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Study of healing Wistar Rat incision wounds through the use of ointments containing Andaliman fruit extract

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Abstract
Andaliman (Zanthoxylum acanthopodium DC) is a plant that supports the UNESCO Toba Caldera Geopark and is a traditional spice of the Batak tribe. The content of terpenoids makes it have cultural value and health potential. Herbal products from andaliman are effective in wound healing without excessive side effects. Research on Wistar rats shows the potential of andaliman ointment as a safe natural alternative in health care. The experimental study was conducted in January 2024 at the Laboratory of Universitas Prima Indonesia with 25 male Wistar rats divided into 5 groups. Tests of the effectiveness of Andaliman Fruit ointment in wound healing in Wistar rats showed significant differences in response to Andaliman extract, strengthening its potential influence in wound healing. Andaliman Fruit Extract contains bioactive compounds such as alkaloids, flavonoids, saponins, and tannins that play an important role in healing incision wounds in white rats. The optimum concentration for best effectiveness was identified at 9%, showing results competing with Bioplacenton® in wound healing. In conclusion, Andaliman fruit has the potential as an effective alternative in healing incision wounds in white rats, showing results that compete with Bioplacenton®.

Keywords: Andaliman plant, Traditional Batak spice, Wound healing potential

Introduction

Andaliman, which has the Latin name Zanthoxylum acanthopodium DC, is a very distinctive plant and limited in number [1]. This plant becomes very important in the context of the development of the Toba Caldera Geopark by UNESCO Global Geopark (UGG) [2]. The Toba Caldera Geopark is one of the few geoparks in the world selected as part of UNESCO's Global Geopark Network (GGN). Geopark itself is an area that has geological wealth, biodiversity, and important cultural heritage and is considered a model for sustainable development [3]. Andaliman has an important role in supporting the Toba Caldera Geopark because this plant is a typical plant that grows around the Lake Toba area and its surroundings, especially in the North Sumatra region. The use of andaliman as a spice in traditional Batak cuisine also makes this plant have high cultural value in the context of local society [4]. Andaliman is often used as a spice in typical Batak dishes such as risk, natinombur, and sangsang. The limited number of andaliman and its unique existence make it an important symbol in environmental and cultural conservation efforts in the Toba Caldera Geopark [5]. This plant is one of the attractions for tourists visiting the geopark area, both to enjoy its natural beauty and cultural wealth. Thus, Andaliman has a very significant role in supporting the development of the Toba Caldera Geopark and promoting natural and cultural diversity in Indonesia [6].

Andaliman does have a close relationship with the Batak tribal community around Lake Toba and its surroundings. Its use as a spice in traditional dishes such as arsik, natinombur, and sangsang has become an inseparable part of the culinary heritage of the Batak tribe [7]. This shows the importance of andaliman in enriching the taste of the typical cuisine of the region. In addition, different nicknames for andaliman in various regions such as Sinyarnyar, itir-itir, and tuba show the linguistic and cultural diversity in Indonesia [8]. This also shows how well known this plant is in the local community, because usually plants that are culturally important will have a variety of names in regional languages. Not only as a spice in cooking, andaliman is also known for its terpenoid substance content which has a variety of health benefits [9]. The antioxidant, antimicrobial, and immunostimulant effects of andaliman add to its added value as a potential plant in the field of health and medicine. This also supports the value of biodiversity in Indonesia, because local plants such as andaliman have potential in the development of natural medicines that benefit human health [10].

Wound healing is indeed a complex process, which consists of several phases such as inflammation, proliferation, and remodeling. The inflammatory phase is the body's response to injury that leads to the formation of blood clots and inflammatory reactions [11]. The proliferation phase involves the growth and migration of cells to form new granulation tissue, while the remodeling phase involves tissue restructuring and scar tissue formation [12, 13]. Fibroblasts are the main cells that play an important role in the wound healing process [14]. They are responsible for producing the extracellular matrix, including collagen, which provides structural strength to newly formed tissues. The involvement of fibroblasts is very important in speeding up the wound healing process. Herbal products, such as ointments from andaliman fruit, have been recognized as effective in wound healing without causing excessive side effects such as chemical drugs. This is due to the natural ingredients in herbal products that can provide therapeutic benefits without the risk of serious side effects [15].

