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Original Article

Effectiveness of stingless bee (Kelulut) honey versus conventional gel dressing in diabetic wound bed preparation: A randomized controlled trial

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الملخص

أهداف البحث: يحتوي عسل كيلولوت على تريهالولوز ويحتوي على نسبة عالية من مضادات الأكسدة، مثل المواد الفينولية والفلافونويد، والتي يمكن أن تعزز التئام الجروح. تهدف هذه الدراسة إلى تقييم فعالية عسل كيلولوت في التئام جروح مرضى السكري مقارنة بضمادات الجل التقليدية المتوفرة تجاريا (جل انتراسايت من سميث-نيفيو).

طريقة البحث: تم إجراء تجربة مراقبة مستقبلية عشوائية وحيدة التعمية على مرضى السكري المؤهلين الذين يعانون من جروح تجويف كاملة السماكة. تم تسجيل التركيبة السكانية للمرضى، وحجم وموقع الجروح، وفحوصات الدم الروتينية الأساسية. تم تضميد الجروح كل يومين إما بعسل كيلولوت لمجموعة التدخل أو الجل للمجموعة الضابطة. تم حساب نسبة تقليل حجم الجرح وتكوين الأنسجة الحبيبية كل ستة أيام لمدة شهر واحد.

النتائج: تم اختيار واحد وسبعون مريضا بصورة عشوائية. وبعد 30 يوما من المتابعة، أصبح 62 مشاركا متاحين للتحليل: 30 و32 من مجموعتي المراقبة والعلاج، على التوالي. كان لدى المجموعة الضابطة أنسجة حبيبية أعلى عند خط الأساس وأظهرت المزيد من الجروح في الطرف السفلي والجذع الخلفي. أظهرت كلا المجموعتين زيادة في متوسط ومتوسط النسبة المئوية لظهارة الجرح والأنسجة الحبيبية بمرور الوقت، مع ارتفاع القيم بشكل ملحوظ في كل نقطة زمنية في مجموعة العسل. ومع ذلك، كشفت القياسات المتكررة "أنوفا" و "أنكوفا" عن عدم وجود تأثير تفاعل كبير بين العلاجات المختلفة والوقت.

الاستنتاجات: كشفت هذه التجربة أن عسل كيلولوت كان مشابها للجل التقليدي وفعالا مثله في علاج جروح مرضى السكري من حيث تعزيز تكوين الظهارة وتكوين الأنسجة الحبيبية.

الكلمات المفتاحية: عسل النحل غير اللاسع؛ عسل كيلولوت؛ داء السكري؛ الجروح؛ التئام الجروح

Abstract

Purpose: Kelulut honey contains trehalulose and has high antioxidant content, such as phenolic and flavonoid substances, which can promote wound healing. This study evaluated the effectiveness of Kelulut honey in diabetic wound healing compared to a commercially available conventional gel dressing (Intrasite gel).

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Methods: A prospective, randomized, single-blinded control trial was performed on eligible diabetic patients with full-thickness cavity wounds. Patients' demographics, size and site of wounds, and baseline routine blood investigations were recorded. The wounds were dressed every other day with Kelulut honey for the intervention group or gel for the control group. The wound size reduction and granulation tissue formation percentage were calculated every 6 days for 1 month.

Results: Seventy-one patients were randomized. After 30 days of follow-up, 62 participants were available for analysis: 30 from the control group and 32 from the treatment group. The control group had increased granulation tissue at baseline and more wounds on the lower limb and posterior trunk. Both groups showed an increasing mean and median percentage of wound epithelialization and granulation tissue over time, with significantly higher values at every timepoint in the honey group ($p < 0.05$). However, repeated measures analysis of variance and analysis of covariance revealed no significant interaction effect between the different treatments and time, with $F(2.02, 121.28) = 0.88$, $p = 0.417$ and $F(1.60, 93.95) = 0.79$, $p = 0.431$, respectively.

Conclusion: This study revealed that Kelulut honey was comparable to and as effective as the conventional gel in treating diabetic wounds in terms of promoting epithelialization and granulation tissue formation.

