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Incision Wound Healing Activity of Red Betel Leaf (*Piper crocatum*) in Wistar Rats

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Abstract

Background: Incisional wounds are tissue injuries that require appropriate management to prevent complications. Red betel leaf (*Piper crocatum*) contains bioactive compounds with anti-inflammatory, antioxidant, and antimicrobial properties that may enhance wound healing. **Objective:** This study aimed to evaluate the wound-healing activity of red betel leaf extract in Wistar rats with incisional wounds. **Methods:** The research used an experimental laboratory design in which test animals were divided into five groups.: three treatment groups with extract concentrations of 5%, 10%, and 15%, a positive control group using 10% povidone iodine, and a negative control group using 0.9% NaCl. Observed parameters included redness, edema, exudate, granulation tissue formation, and wound length changes during the healing process. **Result:** The results demonstrated that *Piper crocatum* extract, particularly at a concentration of 15%, significantly reduced inflammatory signs (erythema, edema, and exudate) and accelerated granulation tissue formation and wound contraction compared with the control groups ($p < 0.05$). **Conclusion:** These findings suggest that red betel leaf extract possesses pharmacological activity that accelerates wound healing and has potential as a complementary therapy in wound management.

Keywords: Incisional wound, *Piper crocatum*, red betel leaf, Wistar rats, Wound healing

Original Research Article

INTRODUCTION

The skin is the largest organ of the human body, accounting for approximately 15% of an adult's body weight, and serves as a protective barrier for internal tissues against trauma, ultraviolet radiation, extreme temperatures, toxins, and microorganisms (Agustina et al., 2019). One of the common conditions affecting the skin is injury, which can cause both physical and emotional impacts, ultimately affecting the patient's quality of life (Kurniasari et al., 2023). Although the skin has an inherent ability to repair damage, the wound-healing process can be hindered by various factors such as infection, metabolic disorders, or hypoxia, thereby requiring additional treatment that often incurs substantial costs (Liste, 2020).

Epidemiological data indicate an increasing prevalence of wound cases worldwide. In the United

States, the prevalence of chronic wounds reaches 3.5 per 1,000 population, while the World Health Organization estimates that approximately 6 million people globally suffer from acute or chronic wounds (Dinas Kesehatan Kota Surabaya, 2022). In Indonesia, the 2023 National Basic Health Research (Riskesdas) reported a national injury rate of 8.2%, with falls and traffic accidents as the leading causes (Riskesdas, 2023). These data highlight the need for effective wound management strategies to achieve optimal healing outcomes (Nasution, 2020).

In recent years, herbal-based therapies have gained attention as alternative or complementary approaches in wound care. Traditional medicines have been shown to contain bioactive compounds that support tissue repair (Liste, 2020). One widely used medicinal plant is red betel (*Piper crocatum*), traditionally applied as an antiseptic and in the treatment of various conditions (Nurchayati et al., 2021). Its active constituents, including flavonoids, alkaloids, tannins, and saponins, exhibit anti-inflammatory, antioxidant, and antimicrobial activities that can accelerate tissue regeneration (Windono & Parfati, 2016).

Several studies have reported the pharmacological potential of *Piper crocatum* in wound healing. However, evidence regarding the topical effectiveness of red betel leaf extract on incisional wounds, particularly across different extract concentrations, remains limited, indicating the need for further investigation using animal models such as Wistar rats (Windono & Parfati, 2016). Therefore, this study was designed to evaluate the wound-healing efficacy of topical *Piper crocatum* extract at concentrations of 5%, 10%, and 15% on incisional wounds in Wistar rats.

Based on these considerations, this study was designed to evaluate the wound-healing efficacy of topical red betel leaf (*Piper crocatum*) extract on incisional wounds in Wistar rats. This study hypothesized that topical red betel leaf (*Piper crocatum*) extract at concentrations of 5%, 10%, and 15% would significantly reduce erythema, edema, and exudate, enhance granulation tissue formation, and accelerate wound contraction in incisional wounds of Wistar rats compared with a positive control (10% povidone iodine) and a negative control (0.9% NaCl). These clearly d efined and measurable outcomes are expected to provide robust evidence regarding the potential of *Piper crocatum* extract as a therapeutic agent in wound management.

MATERIALS AND METHODS

The study employed a laboratory experimental design using a pre-test and post-test control group approach. Five groups were included (three treatment groups and two control groups) with random allocation: treatment groups receiving topical red betel (*Piper crocatum*) leaf extract at concentrations of 5%, 10%, and 15%; a positive control group treated with 10% povidone-iodine ointment; and a negative control group treated with 0.9% NaCl. Observations were performed before and throughout the wound-healing process (Siregar et al., 2022).