The study, designed to test the effectiveness of andaliman fruit ointment in the healing process of incision wounds in Wistar rats, is a positive step toward using more natural and safe traditional medicine in health care. Wistar rats are often used in medical research because they have biological similarities with humans, so the results of research on Wistar rats can provide a relevant picture regarding the

effectiveness of these herbal products in humans [16, 17]. The safe and natural use of traditional medicine has the potential to be an attractive alternative in medicine and healthcare, especially if it can prove its effectiveness in clinical trials and follow-up research. As such, this research could be an important first step in developing more holistic, nature-based treatments for society.

Research Methods

This study is an experimental study using male wistar rats as experimental animals, with a Pre-test and Post-test group only control design approach. Conducted in January 2024 at the Laboratory of Universitas Prima Indonesia. The study sample involved 25 male white rats aged 6-8 weeks and weighing 150-200 gr, randomly selected and divided into 5 groups (4 treatments and 1 control). The determination of the number of samples followed Frederer's formula with a result of $n \geq 4.75$, so that each experimental group used 5 mice. This sample was measured daily for 1 week before testing. Materials used include alcohol, aluminum foil, aquadest, Andaliman Fruit, 96% ethanol, rat test animals (mus muscles), sterile gauze, whatman filter paper, methyl paraben, petroleum ether, plaster, propylene glycol, gloves, and triethanolamine. The tools used include glass tools (pyrex®), autoclaves, maceration vessels, blenders (Maspion), porcelain dishes, calipers (Tricle brand®), ovens, tweezers, rotavator (Heidolf®), iron spoons, analytical scales (Precisa®®), and water baths. The working procedure includes the extraction of Andaliman Fruit from sample processing to essential oil making, washing, drying, and grinding to powder. Andaliman Fruit essential oil is produced through a Hydro-distillation process for 4 hours at a temperature of 80oC with elimination of water residues using anhydrous sodium sulfate.

Phytochemical tests are performed to identify groups of compounds in Andaliman Fruit Essential Oil, including flavonoids, tannins, alkaloids, phenols, terpenoids, and saponins. The identification procedure involves examining discoloration or precipitate formation using various reagents and modified techniques, such as testing with FeCl3 for tannins and phenols, testing dragendroff and mayer reagents for alkaloids, and yellow undercoat formation tests for terpenoids [18, 19]. Furthermore, the preparation of ointment preparations from Andaliman Fruit Essential Oil involves formulations with various concentrations of ingredients such as Andaliman Fruit extract, lanolin, solid paraffin, cetostearyl alcochol, and white vaseline. Before the study, test animals (male white rats) were adapted for 7 days and given incision wounds in the dorsal region along 2 cm, with inclusion and exclusion criteria to ensure animal health during the treatment [20].

In this study, rats were adapted for 7 days and given standard feed before treatment. The treatment group was divided into five groups with each given Andaliman fruit ointment preparations with different concentrations (3%, 6%, 9%, and 12%), and one positive control group given Bioplacenton®. Incision wounds on rats' backs were given after the rats were anesthetized with ether liquid, shaved rat fur, and disinfected the skin before incisions. Furthermore, an antioxidant test was carried out to measure the antioxidant activity of Andaliman Fruit extract with the DPPH concentration reduction method. The data obtained will be processed using statistical analysis techniques, including normality test and ANOVA test to evaluate the effectiveness of ethanol extracts of Andaliman Fruit and Bioplacenton® in healing incision wounds on rat backs [21].

Results of Analysis and Discussion

Table 1: Phytochemical Screening of Andaliman Fruit.

Test	Result	Information
Alkaloid	Red-brown sediment	(+)
	White sediment	(+)
	Chocolate sediment	(+)
Flavonoid	Red color on the layer of amyl alcohol	(+)
Saponins	Permanent foam	(+)
Tannins	Blackish-green color	(+)

From table 1. It can be known that Andaliman Fruit extract contains chemical compounds of alkaloids, flavonoids, saponins and tannins. In the alkaloid test, a red-brown precipitate was found to form for Dragendorff reagent, a white precipitate resulting from the addition of Mayer's reagent, and a brown precipitate for Bouchardt's test. Antioxidant testing was performed using UV-Vis spectrometry method at wavelength 517 nm with 2-2-Diphenyl-1-picrylhydrazil (DPPH). The results of antioxidant testing of Andaliman Fruit extract can be seen in the following table:

Table 2: Data on the percentage of inhibition of Andaliman Fruit extract extract against DPPH.

