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Effectiveness analysis of piper crocatum linn. extract cream. for wound healing in wistar rats

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Abstract
A wound is damage or loss of body tissue due to a factor that disrupts the body's protective system. The wound healing process can be divided into three main phases, namely, the inflammatory phase, the proliferation phase, and the remodeling phase. Red betel leaf is one of the natural ingredients that can be used as an alternative medicine for wound healing. This study aims to analyze the effectiveness of cream preparations of red betel leaf extract (piper crocatum linn.) in accelerating the healing of cut wounds. This type of research is experimental, with a Pre-test and Post-test group-only control design approach conducted in March 2023. Determination of sample size according to Frederer's formula, namely with a minimum sample size of 5 rats for each group, testing with the distribution of red betel extract with a concentration of 2%, 4%, 6^, and 8%. Data analysis using statistical data test with normality test and ANOVA test. The results of red betel extract contain chemical compounds of alkaloids, flavonoids, saponins, and tannins. ANOVA test obtained a Fcount value of 6.033 ≥ Ftable of 2.67, with a p-value of 0.014 ≤ 0.05. Conclusion The optimum concentration of red betel ethanol extract that can heal cut wounds in white rats is 8%; red betel ethanol extract cream can approach Bioplacenton® in healing cut wounds in rats.

Keywords: Red betel, cream, wounds

Introduction
A wound is damage or loss of body tissue due to a factor that disrupts the body's protective system. The wound-healing process can be divided into three phases: inflammatory, proliferation, and remodeling [1]. Fibroblasts are more active in synthesizing matrix components in response to wounds by proliferating and increasing fibrinogenesis [2]. Herbal products have been used since long ago 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 cause fewer side effects than chemical drugs. The World Health Organization (WHO) recommends using traditional therapies, including herbs, in public health maintenance, prevention, and treatment of diseases, especially chronic diseases, degenerative diseases, and cancer. Red betel leaf is one of the natural ingredients that can be used as an alternative wound-healing medicine. Red betel leaves contain phytochemical compounds: alkaloids, saponins, tannins, and flavonoids [3, 4]. The flavonoid content as an immunostimulant substance and the production of growth hormones such as EGF, TGFα, PDGF, VEGF, FGF, and TGFβ will also increase to accelerate wound healing [5]. Saponin has the ability as a cleanser and antiseptic that functions to kill or prevent the growth of microorganisms that commonly arise in wounds so that the damage does not cause severe infection. This study aims to analyze the effectivity of cream preparations of red betel leaf extract (piper crocatum linn.) in accelerating the healing of cut wounds.

Research methods
This type of research is experimental, with a Pre-test and Post-test group-only control design approach conducted in March 2023. Determination of sample size according to Frederer's formula, namely with a minimum sample size of 5 rats for each group. The materials used were alcohol, aluminum foil, distilled water, red betel, 96% ethanol, rat test animals (Mus musculus), sterile gauze, Whatman filter paper, methylparaben, petroleum ether, plaster, propylene glycol, gloves, triethanolamine. The tools used included glassware (pyrex®), an autoclave, a maceration vessel, a blender (Maspion®), a porcelain cup, a caliper (Tricle brand®), an oven, tweezers, a rotavapor (Heidolf®), iron spoon, analytical balance (Precisa®), and water bath. An antioxidant test was conducted to see the antioxidant activity of red betel extract with concentrations of 2%, 4%, 6^, and 8%. The method used was 1, 1- difenil-2-pikrilhidrazil (DPPH) concentration reduction. EC50 (extract concentration in reducing 50% DPPH) is the parameter used. DPPH test was conducted by preparing 50 ppm DPPH in ethanol. Data analysis used statistical data tests with normality tests and ANOVA tests.

Results and discussion
Skrining fitokimia ekstrak sirih merah
Based on the results of the identification of chemical compound groups can be seen in the following table:

Table 1: Phytochemical screening of red betel

Test	Result	Description
Alkaloids	Red-brown precipitate	(+)
	White precipitate	(+)
	Brown precipitate	(+)
Flavonoids	Red color in the amyl alcohol layer	(+)
Saponins	Permanent foam	(+)
Tannins	Blackish green color	(+)

From the table, it can be seen that red betel extract contains alkaloid, flavonoid, saponin, and tannin chemical compounds. Tannin compounds can act as astringents in

wounds, while saponins work to increase the speed of epithelialization. Flavonoid compounds also play a role in wound healing by stopping bleeding, namely through vasoconstriction in blood vessels, accessible radical antidotes, inhibitors of hydrolysis and oxidation of enzymes, and anti-inflammatory [1].

