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Effect of Andaliman Fruit Extract (Zanthoxylum Piperitum) in Accelerating Wound Healing After Tooth Extraction in Rats

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ABSTRACT: *The potential of andaliman as an antimicrobial, antioxidant, anti-inflammatory, xanthine oxidase inhibitor, and cytotoxic. Other studies have also reported the antibacterial activity of andaliman extract against food-pathogenic bacteria such as Bacillus cereus, Escherichia coli, Staphylococcus aureus, and Salmonella typhimurium. This study aimed to analyze the effect of giving 50% and 100% Andaliman (Zanthoxylum piperitum) fruit extract in accelerating wound healing time after tooth extraction in Wistar rats. This study is a laboratory experiment using a complete randomized design with a post-test-only control group design pattern. Wistar rats, 32 rats, male, physically healthy, 2-3 months old, with body weight between 200-250 grams, were divided into two groups, namely 16 rats treated with 50% Andaliman fruit (Zanthoxylum Piperitum) and 16 rats treated with 100% Andaliman fruit (Zanthoxylum piperitum) to see the comparison of accelerated wound healing after tooth extraction. Data analysis using the SPSS 16 program. Research using a pure experiment with a non-parametric Chi-Square Test, after testing, showed that (p <0.05) means there is a significant difference between groups. Andaliman Fruit Extract (Zanthoxylum piperitum) 50% and 100% effectively accelerate wound healing time after tooth extraction of Wistar rats. Andaliman fruit extract (Zanthoxylum piperitum) 100% is more effective than Andaliman fruit extract (Zanthoxylum piperitum) 50% in accelerating wound healing time after tooth extraction of Wistar rats because the flavonoid content in Andaliman fruit extract (Zanthoxylum piperitum) 100% which helps accelerate wound healing is higher than Andaliman fruit extract (Zanthoxylum piperitum) 50%.*

Keywords: Andaliman Fruit, Wound Healing, Extraction

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I. INTRODUCTION

Batak pepper or andaliman, which has the Latin name Zanthoxylum acanthopodium DC, is a typical plant that is very limited in number and supports the development of the Toba Caldera Geopark by UNESCO Global Geopark (UGG). Andaliman is a specific plant in the Lake Toba region. It is closely related to the Batak tribe because andaliman fruit is often used as a seasoning for traditional Batak cuisine in North Sumatra. Such as carp arsik, natinombur and sangsang (Shasti, 2017); (Gultom et al., 2021). Andaliman has a different nickname in each region, as in South Tapanuli has the name Sinyarnyar; in Tanah Karo, the name itir-itir; and in Simalungun, the name tuba. Not only utilized as a spice, but andaliman also has benefits as a producer of terpenoid substances with antioxidant activity and antimicrobial and immunostimulant effects. Tooth extraction will cause a wound in the form of exposed alveolar bone in the oral cavity. An injury is an anatomical damage or partial tissue destruction due to trauma (Helmalia, 2019). The severity of the wound depends on the amount of trauma received by the tissue. Physiologically, the body can repair damage to its skin tissue (injury), known as wound healing. Routine wound healing is a complex and dynamic process. The wound-healing process can be divided into three phases: inflammatory, proliferation, and remodeling. These phases continue from the onset of the wound until wound closure. The inflammatory phase is the body's reaction to the damage that starts after a few minutes and lasts about three days after the injury. The proliferation phase is characterized by the appearance of new blood vessels resulting from reconstruction and occurs within 3-24 days. The maturation phase is the final stage of the wound-healing process (Burnett & Zager, 2004).

The primary cells involved in the wound-healing process are fibroblasts. Fibroblasts are stem cells that form and lay down fibers in the matrix, especially collagen fibers. They secrete small tropocollagen molecules that combine with the primary substance to form collagen fibers. Collagen will provide strength and integrity to any well-healed wound. Fibroblasts more actively synthesize matrix components in response to the damage by proliferating and increasing fibrinogenesis (Govindaraju et al., 2019). Therefore, fibroblasts are the leading agents in the wound-healing process. Herbal products have been used for a long time in the medical world. Nowadays, herbs are widely used for various treatments. Modern research results also show that herbal

medicines are proven effective for health and do not cause side effects as much as chemical drugs (Kumar & Jaitak, 2019).