This research assessed the activity of red betel leaf extract on the healing of incisional wounds in Wistar rats. The evaluated parameters included erythema, edema, exudate, granulation tissue formation, and wound length.

Figure 1. Drying process of red betel (*Piper crocatum*) leaves

Figure 2. Preparation of powdered simplicia and maceration process.

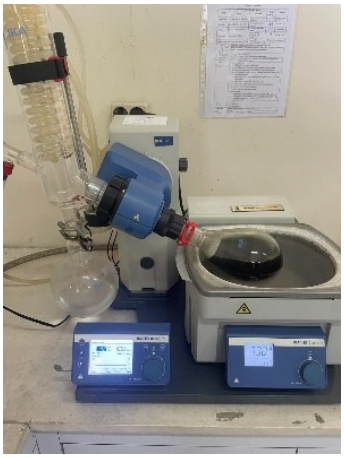

Figure 3. Extract evaporation.

Figure 4. Determination of vaseline for the treatment groups 5%, 10% and 15%.

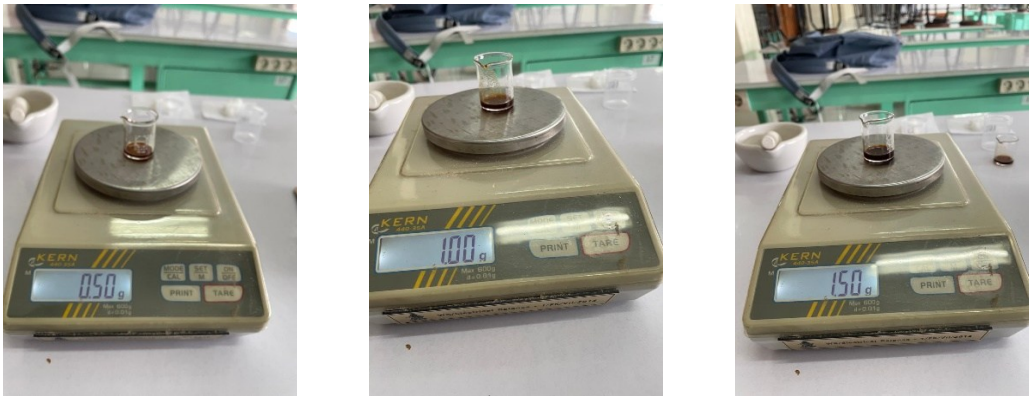

Figure 5. Determination of red betel leaf extract for the treatment groups 5%, 10%, and 15%.

The tools used in this study consisted of an analytical balance, blender, beaker, measuring cylinder, rotary evaporator, minor surgical instruments, syringes, and extract containers. The materials included dried red betel leaves, 96% ethanol for maceration for 3×24 hours, followed by filtrate evaporation using a rotary evaporator to obtain a concentrated extract. Additional materials were: ointment base (vaseline), 0.9% NaCl, 10% povidone-iodine ointment, cotton, sterile gauze, and ketamine–xylazine for anesthesia. The instrument used for data collection was a wound-healing observation sheet.

The study began with a seven-day acclimatization period during which the test animals were provided standard feed and water ad libitum. Incisions were made under ketamine–xylazine anesthesia. A linear incision measuring 2 cm in length and approximately 0.2 cm in depth was created aseptically on the dorsal region of each rat. The wound was then cleansed with 0.9% NaCl and treated with the assigned topical preparation. Treatments were administered once daily for 14 days, and daily observations were carried out to assess erythema, edema, exudate, granulation tissue formation, and changes in wound length throughout the healing process. Data were coded, tabulated, and statistically analyzed using the Kruskal–Wallis test followed by Dunn's post hoc test, with a significance level of $p < 0.05$.

This study received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, under ethics approval number: No. 29/SLE/FK/UWKS/2025.

RESULTS

This study used 25 Wistar rats, which were divided into five groups: a positive control group (povidone-iodine), a negative control group (0.9% NaCl), and three treatment groups receiving red betel (*Piper crocatum*) leaf extract at concentrations of 5%, 10%, and 15%. The observed parameters included erythema, edema, wound exudation, granulation tissue formation, and wound length.

Figure 6. Erythema around the wound area.

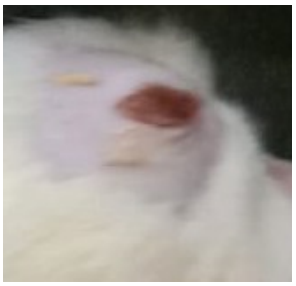

Figure 7. Wound edema.

