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ORIGINAL RESEARCH

Effectiveness of Indonesian Honey on the Acceleration of Cutaneous Wound Healing: An Experimental Study in Mice

Haryanto, RN, MS;[1,2] Tamae Urai, RN, MS;[1] Kanae Mukai, RN, MS;[1] Suriadi, RN, PhD;[2] Junko Sugama, RN, PhD;[1] Toshio Nakatani, MD, PhD[1]

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From the [1]Department of Clinical Nursing, Graduate School of Medical Science, Kanazawa University, Japan; [2]Institute of Nursing, Muhammadiyah Pontianak, Indonesia

Address correspondence to:
Toshio Nakatani, MD, PhD
Department of Clinical Nursing,
Graduate School of Medical Science
Kanazawa University
5-11-80 Kodatsuno
Kanazawa 9200942
Japan
nakatosi@staff.kanazawa-u.ac.jp

Abstract: The purpose of this study was to investigate the effectiveness of Indonesian honey in wound healing compared to Tegaderm hydrocolloid dressing and Manuka honey. Three groups of male mice were treated to produce 2 circular, full-thickness skin wounds on the dorsum. They were then randomly allocated to receive daily Indonesian honey, Manuka honey, or hydrocolloid (control). Macroscopic findings were observed from day 0 to 14 after wounding. Microscopic findings on days 3, 7, 11, and 14 after wounding were obtained. The ratios of wound areas for honey groups on day 3 were smaller than those of the control group. Wound areas of honey groups gradually decreased to almost the same wound area as the control group on day 14, while the control group wound area peaked on day 5 and rapidly decreased until day 14. On day 3, myofibroblasts and new blood capillaries in wound tissue of honey groups were observed, but were not seen in the control group. After day 7, microscopic findings were almost the same among the 3 groups. These results indicate that Indonesian honey is almost as effective for wound healing as Manuka honey and hydrocolloid dressing.

Wound healing is a dynamic physiological process initiated and influenced by many factors. The process can be divided into 4 stages: hemostasis, inflammation, proliferation (granulation, contraction, and epithelialization), and remodeling.[1]

Many modern dressings, such as hydrocolloids, gels, and foams, commonly have been used in clinical settings. However, these dressings are expensive in many developing countries. As an alternative, honey can be used as a topical dressing for wound care.

Honey is a byproduct of flower nectar and the upper aero-digestive tract of honey bees, which is concentrated through a dehydration process inside the beehive.[2] The use of honey as a medication has been known for thousands of years, for example, in the treatment of digestive organ disease, the eye, and respiratory issues.[3] Additionally, honey can be used as a topical therapy for burns, infections, and skin ulcers.[4]

To date, research has shown that honey is effective for the treatment of

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wounds, both clinically and in the laboratory. Several studies have shown honey to be effective at increasing granulation tissue and collagen, as well as epithelialization, when it is used as topical therapy in wound care.[5] Another study has reported that honey can also decrease wound area.[6] Generally, pure commercial unboiled honey is composed of approximately 40% glucose, 40% fructose, 20% water, amino acids, biotin, aminonicotinic acid, folic acid, pantothenic acid, pyridoxine, thiamine, enzymes (diastase, invertase), glucose oxidase and catalase, and the minerals calcium, iron, magnesium, phosphorus, and potassium.[6] Another study showed that honey is a mixture of sugars (about 40% fructose, 30% glucose, and 10% maltose), including oligosaccharides, minerals, carbohydrates, enzymes, and phytochemicals, such as flavonoids, and ferulic and caffeic acids.[7]

The purpose of this study is to investigate the effectiveness of Indonesian honey in accelerating wound contraction, granulation, epithelialization, and myofibroblast activity in wound healing in comparison with a modern dressing, Tegaderm™ hydrocolloid dressing (3M Health Care, Tokyo, Japan), and Manuka honey.

Keypoints

- Several studies have shown honey to be effective at increasing granulation tissue, collagen, and epithelialization when used as topical therapy in wound care.[5] Another study has reported that honey can also decrease wound area.[6]
- Wounds of the experimental groups were treated with either 0.1 mL Indonesian or 0.1 mL Manuka honey and were covered with gauze, as a secondary dressing, to prevent honey run-off and to absorb any exudate from the wound surface. This was compared to wounds treated with hydrocolloid dressings.

