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Original Article

Development and preclinical evaluation of an Aceh kelulut honey-based hydrocolloid dressing for wound healing

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Abstract

Honey has long been used in wound care because of its antibacterial and anti-inflammatory properties, while hydrocolloid dressings provide a moist and protective environment that supports tissue repair. This study aimed to evaluate the macroscopic and microscopic effects of an Aceh kelulut honey–based hydrocolloid dressing on wound healing in mice. Twenty-seven healthy male mice (*Mus musculus*) were assigned to three groups: control treated with 0.9% NaCl, pure Aceh kelulut honey (KH), and Aceh kelulut honey–based hydrocolloid (KHHC). Two full-thickness excisional wounds, each 4 mm in diameter, were created on the dorsal skin of each mouse. Wound diameter was measured daily for 14 days. Histopathological evaluation was performed on days 3, 7, and 14 to assess neutrophil and macrophage counts, epithelialization ratio, myofibroblast ratio, and collagen fiber density. The KHHC group showed faster macroscopic wound closure than the KH and control groups. Significant differences were observed among groups in neutrophil count, macrophage count, epithelialization ratio, myofibroblast ratio, and collagen fiber density. KHHC reduced inflammatory cell infiltration, increased myofibroblast ratio, and enhanced collagen fiber density, suggesting accelerated wound contraction and tissue remodeling. However, epithelialization was lower in the KHHC group during the early healing phase. These findings indicate that Aceh kelulut honey–based hydrocolloid dressing may improve several key aspects of wound healing, particularly inflammation control, wound contraction, and collagen deposition. Further studies are required to optimize the formulation and clarify its effect on reepithelialization.

Keywords: Aceh kelulut honey, hydrocolloid Aceh kelulut honey, wound healing, *Mus musculus*, collagen fiber density

Introduction

A wound is generally characterized by damage to the skin membrane and is often accompanied by injury to the underlying tissues or organs. Anatomically, a wound represents an external or internal disruption of the normal continuity of the extracellular matrix and epithelium, resulting in the loss of the protective function of the skin, with or without damage to underlying connective

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tissues such as blood vessels, nerves, muscles, or bones. Although wounds are commonly encountered in daily life and clinical practice, they remain an important health problem because they may arise from both acute events and chronic diseases and can impose a considerable clinical burden. This burden is particularly evident in chronic or non-healing wounds, which are associated with delayed tissue repair, prolonged inflammation, increased risk of infection, pain, functional impairment, repeated healthcare visits, longer treatment duration, reduced quality of life, and increased healthcare utilization [1-2]. Wound care, particularly in chronic wounds, represents a major challenge for medical professionals. Consequently, wound management plays a critical role in determining both the quality and duration of wound healing [3]. Effective wound management encompasses wound assessment, cleaning, appropriate therapeutic approaches, and scar management. Proper wound care facilitates optimal healing, thereby improving patients' quality of life [4, 5].

Honey is considered effective in the topical management of wounds and burns because of its antibacterial properties and its ability to promote wound healing [6, 7]. The high sugar content of honey exerts an osmotic effect that inhibits microbial growth [6,7]. Honey also possesses direct anti-inflammatory properties, which reduce wound inflammation, edema, and exudate, thereby enhancing healing and alleviating pain [8-10]. However, the biological activity of honey may vary depending on its botanical source, geographical origin, bee species, and physicochemical composition. One local honey with potential relevance to wound management is Aceh kelulut honey, which is produced by stingless bees locally known as kelulut in Aceh, Indonesia. Kelulut honey is different from general honey mainly in its bee origin and physicochemical characteristics, including its relatively acidic nature and bioactive compounds such as phenolics and flavonoids, which have been associated with antibacterial, antioxidant, anti-inflammatory, and wound-healing activities [11,12]. Previous studies have also reported the potential effectiveness of stingless bee or KH in wound management, including its role in promoting epithelialization and granulation tissue formation [13,14].

To deliver the benefits of honey more effectively in wound management, it can be incorporated into modern dressings such as hydrocolloids (HC). HC dressings have gained popularity due to their ease of application, durability, and pain-free removal. They consist of hydrophilic colloidal particles embedded in an adhesive film or foam [15], which interact with wound exudate, swell, and form a barrier against contaminants [4]. HC also provide effective exudate absorption and a microenvironment conducive to angiogenesis and granulation [16]. Their occlusive nature prevents the entry of water, oxygen, or bacteria into the wound, inhibiting bacterial growth [17]. HC dressings are generally indicated for wounds with low to moderate exudate, granulating or necrotic wounds, superficial burns, and pressure ulcers, and some hydro fiber products provide additional bactericidal activity, particularly against Gram-negative species [2].