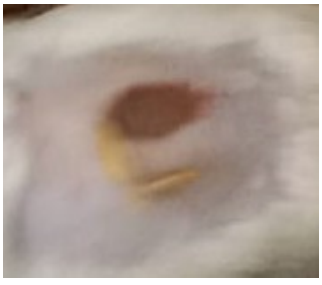

Figure 8. Wound exudation.

Figure 9. Wound granulation tissue formation.

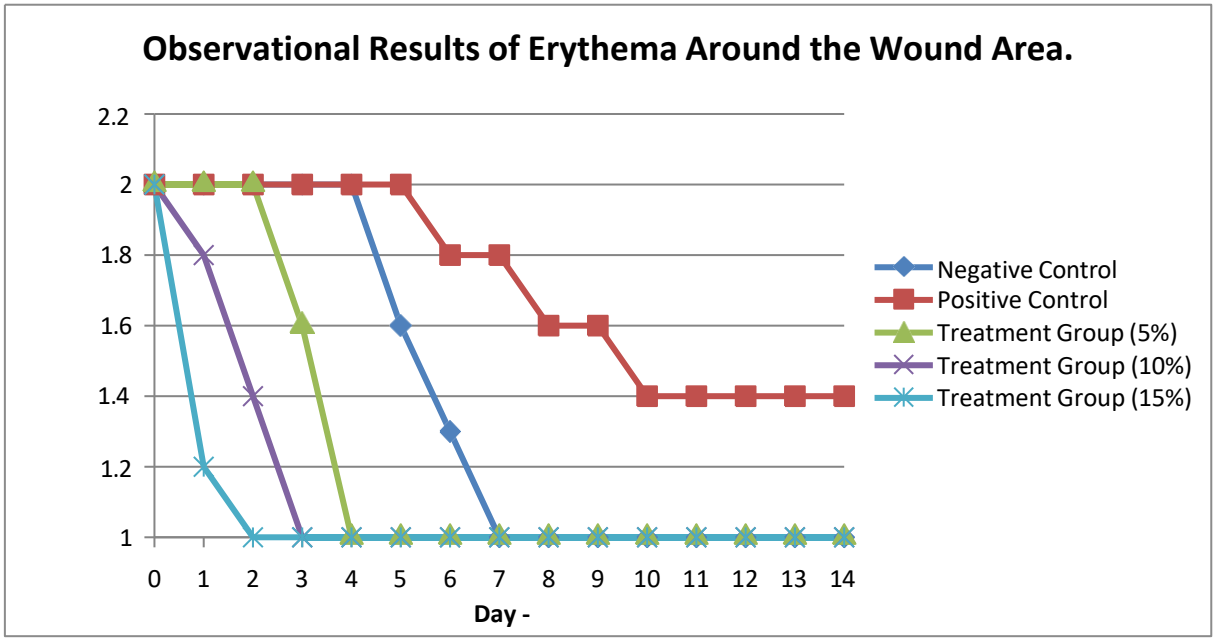

Figure 10. Observational results of erythema around the wound area.

Figure 10. The treatment groups demonstrated a faster reduction in wound erythema compared with the control groups. The 15% extract concentration showed a noticeable decrease in erythema by Day 2, followed by the 10% concentration on Day 3 and the 5% concentration on Day 4. In contrast, the positive control group continued to exhibit higher erythema scores throughout the observation period.