Methods

Animals. Thirty-six BALB/cCrSlc 8-week-old male mice weighing 22.0–23.8 g were used. Each mouse was caged individually in an air-conditioned room at 25.0˚C ± 2.0˚C with lighting from 08:45 to 20:45. Water and laboratory feed were given ad libitum. The experimental protocols were in accordance with the Guidelines for Care and Use of Laboratory Animals of Kanazawa University, Japan.

Honey. Two types of honey were used: Indonesian pure honey (*Apis dorsata*) and commercial honey, namely, Manuka honey (*Leptospermum scoparium*).

Wounding. Mice were anesthetized with intraperitoneal (IP) injection of sodium pentobarbital (0.05 mg/g weight). Two circular (4 mm in diameter), full-thickness skin wounds, including the panniculus on both sides of the dorsum of the mouse, were made with a sterile disposable biopsy punch (Kai Industries Co. Ltd., Gifu, Japan). The day when wounds were made was designated as day 0. Wounds of the experimental groups, Indonesian honey, and Manuka honey groups, were treated with either 0.1 mL Indonesian or 0.1 mL Manuka honey, respectively. Treatments were applied using a 1 mL syringe. All wounds on an individual animal received the same treatment. The wounds to which honey was applied were covered with gauze, as a secondary dressing, to prevent honey run-off and to absorb any exudate from the wound surface. The sterilized gauze was 28 mm x 10 mm. The gauze was changed and all wounds were treated with honey every day. Mice were wrapped twice with sticky bandages (Meshpore Tape, Nichiban, Tokyo, Japan) to prevent the gauze from slipping out of position. Wound healing progress was observed once daily from day 0 to day 14 after wounding. Meanwhile, wounds of the control group were covered with hydrocolloid dressing (Tegaderm). All mice were wrapped twice with sticky bandages, which were changed every day. Wound areas were traced on polypropylene sheets and photographs were taken every day. Wound areas were evaluated using Scion Image Beta 4.02 and Adobe Photoshop Elements 6.0.

Histological procedure. The mice were euthanized by a massive sodium pentobarbital IP injection on day 3, 7, 11, or 14 post wounding. The wounds and the surrounding normal skin were excised for an area of about 15 mm x 15 mm square, stapled onto polypropylene sheets to prevent over-contraction of the samples, and fixed in 4% paraformaldehyde in 0.2 mol/L phosphate buffer (pH 7.4) for 12 hours. The samples were dehydrated in an alcohol series, cleaned in xylene, and embedded in paraffin to prepare serial 5-µm sections.

Alternate sections of the wound center were stained with hematoxylin-eosin (H&E) or Azan, and immunohistologically stained with anti-alpha smooth muscle actin (α-SMA) antibody. The immunohistological staining was performed as follows: the paraffin of the sections was removed with xylene, washed with 0.01 mol/L phosphate-buffered saline (PBS), pH 7.4, covered with 0.03% hydrogen peroxide to block endogenous peroxidase for 20 minutes at room temperature, rinsed with PBS, incubated in a solution of monoclonal mouse anti-human alpha smooth muscle actin for 60 minutes at room temperature, rinsed with PBS, followed by incubation with Dako

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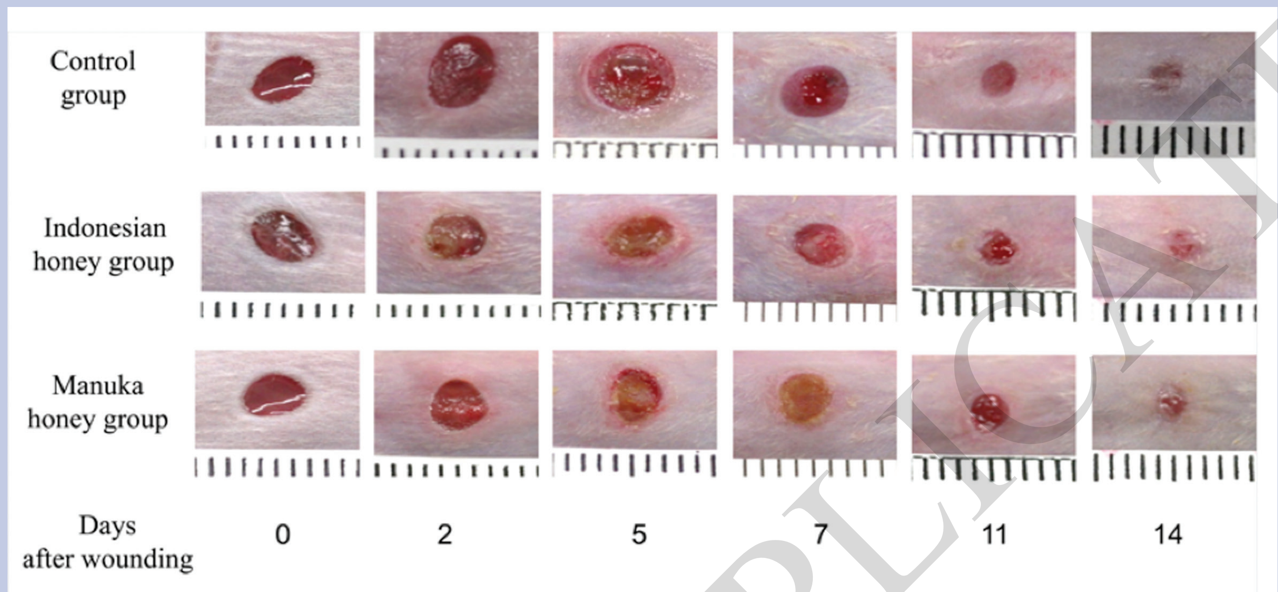

