In vivo evaluation of *Pandanus tectorius* fruit ethanol extract gel on skin incision wound healing

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Abstract. *Pandanus tectorius* is a plant belonging to the Pandanaceae family. *Pandanus tectorius* fruit contains bioactive compounds with antioxidant and anti-inflammatory properties that may accelerate wound healing. However, scientific evidence regarding its efficacy in incision wound repair remains limited. This study evaluated the wound-healing activity of *Pandanus tectorius* fruit ethanol extract gel at concentrations of 10%, 20%, and 30% in male white rats (*Rattus norvegicus*). Wound length was measured on day 10 and analyzed using the Kruskal–Wallis test, followed by Mann–Whitney post-hoc comparisons. Includes organoleptic evaluation, non-specific parameter testing, homogeneity assessment, spreadability measurement test, and pH analysis. The data were non-normally distributed (Shapiro–Wilk, $p < 0.05$). The Kruskal–Wallis test showed a significant difference among groups ($p = 0.031$). The 20% extract concentration had the shortest median wound length (0.81 mm; Q1–Q3: 0.75–1.04) and the smallest IQR (0.29), indicating the most consistent healing, while the 30% concentration had a median of 0.93 mm. In contrast, the 10% concentration (median 1.26 mm; IQR 1.25) had a less consistent effect. The result of organoleptic evaluation shows that the semi-solid mixture is yellowish-white at 10% concentration, orange-yellow at 20%, and brown at 30%, it also has a smell that is typical of extracts. *P. tectorius* ethanol extract gel, particularly at 20% and 30%, significantly accelerated wound healing through antioxidant and collagen-stimulating mechanisms. Future studies should include multiple observation points and histopathological evaluation to validate its clinical potential as a natural wound-healing agent.

1 Introduction

Wound healing is a complex, sequential biological process that restores the skin's structure following damage from many factors, such as chemicals, friction, or radiation. Open wounds, including incised wounds, exhibit distinct lacerations and external hemorrhage. Poorly healed or chronic wounds significantly increase the global health burden, resulting in an estimated 5 million deaths each year. Periodical application of topical antibiotics for open

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wounds causes considerable challenges in clinical practice, leading to a high risk of antimicrobial resistance (AMR) and skin inflammation [1]. Additionally, approximately 80% of the global population relies on traditional remedies for wound management, according to the World Health Organization (WHO) Investigation of natural plant extracts, especially those containing active compounds such as flavonoids, is necessary to improve the healing process, reduce complications, and provide a safe, effective, and sustainable alternative to conventional antimicrobial agents [2, 3].

Pandanus tectorius fruit has recently attracted scientific interest due to its remarkable and strong free radical–scavenging activity and also rich phytochemical composition. It contains a wide range of bioactive compounds, including flavonoids (naringenin, tangeretin, and chrysin), triterpenoids, saponins, glycosides, and phenolic compounds [4, 5]. Among these, naringenin has been demonstrated to enhance fibroblast migration, collagen formation, and also angiogenesis by modulating the TGF-β and VEGF signaling pathways [6]. Tangeretin demonstrates strong anti-inflammatory properties by inhibiting COX-2 and TNF-α expression [7]. These molecular mechanisms collectively support wound healing, re-epithelialization, and also extracellular matrix remodeling, suggesting that *Pandanus tectorius* could accelerate the healing cascade via antioxidant and anti-inflammatory pathways. Compared to other tropical medicinal plants that are commonly used for wound healing, such as *Centella asiatica* and Aloe vera, *Pandanus tectorius* exhibits a unique combination of bioactive flavonoids, including tangeretin and naringenin, that provide synergistic antioxidant and anti-inflammatory effects. Moreover, its fruit extract showed higher total phenolic content and stronger free radical scavenging activity than the leaves or those of other comparable plant species, which indicates superior therapeutic potential for tissue repair.

Although *Pandanus tectorius* has been investigated for its pharmacological potential, studies have shown that its ethanol-based gel formulation for in vivo wound healing remains limited. Previous reports also primarily focused on methanol extracts or in vitro antioxidant activity, leaving a gap in evidence regarding the efficacy, stability, and biocompatibility of ethanol-extracted formulations. Ethanol, as a green solvent, enables the efficient isolation of both polar and non-polar compounds and aligns with eco-friendly pharmaceutical principles [8].