Given the therapeutic potential of honey, especially Aceh kelulut honey, in wound care, further investigation is warranted to evaluate its incorporation into modern dressing formulations. The aim of this study was to evaluate the macroscopic and microscopic effects of Aceh kelulut honey–based hydrocolloid (KHHC) dressing on wound healing. It is expected that KHHC could serve as a valuable wound care modality, particularly for wounds with moderate exudate and those at risk of contamination or infection.

Methods

Aceh Kelulut honey–based hydrocolloid (KHHC) formulation

The KHHC formulation was prepared following the previously developed method [18] with minor modifications. Briefly, distilled water was heated to boiling, followed by the addition of chitosan (3%), polyvinyl alcohol (6%), and sodium carboxymethylcellulose (6%). The solution was stirred until all components were completely dissolved. Polysorbate-80 (3%) and glycerol (3%) were then added gradually with continuous stirring until a homogeneous mixture was achieved. The prepared solution was stored in a refrigerator for 24 hours. Subsequently, Aceh kelulut honey (9%) and distilled water (70%) were incorporated, and the solution was stirred again until homogeneous, yielding the KHHC formulation.

Experimental animals and husbandry

Twenty-seven healthy male mice (*Mus musculus*), aged 8 weeks and weighing 23.5±0.6 g, were used; obtained from the Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia. The mice were housed individually at room temperature with *ad libitum* access to water and standard chow. The sample size was calculated based on Federer's formula. Prior to the experiment, the animals underwent a one-week acclimatization period. All animals received standard food and water, housed in cages that had been previously dried and lined with sawdust. The cages were placed in well-ventilated rooms with indirect exposure to natural sunlight [19]. The study protocol on animals was approved by the Animal Experiment Committee of the Faculty of Veterinary Medicine, Universitas Syiah Kuala.

Preparation and care of experimental animals

The mice were divided into three treatment groups: control group treated with saline solution; kelulut honey (KH) group treated with kelulut honey; and KHHC group treated with KHHC. Nine animals were used for each group. Full-thickness excisional wounds were created on the dorsal region of all mice. Before wound creation, the dorsal hair was shaved and the exposed skin was disinfected with 70% ethanol. Local anaesthesia was then administered using lidocaine. Two full-thickness excisional wounds, each 4 mm in diameter, were created on the shaved dorsal surface using a sterile surgical blade for each animal (**Figure 1**). Treatments were applied daily starting immediately after wound creation: control group treated with 0.9% NaCl; KH group treated with 0.1 mL of pure Aceh kelulut honey, and KHHC group treated with 0.1 mL of KHHC. The macroscopic evaluations were conducted every day post-treatment, while microscopic evaluation was performed on days 3, 7, and 14 post-treatment.

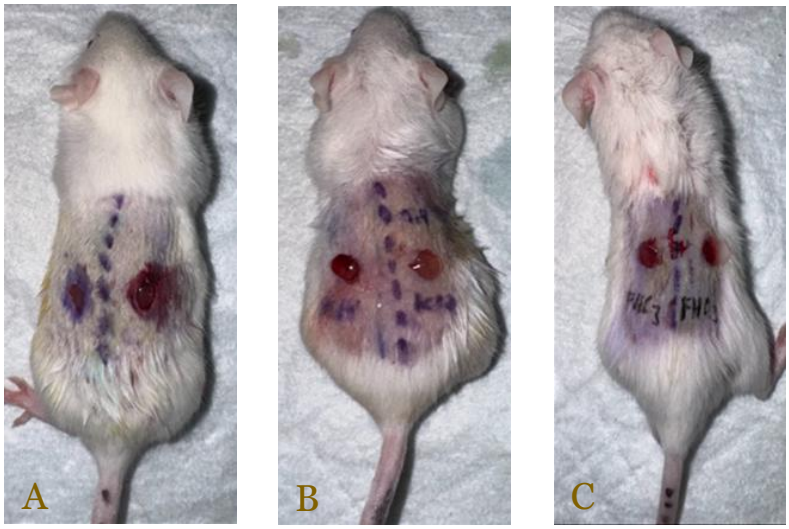

Figure 1. Representative 4-mm full-thickness excisional wounds on the dorsal skin of mice assigned to (A) the control mice untreated; (B) KH group treated with 0.1 mL of kelulut honey; and (C) KHHC group treated with 0.1 mL of Aceh kelulut honey–based hydrocolloid (KHHC).