Keywords: Diabetes mellitus; Kelulut honey; Stingless bee honey; Wound; Wound healing

Introduction

Diabetes mellitus (DM) is a major health issue with increasing prevalence worldwide.[1] According to the US National Diabetic Statistic Report 2020, it was estimated that a total of 34.2 million people or 10.5% of the US population had DM in 2018. Among these, 1.5 million were new cases of DM, which is about 6.9 per 1000 persons.[2] It is well known that wound healing in diabetic patients is often impaired. Various treatment modalities such as surgical debridement, infection control with antimicrobial agents, dressing selections, wound offloading, vascular assessment, and strict glycemic control have been employed to expedite the healing process.[3−5]

One of the most commonly researched adjuvants to wound therapy is honey. Honey has been used since ancient times in wound management, dating back to 2500 BC.[6] It fell out of favor in modern medicine due to the development of modern synthetic medicine; however, interest was rekindled in recent years.[7] Honey contains pro-healing properties such as antioxidant and free radical scavenging activity, anti-inflammatory effects, and antimicrobial activity. Globally, honey derived from European honey bees, such as Manuka honey, has been well studied and the evidence of its benefits in promoting wound healing has been established.[8]

There has been no study on the effect of stingless bee honey (Kelulut honey) produced by Melipolini sp. on diabetic wound healing. Kelulut honey has better antioxidant capacity, anti-inflammatory effects, and free radical scavenging activity than other local honey, and also possesses similar pro-healing properties as other kinds of honey.[9] These effects are due to the much higher content of phenolic and flavonoid substances in Kelulut honey, and the key bioactive factors promoting wound healing and preventing oxidative stress-related injury.[9] Australian researchers also recently discovered a novel source of the rare disaccharide trehalulose in the honey of stingless bees, which has antidiabetic and antioxidant activities.[10]

This study evaluated the effectiveness of Kelulut honey for wound bed preparation in diabetic patients compared to a commercially available conventional gel used to manage wounds. We postulated that Kelulut honey would be more efficient in promoting wound epithelialization and granulation tissue formation in diabetic patients, given its better pro-healing properties.

Materials and Methods

Research design

This paper was written according to the Consolidated Standards of Reporting Trials (CONSORT) statement and in accordance with the Declaration of Helsinki. We performed a prospective, single-blind, randomized controlled trial (RCT) comparing the effectiveness of Kelulut honey versus conventional gel dressing (Intrasite gel; Smith & Nephew, London, UK) in wound size reduction or wound epithelization, and granulation tissue formation percentage in diabetic patients with cavity wounds (Figure 1). Each participant was followed up for 30 days.

Patient selection

Eligible participants were adults aged 18−70 years old, requiring admission for wound management to the Hospital Universiti Sains Malaysia (Kelantan, Malaysia) or attending wound clinics in the Hospital Universiti Sains Malaysia, with a full-thickness cavity wound, and controlled DM status defined as fasting blood glucose (FBG) < 10 mmol/L upon selection. Exclusion criteria were those with severely contaminated or infected wounds, a history of allergy to honey or stingless bee product, immunocompromised patients or those on chronic steroid use (defined as the use of a steroid for more than 2 weeks), pregnant women, or patients diagnosed with end-stage renal disease. The FBG cut-off point value of 10 mmol/L was chosen based on the guidelines by the American College of Endocrinology, American Association of Clinical Endocrinologists, and American College of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement.[11−13]

The study protocol and voluntary nature of their participation were explained. Patients were also reassured that they would still receive the standard treatments, even if they opted not to participate or withdraw from the study at any time.

