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Original Article

Date and honey mixture compared with honey alone for diabetic foot ulcer healing

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Abstract

Purpose

A date and honey mixture is used in Indonesia to promote wound healing. However, no studies have evaluated its effects. Thus, this study evaluated the effectiveness of the date and honey mixture in promoting diabetic foot ulcer（DFU）healing, and its effects on biofilm intensity and biomarker levels.

Methods

This observational study enrolled 30 patients with recurrent DFU treated using the date and honey mixture and 30 patients with recurrent DFU treated only using honey. Both groups were observed every 2 weeks for up to 8 weeks. The Kaplan-Meier method and log-rank test were used to compare the DFU healing proportion. Moreover, the Cox proportional-hazards model was used to assess the effects of the date and honey mixture on wound healing. Superoxide dismutase 3（SOD3）and interleukin（IL）-6 were evaluated as oxidative stress and inflammatory status markers, respectively. These biomarkers and biofilms were collected using wound blotting every 2 weeks. The linear mixed-effect model was performed for biomarkers.

Results

No significant difference was noted between the two groups in patient or wound characteristics at baseline,

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except for the diabetes duration. The proportion of wound healing was significantly higher in DFU treated by the date and honey mixture than when treated only using honey (p=0.015). The adjusted hazards ratio of the date and honey mixture was 8.55 (95% confidence interval=1.03-70.72; p=0.046), which was also significantly different for the biofilm intensity (p=0.008), IL-6 (p=0.015), and SOD3 (p<0.001).

Conclusion

The date and honey mixture may promote wound healing in recurrent DFU.

Key Words：biomarker, date fruit, diabetic foot ulcer, honey, wound healing

Introduction

Diabetic foot ulcer (DFU) recurrence is prevalent and can be difficult to treat. Several previous studies reported the prevalence of recurrent DFU to be as high as 59.3%[1)-3)] and 54.3%[4)] in Europe and Indonesia, respectively, which burdens both the patient and the national healthcare system because treatment can be expensive. Thus, promoting wound-healing techniques using local wound management is essential to reduce costs.

The recommendations promoted by the International Working Group on the Diabetic Foot[5)], especially intervention guidelines, to promote DFU healing, should be applied. However, one barrier to DFU treatment in Indonesia is the medication cost[6)]. Access to the recommended medications, including modern dressings and biophysical therapeutic agents, is limited. Thus, complementary therapy is a common method to manage DFU in Indonesia.

Honey is the most common first-choice DFU treatment in Indonesia. Clinical randomized controlled trials (RCTs)[7)-10)] reported that the healing rate (50%–97%) among patients with DFU treated by honey was higher than that in the control group. In these RCTs, the wounds were Wagner grades I and II, and glycemic control was good (<10.0%). However, 5.7%–70% of DFU wounds in Indonesia are grade III or higher[4)11)12)], and glycemic control is often poor (>10.0%)[12)]. Previously, a prospective study revealed that the DFU healing rate within 12 weeks of receiving honey treatment is 38% in Indonesian wound-care clinics[13)]. Thus, the effectiveness of honey in promoting wound healing is limited for severe DFU stages or for DFU that develops in patients with poor glycemic control.

One factor that impedes DFU healing is bacterial colonization and biofilm formation. DFU wounds harbor several bacterial species[14)], causing the formation of polymicrobial biofilms[15)]. Encapsulation in biofilms increases bacterial resistance to antibiotic treatment[16)], and persistent bacterial colonization can delay wound healing because of the release of virulence factors and sustained inflammation[17)]. Reducing biofilm formation has therefore been considered important for the successful healing of chronic wounds[18)].

Glycemic control is poor among patients with recurrent DFU in Indonesia. High blood sugar levels can stimulate macrophages, increasing the production of proinflammatory cytokines (e.g., interleukin (IL)-1β, IL-6, IL-12, IL-18, and tumor necrosis factor-α)[19)]. Previous studies reported that IL-6 increased significantly in patients with diabetes with ulcers compared with patients with diabetes without ulcers[20)]. Moreover, hyperglycemia may also result in the increased production of reactive oxygen species (ROS)[21)]. Furthermore, ROS are formed due to glucose autooxidation, metabolism, and advanced glycosylation end-product development. Therefore, reducing inflammation and oxidative stress may represent an essential strategy to promote wound healing under poor glycemic control conditions.