According to Silalahi (2021), andaliman contains phenol compounds, monoterpenes, sesquiterpenes, nones, and essential oils, which of terpenoid compounds. Based on its chemical content and physiological activity, the utilization of andaliman can be increased; no longer just a seasoning but also a preservative, medicinal material and supplement, and vegetable pesticide (Silalahi & Lumbantobing, 2021). Several studies have reported the potential of andaliman as an antimicrobial, antioxidant, anti-inflammatory, xanthine oxidase inhibitor, and cytotoxic. Other studies have also reported the antibacterial activity of andaliman extract against food-pathogenic bacteria such as Bacillus cereus, Escherichia coli, Staphylococcus aureus, and Salmonella typhimurium (Sitanggang et al., 2019); (Anggraeni, 2020). Because of the above, the author is interested in examining the effectiveness of 50% and 100% Andaliman Fruit (Zanthoxylum piperitum) extract in accelerating wound healing time after tooth extraction in Wistar rats.

II. RESEARCH METHODS

This experimental laboratory study uses a randomized controlled design with a post-test only control group design pattern. The experimental animals used in this study are Wistar rats, 32 males, physically healthy, 2-3 months old, with a body weight between 200-250 grams. The rats will be divided into two groups, namely, 16 treated with 50% Fruit Andaliman (Zanthoxylum Piperitum) and 16 treated with 100% Fruit Andaliman (Zanthoxylum Piperitum) to see the comparison of accelerated wound healing after tooth extraction. The sample size was determined by the Federer formula, namely: $(t - 1)(r - 1) \geq 15$. Where t = several treatments; (2 treatments) r = several replications. Thus, the minimum sample size for each treatment was 16 rats.

$= (t-1)(r-1) \geq 15$
$= (2-1)(r-1) \geq 15$
$= (r-1) \geq 15$
$= (r-1) \geq 15$
$= r \geq 15 + 1$
$= r \geq 16$

Tools

Tools used in research :

1. Number-coded experimental animal cages.
2. Diagnostic set (mouth glass, sonde, tweezers).
3. Nierbeken.
4. Dental extraction forceps (in this case a needle holder is used) under sterile conditions.
5. Syringe.
6. Gloves.
7. Mask.
8. Petri dish of jaw preparation.
9. A set of tools for making histology preparations.
10. Microscope.

Material

Materials used in the study:

1. Fruit Andaliman (Zanthoxylum Piperitum) Extract 50%
2. Fruit Andaliman (Zanthoxylum Piperitum) Extract 100%
3. Ketamine.
4. Formalin 10%.
5. Histology preparation material with Hematoxylin Eosin (HE) staining.
6. 70% alcohol as sterilization material.
7. Cotton pellet.

Data Type

The type of data collected in this study is primary data obtained from the results of measurements (scoring) on the histological picture of the process of accelerating wound healing after tooth extraction by administering Fruit Andaliman (Zanthoxylum Piperitum) 50% and Fruit Andaliman (Zanthoxylum Piperitum) 100%.

Extraction on Fruit Andaliman (Zanthoxylum Piperitum)

Collecting 3 kg of Fruit Andaliman (Zanthoxylum Piperitum), the Fruit Andaliman (Zanthoxylum Piperitum) was washed and divided into two parts to take the inner meat to obtain the gel. After washing, the flesh of the Fruit Andaliman (Zanthoxylum Piperitum) was dried in an incubator at 500 ℃ for 72 hours. The dried flesh of the Fruit Andaliman (Zanthoxylum Piperitum) was then pulverized using a blender until it became powder. Fruit Andaliman (Zanthoxylum Piperitum) meat that had become powder was then extracted by maceration while stirring. The extraction process uses a water solvent. The powder was put into a maceration vessel or container with a watertight lid and then filtered using filter paper; the pulp was macerated up to 2 times. The obtained maceration results were collected and evaporated using a rotary vacuum evaporator at a temperature of 500C until there was no more solvent condensation on the condenser. After the solvent was evaporated using a rotary vacuum evaporator, the evaporation was continued using a 70°C water bath to obtain a pure extract. The Fruit Andaliman (Zanthoxylum Piperitum) extract was then diluted with water to get 50% and 100% extract concentrations.

