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Wound Healing Activity of Ethyl Acetate Extract of *Piper crocatum* Leaves Combined with *Geniotrigona thoracica* Propolis

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ABSTRACT

Wounds are a common health issue caused by various types of injuries, burns, or infections. Although several wound healing methods are available, many rely on synthetic chemicals that may have side effects. Therefore, there is a need for safer and more effective alternatives. *Piper crocatum* leaves and *Geniotrigona thoracica* propolis are known to contain flavonoid compounds that have the potential to accelerate wound healing naturally. However, limited research has explored the combination of these two substances to enhance wound healing effectiveness. This study aims to provide scientific evidence regarding the potential of the combination of ethyl acetate extract of *P. crocatum* leaves and *G. thoracica* propolis as a more effective, safe, and natural alternative for wound healing treatment. The research involved creating wounds on the backs of male rabbits, which were divided into seven groups. Each group received different treatments, including ethyl acetate extract of *P. crocatum* leaves and *G. thoracica* propolis, combinations of both (P1-P5), and a positive control (bioplacenton), while the negative control received no treatment. The preparations were applied topically, and wound healing was monitored daily. The results indicate that the combination of ethyl acetate extract of *P. crocatum* leaves and *G. thoracica* propolis (1:3) promoted faster wound healing compared to other combination.

Keywords : *Piper crocatum*, *G. thoracica*, Wounds, Rabbits

INTRODUCTION

The skin serves as a highly effective barrier against the invasion of bacteria and other foreign bodies. However, skin tissue can be damaged or lost due to various factors, including trauma, temperature changes, chemical exposure, explosions, electric shocks, and animal bites, resulting in wounds. Wounds are disruptions to tissue function that can lead to a loss of the skin's protective role and cause damage to other tissues (Zahran et al., 2022). Wound healing is the process through which the body repairs damaged tissue to restore its structure and function. If left untreated, wounds may become infected, bleed, and require proper wound care. Effective wound care often involves the use of compounds that possess wound-healing properties, such as flavonoids.

In Indonesia, medicinal herbs from plants have been widely utilized for their therapeutic properties. These plants contain secondary

metabolites, such as flavonoids, saponins, alkaloids, steroids, triterpenoids, and tannins, which are known to have medicinal benefits (Khafid et al., 2023). Red betel (*Piper crocatum*) contains secondary metabolites, including flavonoids, alkaloids, tannins, lignan and saponins, which have been found to contribute to various health benefits (Aisyiyah et al., 2021; Faizal & Alifah, 2023). Specifically, tannins and saponins in red betel leaves play a significant role in stimulating collagen formation, a key component in the wound healing process (Widyawati et al., 2021).

Flavonoids can be extracted from plants through maceration, a process that uses a solvent to dissolve the active compounds from plant material. This method is effective in obtaining compounds that are heat-sensitive or not easily extracted by other means (Soleha et al., 2018). Ethyl acetate is commonly used as the solvent in this process due to its semi-polar nature, which allows it to effectively extract both polar and non-polar flavonoid compounds

(Kanifah et al., 2015). Flavonoids are known for their anti-inflammatory and antioxidant properties, which contribute to their wound healing potential. Antioxidants, in particular, can prevent cellular damage caused by oxidative stress, further supporting the healing process.

In addition to flavonoids, bee propolis from *Geniotrigona thoracica* has shown promise in wound healing. Propolis contains bioactive compounds rich in flavonoids and phenolic compounds, which are known to combat free radicals and contribute to tissue repair (Kustiawan, Zulfa, et al., 2022; Segueni et al., 2016). Previous studies have explored the wound healing potential of red betel leaves, such as the combination of red betel leaf extract with soursop leaf extract, which demonstrated improved wound healing efficacy. Other studies have investigated the effectiveness of chitosan emulgel formulations containing red betel leaves extract and binahong leaves extract, which proved successful in treating burn wounds (Fakhruddin et al., 2019; A. J. Pratama & Rolan R, 2016).