Therefore, this study has a significant purpose to evaluate the in vivo wound-healing efficacy of an ethanol extract gel of *Pandanus tectorius* fruit on incisional wounds in *Rattus norvegicus*. The methodology includes macroscopic and organoleptic evaluation, non-specific parameter testing, homogeneity assessment, spreadability measurement test, and pH analysis to establish a scientific basis for utilizing this natural resource. We hypothesize that, in this case, topical application of *Pandanus tectorius* fruit ethanol extract gel enhances wound healing through antioxidant and anti-inflammatory mechanisms mediated by flavonoids such as naringenin and tangeretin. This research further contributes to the Sustainable Development Goals (SDG 3: Good Health and Well-being; SDG 15: Life on Land) by promoting the therapeutic potential of locally sourced, natural plant-based products.

2 Material and methods

2.1 Research location and time

This research was conducted at the Biomolecular Laboratory of Hang Tuah University, Surabaya, and the Pharmacy Laboratory of Hang Tuah University, Surabaya.

2.2 Equipment and materials

The equipment used in this study included: maintenance cages, treatment cages, food and water containers, analytical scales, scalpels, handscoon, razors, gel containers, and Heidolph Rotary Evaporators.

The materials used in this study included: white rats, rat food and water, *Pandanus tectorius* fruit, 96% ethanol solution, water, Bioplacenton ge, gel base, CMC-Na, glycerin, benzoic acid, and ketamine 10% mg/kg.

2.3 Research type and design

This research was an experimental study using a post-test control group design, where all aspects were homogeneous except for the treatment. The test animals were divided into 5 treatment groups:

Treatment 1: Given 10% *Pandanus tectorius* fruit ethanol extract gel
Treatment 2: Given 20% *Pandanus tectorius* fruit ethanol extract gel
Treatment 3: Given 30% *Pandanus tectorius* fruit ethanol extract gel

2.4 Research procedure/implementation

2.4.1 Pandanus tectorius fruit extract preparation

Preparation began by thoroughly cleaning and cutting the *Pandanus tectorius* fruit into small pieces. After that, the sample was oven-dried and then subjected to extraction. The extraction was carried out by macerating for 3 × 24 hours. After the maceration, the mixture was filtered and evaporated to obtain a thick extract.

2.4.2 Test animal preparation

All experimental procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of the Faculty of Medicine, Universitas Hang Tuah, Surabaya, Indonesia, under (Approval No. I/060/UHT.KEPK.03/VIII/2025). The study was conducted in accordance with the ethical principles outlined in the ARRIVE guidelines and the Declaration of Helsinki for animal research.

For the preparation of test animals, *Rattus norvegicus* were selected as the experimental subjects. The animals were acclimatized to the laboratory environment for 1 week. Next, they were weighed and subsequently divided into 5 groups, with 6 white rats in each group.

2.4.3 Pandanus tectorius fruit extract gel formulation

In this research, the next stage involved formulating *Pandanus tectorius* fruit extract gels with extract concentrations of 10%, 20%, and 30%. These gels were applied twice daily for a 10-day observation period. The dosage calculation for each concentration is as follows:

Formulation of 10% *Pandanus tectorius Fruit* ethanol extract gel

R/	Extract	20 g
	CMC Na	3.5 g
	Benzoic acid	0.2 g
	Glycerin	5 g
	Aquadest	ad 200 g

Formulation of 20% *Pandanus tectorius Fruit* ethanol extract gel

R/	Extract	40 g
	CMC Na	3.5 g
	Benzoic acid	0.2 g
	Glycerin	5 g
	Aquadest	ad 200 g

Formulation of 30% *Pandanus tectorius Fruit* ethanol extract gel

R/	Extract	60 g
	CMC Na	3.5 g
	Benzoic acid	0.2 g
	Glycerin	5 g
	Aquadest	ad 200 g

The total mass of each gel formulation was adjusted to 200 g. The ethanol extract of *Pandanus tectorius* fruit was incorporated at concentrations of **10%, 20%, and 30% w/w**, corresponding to **20 g, 40 g, and 60 g of extract**, respectively, mixed with the gel base to reach a total weight of 200 g. This clarification ensures that the stated extract percentages refer to weight per weight (w/w) concentrations relative to the final formulation mass.

