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THE WOUND HEALING POTENTIAL OF HONEY AND PROPOLIS FROM STINGLESS BEES IN ACUTE WOUNDS

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ABSTRACT

Honey and propolis from stingless bees have been reported to promote wound healing due to their anti-inflammatory, antioxidant, antibacterial, and moisturizing activities. However, variations in compounds and biological activities of these products can arise due to geographical and bee origin differences. This study aimed to investigate the wound healing potential of stingless bee honey and propolis from East Kalimantan in an acute wound animal model. Honey and propolis from stingless bees have been reported to promote wound healing due to its anti-inflammatory, antioxidant, antibacterial, and moisturizing activities. However, variation of compounds and biological activities of these products can arise due to geographical and bee origin differences. This study aimed to investigate the wound healing potential of stingless bee honey and propolis from East Kalimantan in acute wound animal model. A post-test only control group design was employed in this study. Fifteen Wistar rats were divided into 3 groups, i.e., a control receiving tulle and treatment groups receiving stingless bee honey and propolis, respectively. Wound healing activity was evaluated from wound diameter changes and histological evaluations following hole punch wound. Kruskal Wallis test results showed no significant changes in the proliferation phase of wound healing, as reflected by the diameter changes ($p = 0.989$), the rate of histopathological re-epithelization ($p = 0.730$) as well as number of fibroblasts ($p = 0.779$), collagen ($p = 0.779$), and neovascularization ($p = 0.756$) among the groups. Honey and propolis from stingless bees have the potential to treat acute wounds in the proliferation phase where their wound healing properties are equivalent to tulle.

Keywords: Acute Wound, Stingless Bee, Honey, Propolis.

INTRODUCTION

A wound is defined as a disruption in the continuity of the epithelial layer of the skin or mucosa due to physical or thermal damage. Wound healing is a complex and dynamic process supported by various cellular processes that are coordinated to efficiently repair damaged tissue. (Wilkinson & Hardman, 2020) Skin wound healing shows a unique mechanism of cellular function and involves the interaction of several growth factors, cells, and cytokines. In the wound healing process, there are several stages, i.e., hemostasis, inflammation, angiogenesis, growth, re-epithelialization, and remodeling.(Rodrigues et al., 2019) Although physiological wound healing is able to restore tissue integrity, in various cases, this process is frequently restricted to wound repair.(Tottoli et al., 2020)

According to the length and nature of the healing process, wounds are categorized into acute and chronic wound.(Dhivya, 2017) Treatment of acute wounds in patients requires systematic management for optimal results, starting with a physical examination and selection of appropriate wound care interventions.(Hendie et al., 2024) Management of acute wounds begins by cleaning the wound, removing dead tissue, and applying wound dressings and topical medications to accelerate the wound healing process. Currently, intensive research is being conducted to find effective agents for wound treatments.(Jayalakshmi et al., 2021)

Propolis and honey are produced by bees and are non-timber forest products that are full of benefits. There are many types of bees that can produce honey, one of which is the stingless bee (Heterotrigona iitama), also known as Meliponini.(Hakim, 2021) Stingless bee honey differs from other local honey species, as it is reported to have stronger antioxidant activity and higher phenolic content. The better antioxidant activity and higher phenolic content lead to their potential to treat numerous medical conditions, including infections and cancer. (Ramli et al., 2019) Further, propolis and honey from stingless bees have been reported to exert therapeutic properties, such as anti-inflammatory, antioxidant, and antibacterial properties. They are also natural moisturizers. The high amount of polyphenolic compounds in propolis and stingless bee honey can promote cell proliferation, protect cell structure, and fight free radicals in injured areas.(Ramli et al., 2019)

Although there are various studies that have examined the wound healing activities of propolis and stingless bee honey. (Ramli et al., 2019) there has been any studies investigating the wound healing properties of propolis and stingless bee honey from Indonesia in acute wounds. Moreover, previous research reported variations in the physicochemical properties, content, and biological activities of propolis and stingless bee honey due to geographical differences and the origin of the bees. (Leonhardt et al., 2013) This highlights the importance of conducting studies on products originating from Indonesia. Therefore, this study aimed to evaluate the wound healing activity of honey and propolis from Indonesia's stingless bee in an animal model of acute wounds. This aim was achieved by examining changes in wound diameter, speed of re-epithelialization, and the number of fibroblasts, collagen, and neovascularization through histological observations. The results of this research can become the basis for scientific evidence of stingless bee honey's and propolis's wound healing properties, enabling them to be developed until they can finally be used clinically.