Extract Concentration (ppm)	Absorbansi Extract	Absorbansi Control	Inhibisi (%)
3	0.345	0,538	56.08
6	0.285	0,538	57.11
9	0.224	0,538	57.54
12	0.121	0,538	59.14

In Table 2, data on the percentage of inhibition of Andaliman fruit extract against 2,2-diphenyl-1-picrilhydrazil (DPPH) at various concentrations are shown. At a concentration of 3 ppm, the absorbance value of the extract was recorded at 0.345 with an inhibition percentage of 56.08%, which increased to 57.11% at a concentration of 6 ppm. The concentration of 9 ppm showed an extract absorbance value of 0.224 with an inhibition percentage of 57.54%, while at the highest concentration, which was 12 ppm, the percentage of inhibition reached a peak of 59.14% with an extract absorbance value of 0.121. These data show a tendency to increase the percentage of inhibition along with an increase in the concentration of Andaliman Fruit extract, indicating the potential of the substance in significantly inhibiting DPPH.

Table 3: Changes in wound length with varying concentrations of Andaliman Fruit extract

Day 1-	Change in Wound Length (cm)				
	Concentration: 3%	Concentration: 6%	Concentration: 9%	Concentration: 12%	Bioplacenton
1	2	2	2	2	2
3	1.8	1.8	1.7	1.7	1.4
5	1.6	1.4	1.5	1.4	1.1

7	1.4	1.1	1.2	1.2	0.7
9	1.1	0.8	0.6	1	0.5
11	1	0.5	0.3	0.8	0.2
14	0.9	0.4	0.1	0.6	0.1

Table 3. showed changes in wound length with administration of various concentrations of Andaliman fruit extract over a period of time, compared to a control group using Bioplacenton. On the first day, all groups showed an equivalent wound length, which was 2 cm. However, on the third day, changes were seen with concentrations of 6%, 9%, and 12% showing a decrease in wound length to 1.8 cm, 1.7 cm, and 1.7 cm respectively, while the control group (Bioplacenton) remained at 1.4 cm. The difference was even more noticeable on the fifth day, where concentrations of 6%, 9%, and 12% showed changes to 1.4 cm, 1.5 cm, and 1.4 cm, while Bioplacenton reached 1.1 cm. On the seventh day, further changes were seen, and on the ninth day, concentrations of 9% and 12% showed a more significant reduction in wound length compared to Bioplacenton. On day 14, concentrations of 9% and 12% showed a steadily decreasing wound length, while Bioplacenton reached 0.1 cm. These data show the potential of Andaliman fruit extract in accelerating the wound healing process, with concentrations of 9% and 12% showing better effects compared to the contro group. Bioplacenton in the observed time span. It can be concluded that Andaliman fruit extract has the ability to heal wounds, although the healing speed is not as fast as Bioplacenton® when viewed from reducing wound length from day to day. The ability to heal wounds may be influenced by the content of compounds in extracts such as flavonoids, alkaloids, saponins, and tannins.

Secondary metabolite compounds contained in Andaliman fruit extract have bioactive properties such as flavonoids that play a role in the inflammatory process. When wounds occur on the skin of mice, flavonoids play a role in inhibiting the formation of prostaglandins and other inflammatory mediators such as leukotrienes. Inhibition of the production of these two compounds accelerates the inflammatory process to the next process, namely proliferation. In addition, the alkaloids contained in Andaliman fruit extract can inhibit bacterial growth by disrupting peptidoglycan in bacterial cells which causes the formation of cell walls.