Figure 1. Macroscopic observation of wound healing. Wounds were created on Day 0. The wound areas of the control group and the hydrocolloid dressing group expanded more than that of the Indonesian and Manuka honey groups until day 10 after wounding. The wound areas of the honey groups decreased gradually. Wounds in all groups on day 14 were nearly the same size with minimal scarring. The width between marks is 1 mm.

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EnVision+System-HRP Labeled Polymer Anti-Mouse (Dako North America, Inc., Carpinteria, CA), and washed in PBS. The final reaction product was developed for 5–10 minutes with a 3,3'-diaminobenzidine substrate (Dako ENVISION Kit/HRP, Kyoto, Japan). The sections were washed in PBS and then counterstained with H&E and washed again in tap water. Negative controls were obtained by omitting primary antibody.

Neutrophil, capillary, and myofibroblast counting. The numbers of neutrophils, capillaries, and myofibroblasts in granulation tissue were counted by observation through a light microscope at 400x magnification. Five to 6 sections from 3 different mice for days 3, 7, 11, and 14 after wounding were used for the entire area from the center of the wounds, and were expressed in millimeters squared.

Measuring re-epithelialization and wound tissue thickness. Wound epithelialization was defined as the length of new epithelium (mm) divided by the length of wound on the day (mm), as determined using Adobe Photoshop Elements 6.0 and Scion Image Beta 4.02. Five to 6 sections were used from 3 different mice for days 3, 7, 11, and 14 after wounding. The thickness of wound tissue (mm) was measured at the midpoint of the wound on the section using Adobe Photoshop Elements 6.0 and Scion Image Beta 4.02. The thickness of the wound was the length of the perpendicular line to the wound surface from the line linking both panniculus muscles.

Keypoints

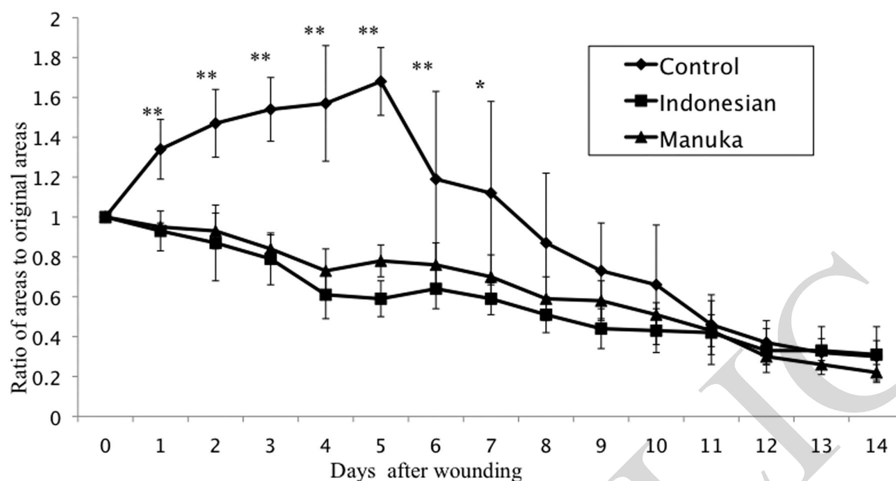
- The numbers of neutrophils, capillaries, and myofibroblasts in granulation tissue were counted by observation through a light microscope at 400x magnification.
- Wound epithelialization was defined as the length of new epithelium (mm) divided by the length of wound (mm) on the day of evaluation. Five to 6 sections were used from 3 different mice on days 3, 7, 11, and 14 after wounding.