Macroscopic examination

Macroscopic evaluations were conducted from day 0 to day 14. Wound diameter was measured daily using a digital caliper in both horizontal and vertical directions before treatment application.

Microscopic examination

On days 3, 7, and 14, three animals per group were terminated at each time point via cervical dislocation. Wounds, together with adjacent healthy skin (approximately 3 mm thick), were excised. Tissue samples were fixed in 4% paraformaldehyde for 18 hours, dehydrated in a graded ethanol series, cleared in xylene, and embedded in paraffin. Serial sections of 5 µm thickness were prepared and stained with hematoxylin-eosin (HE) and Masson's trichrome. Microscopic evaluation was performed using a Meiji Techno EMZ5-V7 microscope (Meiji Techno Co., Ltd., Saitama, Japan).

Five microscopic wound-healing parameters were measured: neutrophil count, macrophage count, epithelialization ratio, myofibroblast ratio, and collagen fiber thickness ratio. Neutrophils and macrophages in granulation tissue were quantified using a light microscope at 40× magnification. Stained cells were counted in three microscopic fields: two fields near the wound edges and one field at the wound center. The area of each field was measured using ImageJ software (National Institutes of Health, Bethesda, Maryland, USA). The mean neutrophil and macrophage counts were calculated by dividing the total number of cells counted in the three fields by three.

The epithelialization ratio, myofibroblast ratio, and collagen fiber thickness ratio were also assessed. The epithelialization ratio was calculated as the length of newly formed epithelium divided by the total wound length, presented in percentage. Similarly, the myofibroblast ratio was calculated as the myofibroblast area divided by the total wound area and the collagen fiber thickness ratio was calculated as the collagen-positive area divided by the total wound area; both also presented in percentage.

Statistical analysis

Quantitative data were first assessed for normality using the Shapiro–Wilk test. For variables with a normal distribution, differences among the three groups were analyzed using one-way ANOVA. For variables that were not normally distributed, the Kruskal–Wallis test was used. Post hoc pairwise comparisons were performed using the Mann–Whitney U test with Bonferroni adjustment.

Results

Macroscopic analysis on wound diameter

The effects of the three treatments on wound diameter were assessed daily using a digital caliper over a 14-day observation period and the results are presented in **Figure 2**. The KHHC group exhibited faster wound healing beginning on day 2, with progressive reduction in wound diameter until day 14. Macroscopically, the KHHC treatment also accelerated dorsal hair regrowth, particularly between days 7 and 14. In contrast, wound closure was slower in the KH and control groups. In the KH group, significant wound closure was first observed on day 9, whereas in the control group, notable closure was observed only after day 7. Additionally, mice in the control group showed delayed hair regrowth up to day 14.

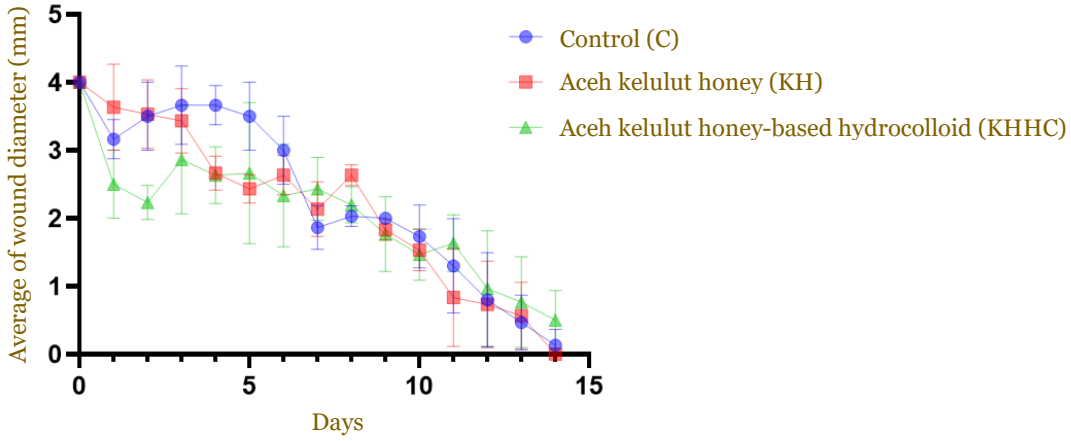

Figure 2. Average wound diameter (mm) of mice from day 1 to day 14 in the control group (C), Aceh kelulut honey group (KH), and Aceh kelulut honey–based hydrocolloid (KHHC). Data are presented as mean ± standard deviation.