Several studies reported that the chemical compounds found in dates possess phytochemical functions (e.g., antibacterial[22)-24)], antibiofilm[22)25)], anti-inflammatory[24)26)-28)], and antioxidant[27)-31)], which can promote the wound-healing process. Consequently, dates may be used as a topical dressing instead of honey, based on the effects of the chemical compounds and phytochemicals identified. Similar to dates, honey has phytochemical functions (e.g., flavonoids, ferulic and caffeic acids[18)32)], antibacterial[19)33)], antibiofilm[20)-22)34)-36)], immunostimulatory[23)24)37)38)], and anti-inflammatory effects[25)26)39)40)], which can promote the wound-

healing process. Both dates and honey have good phytochemical functions, and both were combined as topical dressings for greater wound healing-promoting effects. In addition, dates promoted wound healing in an animal study[41]. However, the effectiveness of dates in clinical use to treat recurrent DFU or DFU that develops in patients with poor glycemic control remains unclear.

This study hypothesized that a mixture containing both dates and honey is effective for wound healing by eliminating biofilms and inflammatory cytokines, and reducing oxidative stress in DFU. This study investigated the effectiveness of the mixture of dates and honey in promoting wound healing in patients with recurrent DFU.

Materials and Methods

1. Study design

This study was a prospective, observational design performed between September 2018 and March 2019. The total number of patients and the number of patients for each group were estimated based on the preliminary survey at the study clinic. Each patient's local wound care was selected by the wound specialist nurse in the clinic.

2. Setting and patients

The study was conducted at the Kitamura Clinic, a private wound-care clinic in a rural area of West Borneo, Indonesia. Moreover, wound care was based on the wound status using modern dressings and complementary therapy.

The study populations were patients using recurrent DFU treated with the date and honey mixture who met the following criteria: diabetes, type 2; age, ≥ 26 years (early adult to older);[42] level of hemoglobin A1c (Hb A1c), ≥ 6.5%; ankle-brachial index (ABI), 0.9–1.2 mmHg; wound recurrence; and wound grade 1–4 according to the Wagner classification. A recurrent ulcer was defined as any secondary ulcer, regardless of its location[43]. The exclusion criteria were participants who had a wound above the ankle, DFU with systemic infection, wound size <1 cm^2, whole-foot gangrene, severe disease, congestive heart failure, chronic renal failure, and peripheral arterial disease. Patients who were unable to visit the clinic regularly were also excluded.

Patients with DFU treated by honey alone were also enrolled in this study as controls during the same study period. The inclusion and exclusion criteria were the same as those for patients with DFU treated using the date and honey mixture.

3. Materials

This study used two materials. The first material was the date extract. The University of Tanjungpura Pontianak (West Kalimantan, Indonesia) pharmacy provided extracts from Ajwa date palms, commonly known as *Phoenix dactylifera* L., cultivated in Medina, Saudi Arabia. The dates were dried at room temperature for 2 weeks and pulverized. The pulverized dates were macerated in 96% ethanol for 48 h. The mixture was filtered, and the extract was then concentrated using a rotary evaporator set at 40℃ after 48 h and stored at 4℃–8℃ until further use. The second material used for the control treatment was *Trigona thoracica* honey[44]. The volume of mixing between the date extract and honey was 1,000 mL, and the volume of each was equal. The mixture was then stored at 4℃–8℃ . Either honey alone or the date and honey mixture was applied to the wound surface by applying the material to wet gauze, which was then placed on the wound surface. The frequency of use depended on the wound condition.

4. Outcome measures

1) Primary outcome

The primary outcome was wound healing, which was defined as complete wound epithelialization based on an observation within 8 weeks using the Diabetic Foot Ulcer Healing Scale (DMIST)[45], which can assess the DFU wound status. The DMIST consists of 11 domain items, and the total score ranges from 0 to 34. A score of zero indicates DFU healing.

2) Secondary outcomes

Three secondary outcomes were evaluated: biofilm intensity, superoxide dismutase 3 (SOD3) level, and IL-6 level. The biofilm intensity was used as an indicator of the local bacterial colonization status. Furthermore, SOD3 and IL-6 were evaluated as oxidative stress and inflammatory status markers, respectively.

5. Confounding factors

Demographic data, including sex, age, education, ethnicity, occupation, diabetes mellitus (DM) duration, medical history, smoking status, and DM therapy type, were obtained from the patients' medical records. One of the researchers measured the Wagner grading system, blood pressure, glycemic status, body mass index (BMI), sensory status tested by the monofilament test, and ABI.

6. Procedure

The bedside procedure was as follows: (1) The dressing was removed from the wound surface; (2) the nitrocellulose membranes were moistened with normal saline; (3) the first membrane was attached to the wound bed for 10 s and removed (for biofilm detection); (4) the same procedure was performed for the second membrane (for IL-6 and SOD3 detection); (5) the membranes were stored in plastic bags; (6) a photograph of the wound was taken, and the ABI, blood pressure, and monofilament test were evaluated; (7) a new dressing containing the date and honey mixture or honey alone was applied; and (8) the BMI and glycemic status were measured.