Statistical Analysis

Data are expressed as mean ± SD, and were analyzed using JMP® 8.0.1 (SAS, Cary, NC). ANOVA and Tukey-Kramer multiple comparison test were performed. The differences were considered significant at $P < 0.05$.

Results

Macroscopic observation of wound healing. On the second through fifth days after wounding, the area surrounding the wound in Indonesian and Manuka honey groups had apparent redness, but no edema or odor (Fig-



Value was expressed Mean±SD. n = 6 per group . ANOVA, Tukey-Kramer
(* $p < 0.05$, ** $p < 0.01$)

Figure 2. Ratio of the wound area to the initial area on day 0.
On day 5, the wound areas in the control, Indonesian, and Manuka honey groups were 1.68 ± 0.12, 0.59 ± 0.02, and 0.78 ± 0.01 times as large as on day 0, respectively. There were significant differences between the control group, the Indonesia honey group (P =0.0001), and the Manuka honey group (P =0.0001). On day 14, the wound areas in control, Indonesian, and Manuka honey groups were 0.30 ± 0.08, 0.31 ± 0.14, and 0.22 ± 0.04, respectively. There were no significant differences between the control group, the Indonesian honey group (P = 0.98), or the Manuka honey group (P =0.35).

ure 1). This condition was the same as that of the control group, but the wound area in the control group was larger than those of the Indonesian and Manuka honey groups. On day 7, the area surrounding the wound in Indonesian and Manuka honey groups had no redness. The wound areas of both groups were smaller than on day 0. Granulation and new epithelium were observed. In the control group, granulation and new epithelium were apparent, but the wound area was larger than those in the Indonesian and Manuka honey groups. On day 11, the entire wound areas of all groups were covered by new epithelium, and the wound areas of all groups were almost the same. On day 14, wounds of all groups healed with scarring and were not infected.

The ratio of wound area. The ratios of wound areas on day 0 to day 14 after wounding to the initial wound area on day 0 were calculated (Figure 2). There was no significant difference between the wound area of the Indonesian honey group and that of the Manuka honey group throughout the entire period (day 0 to day 14 post wounding). Conversely, wound area in the control group increased after wounding, peaked on day 5, and then decreased rapidly. While there were significant differences between the control group and the Indonesian and Manuka honey groups from 1 day to 10 days after wounding, on day 11 post wounding, the wound areas in control, Indonesian, and Manuka honey groups were 0.46 ± 0.15, 0.42 ± 0.16, and 0.43 ± 0.08 times smaller, respectively, on day 11 than day 0, and there were no significant differences between the control group and the Indonesian honey (P = 0.87) and Manuka honey groups (P = 0.92) on day 11 after wounding.

Histological observations. On day 3 post wounding, during the inflammation phase, new epithelium along the wound edge appeared in all groups and expanded toward the center of the wound (Figure 3). The wound floor in the control group expanded more so than in the experimental groups, possibly due to edema. In the control group, no granulation tissue was observed. Thin collagen fibers colored blue by Azan staining were observed in the wound tissue of all groups. Many neutrophils and macrophages were already present in the wound tissue of all groups. New blood capillaries and myofibroblasts containing α-smooth muscle actin stained brown were

