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Comparison of Clove Leaf Oil Ointment Dosages on Wound Healing in Wistar Rats

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Abstract

In Indonesia, clove (*Syzygium aromaticum*) has long been utilized both as a culinary spice and as a traditional herbal medicine due to its wide range of biological activities, including antimicrobial, anti-inflammatory, antioxidant, analgesic, and immunomodulatory effects. Its major active compound, eugenol (72–90%), plays a crucial role as an antiseptic and analgesic agent, supported by other constituents such as caryophyllene, α-cadinol, limonene, phenolics, and flavonoids, which contribute to its antioxidant and free radical–scavenging properties. Clove leaf oil used in this study was obtained through steam distillation, ensuring consistency and stability of its bioactive components. This research employed a true experimental design with a pretest–posttest control group approach involving 25 male Wistar rats, divided into five groups: a positive control (10% povidone-iodine), a negative control (0.9% NaCl), and three treatment groups receiving clove leaf oil ointment at concentrations of 5%, 10%, and 15%, respectively. The wound-healing parameters observed included erythema, edema, exudate, granulation tissue formation, and wound length reduction. The Kruskal–Wallis test revealed statistically significant differences across all treatment groups for each variable erythema, edema, exudate, granulation tissue, and wound length ($p < 0.05$).

Conclusion: Clove leaf oil (*Syzygium aromaticum*) effectively accelerates wound healing, as evidenced by the reduction of erythema, edema, and exudate, along with enhanced granulation and shortened wound length. Among all groups, the 15% concentration demonstrated the most optimal healing effect, suggesting its potential as a promising herbal-based topical therapy for wound management.

Keywords: *Syzygium aromaticum*; Ointment formulation; Incised wound; Wistar rats; Wound healing

1. Introduction

Clove (*Syzygium aromaticum*) is a medicinal plant widely utilized in Indonesia both as a culinary spice and a traditional remedy. Its leaves contain essential oils rich in the bioactive compound eugenol (72–90%), which has been extensively reported to exhibit antimicrobial, anti-inflammatory, analgesic, and antioxidant activities. In addition to eugenol, other constituents such as caryophyllene, α-cadinol, limonene, phenolic compounds, and flavonoids contribute to free radical neutralization, oxidative stress reduction, and tissue regeneration support. The combination of these pharmacological properties provides a strong scientific basis for the potential use of clove leaf oil as a topical agent for wound healing [1-10].

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Wounds are a common medical condition resulting from trauma or surgical procedures, and inadequate healing may lead to complications such as infection, prolonged inflammation, and scar formation. Therefore, it is crucial to develop topical therapies that are effective, safe, and easily accessible to enhance the healing process [11-15]

Based on this background, the present study aims to determine the effective concentration of clove leaf oil ointment for promoting wound healing in Wistar rats (*Rattus norvegicus*), evaluated through macroscopic parameters including wound color, edema, exudate, granulation tissue, and wound length. The findings are expected to provide a scientific contribution to the development of herbal-based alternative therapies for wound management [1,2,9,11,13-16].

2. Material and methods

2.1. Study Design

This study employed a true experimental design using a pretest–posttest control group approach, in which the samples were divided into five groups receiving different treatments. Experimental animals consisted of male Wistar rats (*Rattus norvegicus*) treated with clove leaf oil (*Syzygium aromaticum*) ointment, and compared with control groups receiving 10% povidone-iodine and 0.9% NaC [12,16].

2.2. Sample Size and Inclusion Criteria

A total of 25 male Wistar rats, aged approximately 2.5 months and weighing 200–250 g, were randomly assigned into five groups: three treatment groups (clove leaf oil ointment concentrations of 5%, 10%, and 15%) and two control groups (10% povidone-iodine and 0.9% NaCl). Inclusion criteria included healthy and active rats with no apparent illness. Animals that died during the experiment were excluded from the final analysis and recorded as dropouts [11-13,16.]