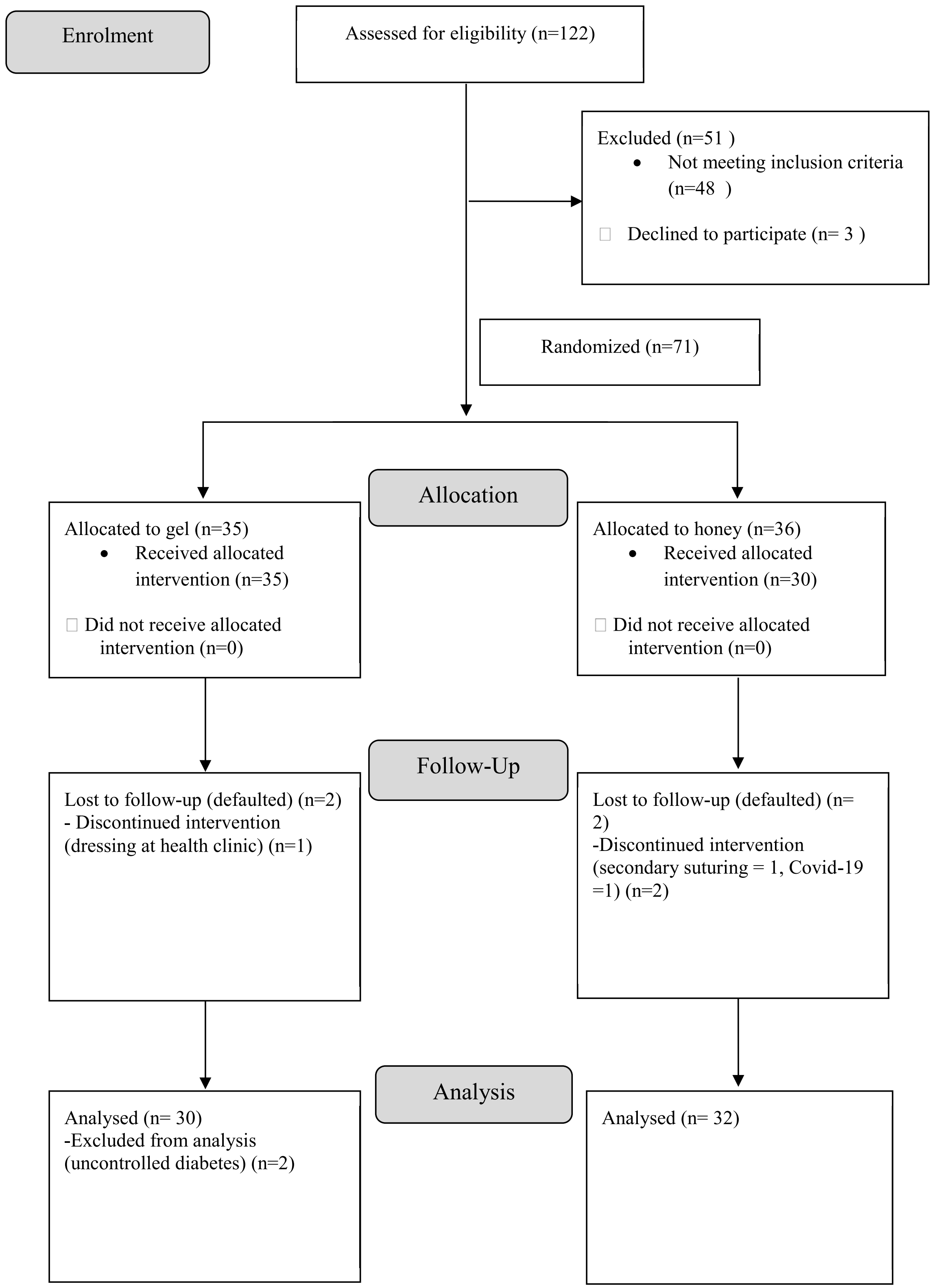

Figure 1: CONSORT flow diagram.

After receiving written informed consent, complete information including age, sex, race, smoking status, site and size of the wounds, and baseline blood investigations including full blood count, urea, creatinine, total protein, albumin, hemoglobin A1C (HbA1c), and FBC, together with extensive medical and surgical history were obtained.