Microscopic analysis of neutrophil and macrophage, myofibroblast and reepithelialization

The microscopic effects of KHHC dressing on neutrophil and macrophage counts, myofibroblast ratio, and reepithelialization ratio were evaluated using HE staining and the results are presented

in **Figure 3A-C**. Overall, clear differences were observed between the control group and the two treatment groups (KH and KHHC) across the parameters measured. Statistical analyses were conducted, including tests for normality and homogeneity of variance, followed by comparative analysis among the three groups. The results are presented graphically in **Figure 4**.

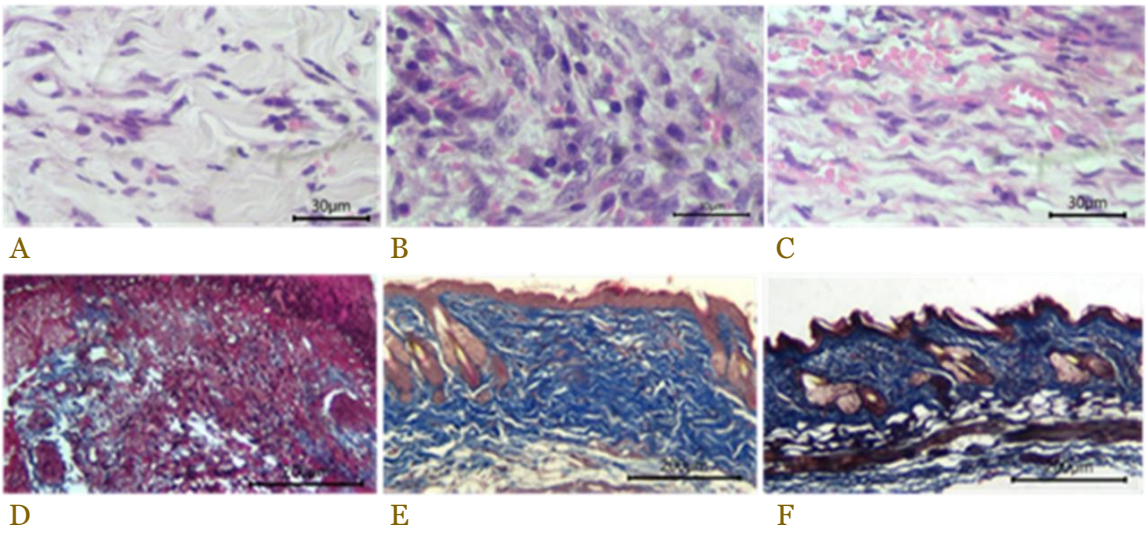

Figure 3. Histological evaluation of wound healing. Hematoxylin–eosin (HE) staining for the evaluation of neutrophil and macrophage counts, myofibroblast ratio, and reepithelialization ratio on day 7 revealing variable distributions of neutrophils and macrophages were observed in (A) control group (treated with 0.9% NaCl), (B) KH group (treated with pure Aceh kelulut honey), and (C) the KHHC group (treated with Aceh kelulut honey–based hydrocolloid dressing). Myofibroblasts appeared and were distributed across all groups. Masson's Trichrome (MT) staining for the evaluation of collagen fiber thickness on day 7 reveals collagen fibers in control group appeared relatively thin and aligned (D), whereas in KH group (E) and KHHC group (F) the collagen fibers appeared thicker, denser, and more irregular.

Neutrophil and macrophage counts

A significant difference in the mean neutrophil count was observed on days 3 and 7 among the three treatment groups ($p<0.001$) (**Figure 4A**). The highest mean neutrophil count was found in the control group (12.50/mm²), followed by the KHHC group (7.0/mm²), and the KH group (3.20/mm²). In contrast, no significant difference was observed among the three groups on day 14 ($p=0.120$) (**Figure 4A**). The findings indicate a gradual decline in neutrophil counts through day 14 across all treatment groups.