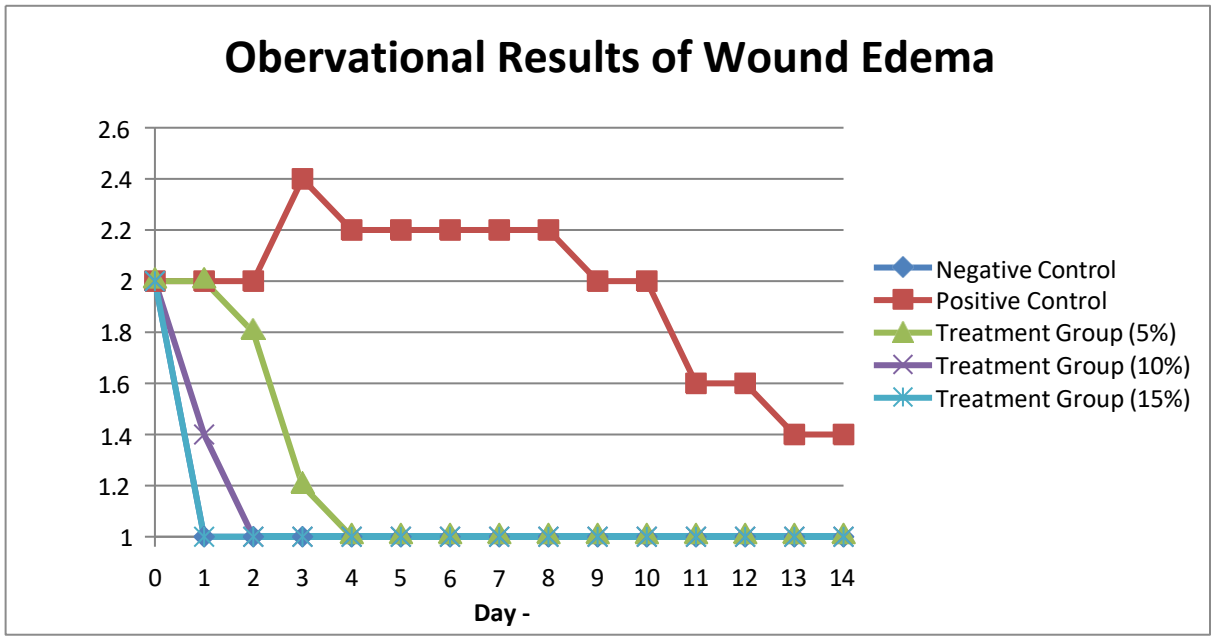

Figure 11. Observational results of wound edema.

Figure 11. illustrates that the extract-treated groups demonstrated a more rapid reduction in edema compared with the control groups. The 15% treatment group showed the earliest and most notable decrease in edema, followed by the 10% and 5% treatment groups, which exhibited a more gradual decline. In contrast, the negative control group showed a slow, progressive reduction, while the positive control group maintained relatively higher edema levels throughout the observation period.

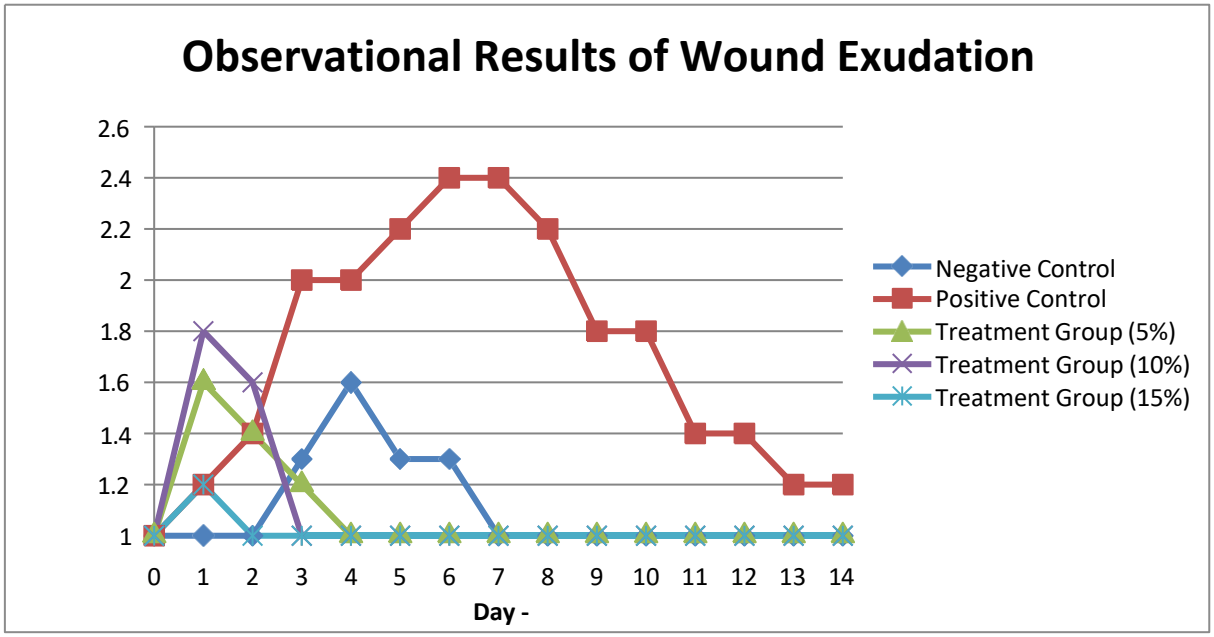

Figure 12. Observational results of wound exudation

Figure 12. indicates that the treatment groups were able to suppress wound exudate production more rapidly than the control groups. The 15% treatment group demonstrated the earliest stabilization of exudate levels, whereas the 5% and 10% treatment groups showed an initial increase during the early observation period, followed by a rapid decline until stabilization was achieved. The negative control group exhibited fluctuating exudate levels, while the positive control group showed a marked increase that remained elevated for a longer duration before decreasing toward the end of the observation period.