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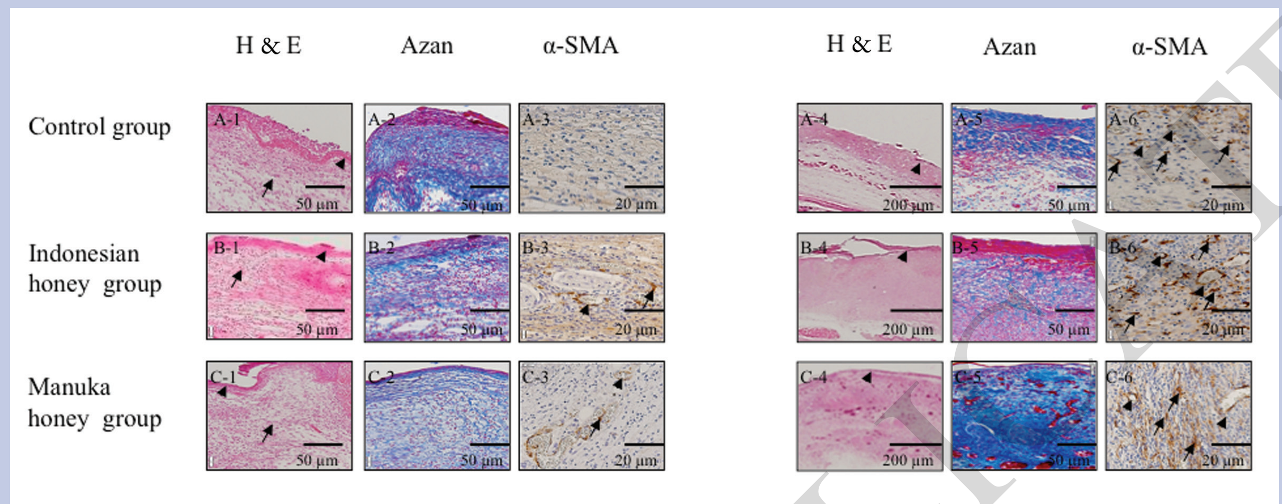

Figure 3. Histology on day 3 (above left) and day 7 (above right) after wounding. Control (hydrocolloid dressing) group on day 3 (A-1–A-3) and on day 7 (A-4–A-6). Indonesian honey group on day 3 (B-1–B3) and day 7 (B-4–B6), and Manuka honey group on day 3 (C-1–C3) and day 7 (C-4–C-6). Many neutrophils (arrows) were observed in wound areas of all groups on day 3, and decreased slightly on day 7; edges of new epithelium (arrowheads) were present at the wound edge on day 3 (A-1, A-4, B-1, B-4, C-1, C-4). Thin collagen fibers stained dark blue were present across the wound area in all groups on day 3, and became bundles of collagen comprising part of the granulation tissue on day 7 (A-2, A-5, B-2, B-5, C-2, C-5). Although nonspecific staining was present in the wound tissue of the control group on day 3 (A-3), neither myofibroblasts nor new blood vessels could be found. On the other hand, myofibroblasts (arrows in B-3, C-3) and new blood vessels (arrowheads in B-3, C-3) were observed. On day 7, numerous myofibroblasts (arrows in A-6, B-6, C-6) and new blood capillaries (arrowheads in A-6, B-6, C-6) were present in the wound area of all groups, which were related to the granulation tissue.

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already observed in the wound tissue of Indonesian honey and Manuka honey groups, but not in the control group. This may indicate that granulation tissue consisting of collagen fibers and new blood capillaries formed more rapidly as a result of the Indonesian and Manuka honey.

On day 7 after wounding, granulation tissue consisting of collagen fibers and new blood capillaries was observed and filled the concave space of the wound in the control group (Figure 3). New epithelium formed along the wound edge and almost covered the wound surfaces in all groups, while new epithelium covered the wound surface of the control group more widely than those of the experimental groups. Collagen bundles in the Indonesian honey group seemed to be thicker than those of the other groups in the granulation tissue. In the Indonesian honey and Manuka honey groups, many myofibroblasts and blood capillaries appeared in granulation tissue, which were more abundant than those on day 3. Myofibroblasts in granulation tissue of the Indonesian honey group seemed to be more abundant than those in Manuka honey and control groups.

On day 11, the wound surface was almost completely covered with new epithelium. All groups exhibited collagen throughout the granulation tissue. Myofibroblasts appeared throughout the granulation tissue in the Indonesian honey group and were more abundant than those in the control group. Myofibroblasts in the Manuka honey group appeared in the granulation tissue and were more abundant at the wound edges, and were also more abundant than those of the control group.

On day 14, the wound surface was completely covered with new epithelium. Tight bundles of collagen filled the whole of the granulation tissue of all groups and produced scars. Myofibroblasts appeared throughout the granulation tissue and underneath the new epithelium in all groups. A few blood capillaries were observed in the scars of all groups.

Neutrophils. On day 3, the numbers of neutrophils in the Indonesian honey and Manuka honey groups were larger than that of the control group (Table 1). There were significant differences between the control group and the Indonesian honey group (P = 0.0003) and the Manuka honey group (P = 0.0010). However, there was no

Table 1. Number of neutrophils, myofibroblasts, and new blood capillaries (mm^2) .