A significant difference was also found in macrophage counts on day 7 (**Figure 4B**). The Kruskal–Wallis test revealed significant differences among the three treatment groups ($p=0.020$), with the highest mean macrophage count in the control group (1.90/mm²), followed by the HC group (1.2/mm²) and the KH group (0.7/mm²). Post-hoc analysis using the Mann–Whitney test showed a significant difference between the control group and KH group on day 7 ($p=0.006$). On days 3 and 14, no significant differences were observed among the three groups ($p=0.621$ and $p=0.403$, respectively) (**Figure 4B**). The results demonstrated that macrophage counts tended to decrease markedly in all groups, particularly in the control group.

Reepithelialization ratio

There was a significant difference in the mean reepithelialization ratio among the three groups on days 3 and 7 (**Figure 4C**). Post-hoc Mann–Whitney analysis revealed significant differences between the control group and the KH group ($p=0.004$) and between the control group and the KHHC group ($p=0.004$) on day 3. On day 7, a significant difference was observed only between the control group and KHHC group ($p=0.010$). By day 14, no significant differences were detected among the three groups (**Figure 4C**).

Myofibroblast ratio

There was a significant difference in the mean myofibroblast ratio on day 3 among the three treatment groups (p=0.036) (**Figure 4D**). The mean ratios were 8.90 in the control group, 11.40 in the KH group, and 10.70 in the KHHC group. Post-hoc analysis showed a significant difference between the control group and KH group on day 3 (p=0.017) (**Figure 4D**).

One-way ANOVA showed a significant difference in the mean myofibroblast ratio on day 14 among the three groups (p<0.001) (**Figure 4D**). The mean ratios were 15.00 in the control group, 20.90 in the KH group, and 19.70 in the KHHC group. Post-hoc analysis using the Games–Howell test indicated significant differences between the control group and the KH group (p=0.040) and between the control group and the KHHC group (p=0.010). On day 7, no significant differences were observed among the groups. The myofibroblast ratio increased from day 7 to day 14 across all treatment groups (**Figure 4D**).

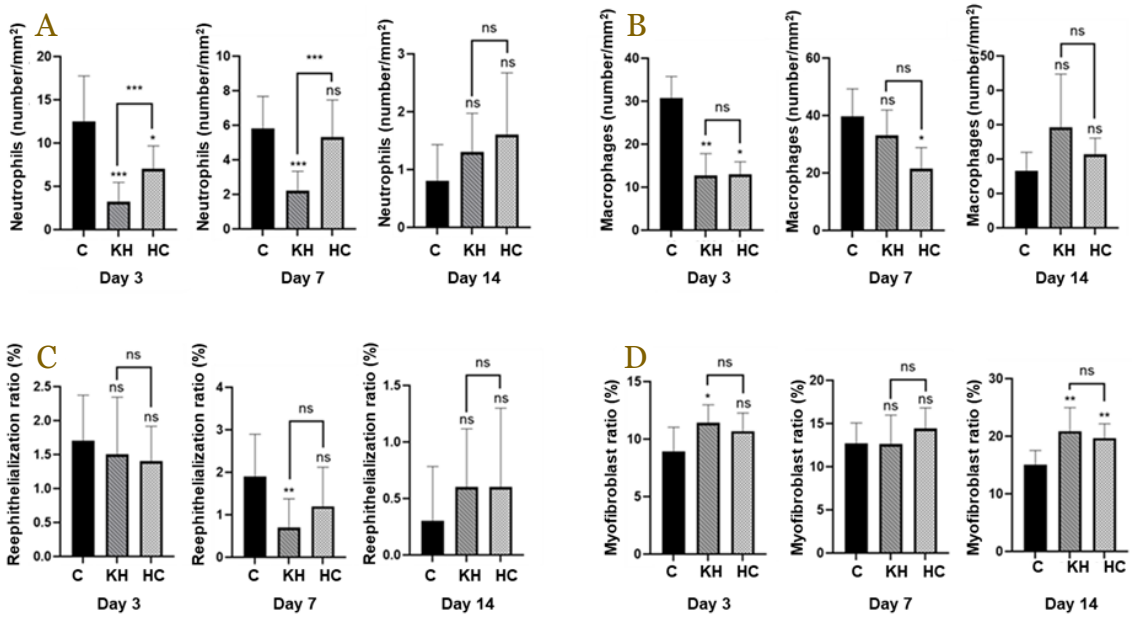

Figure 4. Comparisons of neutrophil count, macrophage count, reepithelialization ratio, and myofibroblast ratio on days 3, 7, and 14. (A) Comparison of neutrophil counts per mm², (B) comparison of macrophage counts per mm², (C) comparison of reepithelialization ratio (%), and (D) comparison of myofibroblast ratio (%). Data are presented as mean ± standard deviation. C (control, treated with 0.9% NaCl), KH (treated with Aceh kelulut honey), and KHHC (treated with Aceh kelulut honey–based hydrocolloid dressing). Statistical significance was assessed against the control group (C). Significance levels: ns=p≥0.050, *p<0.05, **p<0.01, ***p<0.001.