LITERATURE REVIEW

Wounds and Their Healing

A wound is a disruption of the integrity of biological tissues, including the skin, mucous membranes, and organ tissues. Wounds can be caused by various types of trauma, making it crucial to ensure wounds are properly cleaned and dressed to limit the spread of infection and further injury (Dattani & Farouk, 2007). Wounds can be classified into different types, ranging from mild, moderate, to severe; from small to large; from superficial to deep; from non-infectious to infectious; and including burns, bruises, knife wounds, crush injuries, needle punctures, and gunshot wounds (Wintoko et al., 2020).

Wound healing is a complex and dynamic process supported by various cellular processes coordinated to efficiently repair damaged tissue (Wilkinson & Hardman, 2020). Skin wound healing demonstrates unique cellular mechanisms involving the interaction of several cells, growth factors, and cytokines. Physiological wound healing restores tissue integrity, but in many cases, the process is limited to wound repair (Tottoli et al., 2020).

Skin wound repair requires the intricate synchronization of several different cell types. The wound healing process involves several stages, including hemostasis, inflammation, angiogenesis, growth, re-epithelialization, and remodeling (Rodrigues et al., 2019). Repair begins with hemostasis, where a platelet plug prevents blood loss and an initial fibrin matrix forms. Inflammation then occurs to prevent infection, starting with the influx of neutrophils, driven by the release of histamine from mast cells. Monocytes differentiate into tissue macrophages to clear cellular debris and neutrophils. During the proliferation phase, keratinocytes migrate to close the wound gap, blood vessels reform through angiogenesis, and fibroblasts replace the initial fibrin clot with granulation tissue. Macrophages and regulatory T cells (Treg) are also essential for this healing stage. The deposited matrix is further remodeled by fibroblasts, and blood vessels regress, while myofibroblasts cause overall wound contraction (Figure 2.1) (Wilkinson & Hardman, 2020). When wound healing does not progress normally, chronic wounds can occur, and this condition is a significant burden for both patients and the medical system (Han & Ceilley, 2017). Chronic wounds are an extraordinary burden on the healthcare system and lead to significant patient morbidity and mortality (Ellis et al., 2018).

Wound Management

The management of acute wounds is based on the etiology of the wound, to ensure the proper wound care management, thereby accelerating the wound healing process, starting from wound cleaning, selection of wound dressings, and topical agents for wound care (Figure 2.5) (Ubbink et al., 2015).

Wound Dressings

Wound healing requires proper care to prevent infection. Covering wounds with dressings can prevent bacterial contamination. Dressings are designed to be in contact with the wound, unlike bandages, which hold the dressing in place. Traditional wound dressing products include gauze, fibers, plasters, bandages (natural or synthetic), and dry cotton used as primary or secondary dressings to protect wounds from contamination. Gauze dressings, made from woven and non-woven fibers of cotton, rayon, and polyester, provide some protection against bacterial infection. Some sterile gauze pads are used to absorb exudate and fluid from open wounds with the help of fibers in the dressing. These dressings need to be changed frequently to protect against maceration of healthy tissue. Gauze dressings are less cost-effective. Due to excessive wound drainage, dressings become moist and tend to adhere to the wound, causing pain upon removal. Bandages made of natural cotton and cellulose or synthetic bandages made of polyamide materials have different functions (Dhivya et al., 2015).