2.4.4 Gel preparation

The ingredients were weighed according to the formula. A 10% extract was dissolved in a portion of water heated to 75°C. Water was added with continuous stirring until a gel formed. The formed gel was then stored at room temperature overnight. The same procedure was performed for the 20% and 30% extracts.

2.4.5 Gel preparation stability test

Gel stability tests were conducted before and after storage. Test parameters included organoleptic observations, spreadability tests, and homogeneity tests.

2.4.6 Test animal treatment

For the preparation of animal test, *Rattus norvegicus* were selected as the experimental subjects. The animals were acclimatized to the laboratory environment for a week under controlled temperature and humidity. Next, they were weighed and divided into five groups, with six white rats per group. They were anesthetized using ketamine-xylazine at a dose of 5-10 mg/kgBW. The incision wound was created under aseptic conditions after shaving and disinfecting the dorsal skin of the rats using 70% ethanol. A standardized cut measuring approximately 2 cm in length and 2 mm in depth was made using a sterile scalpel. The wounds were then treated with *Pandanus tectorius* fruit extract gel at concentrations of 10%, 20%, and 30%, as well as a positive control (bioplacenton gel), and a negative control (gel base). The wound length was then measured on day 10. Postoperative care included individual cage separation to prevent cannibalism and cross-licking among the rats. The wounds were observed daily, and all animals were provided with standard feed and water ad libitum during the experimental period.

Bioplacenton gel was used as a positive control. It contains placenta extract (0.1 g) and neomycin sulfate (0.5 g) per 100 g of gel, which function as a tissue-regenerating agent and a topical antibiotic, respectively. The placenta extract promotes epithelial regeneration and fibroblast proliferation through growth factor stimulation, while neomycin sulfate prevents secondary bacterial infection at the wound site. Therefore, Bioplacenton was selected as a comparator to evaluate the wound-healing efficacy of *Pandanus tectorius* fruit extract gel.

2.4.7 Observation of incision wound healing

Incision wound length measurements began on day 10 using a vernier caliper for macroscopic assessment. The analysis focused on the distribution of wound length data, presented as median (Q1–Q3) and interquartile range (IQR), due to the non-normal distribution confirmed by the Shapiro–Wilk test ($p < 0.05$). The use of boxplots allowed for a clearer comparison of wound-healing performance among treatment groups by illustrating the variability and central tendency of wound lengths. This method provided a more accurate and representative evaluation of healing consistency and treatment efficacy across the different concentrations *of Pandanus tectorius* fruit extract.

2.4.8 Data analysis

To support the differences in wound healing in *Rattus norvegicus*, the data were analyzed using the Kruskal-Wallis test, which indicated statistically significant differences ($p = 0{,}031$).

3 Results

3.1 *Pandanus tectorius* fruit ethanol extract test gel

A filtrate was obtained through maceration with 96% ethanol, followed by filtration and evaporation, yielding 120 grams of concentrated *Pandanus tectorius* fruit extract.

After extraction, the *Pandanus tectorius* fruit ethanol extract was incorporated into a gel formulation. Pre-mixing sodium carboxymethyl cellulose (Na-CMC) with distilled water ensured uniform integration of benzoic acid, glycerin, and the ethanol extract.

3.2 Gel base formulation

The gel base, serving as the negative control, contained Na-CMC, benzoic acid, glycerin, and distilled water. Na-CMC, benzoic acid, and glycerin dissolved completely in distilled water, resulting in homogeneous mixing without granule formation.

3.3 Organoleptic observation results and non-specific parameters

Table 1 shows the color differences among gel preparations of FI, FII, and FIII, which contain 20 grams for the FI, 40 grams for the FII, and 60 grams for the FIII. The table also shows the information on the shape, odor, and color of the gels. Table 2 summarizes the non-specific parameter tests, including ash content, moisture content, fat content, and protein content.

Table 1. Results of organoleptic test observations of preparations.

Formula	Shape	Color	Odor
F I (10%)	Gel	Yellowish White	Typical Extract
F II (20%)	Gel	Yellow Orange	Typical Extract
F III (30%)	Gel	Brown	Typical Extract

Table 2. Non-specific parameter test results.