Microscopic analysis on collagen fiber density

Collagen density was evaluated on days 3, 7, and 14 using Masson's Trichrome (MT) staining, as shown in **Figure 3D-F**. For comparison, collagen analysis was also performed on healthy skin. The results demonstrated that collagen fiber density tended to increase on day 7 in control, KH, and KHHC groups.

The Kruskal–Wallis statistical test revealed significant differences in the mean collagen fiber density ratio among the three treatment groups on days 3, 7, and 14, with p-values of 0.026, 0.031, and 0.034, respectively (**Figure 5**). On day 3, the post-hoc Mann–Whitney test showed significant differences in the mean collagen fiber density ratio between the control group and KH group (p=0.025), as well as between the control group and KHHC group (p=0.025). On day 7, the post-hoc Mann–Whitney test revealed significant differences in the mean collagen fiber density ratio between the control group and KHHC group (p=0.016), as well as between the KH group and KHHC group (p=0.037). On day 14, significant differences were also observed between the control group and the KH group (p=0.037), and between the control group and the KHHC group (p=0.025) (**Figure 5**).

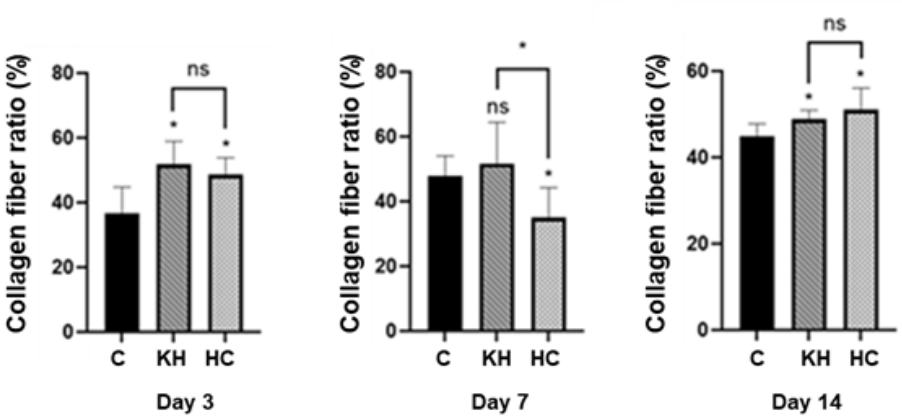

Figure 5. Comparison of collagen fiber thickness ratio on days 3, 7, and 14. Data are presented as mean ± standard deviation, n=6 per group; C (control, treated with 0.9% NaCl), KH (treated with kelulut honey), and KHHC (treated with Aceh kelulut honey-based hydrocolloid dressing). Significance is expressed relative to the control group (C). Significance levels: ns=$p \geq 0.05$, *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Discussion

Honey has long been used as a wound care modality since ancient times, including in Indonesia. The diversity of honey types in Indonesia is influenced by climate, insect species, and nectar sources [5]. Aceh Province is one of the honey-producing regions in Indonesia, yielding several varieties such as kelulut honey, yellow honey, and black honey. Our initial study investigated the antibacterial activity of Aceh kelulut honey, yellow honey, and black honey against wound-associated bacteria, including *Staphylococcus aureus*, *Staphylococcus hominis*, *Escherichia coli*, and *Pseudomonas aeruginosa* [20]. The study concluded that the highest antimicrobial activity was observed in Aceh black honey, followed by kelulut honey and yellow honey. The study also noted that kelulut honey demonstrated sufficient antibacterial activity to inhibit the growth of wound-associated bacteria.

