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Sub-Acute Toxicity and Allergy Studies of Bidara Leaf (*Ziziphus Mauritiana*) Extract as A Wound Healing Material

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Abstract

Background: In dentistry, the wound healing process is often encountered in tooth extractions, incisions, oral and facial surgery, gingival flaps and biopsies. Post-tooth extraction wound is a medium that allows pathogenic microbes to breed and infect the wound. Wound management must be carried out as soon as possible to restore mucosal integrity so as to prevent bacterial infections penetrates the body. Bidara (*Ziziphus mauritiana*) is one of the plants used as traditional medicine by the community. Research on this plant as a medicinal raw material is increasing, so further research needs to be carried out to prove the safety of this medicinal plant. This study aims to determine the effects of sub-acute toxicity and allergic reactions caused after administering bidara leaf extract on the liver histopathology of mice.

Methods: In vivo laboratory experimental study using a post-test only control group design with 24 mice (*Mus musculus*). The research sample consisted of 4 groups, namely the control group given 0.3% Na-CMC, the treatment group given bidara leaf extract at a dose of 500 mg/kg BW, 600 mg/kg BW, and 700 mg/kg BW. The treatment extract was given orally for 28 days.

Results: The results of the study showed that the dose of bidara leaf extract had an effect on the liver histopathology of mice, namely at doses of 600 mg/kg BW and 700 mg/kg BW it had a toxic effect that was visible from changes in liver cell structure. Allergy tests showed that bidara leaf extract did not cause allergic reactions in mice.

Conclusion: It can be concluded that bidara leaf extract (*Ziziphus mauritiana*) does not cause allergies and at certain doses does not have toxicity in the liver of animals study.

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INTRODUCTION

Wounds are injuries that are often experienced by every human being characterized by the loss or damage of some body tissues caused by trauma from sharp objects, temperature changes, chemicals, explosions, electric shock or animal bites. In dentistry, the wound healing process is often found in tooth extraction, incision, oral and facial surgery, gingival flap and biopsy. The wound after tooth extraction is one of the media that allows pathogenic microbes to multiply and infect the wound. Wound management must be done as soon as possible to restore mucosal integrity so as to prevent bacterial infection from entering the body. Proper and consistent wound care is needed to prevent infection and inflammation so as to accelerate the healing process.¹ The wound healing process in the human body consists of several phases, namely the hemostasis and inflammation phase, the proliferation phase and the maturation phase.²

Traditional medicine studies in Indonesia were increasing to obtain phytopharmaceuticals that can be aligned with modern medicine.³ Traditional medicine has been widely accepted in almost all countries in the world. According to WHO, countries in Africa, Asia, and Latin America use traditional medicine as a complement to the primary treatment they receive. In Africa, as much as 80% of the population uses traditional medicine for primary treatment.⁴ The use of traditional medicine is generally considered safer than the use of modern medicine, this is because traditional medicine has relatively fewer side effects than modern medicine. One of the plants used as traditional medicine by the community is bidara. The use of bidara plants in India is as a medicine for diarrhea, diabetes, fever, and malaria, while in Malaysia the bark decoction is used as a medicine for stomach pain. Bidara leaf

(*Ziziphus mauritiana*) is used as a traditional medicine because it has potential as an antidiabetic, antimicrobial, anti-inflammatory, antioxidant, and anticancer.⁵

Based on previous study,⁶ bidara leaves have potential in wound healing in experimental animals. The study showed that bidara leaf extract effectively increased the number of fibroblasts in the wound healing process of wistar rat gingival incision. The effectiveness of this plant in wound healing is due to active ingredients including alkaloids, flavonoids, polyphenols, tannins, saponins, and terpenoids. The content of alkaloid compounds functions as an analgesic, while saponin compounds function to spur collagen growth in the wound healing process and stimulate the formation of new cells.