Tulle (Continued)

Commonly used wound dressings are "passive" dressings including gauze, lint, non-adherent dressings, and tulle. These dressings fulfill very few of the properties of an ideal dressing and have very limited use as primary dressings, but some are still useful as secondary dressings. Passive dressings maintain moisture, thereby accelerating epithelialization in superficial acute wounds compared to wounds exposed to air. Tulle/paraffin dressings are one of the earliest modern dressings. Many variations have been developed over the years by altering the paraffin loading in the dressing base. These dressings form a waterproof paraffin coating over the wound, but they can cause maceration because water vapor and exudate cannot escape and become trapped inside the wound. These dressings are permeable to bacteria, can adhere to the wound, and in some cases can cause trauma upon removal, requiring a secondary dressing. The use of these dressings is limited to simple, clean, superficial wounds, minor burns, and they are also used as primary dressings over skin grafts (Ilenghoven, 2017).

Stingless Bee Honey

Stingless bees are the oldest known bees. There are approximately 500 species of stingless bees worldwide, found in several tropical regions of Australia, Africa, the Americas, and in Southeast Asian countries including Malaysia. Compared to other tropical Asian countries, Malaysia, with over 35 reported species, has the highest diversity of Trigona species. Usually, stingless bees develop their nests on the roots or wood of felled trees (Adenan et al., 2021) and also have key characteristics that distinguish them from stinging bees (Figure 2.6) (Al-Hatamleh et al., 2020).

RESEARCH METHODS

The test animals used were Wistar rats aged 8-10 weeks with a body weight of 200-400 grams obtained. Fifteen rats were used in the experiment and fed with rat chow of 15 grams each and water ad libitum. They were kept for two weeks during acclimatization under standard conditions (temperature of 22 ± 4°C with relative humidity of 55 ± 15% and 12-h light-dark cycle). All animal protocols were approved by the Health Research Ethics Commission, Faculty of Medicine, Mulawarman University (no. 212/KEPK-FK/XI/2023).

The research was conducted using a post-test-only control group design, which was carried out at the Pharmacology Laboratory, Faculty of

Medicine, Mulawarman University, Samarinda, East Kalimantan. The 15 test animals were randomly assigned to three groups, i.e., control (C), stingless bee honey (T1), and stingless bee propolis (T2).(Yanti & Kustiawan, 2023) Before the acute wound was created, the prophylactic antibiotic cefotaxime 100 mg/kg BW was given intraperitoneally, followed by anesthesia using ketamine 20 mg/kg BW intraperitoneally.(Sahlan et al., 2020) A sterile puncher with a diameter of 1.5 cm was used to create 2 punch hole wounds aseptically on the back of the rat that was previously shaved.(Masson-Meyers et al., 2020) Scalpel blade no.11 was also used to help in completely removing the skin. After making the wound, group C was given a wound dressing with tulle, group T1 was given a wound dressing with 1 ml of stingless bee (H. itama) honey, and group T2 was given a wound dressing with 1 ml of stingless bee (H. itama) propolis. All wounds were then closed using sterile gauze and plaster. The honey and propolis, products of Faculty of Forestry, Mulawarman University, used in the tests were dissolved in normal saline in a ratio of 1:1 (v/v).

Wistar rats were treated back in their original cage after wound infliction, and then the wounds were measured on day-0, -2 and -14. After measuring the wounds on day-14, the rats were culled by injecting ketamine 80 mg/kg BW intraperitoneally.(Sahlan et al., 2020) Back wound tissues were extracted and fixed in 10% formalin for histological observation.(Masson-Meyers et al., 2020) The tissues were dehydrated in alcohol gradients, embedded in paraffin, and cut into 5 µm thick sections using a microtome (Leica, Germany). Next, the sections were stained using hematoxylin and eosin (H & E). Histological examination was conducted to assess the level of re-epithelialization and the number of fibroblasts, collagen, and neovascularization. This examination was conducted using a microscope (Olympus Type CX 21) with 40x and 100x magnifications in 5 fields with a zigzag view. The results of these five fields of view were divided by the average and expressed using a scoring system (Tabel 1).