2.3. Research Materials

Research materials included clove leaf oil obtained through steam distillation, 10% povidone-iodine, 0.9% NaCl, and medical equipment such as scissors, sterile scalpels, and bandages. The ointment formulation was prepared by combining clove leaf oil with a base of white petrolatum (vaselin album) and liquid paraffin according to the established formulation [12,14,16].

2.4. Experimental Procedure

The experimental procedure began with a 7-day acclimatization period to allow the rats to adapt to laboratory conditions. A 2 cm long and 0.5 cm deep incised wound was created on the dorsal region of each rat using a sterile scalpel. The treatment groups were topically administered clove leaf oil ointment at concentrations of 5%, 10%, and 15%, respectively. The positive control group received 10% povidone-iodine, while the negative control group was treated with 0.9% NaCl. Wound healing was observed daily for 14 days, and the parameters recorded included wound color, edema, exudate, granulation tissue formation, and wound length [11,13,16].

2.5. Statistical Analysis

Observational data were analyzed using the Kruskal–Wallis test to determine significant differences among groups. If significant results were found, the Dunn's post hoc test was performed to identify specific intergroup differences [17].

2.6. Ethical Approval

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, with ethical clearance number 30/SLE/FK/UWKS/2025. All experimental procedures were conducted in compliance with the ethical guidelines for the use of laboratory animals.

3. Results

Observations showed that all groups exhibited progressive changes in the incised wound healing process during the experimental period. Healing progression was assessed through five parameters: redness, edema, exudate, granulation tissue, and wound length. The following sections describe the comparative wound-healing patterns among the experimental groups.

3.1. Observation of Redness in Wistar Rats

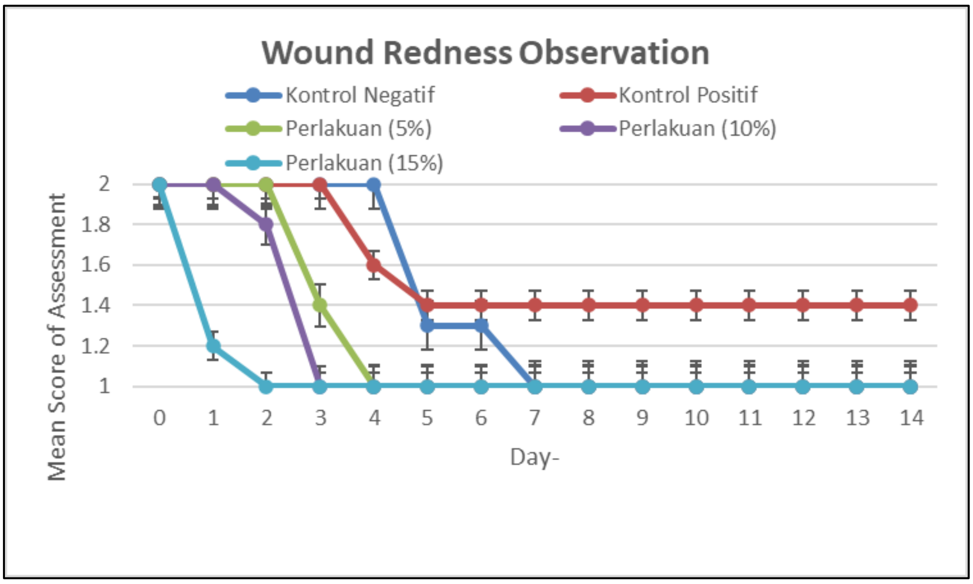

Figure 1 Wound Redness Observation in Wistar Rats

Based on the observation results, the resolution of wound redness varied among groups. In the negative control, redness persisted until day 6, showing the slowest recovery (score decreased to 1 and remained constant). The positive control group showed a reduction in redness from day 4, stabilizing at a score of 1.4. In contrast, the treatment groups demonstrated a faster resolution: the 15% concentration reached a score of 1 (no redness) by day 2, the 10% group by day 3, and the 5% group by day 4.

