification organ of various compounds that enter the body.[17] The more chemical compounds that enter through the gastrointestinal tract , the heavier the liver will work.[17]

Based on the results of research by Wila et al (2018), it is known that ironwood bark contains saponins, terpenoids and alkaloids in moderate quantities.[24] This is in line with the research of Kurniawan et al (2014) which states that the increasing number of hepatocyte cells that experience fatty degeneration can be caused by the presence of alkaloids contained in lamtoro extract.[23] According to Taek et al (2020), secondary metabolites in plants in the form of alkaloids and saponins can cause disruption of hepatocyte membrane permeability, which results in calcium entry into cells.[25] The influx of calcium due to potassium pump failure causes disruption in protein synthesis.[13,22] This causes lipoprotein not to form so that lipid transport is disrupted which results in lipid accumulation in hepatocytes.[13,22] According to Maulina (2016) fatty degeneration is hepatocyte cell damage characterized by the presence of vacuoles in the cytoplasm that can press the cell nucleus to the edge.[13]

The average percentage of hepatocyte cell damage in the form of parenchymatous degeneration and fatty degeneration in the P1, P2, and P3 groups that were not significantly different or close to the control group showed that ironwood bark extract doses of 1,250 mg/kgBW, 2,750 mg/kgBW, and 4,750 mg/kgBW did not have a toxic effect on the liver based on the picture of parenchymatous degeneration and fatty degeneration. This is due to the presence of secondary metabolite compounds such as flavonoids, phenolics, and proanthocyanidins in ironwood bark extract which can act as natural antioxidants.[7] Natural antioxidants work through several mechanisms.[6,19] First, natural antioxidants cause increased activity of endogenous antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GTPx).[6] Second, natural antioxidants inhibit ROS-forming enzymes such as protein kinases, and xanthine oxidase.[19] Third, natural antioxidants work by chelating Fe^{2+} and Cu^{2+} metals which increase ROS formation.[19] Fourth, natural antioxidants can reduce superoxide, peroxyl, alkoxyl, hydroxyl radicals through H^{+} atomic donors.[19] The result of this reaction is an aroxyl radical that can react with other radicals to produce a stable quinone structure.[19] Based on the results of the study, it concluded that there is no toxic effect from giving ironbark extract (*Eusideroxylon zwageri*) doses of 1,250 mg/kgBW, 2,750 mg/kgBW, 4,750 mg/kgBW orally against the liver of Wistar rats (*Rattus norvegicus*) based on histopathological appearance of parenchymatous degeneration and fatty degeneration.

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