Biofilm detection was performed based on the method described by Nakagami et al[18) 46) 47)]. A piece of premoistened nitrocellulose membrane was attached to the wound bed for 10 s. The biofilm was then stained using the CC Steps Biofilm Detection Tools (Saraya Co., Ltd., Osaka, Japan). The stained biofilm was scanned using a document scanner (Canon G2010) and processed using Photoshop CC software (Adobe Systems, San Jose, CA, USA) for background elimination. Lastly, the preprocessed images were used to quantify the area and biofilm intensity using ImageJ software (version 1.51j; National Institutes of Health, Bethesda, MD, USA)[48)] as follows: (1) color images of membranes were changed to color charts for image correction by imprinting color- and size-matching stickers on the subject (CasMatch, Funakoshi, Japan); (2) this image was then changed to a grayscale Tiff file; (3) the next gray image was set at a threshold image with a scale of 240, and then changed to a bitmap image; (4) colors were converted to grayscale and inverted; and (5) the average brightness was measured using ImageJ software. All conditions used during image adjustment with Photoshop and ImageJ were standardized across all images to enable comparisons.

The IL-6 and SOD3 levels on the wound bed were evaluated by the wound blotting method[46)]. Furthermore, another piece of premoistened nitrocellulose membrane was attached to the wound bed after collecting the biofilms, and the membrane was treated with 20% methanol to fix the proteins and inactivate any microorganisms on the membrane. The fixed membranes were stored at −4 ℃ until analysis. The membranes were incubated for 1 h at room temperature with a mixture containing antibodies against IL-6 (sc-130326AF488; Alexa-Fluor 488-conjugated mouse monoclonal; 1: 250; Santa Cruz Biotechnology Inc., Eugene, OR, USA) and SOD3 (sc-271170AF647, Alexa-Fluor 647-conjugated mouse monoclonal; 1:250; Santa Cruz Biotechnology Inc.) for the simultaneous visualization of IL-6 and SOD3 on the membrane. The stained membranes were then scanned using a fluorescence scanner (Typhoon 9400, GE Healthcare, Chicago, IL, USA). The scanner setup was a 526 SP filter, 488-nm blue laser, normal sensitivity, and photomultiplier (PMT) voltage of 550 V for IL-6; and a 670 BP 30 filter, 633-nm red laser, normal sensitivity, and PMT voltage of 550 V for SOD3. The images obtained were used to quantify the intensity of each protein using the same procedure described for biofilm analysis.

7. Statistical analyses

Demographic data and wound characteristics are reported using descriptive statistics. Continuous variables are presented as the means and standard deviations or as medians with interquartile ranges. Categorical variables are reported as counts and percentages. The independent-sample Student's t-test, Mann-Whitney *U* test, chi-squared test, and Fisher's exact test were used to test the significance of differences between groups. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normal distribution of variables.

The Kaplan-Meier method and log-rank test were used to compare the DFU healing proportion between the two groups, and the Cox proportional-hazards model was used to assess the effects of the date and