Non-Spesific Parameter	Result (%)
Ash Content	0,97
Water Content	0,29
Fat Content	0,78
Protein Content	6,50

Ash content determination provides an overview of mineral content, both internal and external, from the initial stages through the process of forming a concentrated extract. Ash content analysis is performed by heating the material at high temperatures, causing organic compounds and their derivatives to decompose and evaporate, leaving residues in the form of mineral elements and inorganic compounds.

Moisture content is determined using a gravimetric method, which aims to determine the water content in the material. This parameter is closely related to the level of purity and the potential for contamination in the sample.

The measurement results showed a fat content of 0.78%, indicating a low energy contribution from the lipid component, which could be relevant in the formulation of low-fat products. On the other hand, the protein was the dominant component at 6.5% The relatively high protein content indicates the potential for significant nutritional value, especially in the context of food ingredients or biological products [9].

3.4 Observation results: Homogeneity test of preparations

The preparations exhibited the homogeneity, indicated by the absence of coarse grains when applied to a transparent glass sheet. Each formula met the gel standard by forming a uniform composition without clumping.

3.5 Observation results: Spreadability test of preparations

Table 3 shows the spreadability measurements. Before storage, the results are : 8.9 cm for FI, 10.4 cm for FII, and 11 cm for FIII.

Table 3. Results of the spreadability test.

	F I	F II	F III
No Load	8,9 cm	10,4 cm	11 cm
2 grams of Load	9,1 cm	10,6 cm	11,1 cm

Spreadability test results demonstrated a clear increase in spread diameter from FI to FII, indicating that higher concentrations of *Pandanus tectorius* fruit extract corresponded to lower gel viscosity. Group of the FI exhibited the lowest spreadability (8.9-9.1 cm), whereas the group of the FIII showed the highest spreadability (11.0-11.1 cm), which may exceed the ideal range of 5-10 cm and suggest an excessively fluid consistency.

The application of the 2 grams of load resulted in a low increase in spreadability for all three formulations (0.1-0.2 cm), indicating favorable thixotropic properties and structural

stability under mechanical stress. These data suggest that FI possessed the most optimal rheological characteristics, providing adequate spreadability for application and sufficient viscosity for retention at the target site.

3.6 pH test observation results

pH measurements were performed using a pH meter. The average pH values for all gel formulations were within the standard range of 4.5 to 6.5. Detailed pH test results are presented in Table 4.

Table 4. pH test results.

Formula	pH
F I (10%)	5,553
F II (20%)	6,315
F III (30%)	6,279

The pH test results show that all gel formulations (FI, FII, and FIII) exhibited pH values within the optimal range for topical application, specifically between 5.553 and 6.315. These values fall within the normal limits tolerated by human skin, which is ideally between pH 4.5 and 6.5. Maintaining this range minimizes the risk of skin irritation, preserves formulation stability, and supports the absorption of active ingredients. FI, with a pH of 5.553, most closely matches the physiological pH of healthy skin and is therefore considered to have the highest biocompatibility. The increase of the extract concentration from 10% of the FI to 20% of the FII and 30% of the FIII resulted in a corresponding increase in pH. The results of the pH test show FIII (pH 6.315) exhibiting the highest value. Despite these differences, all formulations remain safe and suitable for cosmetic and pharmaceutical use on the skin without disrupting the skin's acid mantle [10].

3.7 Wound length measurement results

Wound length data were analyzed using nonparametric tests because the distribution was non-normal, as confirmed by the Shapiro–Wilk test ($p < 0.05$). The Kruskal–Wallis test also identified a statistically significant difference in median wound length among the five experimental groups (Control Negative, Control Positive, Treatment Group 1, Treatment Group 2, and Treatment Group 3) with the value result ($H = 10.666$; $df = 4$; $p = 0.031$). These results demonstrate that at least one treatment group exhibited a significantly different wound closure rate following administration of the ethanol extract of *Pandanus tectorius* fruit. The pairwise comparisons were conducted using the Mann–Whitney U test, which identified a significant difference between the positive control group (Control Positive) and treatment group 3 ($p = 0.004$). The result is that there were no significant differences observed among the other group comparisons ($p > 0.05$). The treatment group 3, which received the highest concentration of *Pandanus* tectorius extract, demonstrated superior wound healing, as indicated by shorter wound length compared to the positive control group.