Building on that preliminary study, the present study evaluated the wound-healing activity of KHHC in animal models. Macroscopically, the KHHC dressing demonstrated a rapid reduction in wound diameter during the early healing phase (days 2–3 of treatment), followed by a gradual decrease throughout the proliferative phase (up to day 14). In contrast, pure kelulut honey exhibited a more delayed effect, with a marked reduction in wound diameter only observed after day 9 of treatment. These findings differ from a previous study, which demonstrated that wounds treated with Japanese honey had a significantly smaller wound area ratio during the inflammatory phase but a larger ratio during the proliferative phase [19]. The microscopic effectiveness of KHHC dressing in this present study was evaluated using five parameters representing the different phases of wound healing. During the inflammatory phase, the migration of inflammatory cells, such as neutrophils and macrophages into the wound area leads to elevated activity of these cells. In this study, both the KHHC dressing and pure kelulut honey significantly reduced neutrophil and macrophage counts, demonstrating their ability to suppress the inflammatory response. This finding is consistent with a previous study, which reported that honey, particularly Japanese honey, was able to attenuate inflammatory responses in wounds but it was less effective in accelerating wound healing compared with KHHC dressings [21]. However, some previous studies found that honey, especially forest honey, did not reduce neutrophil and macrophage levels during the inflammatory phase [22,23]. These discrepancies may be attributed to variations in honey composition, which depend on the specific type and bioactive content of the honey being investigated.

The proliferative phase is a critical stage in the wound healing process, characterized by the formation of granulation tissue within the wound bed and the migration of keratinocytes to regenerate epithelial tissue and restore the continuity of the epidermal layer. New tissue is formed by a matrix composed of collagen, elastin, glycosaminoglycans, and other fibrous proteins, which are stabilized by fibrin and fibronectin. Fibroblasts migrate into the wound area and proliferate

to synthesize additional collagen fibers [1,2]. Importantly, fibroblasts differentiate into myofibroblasts, which play a central role in granulation tissue formation. Myofibroblasts generate contractile force and synthesize extracellular matrix components that facilitate granulation tissue contraction, thereby drawing wound edges together to promote closure [2,18].

In the present study, the proliferative phase was primarily evaluated through the myofibroblast ratio and collagen fiber thickness ratio, both of which were notably facilitated in the KHHC dressing group. This was evidenced by a significantly higher myofibroblast ratio in the KHHC group compared with the control group on day 14. In addition, the collagen fiber density ratio was significantly greater in the KHHC group on day 14 than in the control group. These findings align with previous reports showing that honey application enhances wound contraction [24,25]. However, these results differ from a previous study, which found no effect of honey on wound contraction, as indicated by the lack of increased myofibroblast activity during the healing phase [25].

The findings of this study regarding wound epithelialization rates demonstrated that the KHHC dressing group exhibited a significantly lower epithelialization ratio compared with the control group on days 3 and 7. Therefore, the application of KHHC dressing during the inflammatory and proliferative phases did not result in superior skin wound healing and even appeared to delay reepithelialization. This result is consistent with previous studies, which reported that honey administration inhibited epithelialization activity during the wound healing phase, although it enhanced collagen deposition and promoted wound contraction [25,26].

The study, however, has several limitations that need to be acknowledged. The use of a preclinical mouse model limits direct extrapolation of the findings to human wound healing, particularly in chronic or infected wounds. The sample size was relatively small, and the observation period was limited to 14 days; therefore, longer-term outcomes such as scar quality, tensile strength, and complete tissue remodeling could not be assessed. In addition, the study evaluated only one KHHC formulation and honey concentration, so the optimal dose, formulation stability, and release profile of Aceh kelulut honey from the hydrocolloid matrix remain unclear. Molecular and biochemical markers related to inflammation, angiogenesis, collagen maturation, and epithelial repair were also not assessed, which limits mechanistic interpretation. Further studies using larger sample sizes, different wound models, extended follow-up, and formulation optimization are needed before clinical application can be recommended.

Conclusion

Macroscopically, the KHHC dressing had a marked effect on wound healing in the animal model as evidenced by changes in wound diameter. Microscopically, the dressing significantly influenced neutrophil and macrophage count, epithelialization ratio, myofibroblast ratio, and collagen fiber density. However, given the observed inhibition of reepithelialization despite accelerated wound closure, further studies are recommended to elucidate the mechanisms behind this effect, optimize dressing formulation, and evaluate long-term outcomes in different wound models.

Ethics approval

This study was approved by the Animal Research Ethics Committee of the Faculty of Veterinary Medicine, Universitas Syiah Kuala (Approval No. 373/KEPH/II/2025).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

How to cite

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