However, limited research has focused on the combined effect of ethyl acetate extract of red betel leaves (*Piper crocatum*) and propolis from *Geniotrigona thoracica* in promoting wound healing. Therefore, this study aims to investigate the potential of this combination for enhancing wound healing, filling a gap in the current body of knowledge on natural wound healing therapies.

METHODS

Materials

The materials used in this study include red betel (*Piper crocatum*) leaves, which were identified and verified at the Herbarium Mulawarman, Laboratory of Ecology and Biodiversity Conservation of Tropical Forests, Faculty of Forestry, Mulawarman University, Samarinda, East Kalimantan (No.273/UN/17.4.08/LL/2023). Additionally, propolis from *Geniotrigona thoracica* was obtained from Rumah Sahabat Kelulut, Lempake, Samarinda. This study used rabbits as test animals and has obtained an ethical clearance certificate from the Health Research Ethics Committee, Faculty of Medicine, Universitas

Muhammadiyah Surakarta, with the number 5184/A.1/KEPK-FKUMS/I/2024.

The chemicals employed in the study were 70% ethanol, ethyl acetate, bioplacenton, and various reagents for qualitative phytochemical testing: Wagner's reagent, Mayer's reagent, Dragendorff's reagent, 10% FeCl₃, 5% FeCl₃, and 10% NaOH. These materials were used for extraction, formulation, and analysis throughout the experiment.

Preparation and Extraction of *P. crocatum* Leaves and *G. thoracica* Propolis

The red betel leaves used were taken in Kutai Lama Village, Samarinda, East Kalimantan. All samples obtained must first be washed, dried and blended to powder form and extracted using ethyl acetate solvent and macerated for 3 days and evaporated using a rotary evaporator until a thick extract is obtained (Indrawati et al., 2022).

The propolis used must first be crushed into smaller pieces and then macerated using 96% ethanol and concentrated using a water bath at 60°C until a thick extract is obtained (Y. Pratama & Kustiawan, 2023).

Preparation of The Combination

The *P. crocatum* leaves and *G. thoracica* propolis extract was mixed with several combination (Table 1).

Phytochemical Determination

The test was conducted to determine the phytochemical content in red betel leaves extract and propolis. Phytochemical screening tests were performed based on the method used by Kustiawan (2024), which included testing for alkaloids, flavonoids, phenols, saponins, and tannins.

Wound Healing Determination

Animal preparation and wound healing activity testing refer to Diniatik et al., (2024).

Animal Preparation

The experimental animals used are rabbits. Before the test, rabbits were first kept in a well-ventilated and clean cage and fed twice a day for 7 days.

Table 1. Combination Preparation of *P.crocatum* Leaves Ethyl Acetate Extract and *G.thoracica* Propolis Extract

No.	Formulation	Red betel leaves extract (g)	Propolis extract (g)
1	P ₁	4	0
2	P ₂	0	4
3	P ₃	2	2
4	P ₄	3	1
5	P ₅	1	3

Wound Healing Activity

The treatment of each group is as follows *P. crocatum* leaves, propolis, combination of *P. crocatum* leaves and *G. thoracica* propolis (P1), (P2), (P3), (P4), (P5), negative control without treatment and positive control using bioplacenton. When testing each animal is weighed then numbered and shaved then a wound is made on the rabbit's back using a scalpel then each rabbit is applied topically to the control wound area and test material according to its group. Administration was prepared twice a day every morning and evening for 7-14 days.

Data Analysis

Observations were made by measuring the length of the wound size to see indicators of wound healing speed every day and the research data

obtained were averaged and statistically analyzed using SPSS.

RESULT AND DISCUSSION

Plant Determination

The determination results obtained showed that the plants used in this study were really red betel leaves. The plant identity of red betel leaves is class Magnoliopsida, family Piperaceae, species *Piper crocatum*.