3.2. Observation of Edema in Wistar Rats

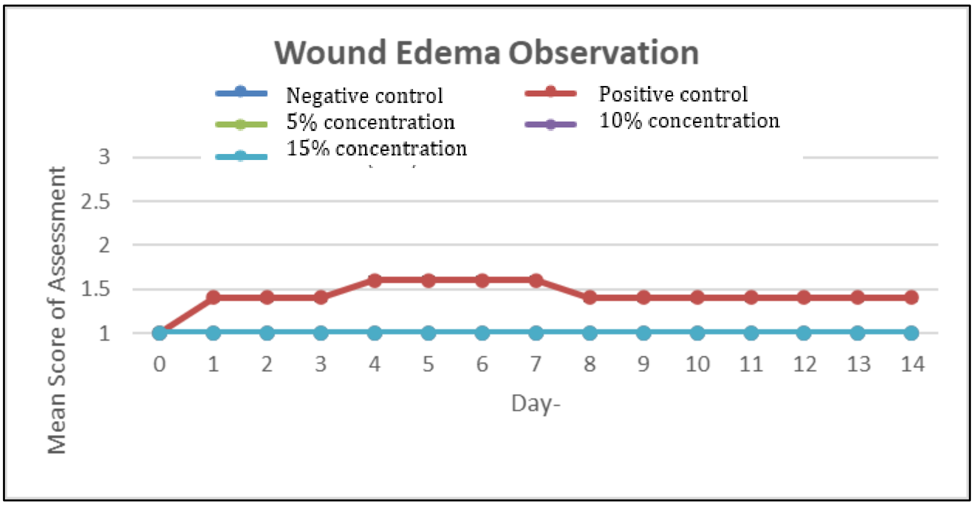

Figure 2 Wound Edema Observation in Wistar Rats

No edema was observed in the negative control or treatment groups (5%, 10%, and 15%) during the observation period (score remained at 1). Conversely, the positive control exhibited localized edema from day 1 (score 1.4–1.6) that persisted without full resolution until the end of the study. These results indicate that clove leaf oil ointment prevented edema formation, whereas persistent edema was still present in the positive control group.