Treatment of Wistar Rats

1. Before treatment, 32 rats were divided into 50% Zanthoxylum Piperitum extract and 100% Zanthoxylum Piperitum extract. After that, all rats were adapted for one week. Then, animals were put into cages, with five rats in each cell in the same environmental conditions, given the same food, and monitored for health.
2. Rat tooth extraction will be performed using a modified needle holder under the anesthetic effect of ketamine 1000 mg/10 ml at a dose of 20 mg/kg bw intraperitoneally.
3. One incisor tooth will be extracted from every five rats daily.
4. After tooth extraction, observe the extraction wound and apply a tampon (cotton pellet) to stop bleeding in the wound for 5 minutes.
5. Dropped Fruit Andaliman (Zanthoxylum Piperitum) 50% in treatment group I and dropped Fruit Andaliman (Zanthoxylum Piperitum) 100% in treatment group II shortly after tooth extraction as much as 0.05 ml every day.
6. After extraction and treatment, the test animals (rats) were fed fine porridge with attention to the health of the test animals.
7. On the 5th day after tooth extraction, rats from each group were physically sacrificed by neck dislocation. The rat's tail was held and then placed on a surface it could reach. The rat will stretch its body; when the rat's body extends, a holder held by the left hand is placed on the nape of the neck. The right hand pulls the tail hard so the rat's neck will be dislocated. Then the jaw of the rat is taken out.
8. Then the tissue was fixed with 10% formalin for 24 hours at room temperature, then the decalcification process was carried out using Ethylene Diamine Tetra Acetic Acid (EDTA 10%) solution at room temperature.
9. Tissue dehydration was then performed using alcohol. First, the specimen was put into toluol alcohol solution (1:1) using pure toluol, then into a paraffin-saturated toluol solution.
10. The following process is infiltration in the oven by inserting the specimen into liquid paraffin.
11. The embedding process is carried out (inserting the tissue into paraffin) and then labeled/coded. After the embedding stage, the tissue is sliced in series with a thickness of approximately 6 microns using a microtome.
12. Evaluating fibroblast cell response using Hematoxylin Eosin (HE) staining. The procedure that must be done is deparaffinization using xylol and alcohol solution, then continued with the rehydration process with alcohol. After that, it is washed with running water, rinsed with distilled water, and then wiped. The glass slide was then placed in Meyer's hematoxylin solution, washed with running water, and then rinsed with distilled water, after which the staining was assessed under a light microscope. If the staining has been considered good, proceed to the next step, namely the dehydration process with alcohol in stages, and then wipe.
13. The next step, put it into xylol solution, and the object glass was covered with deck glass and observed using a light microscope.
14. Fibroblast density was assessed by counting the fibroblasts in 5 fields of view.

Histopathology Scoring Parameters for Fibroblast Counts

Histopathology scoring parameters to determine the distribution of fibroblast tissue is done based on the field of view is:

1. (-) = no fibroblast tissue found
2. (+) = small number of fibroblasts (less than 10% per field of view)
3. (++) = moderate amount of fibroblast tissue (10%-50% per field of view)
4. (+++) = large amount of fibroblast tissue (50%-100% per field of view) 4.

Data analysis using the SPSS 16 program. Research using a pure experiment with a non-parametric Chi-Square Test, after testing, showed that ($p < 0.05$) means there is a significant difference between groups.

III. RESULTS AND DISCUSSION

Data distribution and frequency of the number of fibroblast tissue per field of view in Wistar rats after tooth extraction in groups given 50% and 100% Andaliman Fruit extract (Zanthoxylum Piperitum) can be seen as follows:

Table 1. Distribution and Frequency Data of Fibroblast Tissue Counts Per Field of View After Tooth Extraction

No	Number of Fibroblasts	Fruit Andaliman (Zanthoxylum Piperitum)			
		Concentration 50%		Concentration 100%	
		n	%	n	%
1	No fibroblast tissue found	0	0	0	0
2	Small number of fibroblasts (less than 10% per field of view)	8	25	3	9
3	Moderate amount of fibroblast tissue (10%-50% per field of view)	4	13	5	16
4	Large amount of fibroblast tissue (50%-100% per field of view).	4	13	8	25

Table 1 shows that all samples found fibroblast tissue in the administration of 50% and 100% Andaliman Fruit (Zanthoxylum piperitum) extract after tooth extraction of Wistar rats. The number of fibroblasts found in the small category (less than 10% per field of view) in the administration of 50% Andaliman Fruit (Zanthoxylum piperitum) extract after tooth extraction of Wistar rats was 8 (25%) and in the administration of 100% Andaliman Fruit (Zanthoxylum piperitum) extract as many as 3 (9%). The number of fibroblasts found in the moderate category (10%-50% per field of view) on the administration of Andaman Fruit extract (Zanthoxylum piperitum) 50% after tooth extraction of Wistar rats was 4 (13%). On administering Andaman Fruit extract (Zanthoxylum piperitum), 100% was 5 (16%). The number of fibroblasts found in the large category (50% - 100% per field of view) in the administration of Andaliman Fruit extract (Zanthoxylum piperitum) 50% after tooth extraction of Wistar rats as many as 4 (13%) and in the administration of Andaliman Fruit extract (Zanthoxylum piperitum) 100% as many as 8 (25%). To determine the relationship between the number of fibroblast tissue per field of view in Wistar rats after tooth extraction by administering Andaliman Fruit Extract (Zanthoxylum piperitum) with a concentration of 50% and Andaliman Fruit Extract (Zanthoxylum piperitum) with a concentration of 100%, data analysis was carried out using the Chi-Square test as follows:

Table 2. Relationship between the number of tissue fibroblasts per field of view in Wistar rats after tooth extraction with the administration of Andaliman Fruit Extract (Zanthoxylum Piperitum) at a concentration of 50% and 100%.