Bidara leaf (*Ziziphus mauritiana*) has the potential to be further developed into a standardized herbal medicine⁶, so it is necessary to know the safety level of this extract through toxicity and allergy tests. Toxicity tests can be carried out in various ways, one of which is by using a sub-acute toxicity test,⁷ which is a test to detect toxic effects after administration of test preparations with repeated doses given orally to test animals. Toxicity can cause damage to several organs, especially histopathological changes in the liver or kidney. The liver is the largest parenchymal organ and plays an important role in the body's metabolic processes, making it susceptible to toxicity. The more toxic levels that enter the body, the more liver function can be disrupted.⁸

In addition to toxicity testing, another important safety test is allergy testing. Allergy is an immune failure where the body becomes hypersensitive in immunologically reacting to materials that are generally non-immunogenic. Allergy is a reaction where there is increased reactivity and sensitivity to antigens.⁹ To

determine the cause of allergies, allergy tests can be carried out with two types, namely skin tests which are skin prick tests and skin patch tests. The purpose of this study was to determine the effects of sub-acute toxicity and allergic reactions caused after administration of bidara leaf extract.

Methods

Preparation of Bidara Leaf Extract

Bidara leaves were selected and washed with water, then dried by drying indoors for 3 weeks until dry. After that, the bidara leaves were crushed using a blender until a size of 60-70 mesh was obtained. The dried symplisia was macerated using 70% ethanol for 3x24 hours, filtering the extract every 24 hours, then covered with occasional stirring. The results of maceration were filtered with a buchner funnel lined with filter paper and collected in Erlenmeyer. Simplisia that has been macerated is filtered until the filtrate is obtained. Furthermore, the filtrate was evaporated with a vacuum rotary evaporator and heated with a water bath at 40°C, so that a thick extract of bidara leaves was obtained.⁶ Bidara leaf extract was made at a dose of 500, 600, 700 mg/kg BW,⁶ then the extract was weighed and added 0.3% Na-CMC suspension until evenly distributed.

Sub-acute toxicity and allergy test

Because it uses experimental animals, sub acute toxicity and allergy tests have been carried out ethical clearance at the ethical institution of FKG Unmas Denpasar (No. K.918/A.17.01/FKG-UNMAS/VIII/2021). The samples used in this study were 24 male mice (*Mus musculus*) that met the inclusion criteria, 2-3 months of age, 25-30 g body weight (BW), healthy physical condition and no disability that arose during the experimental period. This study is an in vivo laboratory experimental study using the post-

test only control group design with sample grouping using a completely randomized design (RAL). In the sub-acute toxicity test, animals were given bidara leaf extract orally. The research sample consisted of 4 groups, namely 3 treatment groups and 1 control group. The treatment group consisted of experimental animals given bidara leaf extract at a dose of 500 mg/kg BW, 600 mg/kg BW, and 700 mg/kg BW. The control group was given Na-CMC 0.3% orally. For the allergy test, bidara leaf extract was applied topically at a dose according to the group.

The mice were held on the neck and abdomen in a straight position. Then a syringe cannula containing bidara leaf extract was inserted in the mouth of the mice until it entered the esophagus in an upright position. Each group was given intake once per day.¹⁰ Each experimental animal was observed in the first 30 minutes after administration of the test preparation periodically every 4 hours for the first 24 hours, and thereafter observed once a day for 28 days. On day 29, the mice were euthanized, liver histopathology was examined with hematoxylin eosin (HE) staining and observed using a microscope (Olympus type CX 21) with a magnification of 400 times. Observations made included the presence of parenchymatous degeneration, hydropic degeneration and liver necrosis.

For allergy testing, the test material is applied topically which aims to allow the test material to enter the body directly through the skin layer. Before treatment, mice were shaved with scissors with a size of 0.5 cm x 0.5 cm on the back, then smeared with bidara leaf extract. After administering the extract for 30, 60, and 90 minutes, the animals were observed for signs of allergy including itching, red color, and inflammation.¹¹

Results

Observation of Sub-Acute Toxicity Test

Observations of the descriptive test of sub-acute toxicity of bidara leaf extract in mice were recorded and entered into a scoring table (Table 1).