3.3. Observation of Wound Exudate in Wistar Rats

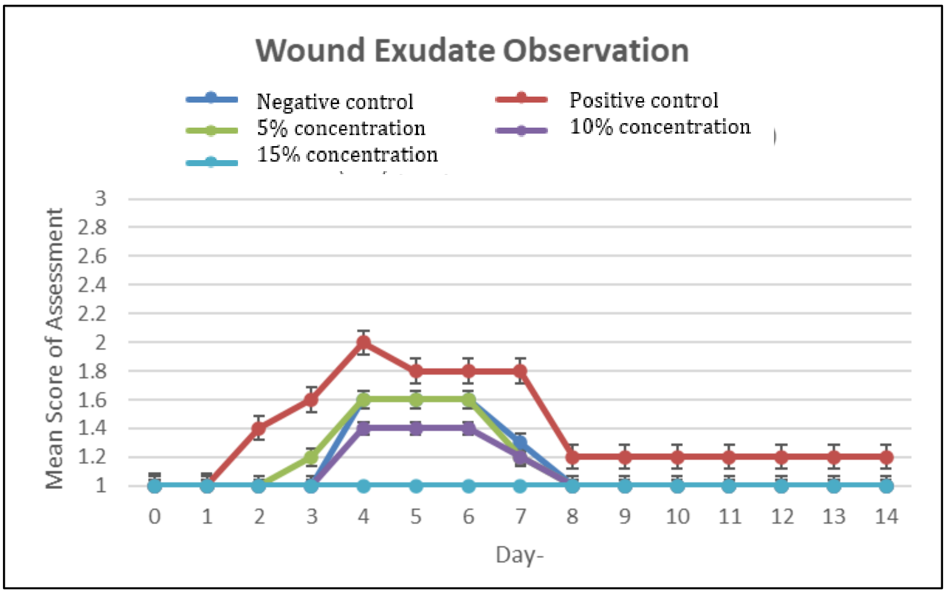

Figure 3 Wound Exudate Observation in Wistar Rats

The negative control group exhibited mild exudation from days 4–7 (score 1.6), returning to normal (score 1) by day 8. The positive control group showed more severe exudation beginning on day 2, peaking between days 4–6 (score 2 = presence of fluid without pus), and only slightly decreasing thereafter, stabilizing at a score of 1.2. The 5% treatment group exhibited mild exudation (score 1.6) between days 4–6, which resolved completely by day 8. The 10% group showed minimal exudation (score 1.4 on days 4–6) and normalized by day 8. The 15% group exhibited no exudation throughout the observation period (score consistently 1).

3.4. Observation of Granulation Tissue in Wistar Rats

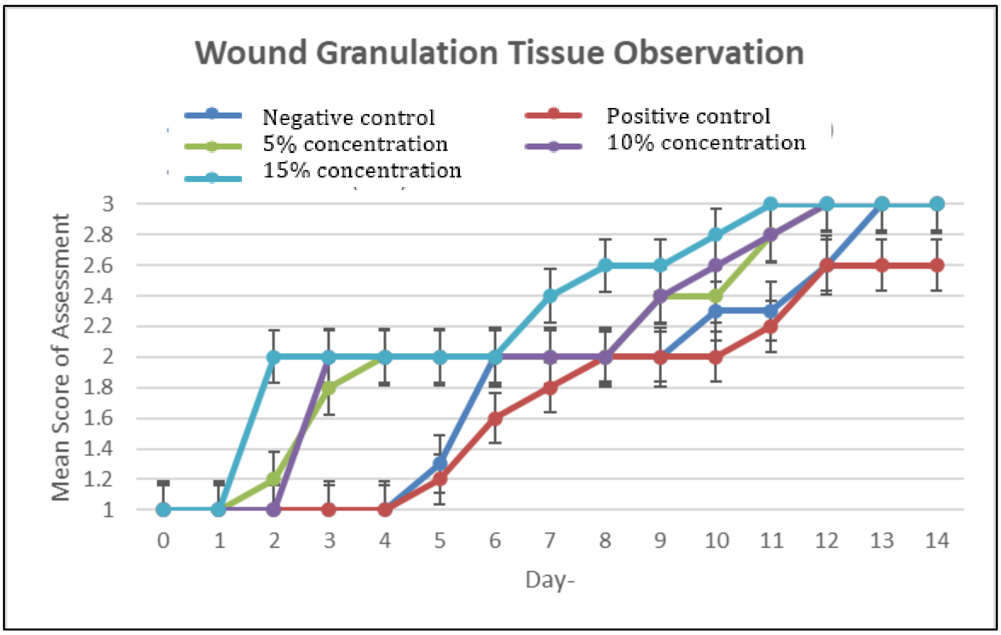

Figure 4 Wound Granulation Tissue Observation in Wistar Rats

Granulation tissue formation progressed at varying rates across groups. The negative control demonstrated the slowest healing, reaching a score of 3 (fully granulated) only on days 13–14. The positive control showed slightly better progress, reaching 2.6 at the end of observation. The 5% and 10% treatments exhibited faster granulation, reaching score 3 by day 12. The 15% treatment group achieved the fastest granulation, with significant improvement starting from day 2 and attaining a maximum score (3) by day 11.