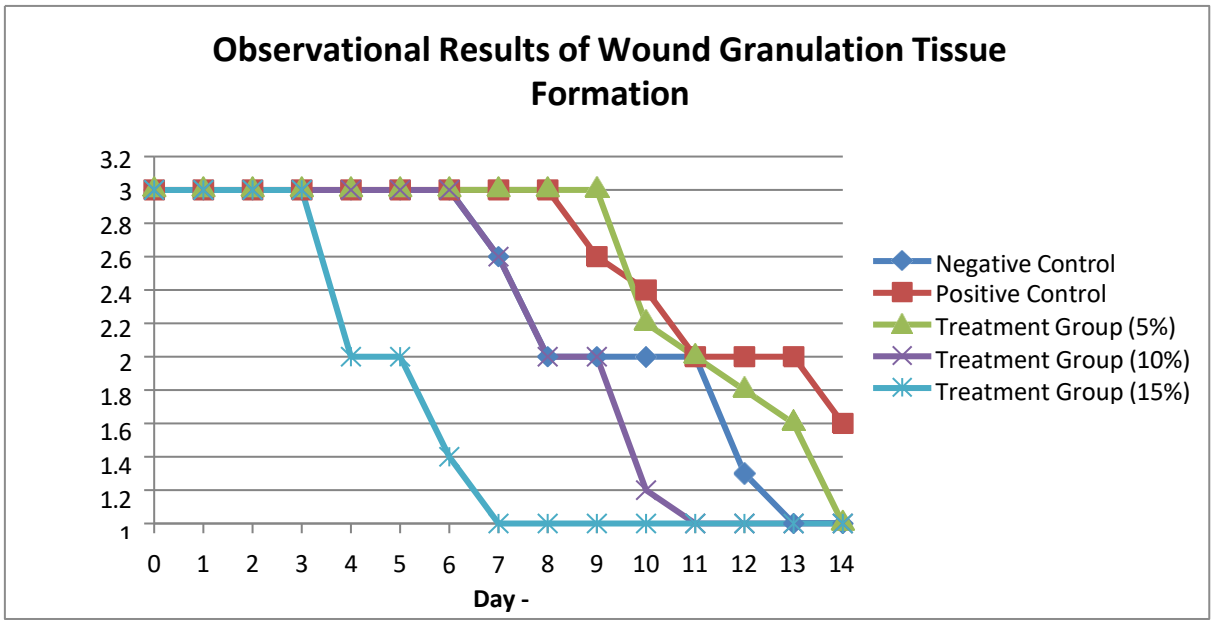

Figure 13. Observational results of wound granulation tissue formation.

Figure 13. demonstrates that the treatment groups exhibited a markedly faster wound-healing progression compared with the control groups. The 15% treatment group showed the most pronounced and earliest decline in granulation tissue scores, achieving the lowest score in a shorter duration than all other groups. This improvement was followed sequentially by the 10% and 5%

treatment groups, both of which demonstrated a gradual yet consistent reduction over the observation period. In contrast, both the negative and positive control groups experienced slight decreases in granulation scores, indicating a more prolonged granulation phase relative to the treatment groups.