Neutrophils				
Groups	**Days After Wounding**			
	3	**7**	**11**	**14**
Control	2268.00±364.96†	1157.83± 88.50*	203.50±42.50	129.20±25.37
Indonesian	3336.67±254.39†	1579.60±407.69*	202.50±30.25	140.66±29.53
Manuka	3177.57±383.84†	1169.67 ± 51.24*	201.80±29.65	108.50± 4.23
Control = 5, Indonesian = 6, Manuka = 6				
Myofibroblasts				
Groups	**Days After Wounding**			
	3	**7**	**11**	**14**
Control	00.00±00.00*†	195.16±54.48	138.16±25.03	127.66±20.76
Indonesian	47.80±27.08*†	210.50±68.31	139.00±25.72	129.00±10.65
Manuka	42.33±27.60†	232.00±37.74	152.60±51.40	106.33±48.42
Control = 6, Indonesian = 6, Manuka = 5				
New Capillaries				
Groups	**Days After Wounding**			
	3	**7**	**11**	**14**
Control	00.00±00.00†	39.00±5.21	43.25±21.26	21.25±8.13
Indonesian	12.33±5.00†	43.00±6.32	46.25±26.51	16.50±12.44
Manuka	16.83±6.61†	42.00±7.79	50.40±11.39	18.00±6.21
Control = 6, Indonesian = 6, Manuka = 6				
Values are expressed as mean ± SD, ANOVA, Tukey-Kramer. *$P < 0.05$ †$P < 0.01$				

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significant difference between the Indonesian honey and Manuka honey groups (P = 0.68).

On day 7, the numbers of neutrophils in Indonesian honey, Manuka honey, and control groups decreased compared with those on day 3. There were significant differences between the control group and the Indonesian honey group (P = 0.02) and the Manuka honey group (P = 0.02). However, there was no significant difference between the Indonesian honey group and the Manuka honey group (P = 0.99). After day 7, the numbers of neutrophils in Indonesian honey, Manuka honey, and control groups decreased. There was no significant difference in this regard between the control group and the Indonesian honey group (P = 0.99) or the Manuka honey group

Table 2. Rate of wound re-epithelialization (%).				
Groups	**Days After Wounding**			
	3	**7**	**11**	**14**
Control	17±14*	59±17	69±41	100±00
Indonesian	26±11*	68±16	84±24	100±00
Manuka	48±27*	56±14	86±13	100±00
Control = 5, Indonesian = 5, Manuka = 5				
Values are expressed as mean ± SD, ANOVA, Tukey-Kramer. *$P < 0.05$				

Table 3. Wound tissue thickness (mm).				
Groups	**Days After Wounding**			
	3	**7**	**11**	**14**
Control	0.23±0.22	0.38±0.13	0.65±0.11	0.83±0.23
Indonesian	0.25±0.02	0.47±0.09	0.61±0.19	0.83±0.36
Manuka	0.22±0.21	0.51±0.13	0.59±0.22	0.79±0.22
Control = 5, Indonesian = 5, Manuka = 5				
Values are expressed as mean ± SD, ANOVA, Tukey-Kramer.				

(P = 0.99), or between the Indonesian honey group and the Manuka honey group (P = 0.99).

Myofibroblasts. On day 3, myofibroblasts in Indonesian and Manuka honey groups were already observed, but no myofibroblasts were observed in the control group (Table 1). There were significant differences between the control group and the Indonesian honey group (P = 0.012) and the Manuka honey group (P = 0.007). However, there was no significant difference between the Indonesian honey group and the Manuka honey group (P = 0.91). On day 7, numerous myofibroblasts appeared in the granulation tissue of the control group, and thus, the significant differences among all groups disappeared. In this period, the number of myofibroblasts of all groups peaked and then decreased gradually on days 11 and 14.

Capillaries. On day 3, new blood capillaries in Indonesian and Manuka honey groups were already observed, but no new blood capillaries were observed in wound tissue of the control group (Table 1). There were significant differences between the control group and the Indonesian honey group (P = 0.0013) and the Manuka honey group (P < 0.0001) in this regard. However, there was no significant difference between the Indonesian honey and the Manuka honey groups (P = 0.26). On day 7, the numbers of capillaries of all groups increased and there was no significant difference among all groups. On day 11, the numbers of blood capillaries of all groups peaked and then decreased rapidly on day 14.