Table 2: Changes in wound length with various extract concentrations

Day-	Change in Wound Length (cm)				
	Concentration 2%	Concentration 4%	Concentration 6%	Concentration 8%	Bioplacenton
1	2	2	2	2	2
3	1.8	1.8	1.7	1.7	1.6
5	1.6	1.4	1.4	1.4	1.3
7	1.5	1.5	1.2	1.2	0.8
9	1.2	0.8	0.8	0.8	0.6
11	1	0.6	0.6	0.5	0.4
14	0.9	0.5	0.4	0.4	0.2

Based on the table above, it can be seen that Bioplacenton®, as the positive control, experienced faster wound healing. On day 3, the wound length was already reduced, and on day 14, the incision wound treated with Bioplacenton® had the highest percentage of recovery. This is because the Bioplacenton® composition has active ingredients of placenta extract and neomycin sulfate, which effectively trigger new tissue formation and prevent infection in the wound area. When viewed from the wound healing rate per day, from day 1 to day seven, the wound healing rate was still linear, but from day 9 to day 14, there was a decrease in the healing rate at 8% concentration compared to the treatment at 6% concentration and far behind when compared to those treated with Bioplacenton®.

When compared, the wound length in the 6% concentration treatment of red betel extract was only 0.2 cm different from Bioplacenton® on day 14. It can be concluded that red betel can heal wounds, although the healing speed is not as fast as Bioplacenton® when seen from the reduction in wound length from day to day. This wound-healing ability may be influenced by the compounds in the extract, such as flavonoids, alkaloids, saponins, and tannins.

Table 4: Test results of the effect of extract administration on wound healing

ANOVA						
		Sum of squares	df	Mean square	F	Sig.
Red betel extract	Between groups	6.343	3	2.245	6.033	.014
	Within groups	36.317	135	.275		
	Total	45.145	137			

The table above shows the F count value of 6.033. To find the value in the F Value Table for df = 3/135 with a probability (α) of 0.05, the F-table value is 2.67. So, the importance of F-count> F-table means that overall, there is a real influence on the administration of red betel extract on wound healing. To emphasize this hypothesis test, it can be seen in the Sig. The count value is 0.014 while the Sig (α) value is 0.05, meaning the Sig. Count value < Sig (α). This means that the administration of red betel extract really affects wound healing in rats.

Table 4: Test results of the effect of bioplacenton® (positive control) on wound length

ANOVA					
	Sum of squares	Df	Mean square	F	Sig.
Between groups	14.933	6	1.112	23.434	.006
Within groups	1.722	28	.076		
Total	13.215	34			

Based on the table above, it can be seen that the Fcount value is 23.434 while the Ftable value is 2.45, which means Fcount> Ftable. When viewed from the significance value, the calculated significance value is 0.001, smaller than the alpha value of 0.06 or $p < 0.05$. From this data, it can be concluded that there is a natural effect of the administration of Bioplacenton® on wound healing. The wound-healing process is essential because the skin is the only organ exposed to the outside world. The skin has specific functions for the body, namely protective, sensory, thermoregulatory, metabolic, and sexual signaling functions. When the skin loses its continuity, these functions cannot perform as they should. Therefore, the wound-healing process requires proper management and treatment so that the wound area does not become infected, eventually leading to chronic wounds.

Based on the healing process, wounds can be classified into primary wound healing, secondary wound healing, and Delayed Primary Healing [6]. In the immediate healing process, the edges of the damage can be reunited, the surface is clean, and there is no tissue loss [7]. Secondary healing occurs when the skin edges are far apart and some tissue is lost [8]. The healing process starts with forming granulation tissue in the wound bed and surrounding area [9]; [10]. Wound healing is the natural repair process of injured tissue involving inflammatory mediators, blood cells, extracellular matrix, and parenchymal cells [11]. Wound healing is a complex biological process that results in the restoration of tissue integrity. Physiologically, the wound healing process can be divided into four stages: hemostasis, inflammation, proliferation, and tissue remodeling. Many factors slow wound healing, including poor nutrition, hypoxia, immunosuppression, chronic diseases, and post-surgical conditions [11, 12]. Surgeons must understand the physiological processes involved in wound healing to minimize patient morbidity from delayed wound healing [13].

Conclusions and suggestions

Based on the results of research and data analysis on the effectiveness of the administration of red betel ethanol extract and Bioplacenton® on wound healing in white rats, it can be concluded that:

1. Red betel ethanol extract has several bioactive compounds, such as alkaloids, flavonoids, saponins, and tannins, that play a role in wound healing.
2. The optimum red betel ethanol extract concentration that can heal cut wounds in white rats is 8%.

3. The highest percentage of healing on day k-14 was in the positive control (Bioplacenton®), which was 96%, followed by 8% v/v extract with a 91% healing percentage.
4. Red betel ethanol extract gel preparation has an ability that is close to Bioplacenton® in healing incision wounds in rats.

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