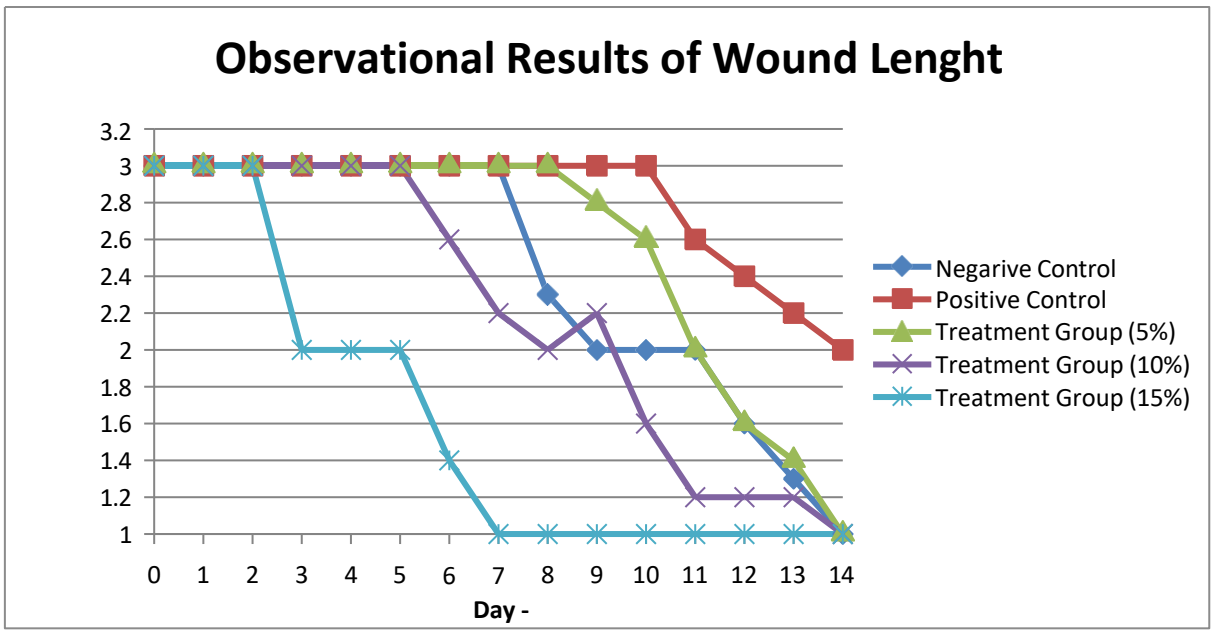

Figure 14. Observational results of wound length.

Figure 14. demonstrates that the treatment groups achieved a more rapid reduction in wound length compared with the control groups. The 15% treatment group exhibited the fastest decrease in wound length, followed sequentially by the 10% and 5% treatment groups. In contrast, both the positive and negative control groups showed a slower wound-healing progression, as indicated by the more gradual reduction in wound length.

Table 1. *Kruskall-Wallis* results test

No	Variable	Groups	Mean ± SD	P Value
1	Erythema around the wound area	Negative control	2.00 ± 0.000	$p < 0.001$
		Positive control	2.00 ± 0.000	
		Treatment group 5%	1.90 ± 0.307	
		Treatment group 10%	1.55 ± 0.510	
		Treatment group 15%	1.15 ± 0.366	
2	Edema	Negative control	1.00 ± 0.000	$p < 0.001$
		Positive control	1.75 ± 0.638	
		Treatment group 5%	1.50 ± 0.512	
		Treatment group 10%	1.20 ± 0.410	
		Treatment group 15%	1.00 ± 0.000	
3	Wound exudation	Negative control	1.08 ± 0.288	$p < 0.001$
		Positive control	1.40 ± 0.502	
		Treatment group 5%	1.30 ± 0.470	
		Treatment group 10%	1.30 ± 0.470	
		Treatment group 15%	1.05 ± 0.223	
4	Wound granulation tissue	Negative control	2.11 ± 0.697	$p < 0.001$
		Positive control	2.55 ± 0.502	
		Treatment group 5%	2.51 ± 0.626	
		Treatment group 10%	1.95 ± 0.796	
		Treatment group 15%	1.15 ± 0.366	
5	Wound length	Negative control	2.25 ± 0.655	$p < 0.001$
		Positive control	2.80 ± 0.404	
		Treatment group 5%	2.48 ± 0.694	
		Treatment group 10%	1.88 ± 0.714	
		Treatment group 15%	1.15 ± 0.366	

Table 2. *Dunn Post Hoc* results test

No	Variable	Group	P Value
1	Erythema around the wound area	Treatment Group 15% - negative control	$p < 0.001$
		Treatment Group 5% - positive control	$p < 0.001$
		Treatment group 10% - negative control	$p = 0.008$
		Treatment Group 10% - positive control	$p = 0.002$
2	Edema	Treatment Group 15% - positive control	$p < 0.001$
		Treatment Group10% - positive control	$p = 0.001$
		Treatment Group5% - negative control	$p = 0.004$
		Negative control - positive control	$p < 0.001$
3	Wound exudation	Treatment Group15% - positive control	$p < 0.001$
		Treatment Group 15% - negative control	$p < 0.001$
		Treatment Group10% - positive control	$p = 0.004$
		Treatment Group10% - negative control	$p = 0.003$
		Treatment Group 5% - positive control	$p = 0.004$
		Treatment Group 5% - negative control	$p = 0.003$
4	Wound granulation tissue	Treatment Group 15% - positive control	$p < 0,001$
		Treatment Group 15% - negative control	$p < 0.001$
		Treatment Group10% - positive control	$p < 0.001$
		Treatment Group 5% - negative control	$p = 0.038$
		Negative control - positive control	$p = 0.022$
5	Wound length	Treatment Group15% - positive control	$p < 0,001$
		Treatment Group15% - negative control	$p < 0.001$
		Treatment Group 10% - positive control	$p < 0.001$
		Negative control – positive control	$p = 0.005$

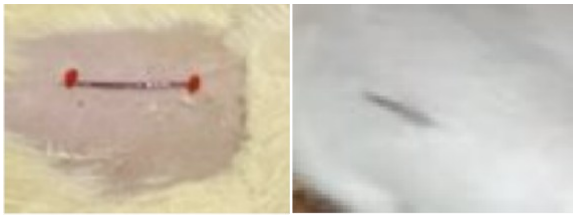

Figure 15. Pre - post Negative Control

Figure 16. Pre - post Positive Control.