3.5. Observation of Wound Length in Wistar Rats

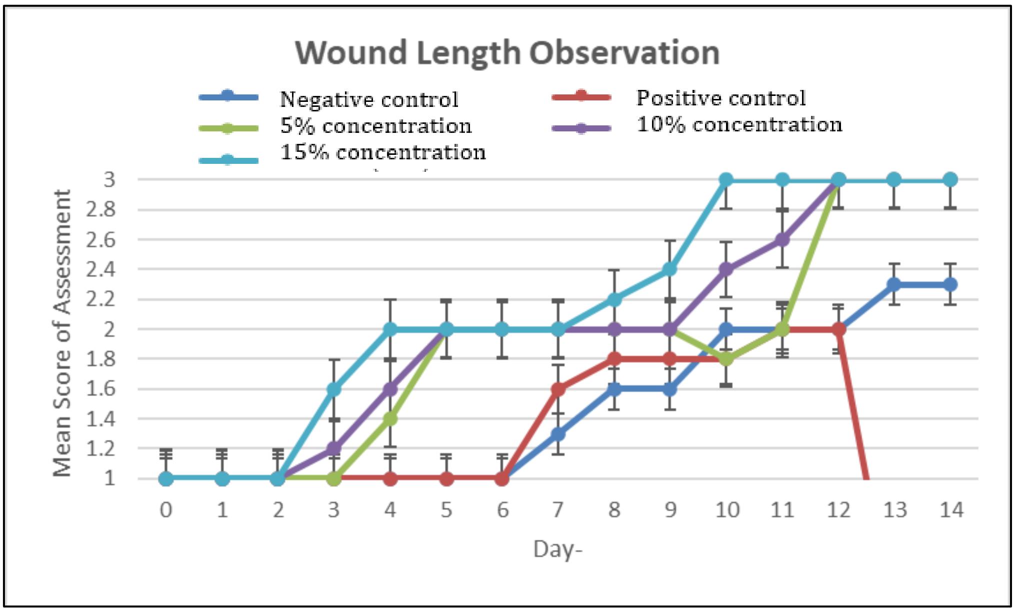

Figure 5 Wound Length Observation in Wistar Rats

Observation of wound length showed varying degrees of contraction among the groups. In the negative control group, wound contraction occurred most slowly, with the wound reaching a score of 2 (1–2.9 cm) on day 10 and remaining at that level until the end of the observation period without achieving the maximum score (3). The positive control group demonstrated slightly better results, reaching a final score of 2.4 on day 14. In contrast, the treatment groups exhibited faster wound healing. The 5% clove leaf oil ointment group began to show improvement on day 4 (score 1.4), reached score 2 on day 5, and achieved the maximum score (3) on day 12. The 10% treatment group showed significant progress starting from day 4 (score 1.2), reached score 2 on day 5, and achieved score 3 on day 12. Meanwhile, the 15% treatment group demonstrated the fastest wound contraction, achieving the maximum score (3 = 0–0.9 cm) as early as day 10..

Table 1 Kruskal–Wallis Test Results for Wound Healing Variables in Wistar Rats

No	Variable	P-Value
1	Wound Redness	0.000
2	Wound Edema	0.000
3	Wound Exudate	0.001
4	Wound Granulation Tissue	0.000
5	Wound Length	0.000

The Kruskal–Wallis test showed that all study variables (wound redness, edema, wound exudate, granulation tissue, and wound length) exhibited statistically significant differences among the treatment groups ($p < 0.05$).

Table 2 Results of the Dunn Post Hoc Test for Wound Healing Variables in Wistar Rats

No	Variable	Group Compared	P-Value
1	Wound Redness	Treatment 15% – Negative Control	0.000
		Treatment 15% – Positive Control	0.000
		Treatment 10% – Negative Control	0.003
		Treatment 10% – Positive Control	0.004
		Treatment 5% – Negative Control	0.028
2	Wound Edema	Treatment 15% – Positive Control	0.000
		Treatment 10% – Positive Control	0.000
		Treatment 5% – Positive Control	0.000
		Negative Control – Positive Control	0.000
3	Wound Exudate	Treatment 15% – Positive Control	0.000
		Treatment 10% – Positive Control	0.002
		Treatment 5% – Positive Control	0.017
		Negative Control – Positive Control	0.022
4	Wound Granulation Tissue	Treatment 5% – Positive Control	0.002
		Treatment 10% – Positive Control	0.001
		Treatment 15% – Negative Control	0.002
		Treatment 15% – Positive Control	0.000
5	Wound Length	Treatment 5% – Negative Control	0.001
		Treatment 5% – Positive Control	0.000
		Treatment 10% – Negative Control	0.000
		Treatment 10% – Positive Control	0.000
		Treatment 15% – Negative Control	0.000
		Treatment 15% – Positive Control	0.000

Based on the Dunn Post Hoc test, all wound healing parameters including redness, edema, exudate, granulation tissue formation, and wound length showed statistically significant differences among the treatment and control groups ($p < 0.05$).