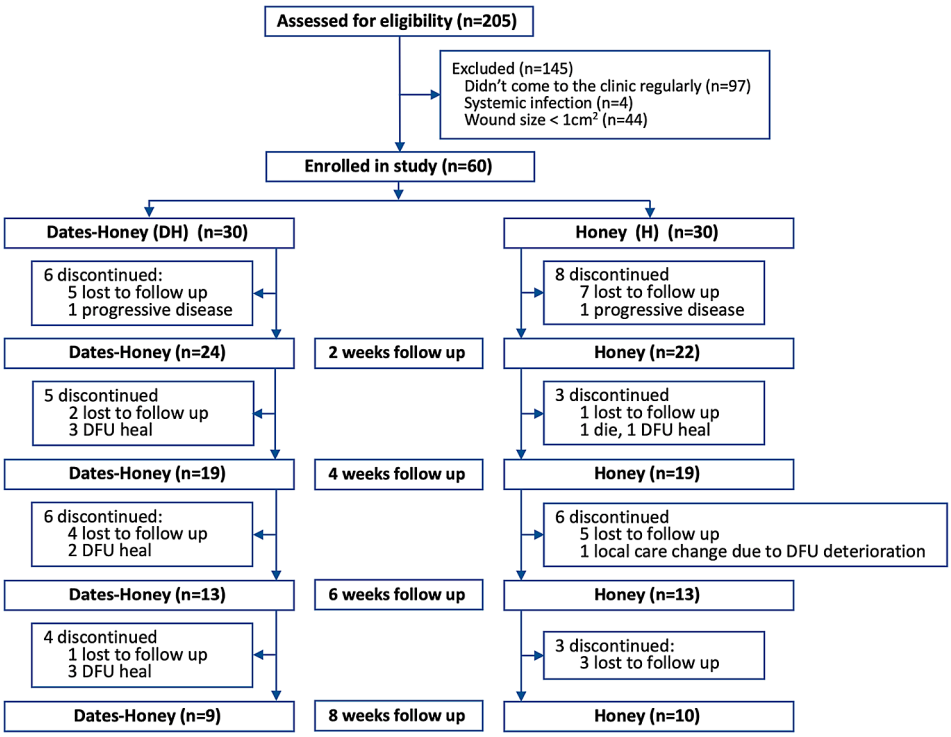

Figure 1　Flow chart of participants

honey mixture on wound healing. A linear mixed-effect model was used to compare secondary outcomes between the two groups and within the group.

The significance level was set at $p < 0.05$. All analyses were conducted using SPSS 22.0 (IBM Cooperation, Armonk, NY, USA).

8. Ethical considerations

The ethics committee of the Department of Medical Sciences at Kanazawa University (approval number 49-1) and the Institute of Nursing Muhammadiyah, Pontianak, Indonesia (approval number: 131/II.I.AU/KET.ETIK/VIII/2018), approved this study. This study was performed following the principles of the Declaration of Helsinki. Informed consent was received from the patients.

Results

1. Patient characteristics

This study recruited 205 eligible patients between September 2018 and March 2019. Of the patients, 145 who did not match the study requirements were excluded after eligibility assessment. In total, 30 patients treated using the date and honey mixture, and 30 patients treated only using honey were enrolled in this study. During this study, eight wounds (8/30; 26.7%) healed in the date and honey mixture (DH) group, and one wound (1/30; 3.3%) healed in the honey (H) group (**Figure 1**).

The baseline characteristics of the patients are shown in **Table 1**. No differences were found between the two groups at baseline in terms of demographic characteristics, except for DM duration (8.0 vs. 3.5 years, $p = 0.034$). The baseline wound characteristics are shown in **Table 2**. Consequently, no significant differences were found among wound characteristics between the groups.

2. Primary outcome

The proportion of wound healing within 8 weeks was significantly higher for DFU treated by the DH mixture than for those treated by only honey ($p = 0.015$; **Figure 2**). The adjusted hazards ratio of the DH mixture for wound healing was 8.55 (95% confidence interval (95% CI) = 1.03-70.72, $p = 0.046$; **Table 3**).

3. Secondary outcomes

The biofilm intensity changes in 8 weeks were significantly different between the two groups ($p = 0.008$; **Figure 3**). The DH group exhibited significantly lower biofilm intensities ($p < 0.001$). Similarly, the H group had significantly lower biofilm intensities ($p = 0.001$).