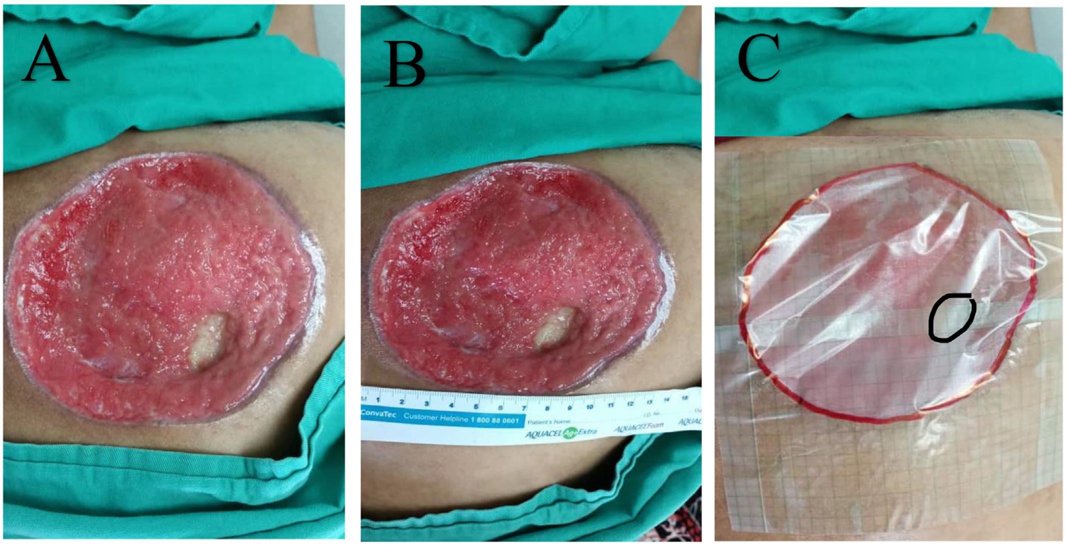

Figure 2: Wound assessment and measurement. A: Wound was cleaned with normal saline to remove residual gel or honey prior to measurement by the masked observers. B: Basic measurements of the wound's width and length. C: The surface area and granulation tissue were traced onto the Opsite Flexigrid for percentage calculation.

Randomization and blinding

The participants were divided into two parallel control and intervention groups at a 1:1 balanced ratio using a simple computer-generated randomization algorithm from a web-based software (http://www.randomization.com). The control group was assigned gel dressing, whereas the intervention group was treated with honey. The study protocols for both gel and honey groups were prepacked in sealed and stapled envelopes and consecutively numbered for each patient according to the randomization schedule. Each patient was assigned an order number and received the study protocol in the prepacked sealed envelope, according to the numbering. The allocation sequence was concealed from the primary researcher and co-researcher enrolling and assessing the wounds. Only the principal supervisor had access to the randomization schedule, which was kept in a safe, locked cabinet in the department. Unique generated random numbers were assigned to identify the study subjects, and no unique hospital registration number was used to maintain confidentiality, allocation concealment, and blinding.

Single blinding was performed on the assessors during wound assessment, data collection, and analysis. The patients and staff performing the dressing were unable to be masked from the treatment allocation due to the honey's prominent appearance and consistency. Nonetheless, to maintain strict blinding during data collection, staff performing the dressing were required to clean the residual gel or honey on the wound bed properly with normal saline before the wound assessment.

Table 1: Baseline characteristics of all patients.

Characteristic	Gel Group (n = 30) Mean (SD)	Honey Group (n = 32) Mean (SD)	P-value
Age (years)	50.9 (12.4)	54.3 (9.4)	0.238[a]
Smoking, n (%)[f]	4 (13.3)	5 (15.6)	0.999[c]
Sex, n (%)[f]			
Male	12 (40.0)	14 (43.8)	0.802[c]
Female	18 (60.0)	18 (56.2)	
Initial wound size (cm^2)[e]	45.5 (87.8)[e]	31.0 (48.4)[e]	0.304[b]
Initial granulation (%)	70.2 (18.9)	58.6 (25.2)	0.045[a]
Site, n (%)[f]			
Upper limb	3 (10.0)	3 (9.4)	
Lower limb	13 (43.3)	12 (37.5)	
Anterior trunk	2 (6.7)	5 (15.6)	0.048[d]
Posterior trunk	12 (40.0)	7 (21.9)	
Head and neck	0 (0)	5 (15.6)	
Total white cell level (g/dL)[e]	9.2 (4.4)[e]	10.6 (5.7)[e]	0.592[b]
Hemoglobin level (g/dL)	11.1 (1.7)	10.4 (1.6)	0.103[a]
HbA1C (%)	9.2 (2.6)	9.5 (2.7)	0.707[a]
Albumin (g/dL)	32.7 (7.2)	33.2 (6.2)	0.789[a]
Urea (g/dL)	4.9 (2.6)	4.7 (2.4)	0.705[a]
Creatinine (g/dL)	73.3 (22.8)	75.1 (19.4)	0.726[a]

[a] Independent t-test.
[b] Mann−Whitney U test.
[c] Fisher's exact test.
[d] Likelihood ratio chi-square test.
[e] Median (IQR).
[f] Frequency, n (%).