4. Discussion

Incisional wound healing is a complex biological process involving several overlapping phases: hemostasis, inflammation, proliferation, and remodeling. The clove leaf oil extract (*Syzygium aromaticum*) contains various bioactive compounds that play crucial roles in accelerating and modulating wound healing, particularly during the inflammatory and proliferative phases. The major constituents of clove leaf oil eugenol, β-caryophyllene, acetyleugenol, α-cadinol, caryophyllene oxide, and limonene contribute significantly to its therapeutic potential. The inflammatory phase is characterized by the activation of the innate immune system, with classical signs such as redness, edema, and exudation. These are part of the body's natural defense mechanism to clear pathogens and cellular debris from the wound area. This phase is followed by the proliferative stage, which includes granulation tissue formation, angiogenesis, and re-epithelialization. The final remodeling stage focuses on collagen maturation and strengthening of the new tissue structure [18]. This discussion focuses on macroscopic parameters observed during the healing process in Wistar rats namely redness, edema, exudate formation, granulation tissue, and wound length.

4.1. Wound Redness

Redness represents an acute inflammatory response resulting from vasodilation and increased local blood flow following tissue injury. In this study, redness appeared in all groups on the first day, but differences emerged in the rate of resolution. The 15% clove oil group showed the fastest reduction, reaching a score of 1 by day 2. The 10% and 5% groups achieved the same score by days 3 and 4, respectively, while the negative control (0.9% NaCl) showed resolution only by day 6. The positive control (10% povidone iodine) failed to reach complete resolution, maintaining a score of 1.4 until the end.

These findings indicate that topical clove leaf oil significantly accelerated the resolution of early inflammatory responses, particularly at 15% concentration. This effect is supported by its pharmacological properties: povidone iodine, though effective as a broad-spectrum antiseptic, can cause tissue irritation and delay cell regeneration due to the absence of anti-inflammatory action. In contrast, eugenol, flavonoids, and tannins in clove oil exert multifactorial benefits. Eugenol inhibits COX-2 and reduces prostaglandin synthesis; flavonoids suppress pro-inflammatory cytokines (TNF-α, IL-1β, IL-6); and tannins limit leukocyte infiltration. Moreover, β-caryophyllene interacts with the endocannabinoid system to reduce inflammation and pain [19], while α-cadinol exhibits antimicrobial and anti-inflammatory effects (Kubo et al., 1998). Previous studies confirm these results, showing that clove extract accelerates inflammatory resolution [1,16] . International evidence also supports eugenol's ability to reduce oxidative stress, modulate NF-κB signaling, and alleviate erythema [21-23]

4.2. Wound Edema

Edema is a hallmark of the inflammatory phase and reflects the vascular response to tissue injury. It occurs due to increased capillary permeability and accumulation of fluid and proteins in the interstitial space, mediated by histamine, prostaglandins, and bradykinin (Gonzalez et al., 2016). Observation results showed that the treatment groups (5%, 10%, 15%) and the negative control did not exhibit edema throughout the study (score = 1). Conversely, the positive control (povidone iodine 10%) displayed mild-to-moderate edema (scores 1.4–1.6) from days 2–7, which persisted until the end.

The absence of edema in the treatment groups is attributed to clove oil's anti-inflammatory and antioxidant properties. Eugenol reduces capillary permeability by inhibiting COX-2/LOX pathways, flavonoids suppress histamine release, and tannins act as astringents that limit leukocyte infiltration. Meanwhile, povidone iodine's cytotoxic effect on fibroblasts and keratinocytes prolongs inflammation and increases fluid accumulation. Previous studies corroborate these findings Utami et al. [2] demonstrated the anti-inflammatory activity of clove extract, while Thomas et al. [24] reported povidone iodine delays fibroblast contraction and migration.