Table 1 Baseline patient characteristics

Characteristics	DH group (n=30)	H group (n=30)	*p*
Sex			
Female	19 (63.3%)	24 (80%)	0.152 [c]
Male	11 (36.7%)	6 (20%)	
Age (years)	57.40 ± 80.07	53.67 ± 9.31	0.102 [a]
Education			
Elementary school	11 (36.7%)	15 (50.0%)	0.626 [d]
Primary school	8 (26.7%)	4 (13.3%)	
High school	5 (16.7%)	4 (13.3%)	
University	3 (10%)	2 (6.7%)	
Uneducated	3 (10%)	5 (16.7%)	
Ethnicity			
Malays	9 (30%)	12 (40%)	0.530 [d]
Madurese	4 (13.3%)	4 (13.3%)	
Javanese	5 (16.7%)	5 (16.7%)	
Buginese	1 (3.3%)	3 (10.0%)	
Chinese	7 (23.3%)	5 (16.7%)	
Sundanese	0 (0%)	1 (3.0%)	
Dayak	3 (10%)	0	
Gorontaloan	1 (3.3%)	0	
BMI (kg/m^2)	22.75 ± 3.07	23.26 ± 3.29	0.530 [a]
Occupation			
Housewife	16 (53.3%)	20 (66.7%)	0.683 [d]
Merchant	2 (6.7%)	3 (10%)	
Farmer	3 (10%)	1 (3.3%)	
Employer	1 (3.3%)	1 (3.3%)	
Private worker	2 (6.7%)	2 (6.7%)	
Retired	3 (10%)	1 (3.3%)	
Stoped working	2 (6.7%)	0	
Police	0	1 (3.3%)	
Security	1 (3.3%)	0	
Freelance	0	1 (3.3%)	
Duration of DM (years)	8.0 (2.8-13.0)	3.5 (1.0-10.0)	0.034 [b]
Oral hypoglycemia			
Yes	23 (76.7%)	20 (66.7%)	0.390 [c]
None	7 (23.3%)	10 (33.3%)	
Insulin			0.644 [e]
Yes	5 (16.7%)	2 (6.7%)	0.424 [d]
None	25 (83.3%)	28 (93.3%)	
Blood Sugar (mg/dl)	255.0 ± 115.1	247.6 ± 132.7	0.562 [a]
HbA1c (%)	10.8 ± 2.4	10.6 ± 2.6	0.690 [a]
Neuropathy			0.645 [e]
Yes	16 (53.3%)	21 (70.0%)	0.184 [c]
None	14 (46.7%)	9 (30.0%)	
Medical history			
Hypertension	2 (6.7%)	3 (10.0%)	1.000 [d]
Gastritis	3 (10%)	2 (6.7%)	
Heart disease	1 (3.3%)	1 (3.3%)	
Typhus abdominals	1 (3.3%)	0	
Asthma	0	1 (3.3%)	
Tuberculosis	0	1 (3.3%)	
None	23 (76.7%)	22 (73.4%)	
ABI wound location	1.02 ± 0.02	1.05 ± 0.02	0.926 [a]
Smoking			
Smoker	4 (13.3%)	1 (3.3%)	0.353 [d]
History of smoking	0	0	
None-smoker	26 (86.7%)	29 (96.7%)	
Blood pressure			
Systole	143 (129-174)	136 (121-148)	0.053 [b]
Diastole	84 (74-94)	83 (78-90)	0.912 [b]

Values represent the mean (standard deviation) or median (IQR) or number (percent).
BMI: body mass index, DM: diabetes mellitus, ABI: ankle brachial index, n: participants
a: t independent test, b: Mann Whitney U test, c: chi-square, d: Fisher's exact test

Table 2 Baseline wound characteristics

Characteristics	DH group (n=30)	H group (n=30)	*p*
DMIST			
Depth	2 (1-2)	2 (1-3)	0.485 [b]
Maceration	1 (0-1)	1 (1-2)	0.058 [b]
Inflammation/infection	2 (1-2)	2 (1-2)	0.506 [b]
Size	4 (3-6)	4 (3-7)	0.642 [b]
Tissue type of wound bed	2 (1-2)	2 (1-2)	0.797 [b]
Type of wound edge	5 (3-5)	3 (3-5)	0.153 [b]
Tunneling	0	0	1.000 [b]
Total score	26.3 ± 8,1	27.4 ± 8.5	0.610 [a]
Wound onset (days)	30 (14.00-41.25)	30 (21.00-60.00)	0.316 [b]
Trigger of wound (%)			
Trauma	12 (40%)	14 (46.7%)	0.604 [c]
Footwear	4 (13.3%)	2 (6.7%)	
Callus	1 (3.3%)	3 (10%)	
Unknown	13 (43.3%)	11 (36.7%)	
Wound site (%)			
Plantar	13 (43.3%)	12 (40%)	0.189 [c]
Dorsal	9 (30%)	4 (13.3%)	
Medial	2 (6.7%)	1 (3.3%)	
Lateral	1 (3.3%)	0	
Heel	1 (3.3%)	2 (6.7%)	
Toe	4 (13.3%)	11 (36.7%)	
Wagner classification (%)			
Grade 1	22 (73.3)	15 (50%)	0.060 [c]
Grade 2	7 (23.3)	15 (50%)	
Grade 3	1 (3.3)	0	

Values represent the mean (standard deviation) or median (IQR) or number (percent).
n: participants, a: t independent test, b: Mann Whitney U test, c: Fisher's exact test

The SOD3 levels were significantly different between the DH and H groups ($p < 0.001$; **Figure 4**). The DH group exhibited no significant changes in SOD-3 levels >8 weeks ($p = 0.630$). In contrast, the H group had significant changes in SOD3 levels >8 weeks ($p < 0.001$). Similarly, the DH and H groups exhibited significant differences in IL-6 values ($p = 0.015$; **Figure 5**). The DH group had significant changes in IL-6 levels ($p < 0.001$). Moreover, the H group had significantly lower IL-6 levels ($p = 0.005$).