Table 1. Descriptive Test of Sub-Acute Toxicity of Bidara Leaf Extract

G	K						P1						P2						P3					
n	I	II	III	IV	V	VI	I	II	III	IV	V	VI	I	II	III	IV	V	VI	I	II	III	IV	V	VI
1	√	√	√	√	√	√	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	√	√	-	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
3	-	-	-	-	-	-	-	-	√	-	-	-	-	√	√	-	-	√	-	√	-	√	-	-
4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	√	-	√	-	√	√	√

Noted: 1: n² mal; 2: parenchymatous degeneration; 3: hydropic degeneration; 4: necrosis; K: Control; P1: dose of 500 mg/kg BW; P2: dose of 600 mg/kg BW; P3: dose of 700 mg/kg BW; n: number of samples

Allergy test

The results of allergy test observations of bidara leaf extract on mice were recorded and entered into a scoring table. The results are presented in Table 2.

Table 2. Allergy Test of Bidara Leaf Extract

n	30'	60'	90'
I	0	0	0
II	0	0	0
III	0	0	0
IV	0	0	0

Noted: 0: no signs of allergy; n: number of samples

The histopathological features of liver damage in various groups including parenchymal degeneration, hydropic degeneration, and necrosis are shown in Figure 1.

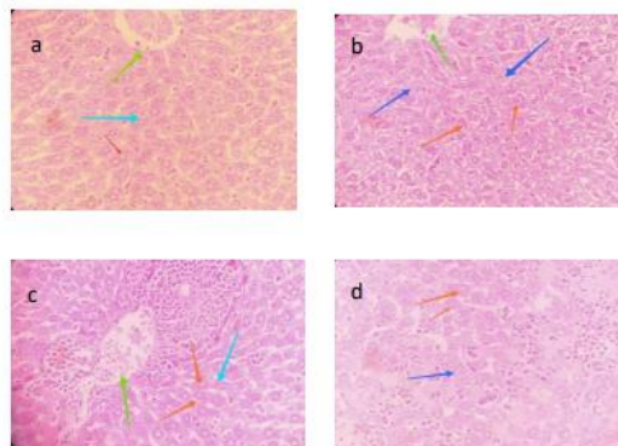


Figure 1: Fibroblast cell appearance

Noted: a. Normal; b. parenchymatous degeneration; c. hydropic degeneration; d. necrosis.

Table 3. Mean test of sub-acute toxicity

Kelompok	n	Mean & SD	Sig
K	6	1,1667±0,40	0,0001
P1	6	2,1667±0,40	
P2	6	2,6667±0,51	
P3	6	3,6667±0,51	

Noted: K: Control; P1: dose of 500 mg/kg BW; P2: dose of 600 mg/kg BW; P3: dose of 700 mg/kg BW; n: number of samples

Table 4. Mann Whitney test between groups

Kelompok	P1	P2	P3
K	0,006*	0,004*	0,002*
P1		0,093	0,004*
P2			0,014*

Noted: K: Control; P1: dose of 500 mg/kg BW; P2: dose of 600 mg/kg BW; P3: dose of 700 mg/kg BW;

Table 5 Allergy Test of Bidara Leaf Extract

Waktu	Z	Sig.
30-90 menit	-0,0001	1,000
60-90 menit	-0,0001	1,000

Discussion

The results of histopathological observations of the liver of mice after the administration of bidara leaf extract for 28 days (Table 1) show that in the control group there were no changes in liver histopathology or in normal conditions. In group P1 (bidara leaf extract dose of 500 mg/kg BW) a picture of parenchymal degeneration was found, in group P2 (bidara leaf extract dose of 600 mg/kg BW) hydropic degeneration began to be found, while in treatment P3 (bidara leaf extract dose of 700 mg/kg BW) most samples had a picture of liver necrosis.

Table 3 shows that there is a significant difference between the treatment groups after being treated ($p < 0.05$). Table 4 shows that the control group has a significant mean difference with the treatment groups (P1, P2 and P3). Similarly, there is a significant mean difference between the P1 group and the P2 and P3 groups.