The analysis of wound length showed that treatment with the ethanolic extract of *Pandanus tectorius* influenced wound-healing outcomes across groups. The 20% extract concentration showed the shortest median wound length (0.81 mm; Q1–Q3: 0.75–1.04) and the smallest interquartile range (0.29) (Table 5), indicating the best and most consistent healing response. The 10% concentration showed the greatest variability (IQR 1.25),

indicating it was not consistently effective. The 30% concentration had a moderate effect, which could be due to it being too high or to slight irritation of the tissue. The boxplot visualization confirmed these results, showing that the 20% group had the most limited distribution and the lowest mean (Fig. 1). The results showed that the exact amount of *Pandanus tectorius* extract helps wounds heal faster by stimulating fibroblast activity, collagen production, and antioxidant defense mechanisms in tissue repair. This happened because the extract contains bioactive compounds like flavonoids, tannins, and saponins.

Table 5. Median, quartile range (Q1–Q3), and interquartile range (IQR) for each treatment group.

Treatment Group	Median (Q1-Q3)	IQR
Control (-)	1.34 (1.23–1.45)	0.22
Control (+)	1.05 (0.55–1.30)	0.75
Treatment Group 1	1.26 (0.10–1.35)	1.25
Treatment Group 2	0.81 (0.75–1.04)	0.29
Treatment Group 3	0.93 (0.50–1.07)	0.57

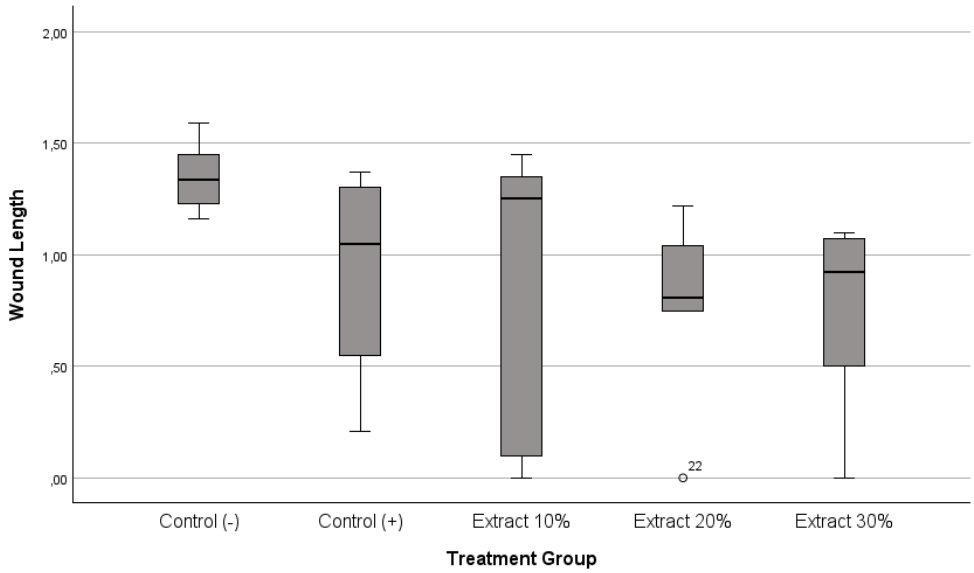

Fig. 1. Wound healing boxplot

The enhanced wound-healing observed in the 20% and 30% treatment group is attributed to the presence of bioactive compounds such as flavonoids, tannins, and saponins in the *Pandanus tectorius* fruit extract. These compounds act synergistically as antioxidants, anti-inflammatory agents, and stimulators of collagen synthesis. Their antioxidant activity helps neutralize free radicals at the wound site, thereby reducing the inflammatory response and promoting fibroblast proliferation, collagen deposition, and epithelial regeneration. As a result, the healing process proceeds more rapidly and consistently across individuals [4-6].