Number of Fibroblasts	Fruit Andaliman (Zanthoxylum Piperitum)		p
	Concentration 50%	Concentration 100%	
No fibroblast tissue found	0	0	0,015*
Small number of fibroblasts (less than 10% per field of view) 3.	8	3	
Moderate amount of fibroblast tissue (10%-50% per field of view)	4	5	
Large amount of fibroblast tissue (50%-100% per field of view).	4	8	

Significant p<0.05. Chi Square Test

From Table 2. it can be seen that there is a significant relationship between the number of fibroblast tissue per field of view in Wistar rats after tooth extraction by giving Andaliman Fruit Extract (Zanthoxylum Piperitum) with a concentration of 50% and Andaliman Fruit Extract (Zanthoxylum Piperitum) with a concentration of 100%, $p = 0.015$ ($p < 0.05$)..

This study compares the effectiveness of Andaliman Fruit extract (Zanthoxylum piperitum) 50% and Andaliman Fruit extract (Zanthoxylum piperitum) 100% in accelerating wound healing time after tooth extraction of Wistar rats. The samples used in this study were Wistar rats. Wistar rats are known to have a physiological body similar to human physiology and have a short average age of 1-2 years, so it is appropriate to use it as an experimental object (Rairisti, 2014). The number of research samples taken was 32 Wistar rats that were physically healthy and 2-3 months old with body weight between 200-250 grams. The model was divided into two groups, namely 16 (50%) for the group treated with 50% Andaliman Fruit (Zanthoxylum piperitum) extract and 16 (50%) for the group treated with 100% Andaliman Fruit (Zanthoxylum piperitum) extract.

Tooth extraction is the process of removing teeth, both whole and the remaining roots, from the alveolar because it cannot be treated anymore. Tooth extraction will cause injury by exposing the alveolar bone in the oral cavity. The wound is anatomical damage or destruction of part of the tissue due to trauma (Sorongan & Siagian, 2015). The body will repair tissue damage (harm), known as the wound healing process, and begins from the time of injury until wound closure. The primary cells involved in the wound-healing process are fibroblasts. The proliferation of fibroblasts determines the outcome of wound healing. This is because fibroblasts will produce collagen that will link the wound and affect the revitalization process that will close the wound.

Rat tooth extraction will be performed under the anesthetic effect of ketamine 1000 mg/10 ml dose of 20 mg/kg bw intraperitoneally. After extraction, the post-extraction wound will be observed, and a tampon (cotton pellet) will be applied to stop bleeding in the damage for 5 minutes. Andaliman Fruit Extract (Zanthoxylum piperitum) 50% was given to treatment group I. Andaliman Fruit Extract (Zanthoxylum piperitum) 100% to treatment group II shortly after tooth extraction as much as 0.05 ml daily by dropping. On the 5th day, the rat jaw was taken and fixed with 10% formalin for 24 hours at room temperature. The decalcification process used Ethylene Diamine Tetra Acetic Acid (EDTA 10%) solution at room temperature. The tissue was then dehydrated in toluol alcohol solution (1:1) using the pure tool.

The fibroblast cell response was evaluated using Hematoxylin Eosin (HE) staining. Fibroblast density was assessed by counting the number of fibroblasts in 3 fields of view. The sample test was carried out on the fifth day because fibroblasts are known to start growing during the third to the seventh day of the wound healing process, so researchers took the average day, namely on the fifth day (Stojanovic et al., 2011). From the results of this study, it was found that all samples found fibroblast tissue in the administration of 50% and 100% Andaliman Fruit (Zanthoxylum piperitum) extract after tooth extraction of Wistar rats. The number of fibroblast tissue in administering Andaman Fruit extract (Zanthoxylum piperitum) was 50% and 100% after tooth extraction of Wistar rats. The number of fibroblasts found in the small category (less than 10% per field of view) in the administration of 50% Andaliman Fruit (Zanthoxylum piperitum) extract after tooth extraction of Wistar rats was 8 (25%) and in the administration of 100% Andaliman Fruit (Zanthoxylum piperitum) extract was 3 (9%). The number of fibroblasts found in the moderate category (10%-50% per field of view) on the administration of Andaman Fruit extract (Zanthoxylum piperitum) was 50% after tooth extraction of Wistar rats was 4 (13%). On administering Andaman Fruit extract (Zanthoxylum piperitum), 100% was 5 (16%). The number of fibroblasts found in the large category (50% - 100% per field of view) in the administration of 50% Andaliman Fruit (Zanthoxylum piperitum) extracts after tooth extraction of Wistar rats as many as 4 (13%) heads and in the administration of 100% Andaliman Fruit (Zanthoxylum piperitum) extract as many as 8 (25%) heads.