Rate of re-epithelialization. On day 3 after wounding, the rates of re-epithelialization of Indonesian honey and Manuka honey groups were faster than that of the control group (Table 2). There was no significant difference between the control group and the Indonesian honey group (P = 0.67) or the Indonesian honey group and the Manuka honey group (P = 0.14). However, there was a significant difference between the control group and the Manuka honey group (P = 0.02).

As the new epithelium of the control group formed rapidly, on day 7 no significant difference of the ratio of re-epithelialization among all groups was observed. On day 11, some wound surfaces were not completely covered with new epithelium. On day 14, all wound surfaces

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Keypoints

- On day 7, the area surrounding the wound in the Indonesian and Manuka honey groups had no redness. The wound areas of both groups were smaller than on day 0. Granulation and new epithelium were observed. In the control group, granulation and new epithelium were apparent, but the wound area was larger than those in the Indonesian and Manuka honey groups.
- Microscopic analysis on day 3 found that the numbers of neutrophils in Indonesian honey and Manuka honey groups were greater than that of the control group; however, by day 7, the numbers of neutrophils in Indonesian honey and Manuka honey groups had decreased rapidly. There was no redness of the skin surrounding the wounds of either honey group. The control group had periwound edema, and number of neutrophils in the control group was greater than the Indonesian and Manuka honey groups.

were completely covered with new epithelium.

Wound tissue thickness. On day 3, the thickness of wound tissue for the Indonesian honey group was greater than that of the control group and the Manuka honey group (Table 3). However, there was no significant difference among groups. As wound healing progressed, the thickness of the wound tissue, that is, granulation tissue and scar, of all groups increased. However, there was no significant difference among the 3 groups on days 7, 11, and 14 post wounding.

Discussion

Indonesia is a developing, tropical country that is home to many types of honey. Indonesian honey has been used frequently in topical therapies and traditional medicine. Therefore, the authors expected that Indonesian honey could be used for wound care. To date, the effects of Indonesian honey on accelerating wound contraction, re-epithelialization, granulation tissue formation, and the distribution of myofibroblasts have not been investigated histologically. Therefore, the authors investigated the effectiveness of Indonesian honey on wound healing in mice. To the best of the authors' knowledge, this study is the first to compare Indonesian honey to Manuka honey and a modern hydrocolloid dressing in mice.

Macroscopic observations revealed that the ratios of wound area in the Indonesian honey group on days 2, 5, and 7 were smaller than those of the control group and that there was a significant difference. On day 7, the areas surrounding the wound in Indonesian honey and Manuka honey groups had no redness. Moreover, both groups exhibited clean, newly formed granulation tissue and new epithelium. In a previous study, on postoperative day 7, lesions treated with honey in rabbits did not show signs of acute inflammation, and epithelialization had occurred[8]; this concurs with what was seen in the present study.

Microscopic analysis on day 3 found that the numbers of neutrophils in Indonesian honey and Manuka honey groups were greater than that of the control group. This was supported by macroscopic findings on days 2 and 5 when redness was observed in the areas surrounding the wounds in the Indonesian and Manuka honey groups. However, on day 7, the numbers of neutrophils in the Indonesian honey and Manuka honey groups decreased rapidly. There was no redness in the area surrounding the wounds in either group. The control group had periwound edema, and the number of neutrophils in the control group was greater than the Indonesian and Manuka honey groups; they were both significantly different from the control group. Antibacterial activity of honey could be due to its high osmolarity, low pH (3.6–3.7), and the presence of hydrogen peroxide.[6,8,9] Hydrogen peroxide forms free radicals[10] that serve to recruit more leukocytes into areas of inflammation, which then promotes the production of proinflammatory cytokines by leukocytes.[11] Another study reported that Manuka honey significantly increased the production of proinflammatory cytokines.[12] Although the effect of the type of honey on the number of neutrophils by topical administration has not been reported, in a previous study of mice treated by injection with jungle honey from a tropical country, it was shown that the number of neutrophils increased and an effective immune function was observed.[13] The authors assumed that honey from Indonesia, a tropical country, may have chemotactic activity on neutrophils. In contrast to the present study, another study using pure honey, the type of which was not reported, found that the number of neutrophils was smaller on day 2 than that of a control group.[8] This difference may be due to the honey's properties.[14,15] However, the present study showed that inflammation processes with Indonesian honey and Manuka honey were shorter than that of the control group.