Discussion

Many previous clinical studies demonstrated the effects of individual applications of honey on DFU, especially for local infection control[49]. Thus, to our knowledge, this is the first study to evaluate the effectiveness of the DH mixture as a complementary topical therapy for DFU wound healing. This study confirmed that using the DH mixture may be more effective for healing recurrent DFU than using honey alone. Consequently, it also suggested that controlling oxidative stress in the wound is a key issue for promoting recurrent DFU wound healing.

The DM duration in the DH group in this observational study was significantly longer than that in the H group. However, the adjusted hazards ratio of the DH mixture for wound healing was 8.6. This reflected the effects of the DH mixture on recurrent DFU wound healing.

Wound healing during DFU is disturbed by a persistent inflammatory phase[50], which may be the result of many factors. Furthermore, wound biofilm formation and oxidative stress were focused on in this study. Significant reductions in the biofilm intensity were observed in both the DH ($p < 0.001$) and H ($p = 0.001$) groups. However, the biofilm intensity in the DH group decreased at a significantly higher rate than that in the H group in 8 weeks ($p = 0.008$). This suggested that the interaction between Trigona honey and Ajwa dates had good effects on biofilm elimination. One potential interaction mechanism may involve vitamin C. Dates are rich in vitamin C[51],

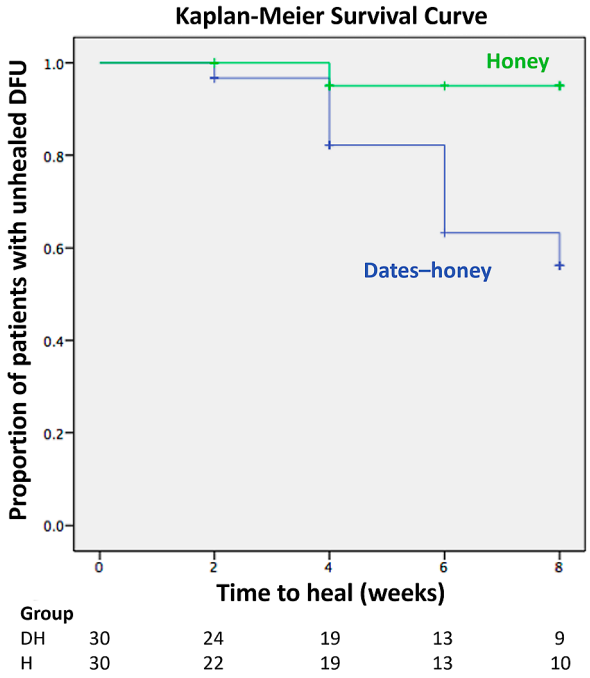

Figure 2　Kaplan–Meier survival curve depicting healing between the two groups
Significant differences were observed between the groups（log-rank test［p=0.015］）.
DH: date and honey mixture group, H: honey group

Table 3　Relationship between contributing factors and wound healing within 8 weeks

Variables	Crude HR	95% CI	p	Adjusted HR	95% CI	p
DH group	8.48	1.06- 67.8	0.044	8.55	1.03- 70.72	0.046
Duration of DM (unit = 1 year)				1.00	0.89-1.12	0.964

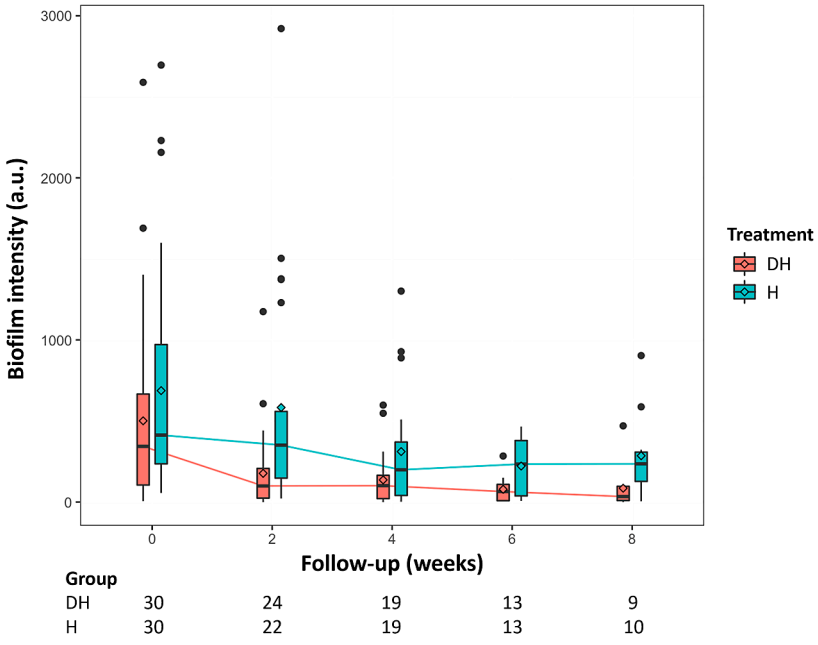

Figure 3　Box-plots of biofilm intensity during follow-up
The effects of DH vs H on biofilm intensity were significantly different（p = 0.008）.
DH: date and honey mixture group, H: honey group