Table 4: Test Results of the Effect of Andaliman Fruit Extract on the Healing of Incised Wounds

ANOVA						
		Sum of Squares	**df**	**Mean Square**	**F**	**Say.**
Andaliman Fruit Extract Ointment	Between Groups	6.784	3	3.221	6.455	.021
	Within Groups	35.445	22	.456		
	Total	42.229	25			

Analysis of Variance (ANOVA) was conducted to evaluate significant differences between group averages in the context of the influence of Red Betel Leaf Extract. The ANOVA results showed a significant difference between the groups tested, with an F value of 6.455 and a significance value of 0.021. This indicates that variations in the effect of Andaliman Fruit Extract on these groups did not occur by chance. Therefore, it can be concluded that there are significant differences in response to Andaliman Fruit Extract among the groups tested, strengthening its potential influence in the context of this study.

Wounds have various classifications based on several factors that include the nature, anatomical structure, healing process, and source of trauma that caused it. Based on its nature, wounds can be divided into several types such as abrasion wounds (friction), contusions (bruises), incisions (incisions), lacerations (tears), penetration (penetration), puncture (puncture), sepsis (infection), and others. While based on its anatomical structure, wounds can be classified as superficial wounds (covering the epidermis), partial thickness wounds (involving the epidermis and dermis), and full thickness wounds (involving all layers of skin to the bone).

The wound healing process also has three main classifications, namely primary, secondary, and delayed primary healing. Primary healing occurs when the edges of the wound can relink with less granulation tissue, resulting in finer scarring. Secondary healing occurs when the edges of the wound are far apart, and the healing process begins with the formation of granulation tissue at the base of the wound which is then followed by contraction and scar tissue formation. Delayed primary healing is a delayed healing process that involves excision and formation of granulation tissue before suturing is performed [22].

The source of trauma that causes injury also varies, ranging from incision wounds (vulnus scissum) caused by sharp objects to puncture wounds (vulnus punctum) due to pointed objects. There are also lacerations (vulnus laceratum) that occur as a result of trauma with uneven surfaces and abrasions (excoriation) due to friction on the skin [23, 24]. In addition, burns (vulnus combustio) can result from heat or chemicals. Knowledge of wound classification is very important in medical treatment because it can help in determining the right healing strategy according to the characteristics of the wound. The wound healing process involves a number of important phases, from hemostasis and inflammation to proliferation, maturation, and remodeling [24]. Hemostasis is the initial phase in which blood clots occur to stop bleeding, while inflammation involves the body's response to the wound with symptoms such as erythema (redness), edema (swelling), pain, and heat, aimed at bringing inflammatory cells to the wound area [25]. After the inflammatory phase, the healing process continues with proliferation, during which the formation of granulation tissue that fills the wound occurs. During this phase, fibroblasts have a key role in producing collagen that strengthens tissues and facilitates the wound closure process. In addition, the maturation and remodeling phases are the stages in which scar tissue forms and undergoes structural and functional changes to achieve optimal integrity [26].

Certain factors can slow the wound healing process, such as poor nutrition, hypoxia (lack of oxygen), immunosuppression (suppression of the immune system), chronic diseases, and post-surgical conditions. It is important for medical practitioners, especially surgeons, to understand deeply the physiological process of wound healing in order to reduce the risk of morbidity and speed up patient recovery [27]. In the context of research on andaliman, andaliman simplisia has been shown to contain a number of active compounds such as alkaloids, flavonoids, glycosides, saponins, tannins, steroids, and triterpenoids [2, 20]. Other studies have also shown that andaliman seeds contain active chemical compounds that have potential as medicinal ingredients, including antibacterial, antimicrobial, antiviral, and protein denaturing compounds [18]. Knowledge of the content of these active compounds can be the basis for the utilization of andaliman as a remedy for other diseases. However, further research is needed to test the effectiveness and safety of using andaliman in the treatment of wounds and other diseases.

Conclusion

Based on this study, Andaliman Fruit extract was proven to have bioactive compounds such as alkaloids, flavonoids, saponins, and tannins that play an important role in the healing process of incision wounds in white rats. The optimum concentration to achieve the best healing effectiveness was identified at 9%. In addition, the results showed that Andaliman fruit has a wound healing ability close to the positive control, Bioplacenton®, with the highest percentage of healing on the 14th day, which is 90%. In conclusion, Andaliman fruit has potential as an effective alternative in wound healing in white rats, showing results that compete with Bioplacenton® in the context of wound healing.

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