Tabel 1. Scoring System for Histopathological Evaluation (Mehrabani et al., 2015)

No	Parameter	Description	Score
1.	Epithelialization	Complete and mature epithelialization	+3
		Epithelialization is complete but immature	+2
		Partial epithelialization	+1
		No epithelialization	0
2.	Fibroblast	The number of fibroblasts is > 50% of the wound tissue	+3
		The number of fibroblasts is < 50% of the wound tissue	+2
		Fibroblasts only exist in the perivasculature	+1
		No fibroblast	0
3.	Collagen	Large amount of collagen	+3
		Medium amount of collagen	+2
		Small amount of collagen	+1
		No collagen	0

4.	Neovascularization	≥ 10 new blood vessels	+3
		6-10 new blood vessels	+2
		1-5 new blood vessels	+1
		No new blood vessels	0

Data analysis

The collected data was tested using a normality test to determine whether the data was normally distributed or not. The data obtained in this study was not normally distributed. Therefore, the data analysis was carried out non-parametrically using the Kruskal-Wallis test. Data analysis was performed in Statistical Package for the Social Science (SPSS) version.(Darby & Hewitson, 2007) Data was presented as the mean ± standard deviation.

RESAERCH RESULTS

Figure 1. Development of re-epithelialization on day-0 (A), -2 (B), and -14 (C)

Changes in wound diameter are associated with the speed of wound re-epithelialization in the test animals. Figure 1 shows the wound closing as the study progressed. This was observed for the all groups. The results of the average re-epithelialization speed in wound healing were assessed by measuring wound diameter changes on day-0 to -2 and on day-0 to -14 (Table 2). The Kruskal-Wallis test results showed that the wound diameter changes on day-0 to -2 and on day-0 to -14 had p values of 0.360 and 0.989 ($p > 0.05$), indicating that the speed of wound healing was not significantly different between groups.

Table 2. Changes in Wistar Rat Acute Wound Diameter with Various Treatments

Group	Diameter change (mm)	
	Day-0 to -2	Day-0 to -14
C	3.5 ± 1.1	1.23 ± 3.0
T1	3.0 ± 1.6	1.33 ± 2.1
T2	4.0 ± 2.2	1.34 ± 1.5

*C is the control group receiving tulle, T1 receiving stingless bee honey and T2 receiving stingless bee propolis

Histological examination

Epithelialization and the presence of fibroblasts, collagen, and neovascularization were clearly visible on histological examination (Figure 2). The results of histological evaluation on the level of epithelialization and the number of fibroblasts, collagen, and neovascularization are shown in Table 3

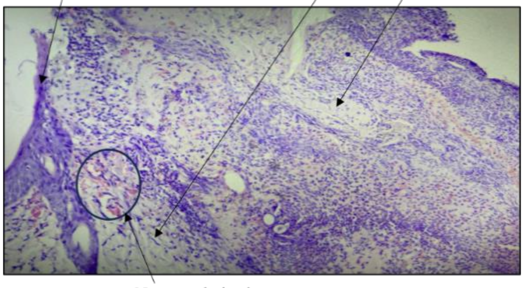

Figure 2. A representative histology image indicating re-epithelialization and the presence of fibroblast, collagen, and neovascularization on 100x magnification

Table 3. Histological Evaluation Results of Acute Wounds Healing on Day-14

Group	Speed of Re-epithelialization	Fibroblast Number	Collagen Number	Neovascularization Number
C	1.00 ± 1.00	1.40 ± 0.54	1.40 ± 0.54	1.40 ± 0.54
T1	1.00 ± 1.00	1.60 ± 0.54	1.40 ± 0.54	1.40 ± 0.54
T2	1.40 ± 0.89	1.60 ± 0.54	1.40 ± 0.54	1.20 ± 0.44

*C is the control group receiving tulle, T1 receiving stingless bee honey and T2 receiving stingless bee propolis

The Kruskal-Wallis test results on re-epithelialization speed, fibroblasts number, collagen number, and neovascularization number showed p values of 0.730, 0.779, 0.779, and 0.756 ($p > 0.05$), respectively. This demonstrated that there were no significant differences among all groups on these four parameters.