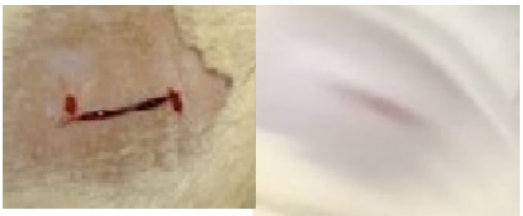

Figure 17. Pre - post Treatment group 5%.

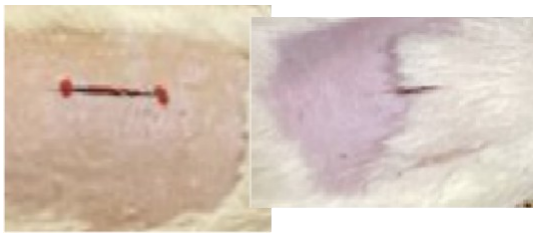

Figure 18. Pre - Post Treatment group 10%.

Figure 19. Pre - Post Treatment group 15%.

DISCUSSION

Wound healing is a dynamic process involving inflammatory and proliferative phases. In the present study, topical application of *Piper crocatum* extract significantly improved wound healing outcomes compared with the control groups. As shown in Figures 10-14 and supported by Tables 1 and 2, extract treated groups particularly the 15% concentration demonstrated faster reductions in erythema, edema, and exudation, along with enhanced granulation tissue formation and wound contraction ($p < 0.05$). These findings indicate a dose dependent wound healing effect of *Piper crocatum*, likely associated with its antiinflammatory and regenerative bioactive compounds, and suggest superior efficacy compared with 10% povidone iodine in this incisional wound model (Putri et al., 2021).

Wound Erythema

Erythema represents one of the characteristic manifestations of the acute inflammatory phase, typically emerging immediately after tissue injury. This response is caused by vasodilation and increased blood flow to the wound area as part of the body's inflammatory reaction (Mewar, 2023). In this study, erythema was observed in nearly all groups from Day 1, with notable differences in the rate at which it subsided.

Erythema reflects local vasodilation and infiltration of inflammatory cells such as neutrophils and macrophages. In this study, the 15% extract treatment group exhibited a significantly faster reduction in erythema than the negative control and even outperformed the 10% povidone iodine group. This effect can be attributed to the flavonoid and tannin content of *Piper crocatum*, which suppresses the release of pro-inflammatory mediators such as prostaglandins and histamine (Agustina et al., 2019). Flavonoids inhibit cyclooxygenase (COX) enzymes involved in prostaglandin synthesis (Salsabila, 2021), thereby reducing vasodilation and capillary permeability, clinically manifested as decreased redness.

Tannins also act as astringents, precipitating proteins in the wound tissue, forming a protective layer, and reducing local irritation (Nuryahya et al., 2021). Additionally, flavonoids exhibit antioxidant activity that neutralizes free radicals, decreasing cellular damage and inflammatory responses (Astuti et al., 2019). (Nuryahya et al., 2021) similarly reported reduced inflammation in second-degree burn wounds treated with *Piper crocatum*. (Safitri et al., 2024) also demonstrated reduced inflammatory cell counts and accelerated wound healing with topical red betel extract in experimental rats. The antimicrobial activity of *Piper crocatum* further prevents secondary infections that can exacerbate inflammation (Oktaviani et al., 2022).

Edema

Edema is a hallmark of the inflammatory phase and arises due to increased vascular permeability, leading to fluid leakage into interstitial tissue. Mediators such as histamine and prostaglandins promote vasodilation and increase capillary permeability (Awaluddin et al., 2020). Thus, the presence or reduction of edema is a crucial indicator of inflammatory progression or resolution.

In the 15% extract group, edema decreased significantly compared with controls. Bioactive constituents such as flavonoids, tannins, and saponins help stabilize cellular membranes and inhibit histamine release from mast cells, thereby reducing capillary permeability and limiting edema formation (Rahmah et al., 2023). The potent antioxidant activity of *Piper crocatum* further attenuates excessive inflammatory responses that may worsen tissue swelling (Ronaldo et al., 2024).