Phytochemical Identification of Samples

The results of phytochemical screening on ethyl acetate extract of *P. crocatum* leaves and *G. thoracica* propolis showed the content of alkaloid, flavonoid, saponin, phenolic, and tannin compounds. The identification results can be seen in Table 2.

Table 2. Secondary Metabolite Results

No.	Compound	Observation Result	
		Red Betel Leaves	Propolis
1	Alkaloid	+	+
2	Flavonoid	+	+
3	Saponin	-	-
4	Phenolic	+	+
5	Tannin	+	+

Description: (+) Positive, (-) Negative

The results of the phytochemical test of *P. crocatum* leaves extract showed positive for alkaloid, flavonoid, phenolic and tannin compounds in accordance with the research of (Jayadi et al., 2023) which states that *P. crocatum* leaves ethyl acetate extract contain alkaloid, flavonoid, saponin, phenolic and tannin compounds, then the phytochemical test of propolis extract contains alkaloid, flavonoid, phenolic and tannin compounds in accordance with the research of Cokro et al., (2023) which states that propolis contains alkaloid, flavonoid, phenolic and tannin compounds.

The *P. crocatum* leaves extract and *G. thoracica* propolis extract do not contain saponins because no foam is formed. This condition proves that the absence of saponin compounds. The foam produced is due to the combination of the structure of the compounds that make up the non-polar sapogenin chain and the polar side chain.

Wound Healing Activity

Activity testing was carried out by first adapting the rabbits for 7 days, using 7 rabbits with 3 incisions each. After the adaptation period, the fur on the rabbits' backs was shaved, and the back area was cleaned with alcohol, followed by sterilization of the tools used. Subsequently, an incision wound of 2 cm in length was made. Measurements were taken daily,

and treatments were applied twice a day for 14 days. The average observation of wound healing can be seen in Table 3. The wound healing process begins with the formation of a scab that progressively gets smaller as the wound heals.

Table 3 shows the average results of wound healing in rabbits over a 14-day period. The data indicates the healing progress of incision wounds treated with different preparations (P1 to P5), as well as the positive control (K+) and negative control (K-). On day 1, all groups, including the treatments and controls, showed identical wound healing scores, with an average score of 2.00 ± 0.00 , indicating no significant difference in wound condition at the start of the experiment. By day 3, the wound healing showed some improvement in all groups.

The combination treatment groups (P2, P3, P4, and P5) showed varied healing rates, with P5 (combination of *P. crocatum* leaves ethyl acetate extract and *G. thoracica* propolis) showing the most significant improvement (1.50 ± 0.00), followed by P4 (1.90 ± 0.12) and P3 (1.70 ± 0.17). The positive control (K+) and negative control (K-) showed slightly better results compared to P1 (2.00 ± 0.00), which showed no improvement. At day 7, further progress was observed in all groups. Group P5 exhibited the most rapid wound healing with an average score of $0.60 \pm$

0.12, followed by P3 (1.03 ± 0.25) and P4 (1.30 ± 0.26). The positive control (K+) showed moderate healing at 1.50 ± 0.00 , while the negative control (K-) showed a healing score of 1.70 ± 0.10 .

On day 10, the healing process accelerated in all groups, with P5 continuing to show the best healing progress (0.15 ± 0.17). Group P3 (0.43 ± 0.21) and P4 (0.50 ± 0.20) also demonstrated significant healing improvements. The positive control (K+) had an average healing score of 1.27 ± 0.06 , while the negative control (K-) remained at 1.43 ± 0.06 . By day

14, all groups except the negative control had completely healed, showing an average score of 0.00 ± 0.00 . The negative control (K-) still showed a noticeable wound (1.20 ± 0.00), indicating that the wound had not completely healed by the end of the experiment. The combination of combination of *P. crocatum* leaves ethyl acetate extract and *G. thoracica* propolis (P5) was the most effective treatment for wound healing, demonstrating the fastest and most complete healing compared to other treatments and controls.