DISCUSSION

This research is an experimental study with a post-test-only control group design, which aims to analyze the potential of honey and propolis from stingless bees in healing acute wounds during the proliferation phase, as assessed from the speed of re-epithelialization and the number of fibroblasts, collagen, and neovascularization.

Wound healing is the body's natural and normal response to injury. Wound healing is a complex and dynamic process for rapid recovery of damaged tissue, enabling it to return to its normal function. This process consists of 4 highly interconnected and overlapping phases, which are hemostasis, inflammation, proliferation, and remodeling.(Rodrigues et al., 2019)

In this study, tulle was used as a control. Tulle dressings are paraffin dressings that are one of the earliest modern dressings.(Sarheed et al., 2016) The dressings are permeable to bacteria and form a waterproof paraffin covering over the wound. However, these dressings can cause maceration because water vapor and exudates cannot escape and are trapped in the wound. Additionally, it can stick to the wound and, in some cases, can cause trauma upon removal and require a secondary dressing. The uses of these dressings are also limited to simple, clean, shallow wounds, minor burns, and are used as the main dressing over skin grafts.(Wardani et al., 2024) The drawbacks of tulle dressings underscore the need for better dressings development.(Huanbutta et al., 2020)

Based on the results of measuring the wound diameter, re-epithelialization in each group showed an improvement in the wound contraction area where the speed of re-epithelialization of groups treated with topical administration of honey and propolis from stingless bees was comparable to that of the control (tulle). This indicates that honey and propolis from stingless bees can meet the criteria for use as alternative dressings where honey and propolis from stingless bees have the ability to act as anti-inflammatory, antioxidants, antibacterials, and moisturizers. (D, 2017) These results also align with the histopathological assessment of the re-epithelialization speed.(Yudhika et al., 2021) Re-epithelialization of wounds following the application of honey and propolis from stingless bees can occur due to the migration of keratinocytes from the surrounding tissue of the epithelium, covering the wound surface. This re-epithelialization process is directly proportional and interconnected with other research variables, namely the number of fibroblasts, collagen, and neovascularization.(Tottoli et al., 2020) To corroborate the findings on re-epithelialization, we also found that the number of fibroblasts, collagen, and neovascularization demonstrated improvements that occurred with the topical administration of honey and propolis from stingless bees, which were equivalent to the control group(Esa et al., 2022). As reported earlier, acute wound repair is characterized by an increase in the number of fibroblasts, collagen, and neovascularization.(Esa et al., 2022)

Fibroblasts produce extracellular matrix which is the main component of scar tissue formation and causes the movement of keratinocytes through the wound filling. Macrophages produce growth factors that stimulate proliferation, migration, and extracellular matrix formation and synthesize collagen that holds wound edges together. (Tottoli et al., 2020)

Collagen is synthesized by fibroblasts, and thus, an increase in the number of fibroblasts is often accompanied by an increase in the amount of collagen.(Esa et al., 2022) Collagen causes primary and secondary hemostasis which occur through two pathways that are interconnected simultaneously and mechanically. Primary hemostasis involves platelet aggregation and platelet blockage brought about by exposure to collagen in the subendothelial matrix. Secondary hemostasis refers to the activation of the coagulation cascade in which soluble fibrinogen is converted into insoluble strands that form a fibrin meshwork. The platelet plug and fibrin network combine to form a thrombus which stops bleeding, releases complements and growth factors, and provides infiltrating cells needed for wound healing.(Rodrigues et al., 2019)

Increased re-epithelialization, fibroblasts, and collagen can stimulate angiogenesis. (Esa et al., 2022) The neovascularization growth begins in the granulation tissue, forming vascular tissue to supply the wound area, and, in the 2-3rd week, the vascularization undergoes regression and maturation.(Han & Ceilley, 2017) Neovascularization occurs after the wound gap is closed in the re-epithelialization process. Next, granulation tissue is formed due to fibrin clots which have been replaced by fibroblasts and then produce collagen that later blocks the platelets and fibrin network. This blockage triggers thrombus formation which stops bleeding, leading to complements and growth factors release, further providing infiltrating cells required for wound healing. Lastly, the blood vessels regress, and myofibroblasts cause overall wound contraction. (Wilkinson & Hardman, 2020)