Dressing application

The Kelulut honey administered to the intervention group was acquired from Brainey Sdn Bhd (Kelentan, Malaysia), a company that provides stingless bee honey certified with Good Manufacturing Practice (GMP), ISO 22000, and Halal. As the honey used is not medical-grade honey, sterilization with 25 kGy gamma-ray irradiation was done for safety purposes to eradicate any potential life-threatening infection,

Table 2: Comparison of percentage of wound epithelialization between dressings across time-points.

	Percentage (%) of Wound Epithelization, Mean (SD)					P value[b]
	Day 6	Day 12	Day 18	Day 24	Day 30	
Honey (n = 32)	25.5 (16.1)	40.2 (20.5)	52.5 (23.4)	65.6 (23.9)	74.7 (22.6)	0.417[b]
Gel (n = 30)	16.8 (11.8)	26.9 (15.4)	40.4 (16.7)	52.0 (19.7)	61.5 (22.1)	
P value[a]	**0.019**[a]	***0.006***[a]	**0.023**[a]	**0.018**[a]	***0.024***[a]	

[a] Independent *t*-test for each time point.
[b] Repeated measures analysis of variance (ANOVA).

Table 3: Comparison of percentage of granulation tissue formation between dressings across time-points.

	Percentage (%) of Granulation Formation, Median (IQR)					P value[b]
	Day 6	Day 12	Day 18	Day 24	Day 30	
Honey (n = 26)	32.5 (46.0)	56.8 (84.8)	73.3 (106.2)	80.0 (123.3)	88.9 (123.3)	0.431[b]
Gel (n = 25)	12.5 (20.5)	18.4 (39.6)	28.7 (54.7)	36.5 (58.8)	41.1 (70.0)	
P value[a]	**0.004**[a]	**0.005**[a]	**0.005**[a]	**0.008**[a]	**0.022**[a]	

[a] Mann−Whitney U test for each time point.
[b] Repeated measures analysis of covariance (ANCOVA).

such as spores from *Clostridium botulinum*. For the control group, the Intrasite gel from Smith & Nephew was used; according to the manufacturer's instructions, approximately 5 mm of gel must be applied over the wound surface.[14] However, this thickness cannot be set as a standard for honey due to honey's high fluidity and consistency. Although honey is very viscous or solid at room temperature, it becomes watery or fluid at body temperature. The thickness of 5 mm could not be sustained, as the honey became watery upon application to the wound surface. Determining a standardized amount of honey is also tricky as no empirical evidence exists for the honey application amount. Khan et al.[15] suggested that the amount of honey required per unit area of the wound would depend on the exudate amount. Hence, for standardization, only a thin layer of either gel or honey was applied during dressing.

Dressings were carried out by trained nurses and medical officers every other day as per the standard of practice. In the honey group, the wound was cleaned with normal saline. A thin layer of honey was applied to the wound and subsequently covered with Opsite film. Sterile gauze and bandages were used as secondary dressing materials. In the control group, a similar approach was undertaken. Pre-prandial capillary blood glucose (CBG) was serially recorded on every dressing day to assess overall diabetic control. More than 60% of CBG readings < 10 mmol/L were considered a reasonable control.[16] One-point CBG daily rather than four points CBG was implemented to eliminate the difficulty of self-monitoring blood glucose at home in those treated as outpatients.

Participants who were unable to comply with the dressing schedule, developed acute complications from uncontrolled DM such as diabetic ketoacidosis, had 40% CBG readings $>$ 10 mmol/L, opted out, or those who contracted coronavirus disease 2019 (COVID-19) were withdrawn from the study. Then alternative treatment and dressing were provided based on the wound condition, which included daily normal saline, iodine, paraffin gauze, or other modern dressing deemed appropriate by the treating physician.

Measurement of outcomes

The baseline participants' data and all clinical characteristics were recorded on standardized proforma by masked observers. The percentage of granulation tissue formation and wound size reduction were calculated based on the surface area of the wound, and granulation tissue was traced and marked on the Opsite Flexigrid with an indelible fine tip marker, as shown in Figure 2. Serial assessments and photo documentation were performed on days 0, 6, 12, 18, 24, and 30. After completion of data collection, two parameters were defined and calculated every 6 days to evaluate the healing process.

Table 4: Comparison of wound epithelialization and granulation between groups.