These results align with the previous research that has been done by Bâldea et al. [6], which reported that a gel preparation containing bioactive compounds with high antioxidant

properties can increase collagen synthesis and accelerate wound tissue regeneration. Therefore, it can be concluded that the ethanol extract gel from *Pandanus tectorius* fruit, particularly at concentrations of 20% demonstrated the optimal effectiveness in accelerating the healing process of incision wounds in white rats (*Rattus norvegicus*).

4 Discussion

The findings of this study demonstrate that the ethanol extract gel of *Pandanus tectorius* fruit promotes significant wound healing in rats, as evidenced by the 20% extract concentration showed the shortest median wound length (0.81 mm; Q1–Q3: 0.75–1.04) and the smallest interquartile range (0.29), indicating the best and most consistent healing response. Kruskal–Wallis test confirmed there is a significant difference among groups ($p = 0.031$), and the Mann–Whitney post hoc analysis identified that the 30% concentration achieved notably greater wound closure compared to the positive control.

The accelerated wound-healing effect is mediated by the synergistic activity of bioactive compounds in *Pandanus tectorius*, including flavonoids (naringenin, tangeretin), saponins, and terpenoids. These compounds accelerate the proliferative phase of wound healing through multiple mechanisms [5]. Flavonoids act as antioxidants that neutralize reactive oxygen species (ROS), thereby reducing oxidative stress and preventing further tissue damage [11]. According to Yen et al. [12], flavonoid-rich extracts stimulate fibroblast proliferation and collagen synthesis through activation of TGF-β and VEGF signaling pathways. Similarly, naringenin enhances fibroblast migration and deposition of extracellular matrix, while tangeretin downregulates COX-2 and TNF-α expression, reducing inflammation and edema [13].

The observed decrease in median wound length from 1.26 mm (10%) to 0.81 mm (20%) and 0.93 mm (30%) indicates a concentration-dependent improvement in wound healing, suggesting that higher concentrations of *Pandanus tectorius*extract enhance tissue repair up to an optimal level. These findings align with previous studies by Bâldea et al. [6], who demonstrated that plant-based gels with high antioxidant content showed superior collagen formation and epithelialization, thereby accelerating wound tissue regeneration. Moreover, the appropriate pH (5.5–6.3) and uniform gel texture ensure its biocompatibility and facilitate the penetration of active compounds.

However, the study itself has several limitations. Wound length was measured only at day 10, providing a single endpoint observation. Wound healing is a dynamic process involving inflammation, proliferation, and remodeling phases; thus, future studies should include multiple observation days (e.g., 0, 3, 7, 10, 14) to evaluate wound contraction kinetics. The relatively high inter-animal variability, reflected in large interquartile ranges, may also have influenced statistical outcomes. Moreover, although the 30% formulation showed the best result, the difference was not statistically significant compared with all groups, so it should be interpreted as a positive trend rather than conclusive superiority.

As a whole, the results indicate that *Pandanus tectorius* fruit ethanol extract gel exerts wound-healing activity through its antioxidant and anti-inflammatory properties, thereby enhancing epithelialization and fibroblast proliferation. Furthermore, in future in vivo and molecular studies focusing on collagen density, growth factor expression, and histopathological assessment are necessary to elucidate the mechanisms in detail and confirm these preliminary findings.

5 Conclusions

In conclusion, this study demonstrates that the ethanol extract gel of *Pandanus tectorius* fruit, particularly at 20% concentrations of extract showed the shortest median wound length (0.81 mm; Q1–Q3: 0.75–1.04) and the smallest interquartile range (0.29) and 30%, especially in comparison to the positive control. The 30% concentration was the most effective in accelerating the wound healing process, as indicated by reduced wound length and improved closure rates. The observed effects are likely mediated by the synergistic activity of bioactive compounds such as flavonoids, tannins, and saponins, which promote fibroblast proliferation, collagen synthesis, and also antioxidant defense, as a result of accelerating tissue regeneration. This research contributes to the growing evidence supporting the therapeutic potential of *Pandanus tectorius* as a natural wound-healing agent. However, the study is limited by wound measurements taken only at a single time point (day 10) and the lack of histopathological analysis to confirm tissue regeneration at the microscopic level. Future studies should include longitudinal wound assessments, histopathological and molecular analyses of collagen formation and growth factor expressionns to validate and optimize the clinical application of *Pandanus tectorius* extract in wound management.

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