Conversely, there was no significant difference in mean between groups P1 and P2. From these statistical tests, it can be said that the administration of bidara leaf extract (in the sub-acute test for 28 days) has a toxic risk to the liver of mice, namely the occurrence of changes in the histopathological structure of liver cells in the form of degeneration and necrosis, especially at doses above 600 mg / kg BW.

Sub-acute toxicity tests are conducted to determine the effect of repeated exposure to a substance at non-lethal doses.¹² There are toxic symptoms caused by mice after being given the test material such as respiratory changes, decreased movement activity and aggressive behavior. The sub-acute toxicity test provides information about the toxic effects on the target organs that are affected. The target organ in this study is the liver because this organ is involved in the metabolism of food substances as well as most drugs and toxicants. Although the liver has

enzyme activity that can metabolize toxicants to become less toxic, if the toxicant level is too high, it can cause damage or death of liver cells.¹³ If the liver is continuously exposed to drugs and chemicals for a long period of time, the cells in the liver will undergo changes including parenchymatous degeneration, hydropic degeneration, and necrosis.¹⁴

The toxic effect of a compound is largely determined by the dose. The higher the dose given, the greater the occurrence of liver cell damage. Liver damage that can occur after being given bidara leaf extract is parenchymal degeneration, hydropic degeneration and necrosis. Parenchymal degeneration is the mildest and most common degeneration because it is reversible. In this degeneration there is swelling and turbidity of the cytoplasm. Hydropic degeneration is a degeneration with a more severe level of damage, namely intracellular accumulation that is more severe than parenchymal degeneration. This degeneration is also reversible, but can be irreversible if the cause of the injury persists.¹⁵ Cells that are injured then experience tears in the plasma membrane and changes in the cell nucleus, causing cell death or necrosis. Necrosis is the irreversible death of cells or tissues in living organisms.¹⁶ Cell death is characterized by cell nuclei that die and turn small. Another opinion says that necrosis in the liver is a toxic manifestation that is dangerous but not always bad because the liver has the capacity to regrow.¹⁷

Damage to the liver causes impaired liver function, but it can also be caused by reduced antioxidant compounds in the body. Reduced antioxidants in the body can cause impaired body tissue function because antioxidants are compounds that can counteract free radicals.¹⁸ Flavonoids are polyphenolic compounds that act as antioxidants that inhibit the oxidation process

triggered by free radicals from toxic compounds.¹⁹ Previous studies have shown that bidara leaf extract contains compounds that can be used as drugs. However, the compounds in bidara leaf extract are not fully medicinal, one of which is a saponin compound. The structure of the saponin compound causes saponins to have soap-like properties and is called a natural surfactant. Saponin compounds can cause toxicity influenced by concentration. The higher the concentration of bidara leaf extract, the higher the foam produced, thus causing the levels of saponin compounds contained in bidara leaf extract to increase.²⁰

In addition to the sub-acute toxicity test that uses the liver as the target organ, there is another safety test, namely, the allergy test. Allergy is an overreaction of the immune system to a substance, known as an allergen. Allergens can be dust particles, drugs, or foods that act as antigens that stimulate an immune response.⁹ If the allergen comes into contact with the skin or enters the eyes, is inhaled, eaten, or injected into the body, an allergic reaction will immediately occur.

Tables 2 and 5 show that bidara leaf extract applied topically does not cause signs of allergy in mice such as itching, redness, and inflammation (score 0). Flavonoid compounds are deliberately produced by plant tissues in response to infection or injury which then function to inhibit fungi or bacteria that will attack.²¹ Steroid compounds in plants commonly called phytosterols have a protective role.²² Flavonoid compounds are divided into several subgroups, each subgroup has different biological and chemical properties.²³ One of the subgroups of flavonoids, namely flavonols, has antioxidant and biological properties. The content contained in flavonols is quercetin which has properties as an antihistamine that can prevent allergies.²⁴

Conclusion

It can be concluded that bidara leaf extract has an effect on sub-acute toxicity in the liver of male mice. It can conclude that start from dose 700 mg/kg BW bidara leaf extract has a toxic effect because it causes changes in cell structure in the liver of male mice. Bidara leaf extract against mice did not show any allergic reactions.

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