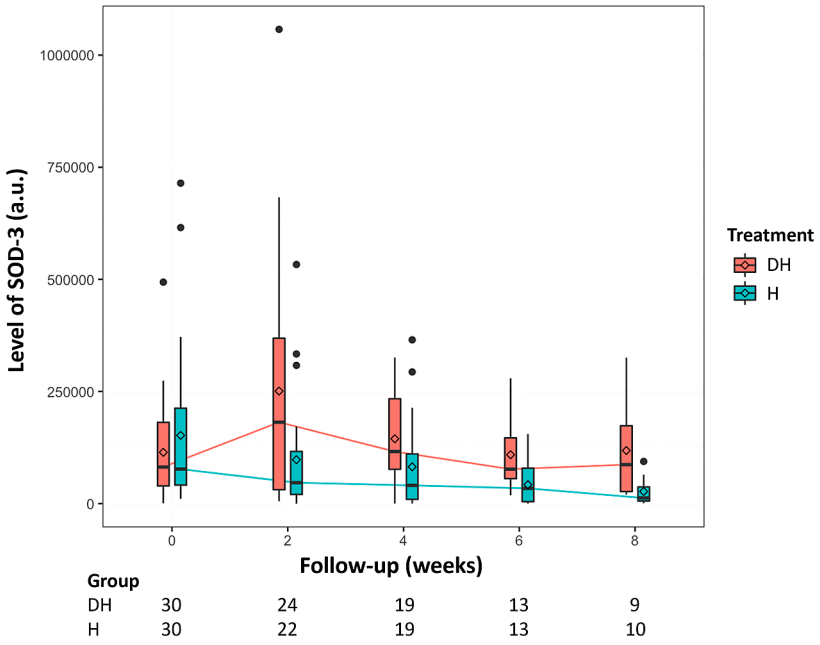

Figure 4　Box-plots of SOD-3 during follow-up
The effects of DH vs. H on SOD-3 were significantly different ($p < 0.001$).
DH: date and honey mixture group, H: honey group

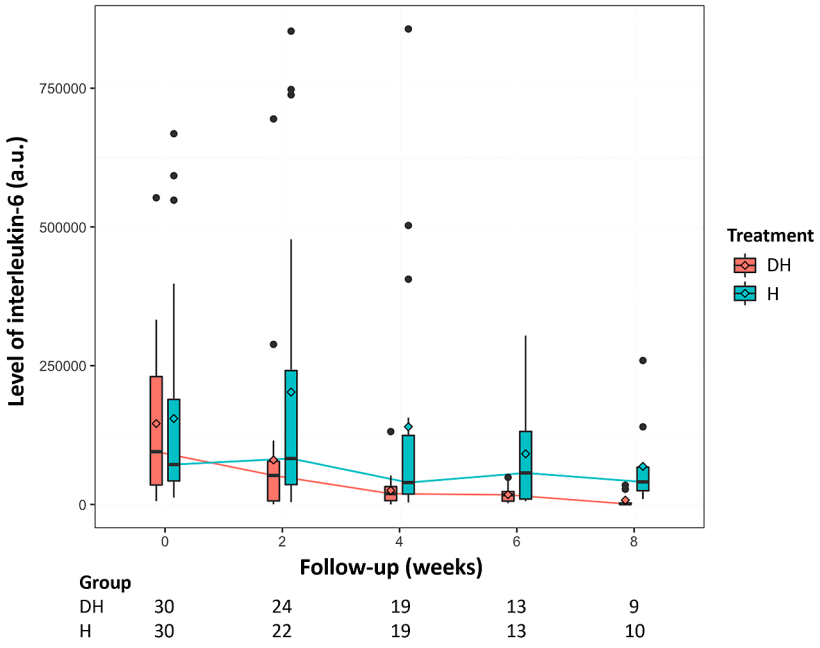

Figure 5　Box-plots of interleukin-6 during follow-up
The effects of DH vs. H on interleukin-6 were significantly different ($p = 0.015$).
DH: date and honey mixture group, H: honey group

and a previous *in vitro* study revealed that vitamin C promotes enhance the antibacterial activities of honey against planktonic and biofilm-embedded bacteria[52]. Moreover, this vitamin C effect increased significantly in a dose-dependent manner. However, the vitamin C concentration in the mixture used in this study was not measured. Therefore, whether a more useful mixture ratio (date vs. Trigona honey) could be formulated was unable to be determined.