Table 3. Average Results of Wound Healing in Rabbits

No.	Day	Average Rabbit Incision Wound Healing (Average $\pm$ SD)						
		P1	P2	P3	P4	P5	K+	K-
1	1	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
2	3	1.80 ± 0.00	1.63 ± 0.06	1.70 ± 0.17	1.90 ± 0.12	1.50 ± 0.00	1.80 ± 0.00	2.00 ± 0.00
3	7	1.37 ± 0.06	1.20 ± 0.00	1.03 ± 0.25	1.30 ± 0.26	0.60 ± 0.12	1.50 ± 0.00	1.70 ± 0.10
4	10	1.07 ± 0.06	0.40 ± 0.10	0.43 ± 0.21	0.50 ± 0.20	0.15 ± 0.17	1.27 ± 0.06	1.43 ± 0.06
5	14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.80 ± 0.00	1.20 ± 0.00

Wound can be caused by sharp objects such as razor blades, knives or the like and can widen the wound so that tissue damage to the skin can occur if not given handling or treatment of the wound. Based on observations that have been made on the healing of incision wounds in rabbits on the third day the wound dries up on all test animals, the edges of the wound begin to narrow and on the seventh day all treatments cause wound scabs, significant results are seen in treatment five which shows that the wound scab has shrunk and on the tenth day treatment five in experiments one and two has completely healed and on the 14 day all treatments are completely healed except for the negative control and positive control, in the positive control the scab results of each experiment have shrunk while the negative control is still quite long (Figure 1).

P5 is a combination of *P. crocatum* leaves ethyl acetate extract and *G. thoracica* propolis extract in a 1:3 g ratio, with a higher propolis composition compared to P4 (3:1 g), and it is more effective than administering each extract individually, such as P1 (ethyl acetate extract of *P. crocatum* only) and P2 (propolis extract of *G. thoracica* only). The results of the combination of *P. crocatum* leaves ethyl acetate extract and *G. thoracica* propolis, was effective in wound healing, this can occur because propolis has several biological and pharmacological activities including antioxidant, antibiotic, anti-inflammatory (Sabir, 2005). The higher proportion of propolis in P5 (compared to P4, which has a 3:1 g ratio) likely contributed to its enhanced wound-healing properties.

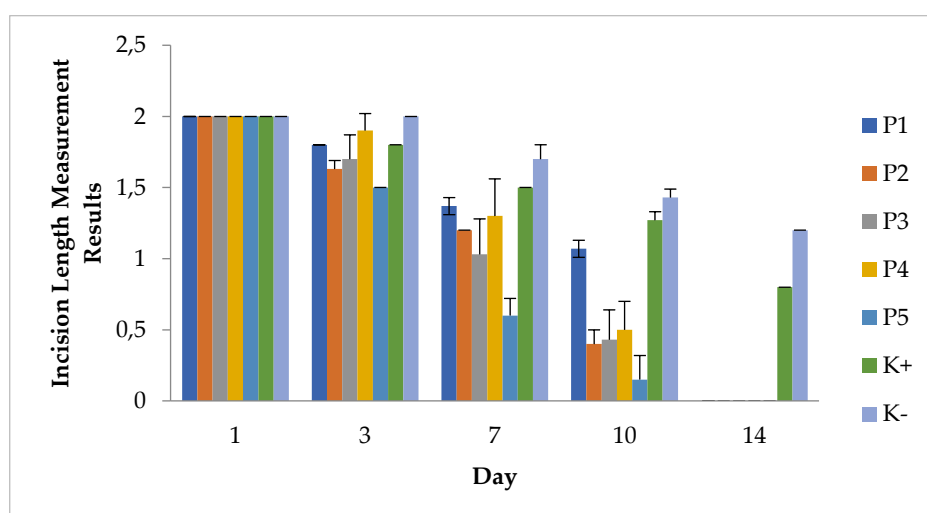


Figure 1. Wound healing measurement result

Propolis contains bioactive compounds, such as flavonoids and phenolics, which have anti-inflammatory, antioxidant, and antimicrobial effects that can accelerate the healing process. The increased concentration of propolis in P5 likely provided a stronger healing effect through its synergistic action with the *P. crocatum* extract. The combination of both extracts in P5 allowed for the benefits of each component to complement each other. *P. crocatum* leaves extract contains compounds like tannins and flavonoids that stimulate collagen production and enhance tissue repair.