Parameters	Time	Treatment	Time*treatment
Epithelialization[a]	$F(2.02, 121.28) = 312.74$ **$p < 0.001$**[a]	$F(1.00, 60.00) = 6.95$ **$p = 0.011$**[a]	$F(2.02, 121.28) = 0.88$ $p = 0.417$[a]
Granulation[b]	$F(1.60, 93.95) = 51.82$ **$p < 0.001$**[b]	$F(1.00, 59.00) = 4.50$ **$p = 0.029$**[b]	$F(1.60, 93.95) = 0.79$ $p = 0.431$[b]

[a] Repeated measures analysis of variance (ANOVA).
[b] Repeated measures analysis of covariance (ANCOVA).

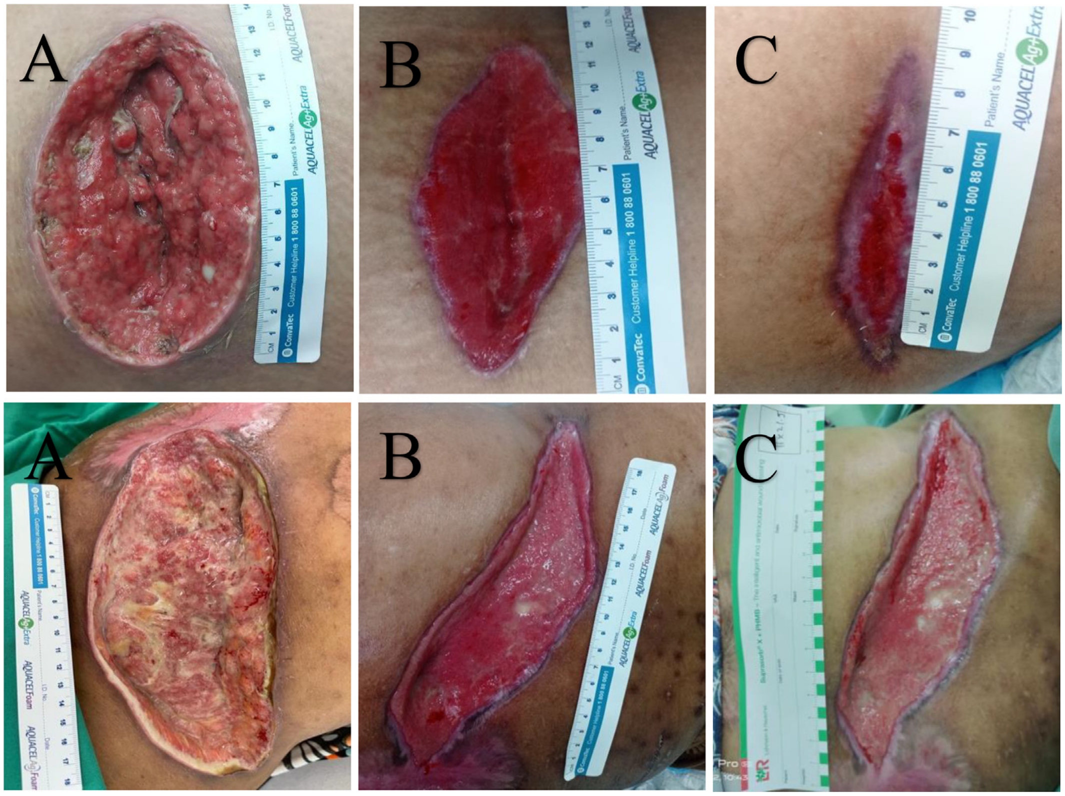

Figure 3: Wound appearance in the honey group. Wound size and granulation tissue upon assessment on, A: recruitment (day 0), B: mid study period (day 12–18), C: upon completion (day 30).