Epithelialization is one of the most important factors in wound healing. A previous study in mice showed that the level of wound re-epithelialization was 0.95 mm on day 3, 1.68 mm on day 6, and increased to 2.27 mm on day 9.[6] Another study reported that acceleration of epithelialization with honey occurred between 6 and 9 days

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clinically and histologically.[9] The present findings were that wound re-epithelialization with Indonesia honey reached 26% on day 3, increased to 68% on day 7, and 69% on day 11, and achieved complete epithelialization on day 14. However, the level of wound re-epithelialization with Manuka honey was higher than those of the other groups on day 3 and was significantly different from that of the control group; it increased to 56% on day 7, 86% on day 11, and reached complete epithelialization on day 14. The results for this variable for Indonesian honey and Manuka honey groups showed no significant differences. On the other hand, on day 3, the re-epithelialization of the control group was about 17% and was slower than that of the experimental group; however, it did rapidly catch up with that of the experimental groups on day 7 and was almost completed on day 11, as in the experimental groups. This indicates that the effectiveness of Indonesian and Manuka honey for re-epithelialization is almost the same as that of the hydrocolloid dressing.

Collagen synthesis requires energy. This energy may be provided by sugars contained in honey, which enters the glycolysis pathway as a source of energy for fibroblasts and enable synthesis of collagen; this could be shown by the fibroblast proliferation and collagen synthesis on day 8.[16] Although the thickness of wound tissue in the present study did not become so thick, as was the case in the study by Ghaderi and Afshar,[17] the levels of effectiveness of Indonesian and Manuka honey on the formation of collagen fibers were almost the same as that of the hydrocolloid dressing—the present results showed that the thickness of wound tissue with Indonesian honey was 0.47 mm on day 7 and reached 0.83 mm on day 14. The results for Manuka honey were 0.59 mm on day 7 with an increase to 0.79 mm on day 14. The results of hydrocolloid dressing were 0.38 mm on day 7 with an increase to 0.83 mm on day 14.

The formation of granulation tissue by honey might also occur via the stimulation of growth of fibroblasts by the hydrogen peroxide contained in honey.[18] Myofibroblasts were seen on day 3 in the Indonesian and Manuka honey groups. They exhibited significant differences compared with the control group. However, the Indonesian and Manuka honey groups were not significantly different in this regard. This result showed that the formation of granulation tissue and the proliferation of fibroblasts in Indonesian and Manuka honey groups was faster than the control group. A new finding of the present study was that, on day 3, new capillaries in the honey groups were observed and they were significantly different from the findings for the control group.

Keypoints

- Indonesian honey and Manuka honey were more effective in depressing the inflammatory reaction in the wound than Tegaderm hydrocolloid sheet dressing. Indonesian and Manuka honey accelerated the formation of granulation tissue more than the hydrocolloid dressing.

In Indonesia, the prices for Indonesian honey, Manuka honey, and hydrocolloid sheet dressings are $6 per 1000 mL, $99.99 per 10 sheets in a box, and $15 per 5 sheets in a box, respectively. In the clinical use of Indonesian honey for wound care, 20 mL is used for covering a wound area of 20 cm^2 for 1 day, so the amount for 14 days is only 280 mL. Manuka honey involves the use of 1 sheet per day, so 14 sheets for 14 days are required. The use of hydrocolloid needs 1 sheet per day with every dressing change; therefore, during 14 days, 14 sheets are required. It can be calculated that the total cost of treatments using Indonesian honey, Manuka honey, and hydrocolloid sheet dressings are $1.68, $139.98, and $37.5, respectively, for 14 days of treatment.

Conclusion

The levels of effectiveness of Indonesian honey and Manuka honey in wound healing were nearly equivalent. Indonesian honey and Manuka honey were more effective in depressing the inflammatory reaction in the wound than hydrocolloid sheet dressing. Indonesian and Manuka honey accelerated the formation of granulation tissue more than the hydrocolloid dressing. Wound contraction during wound healing by topical treatment of Indonesian and Manuka honey was slow, while that of the hydrocolloid sheet dressing was rapid after the wound area enlarged during inflammation. The period before a scar formed in Indonesian and Manuka honey groups was almost the same as that of the hydrocolloid group.

Indonesian honey can be used as a topical therapy as an alternative dressing on various wounds because it is similarly effective for wound healing as Manuka honey and hydrocolloid, while being comparatively less expensive.

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