By combining this with the bioactive compounds in propolis, P5 provided a more potent therapeutic effect compared to the individual extracts (P1 and P2). In contrast, P1 (ethyl acetate extract of *P. crocatum* only) and P2 (propolis extract of *G. thoracica* only) did not show the same level of effectiveness because they lacked the combined synergistic effects of both plant extracts. Thus, the combination in P5 resulted in better wound healing, as it maximized the benefits of each extract while also enhancing the overall therapeutic activity.

Propolis contains non-toxic, balanced nutrients with healing effects, promoting quicker wound drying (Ramelan & Kustiawan, 2024). Propolis in wound healing contains bioflavonoids as antioxidants that can act as cytotoxic free radicals. These flavonoids are rich in vitamins and are considered more effective antioxidants than vitamin E (Manginstar et al., 2024). Propolis also acts as an antibiotic with antibacterial, antiviral, and antifungal properties, which are essential in combating infections that can delay wound healing (Kustiawan, Aziz, et al., 2022; Salatino, 2022). Inflammation is a natural part of the wound healing process, but excessive inflammation beyond four days can inhibit healing. Propolis has been proven to help reduce inflammation (Akhtari et al., 2024; Bhargava et al., 2021). Furthermore, propolis can stimulate various enzymes, cell metabolism, circulation, and collagen formation (Scorza et al., 2024).

The combination of propolis with *P. crocatum* leaves in P5 enhances the healing effect due to the presence of secondary metabolites in the *P. crocatum* leaves, such as essential oils, tannins, and flavonoids. The mechanism of wound healing in secondary metabolites, particularly flavonoids, inhibits the inflammatory process in two ways: by inhibiting capillary permeability and arachidonic acid metabolism, which reduces prostaglandin production. The flavonoids can inhibit the secretion of lysosomal enzymes, which are mediators of inflammation and can further prevent excessive

inflammatory responses. Tannins in red betel leaves have antioxidant activity, acting as anti-inflammatory agents (Ulviani et al., 2016).

Statistical testing was performed using SPSS. The first step involved normality and homogeneity tests to determine whether the data were normally distributed and homogeneous. The normality test (One-Sample Kolmogorov-Smirnov Test) showed that the wound healing data for red betel leaves extract and propolis extract had a normal distribution (significance of $0.200 > 0.05$). In the homogeneity test (Test of Homogeneity of Variances), the results indicated that the data were not homogeneous (significance of $0.01 < 0.05$). Therefore, the non-parametric Kruskal-Wallis Test was used, which revealed significant differences between the 7 treatment groups ($p = 0.010 < 0.05$), indicating that the wound healing effects varied among the groups.

This was followed by the Mann-Whitney Test, which showed a significant difference ($p = 0.007 < 0.05$) between the positive control and formulation 5 in terms of wound healing effectiveness (Handayani, 2022). The combination of *P. crocatum* leaves ethyl acetate extract and propolis extract in P5 demonstrated superior wound healing properties compared to other treatments, with propolis contributing its potent antibacterial, anti-inflammatory, and antioxidant properties, enhancing the overall healing process.

CONCLUSION

The combination of *P. crocatum* Ruiz & Pav leaves extract and *G. thoracica* propolis extract has effectiveness in healing cuts. The combination of *P. crocatum* Ruiz & Pav Leaves extract (1 g) and *G. thoracica* propolis extract (3 g) exhibited the fastest wound healing effect in rabbits. It is recommended to further explore the optimal ratio of *P. crocatum* and propolis extracts for different types of wounds, as well as to conduct additional studies on the potential mechanisms of action behind their synergistic effects.

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