1. Wound surface area on day N (number of the boxes confined within the traced Opsite Flexigrid in cm^2) = W^2_{DayN}

Percentage of wound size or wound surface area ($W^{\%}$) reduction = $[(W^2_{DayN} - W^2_{Day0})/W^2_{Day0}] \times 100\%$

2. Percentage of granulation tissue on day N (number of the boxes represented by the granulation tissue ($G^{\%}$) divided by $W^2_{DayN} \times 100\%$) = G_{DayN}

Percentage of granulation tissue ($G^{\%}$) improvement = $[(G_{DayN} - G_{Day0})/G_{Day0}] \times 100\%$
*O = day 0 (baseline)
*N = day 6, 12, 18, 24, 30

Statistical methods

All data were analyzed using IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, NY, USA). Normal distribution numerical or continuous variables are presented as the mean and standard deviation (SD), whereas the non-normal distribution data are reported as the median and interquartile range (IQR). The independent t-test was used for normally distributed or continuous data, whereas the Mann–Whitney non-parametric U-test was used for non-normally distributed data. The categorical variables are presented as the frequency (n) and percentage (%) and was tested with the Fisher's exact test and likelihood ratio chi-square test. Repeated measures analysis of variance (ANOVA) was conducted for wound epithelialization, whereas the granulation tissue improvement percentage was assessed with repeated measures analysis of covariance (ANCOVA) to correct for the individual differences or baseline characteristics that might influence the outcomes. $P < 0.05$ was considered statistically significant.

Results

Eligible participants were recruited from September 2021 to November 2022. A total of 71 patients were identified and randomized: 35 in the control group and 36 in the intervention groups; each participant was followed up for 30 days. Of these, 62 participants completed the study, with a dropout rate of 12.7% (below 20%). Both groups had a similar number of participants completing the study (30 and 32 from the control and treatment groups, respectively); hence, not suggestive of any bias in the treatment that led to dropout. A total of seven patients were withdrawn during the data collection and two during the analysis phase due to the various reasons described in Figure 1.

For comparisons of baseline characteristics (Table 1), no significant differences were found at baseline. As illustrated in Table 2, both the treatment and control groups showed an increasing mean percentage of wound epithelialization

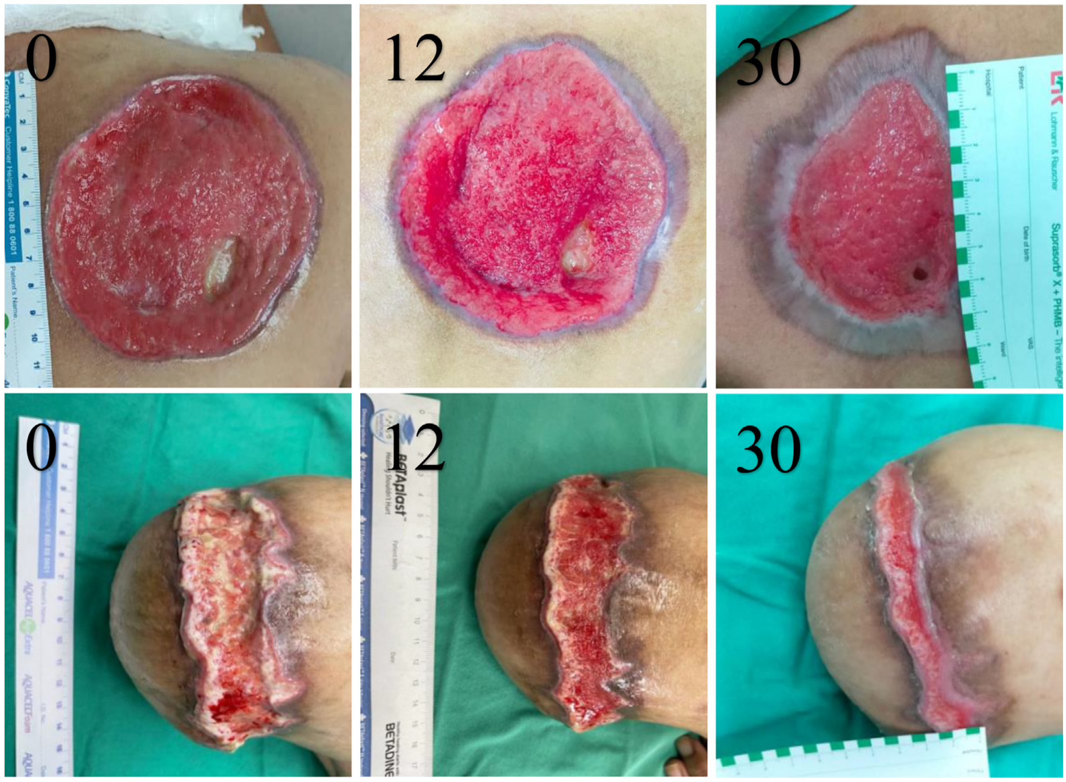

Figure 4: Wound appearance in the gel group. Wound size and granulation tissue upon assessment on, A: recruitment (day 0), B: mid study period (days 12–18), C: upon completion (day 30).