Tannins strengthen capillary walls and reduce plasma leakage, while flavonoids stabilize endothelial cell membranes to prevent excessive fluid transudation (Wahyuni et al., 2021). Hydroxychavicol and chavibetol act as natural anti-inflammatory agents by inhibiting COX and lipoxygenase pathways, reducing inflammatory mediator production (Hariyati, 2018). These results align with (Setiawan & Cholid, 2021), who reported decreased inflammatory responses in animal wound models treated with red betel extract.

Wound Exudation

Wound exudate is produced due to increased immune activity, particularly neutrophils, in

removing cellular debris and microorganisms. Exudation is triggered by increased vascular permeability mediated by histamine and prostaglandins, which disrupt endothelial integrity (Febrianti & Musiam, 2020). Therefore, reduced exudation reflects the resolution of inflammation.

In this study, treatment groups showed faster reductions in exudate compared with controls. Flavonoids and tannins contribute to microvascular hemostasis and form protective layers on the wound surface, preventing excessive fluid leakage (Rahmah et al., 2023). The 15% extract group exhibited significantly lower exudation than the negative control, supported by the antimicrobial effects of alkaloids, hydroxychavicol, and piperol A-B, which limit bacterial growth in the wound area (Hariyati, 2018).

These antimicrobial properties prevent microbial colonization that can intensify inflammation and increase exudate production. (Fadilah et al., 2020) also confirmed significant antibacterial effects of *Piper crocatum* against skin-infecting pathogens. The absence of purulent discharge (pus) in all treatment groups further indicates effective infection prevention, in accordance with the findings of (Oktaviani et al., 2022) regarding inhibition of Staphylococcus aureus and Escherichia coli.

Saponins in *Piper crocatum* enhance tissue contraction and stimulate fibroblast activity, supporting extracellular matrix restoration and reducing excessive exudation (Palumpun et al., 2017). These synergistic effects make red betel extract a potent topical agent for reducing exudation and preventing infection without causing local irritation.

Granulation Tissue

Granulation tissue formation is a key parameter of the proliferative phase and involves fibroblast proliferation, collagen deposition, and angiogenesis. Active compounds in red betel leaf extract stimulate fibroblast proliferation and enhance collagen synthesis essential for structural tissue repair. Saponins also facilitate fibroblast migration and neovascularization (Sutrisno et al., 2022).

In this study, the 15% extract produced significantly greater granulation tissue formation compared with povidone iodine. This effect is linked to the activity of saponins, flavonoids, and alkaloids that promote fibroblast proliferation and collagen synthesis (Setiawan & Cholid, 2021). Flavonoids elevate vascular endothelial growth factor (VEGF) expression, accelerating angiogenesis and granulation tissue development (Suryanto et al., 2020). (Wahyuni et al., 2021) further demonstrated enhanced epithelial regeneration with *Piper crocatum*. These findings reinforce the role of red betel extract as a stimulant for tissue regeneration.

Wound Length

The wound length parameter reflects wound contraction and epithelialization, serving as a clear indicator of healing progression in the proliferative and remodeling phases. Wound narrowing implies active fibroblast migration, collagen deposition, and optimal re-epithelialization (Ekasari & Nugraha, 2020).

The 15% extract group exhibited the most rapid reduction in wound length comparesuryand with controls. Flavonoids and tannins promote fibroblast activity, collagen deposition, and wound edge approximation, while alkaloids provide mild analgesic effects that reduce local oxidative stress (Pratama & Hermawan, 2019). Phenolic compounds act as antioxidants that neutralize free radicals, thereby supporting cellular migration and collagen synthesis.

These combined mechanisms accelerate the transition from the inflammatory to the proliferative phase and subsequently to tissue remodeling (Sari & Lestari, 2015). Consistent with Tan & Ramli (2020), Wistar rats treated with herbal therapy demonstrated faster wound healing than controls. Thus, red betel leaf extract has significant potential to enhance wound contraction and epithelialization.

CONCLUSION

This study provides experimental evidence that topical application of *Piper crocatum* leaf extract may support the wound healing process by promoting inflammation resolution and tissue repair in an incisional wound model. The results demonstrated that *Piper crocatum* extract, particularly at a concentration of 15%, significantly reduced inflammatory signs (erythema, edema, and exudate) and accelerated granulation tissue formation and wound contraction compared with the control groups (p

< 0.05).The findings suggest that red betel leaf extract has potential as a complementary topical agent in wound management. Nevertheless, this study was limited to an animal model and did not include histopathological or molecular evaluations. Future studies are therefore warranted to investigate its safety profile, optimize formulation, and assess clinical efficacy in human subjects.

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