Based on Chi-Square data analysis, there is a significant relationship between the number of fibroblast tissue per field of view in Wistar rats after tooth extraction by giving 50% Andaliman Fruit Extract (Zanthoxylum Piperitum) and 100% Andaliman Fruit Extract (Zanthoxylum piperitum), $p = 0.015$ ($p < 0.05$). This is seen in the distribution of data on the number of fibroblasts (50%-100% per field of view) in Fruit Andaliman (Zanthoxylum piperitum) 100% as many as eight samples and in Fruit Andaliman (Zanthoxylum piperitum) 50% only four pieces. The results of this study are supported by Shasti (2017), which states that Andaliman Fruit Extract, with a concentration of 8%, has the highest clear zone against the growth of S.aureus bacteria. In addition, the antibiotic effect of Andaliman Fruit extract at all concentrations was not significantly different, while cefotaxime with Andaliman Fruit extract at all concentrations had significant inhibition (Shasti, 2017). Andaliman fruit has the potential as an antioxidant and glucosidase inhibitor. Andaliman is a spice widely used by the Batak community as a seasoning. Fruit andaliman has the potential as an antioxidant and glucosidase inhibitor. The extract of andaliman fruit has the best antioxidant activity, with IC50 reaching 30.04 ppm. Fraction C (IC50 16 ppm) has acted as the most active glucosidase inhibitor and also contains flavonoid compounds of the around and flavanone group, which are the most active compounds as glucosidase inhibitors (Helmalia, 2019).

Anggraeni's research (2020) stated that andaliman simplistic contains 7.32% moisture content, 13.62% water-soluble juice content, 29.54% ethanol-soluble juice content, 4.80% total ash content, 0.26% acid-insoluble ash content. In addition, phytochemical screening results show that andaliman simplistic contains alkaloids, flavonoids, glycosides, saponins, tannins, and steroid/triterpenoid compounds (Anggraeni, 2020). Saragih's research (2019) states that the observations made show that the seeds of andaliman contain active chemical compounds that can function as ingredients for treatment. The active chemical compounds in andaliman seeds include phenolics, saponins, flavonoids, tannins, triterpenoids, and alkaloids. These secondary metabolite compounds have antibacterial, antimicrobial, antiviral, and protein denaturing and prevent bacterial growth in digestion. Therefore, knowledge of the content of these active chemical compounds can be used as a basis for further utilization of andaliman seeds as a remedy for other diseases (Saragih & Arsita, 2019). From the results of this study, it can be seen that 100% Andaliman Fruit (Zanthoxylum piperitum) extract is more effective in the wound healing process than 50% Andaliman Fruit (Zanthoxylum piperitum) extract because the higher the concentration of the section, the content in the Andaliman Fruit

(Zanthoxylum piperitum) extract is also higher so that the wound healing process is faster. However, some difficulties in this study are the teeth of Wistar rats that easily fracture when extracted. This is because the anatomy of the Wistar rat teeth is long in the socket and crooked, so when the fracture, the researcher must remove the remaining teeth by slightly tearing the soft tissue from the socket. Another difficulty during the study was finding a comparator substance to check vitamin C levels, so the researcher did not check vitamin C levels and only checked the total flavonoid levels in the turmeric extract 50% with 100%.

IV. CONCLUSION

Based on the results and discussions that have been carried out in this study, it can be concluded:

1. Andaliman Fruit Extract (Zanthoxylum piperitum) 50% and 100% effectively accelerate wound healing time after tooth extraction of Wistar rats.
2. Andaliman fruit extract (Zanthoxylum piperitum) 100% is more effective than Andaliman fruit extract (Zanthoxylum piperitum) 50% in accelerating wound healing time after tooth extraction of Wistar rats because the flavonoid content in Andaliman fruit extract (Zanthoxylum piperitum) 100% which helps accelerate wound healing is higher than Andaliman fruit extract (Zanthoxylum piperitum) 50%.

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