Wound healing properties of honey and propolis from stingless bees are attributed to their antioxidant, antibacterial, anti-inflammatory, and moisturizing activities. The antioxidant (Yudhika et al., 2021)properties of honey and propolis from stingless bees stem from phenolic and flavonoid content which act as electron transporters to neutralize, reduce, and eliminate free radicals. Hence, they protect cell structures from reactive oxygen species (ROS).(Esa et al., 2022) Various phenolics and flavonoids have been successfully detected on both products, including catechin, apigenin, kaempferol, rutin, myricetin, and quercetin.(Ramli et al., 2019) The antibacterial activity of stingless bee honey and propolis prevents the growth of pathogenic bacteria in wounds, preventing damage to wound tissues. (Mama et al., 2019) The antibacterial properties have been tested against Gram-positive (Bacillus subtilis, Micrococcus luteus, Bacillus megaterium, Staphylococcus aureus, and Bacillus brevis) and Gram-negative (Escherichia coli, Pseudomonas syringae, Klebsiella pneumoniae, and Salmonella typhimurium) bacterias.(Al-Hatamleh et al., 2020) The anti-inflammatory effect of honey and propolis from stingless bees functions to prevent a prolonged inflammatory process, thereby preventing fibrosis in wound tissue which has the potential to become a chronic wound.(Esa et al., 2022) The moisturizing effect of the honey and propolis maintain moisture in wounds, enabling the transport of enzymes, growth factors, and hormones, which in turn promote cell growth. (D, 2017) The abilities of the two products as antioxidants, antibacterials, anti-inflammatory, and moisturizer form a good wound bed, thereby increasing the potential for re-epithelialization and the number of fibroblasts, collagen, and neovascularization in acute wounds.(Mama et al., 2019)

The appropriate dressings selection can be chosen based on availability, quantity, and cost. The use of honey and propolis from stingless bees can be alternative dressings options to modern types of dressings that function to protect wounds from dehydration and increase the wound healing speed, for instance, tulle, which is used as a control in this study. These dressings are superior compared to the classic dressings, such as gauze, fiber, plaster, and bandages that can only cover the wound.(Dhivya et al.,

2015) The availability of honey and propolis from stingless bees can now be obtained at affordable prices in liquid form. They are also kept in packaging that is easy to carry so that it can be an alternative for people living in rural areas who are far from health facilities needing to treat their wounds. Additionally, the development of these two products as wound dressings can increase the productivity of honey and propolis farmers of stingless bees, especially in the East Kalimantan area. (Tashkandi, 2021)

Although this study has been carefully designed, it still has a caveat on histological staining. Histological staining using H & E can only illustrate the general tissues and cells conditions and cannot identify fibroblasts and collagen in much details. However, it is still possible to observe fibroblasts and collagen using H & E staining. To overcome this weakness, further investigation using more specific stainings, such as Masson's trichrome staining for collagen (Suyik & Effendy, 2012) or immunohitochemistr (Darby & Hewitson, 2007) should be explored. Apart from that, further research regarding wound healing activity can be carried out for chronic wounds, thereby further strengthening the foundation of the commercialization of stingless bee honey and propolis dressings.

Overall, the results of this study are in accordance with previous studies which have reported the wound healing properties of honey and propolis from stingless bees owing to their antioxidant, antibacterial, anti-inflammatory, and moisturizing properties. These biological activities are attributed to the phenolics and flavonoids contained in the honey and propolis.(Syafrizal et al., 2020) To the best of our knowledge, this is the first research that reported wound healing properties of honey and propolis of Indonesia’s stingless bee.

CONCLUSION

Based on the assessment of speed of re epithelialization and the number of fibroblasts, collagen and neovascularization, honey and propolis from stingless bees have the potential to treat acute wounds in the proliferation phase where their wound healing properties are equivalent to tulle, the primary dressings which are commonly used in health care facilities. Therefore, honey and propolis from stingless bees can be considered as alternative dressings for acute wounds.

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