4.3. Wound Exudate

Exudation is a key indicator of inflammation, representing fluid leakage due to increased vascular permeability. The exudate contains plasma proteins, leukocytes, and inflammatory mediators that cleanse the wound bed and prevent microbial colonization [11]. However, excessive exudation delays healing and increases infection risk.

The 15% clove oil group showed no exudate throughout observation (score = 1). The 10% and 5% groups exhibited mild exudation (score 1.4–1.6) between days 4–6, returning to normal by day 8. In contrast, the negative control showed similar mild exudation (score 1.6) on days 4–7, and the positive control displayed higher exudation (score 2) on days 2–6, persisting until the end.

The effectiveness of clove oil in reducing exudate is linked to its antibacterial and anti-inflammatory actions. Eugenol inhibits prostaglandin synthesis, stabilizes cell membranes, and decreases vascular permeability [8,21]. Notably, no pus or microbial contamination was found in any group, indicating sterile wound maintenance. These results are consistent with Ngajow et al. [3], Sani et al.[4] , and Anggitasari et al. [16], and further supported by international studies showing eugenol reduces biofilm formation and inflammatory mediators [20,25-26].

4.4. Granulation Tissue

Granulation tissue formation marks the transition from inflammation to active healing. It involves fibroblast proliferation, ECM deposition, angiogenesis, and collagen synthesis [27]. Macroscopically, granulation tissue appears pink, moist, and fragile, reflecting new capillary growth and tissue regeneration [18].

The 15% clove oil group showed the fastest granulation response, increasing from day 2 and reaching maximum score (3) by day 11. The 10% and 5% groups achieved the same by day 12, while the negative control reached it on days 13–14. The positive control only reached 2.6 at the end.

This acceleration correlates with eugenol and flavonoid activity that stimulates fibroblast proliferation, angiogenesis, and collagen deposition. Chandini et al. [6] and Wael et al [.1] confirmed that clove oil accelerates the proliferative phase. International studies show eugenol enhances collagen deposition via VEGF and TGF-β regulation [28-29]. Additionally, acetyleugenol acts as an antimicrobial and antioxidant protecting new tissue from oxidative damage [30], while caryophyllene oxide and α-cadinol provide antifungal and antibacterial effects [31].

4.5. Wound Length

Wound length reduction reflects tissue regeneration and healing efficiency. In this study, the clove oil groups exhibited greater wound contraction than controls. The 15% group reached a score of 2 (1–2.9 cm) on day 5 and maximum healing (score 3, 0–0.9 cm) by day 10. The 10% and 5% groups achieved full closure by day 12, while the positive control plateaued at 2.4, and the negative control remained at 2 until the end.

This improvement is due to fibroblast stimulation, collagen synthesis, and re-epithelialization by eugenol, flavonoids, and tannins. Alzohairy [7] reported that eugenol enhances wound contraction through fibroblast activation, while Anggitasari et al. [16] demonstrated similar results in rats. Globally, eugenol has been shown to promote keratinocyte proliferation and tissue remodeling [15,32]. Limonene, another clove component, acts as an antioxidant and antimicrobial, protecting developing tissue from free radical damage [19].

Conversely, povidone iodine exhibited delayed wound contraction due to its cytotoxic effects on fibroblasts and keratinocytes, impairing collagen synthesis and angiogenesis [12,33]

5. Conclusion

This study demonstrated that clove leaf oil (*Syzygium aromaticum*) accelerates incisional wound healing through the reduction of redness, edema, and exudation, and enhancement of granulation tissue formation and wound contraction. Among all groups, the 15% concentration exhibited the most optimal results.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no competing interests related to this research.

Statement of ethical approval

This research is approved ethically by ethical commision health research Wijaya Kusuma Surabaya University with the number 30/SLE/FK/UWKS/2025 at January 31th 2025.

Statement of informed consent

No informed consent is needed because there are no human participant in this study

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