Of note, the changes in the SOD3 levels were different between the two groups. The SOD3 level in the H group decreased significantly in 8 weeks,

whereas there were no significant changes in the DH group in 8 weeks. Manuka honey protected human dermal fibroblasts against oxidative damage by improving the SOD response and promoting wound healing in an *in vitro* study[53]. Thus, the previous study is inconsistent with the current study results for the H group. This difference may be due to poor glycemic control. Moreover, a positive correlation exists between Hb A1c and serum nitric oxide levels, which are oxidative stress markers, suggesting that poor glycemic control leads to increased oxidative stress in patients with type 2 diabetes[54]. Trigona honey may not have sufficient antioxidative stress capacity to treat DFU in patients with hyperglycemia (Hb A1c, 10.6 ± 2.6 in the H group) based on the current and previous studies. In contrast, orally administered Ajwa dates resulted in a significant increase in tissue SOD levels and injury amelioration in a rat cardiac injury model[55]. Similarly, no significant change in SOD levels was observed in 8 weeks in this DH group. Therefore, Ajwa dates may contain sufficient antioxidative stress capacity to treat DFU in patients with hyperglycemia (Hb A1c, 10.8 ± 2.4 in the DH group).

In addition to the antibiofilm and antioxidative stress effects of Trigona honey and Ajwa dates, DFU treated using the DH mixture exhibited a faster decrease in IL-6 levels, which is an inflammatory marker, than DFU treated by honey alone. Studies performed by Al-Yahya et al.[55] and Khan et al.[56] revealed that the Ajwa date extract downregulated IL-6 expression levels in cardiomyopathy and hepatocellular carcinoma models. The reduced IL-6 level in the DH group may be attributed to the anti-inflammatory effects of dates, although the nature of the disease was different in these studies than that examined in the present study. The amelioration of the persistent inflammatory status associated with DFU following treatment using the date and honey mixture promoted wound healing as demonstrated by the proportion of healing between the DH group compared with the H group. Moreover, the healing rate in the DH group was superior to that the H group (**Figure 2**).

This study had several limitations. First, the honey-to-date extract ratio in this study was 1:1. Thus, further studies should evaluate different mixture ratios. Second, this study included only one patient with DFU classified as grade 3 using the Wagner classification guidelines. Therefore, the study results for grade 3 DFU cannot be generalized. Third, IL-6 and SOD3 were measured after the collection of the biofilm. This collection order may affect the levels of these two biomarkers. Lastly, the study design was observational and only a small number of patients was included. Therefore, prospective, well-designed, and large-scale studies are necessary to elucidate the efficacy of the DH mixture in promoting DFU wound healing.

Conclusion

The DH mixture may promote wound healing in recurrent DFU in patients with hyperglycemia.

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原　著

糖尿病足潰瘍におけるなつめやしとハチミツ混合とハチミツ単独の治癒比較

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要　旨

【目的】ナツメヤシとハチミツ混合はインドネシアにおいて糖尿病足潰瘍の局所管理に使用されるが、この局所管理に関する臨床エビデンスはない。本研究の目的は、ナツメヤシとハチミツ混合療法の糖尿病足潰瘍治癒効果の評価である。また創部のバイオフィルムおよびバイオマーカーへの影響も評価した。

【方法】ナツメヤシとハチミツ混合療法を受けた30名の患者（再発）とハチミツ単独療法を受けた30名の患者（再発）が参加した。両群とも2週間ごとに8週まで追跡された。糖尿病治癒についてカプランマイヤー法にて比較した。またCox比例ハザードモデルで治癒の速さの要因を検討した。さらに酸化ストレスマーカーとしてSOD3、炎症反応としてIL-6を調べた。2つのバイオマーカーとバイオフィルムを創面ブロッティング法で採取した。線形混合モデルを用いて局所管理の効果を検討した。

【結果】ナツメヤシとハチミツ混合療法を受けた患者のほうが、有意に治癒割合が高かった（$p = 0.015$）。ハザード比は8.55（95％ CI:1.03-70.72、$p = 0.046$）であった。バイオフィルム染色画像強度（$p = 0.008$）、IL-6（$p = 0.015$）、SOD3（$p < 0.001$）に有意差を認めた。

【結論】ナツメヤシとハチミツ混合は糖尿病足潰瘍（再発）の治癒を促進することが示唆された。

キーワード：バイオマーカー、ナツメヤシ、糖尿病足潰瘍、蜂蜜、創傷治癒