over the study period, with the epithelialization percentage significantly higher in the honey group at each time point. Further analysis with repeated measures ANOVA showed a significant time effect on the epithelialization percentage, $F(2.02, 121.28) = 312.74$, $p < 0.001$, as well as the interaction effect of different dressing material used, $F(1.00, 60.00) = 6.95$, $p = 0.011$. However, there was no significant interaction between the different treatments administered over time, $F(2.02, 121.28) = 0.88$, $p = 0.417$ (Table 4).

Similarly, as shown in Table 3, both arms also showed improvement in the granulation tissue formation, with the intervention group having statistically significant improvements across all time points. Nonetheless, when the initial granulation tissue at baseline was adjusted due to the control group having slightly greater granulation tissue, repeated measures ANCOVA only showed a significant time effect on granulation tissue formation, $F(1.60, 93.95) = 51.82$, $p < 0.001$, and significant effect of the different treatments $F(1.00, 59.00) = 4.50$, $p = 0.029$. Despite both the honey and control groups showing increasing median percentage of wound granulation at the respective time points, no interaction was observed between different treatments and time, with $F(1.60, 93.95) = 0.79$, $p = 0.431$ (Table 4). Our findings suggested no statistically significant difference between the honey and gel in promoting diabetic wound healing, as evidenced by comparable wound progression and improvement in both groups throughout the study period, as illustrated in Figures 3 and 4.

Discussion

Singh et al.[17] reported that diabetic patients have a 25% lifetime incidence of developing foot complications such as diabetic foot ulcers (DFUs). The International Diabetes Federation also stated that 9.1–26.1 million people develop DFUs annually, with one lower limb amputation every 30 s occurring worldwide.[18,19] These complications can result in a socioeconomic burden to the individuals and the healthcare system from the productivity losses incurred by the disease and the public health resources spent on its management.[20]

Non-healing diabetic wounds are usually stalled in the inflammatory phase and fail to progress to the next proliferative and remodeling phase to complete the healing process. The hyperglycemic state causes cellular dysfunction due to the formation of advanced glycation end products and interactions with their receptors, which eventually results in impaired T-cell function, impairment in neutrophil's chemotaxis, activation, phagocytosis, fibroblast proliferation, and epithelial cell migration.[1] There is also an abundance of reactive oxygen species (ROS), hypoxia, and high levels of metalloproteases, which cause extensive tissue damage.[21] Angiogenesis in response to hypoxia is also impaired in DM.[22]

Honey is gaining popularity as one of the commonly researched adjuvants to wound therapy due to its antioxidant property, antimicrobial activity, anti-inflammatory, osmotic effect, acidity, and ability to provide local tissue nutrients.[1] The antioxidants, such as flavonoid and phenolic compounds, help reduce the damaging ROS in the wound bed.[1] A low concentration of hydrogen peroxide is also present in the honey to act as an antibacterial agent; however, it is not cytotoxic to the surrounding tissue due to its low concentration and protective effect of the antioxidating phenolic and flavonoid substances. The hyperosmolarity of honey enables it to draw fluid and lymph from surrounding tissue, subsequently providing a moist environment for better wound healing.[1,7] The high osmolarity environment is also not conducive to the growth and survival of bacteria. Honey's low acidity is bactericidal and promotes oxygen release from the hemoglobin in the wound bed, promoting healthy growth.[1]

Multiple studies have been carried out to assess the effectiveness of honey dressing in diabetic wounds. Three RCTs in the meta-analysis by Wang et al.[23] in 2019 showed that among all of the 267 diabetic patients included, honey dressing groups had a shorter wound healing time. The choices of dressing for the control groups by Guo et al.,[24] Kamaratos et al.,[25] and Siavash et al.[26] in this meta-analysis were povidone-iodine dressing, saline-soaked gauze, and unspecified placebo gel, respectively. Our study selected gel as the control because honey and gel share similar physical properties or consistency. Furthermore, gel efficacy in treating diabetic wounds has also been established. For example, two systematic reviews by Dumville et al.[27] and Wu et al.[28] reported that conventional hydrogel dressing was shown to significantly increase ulcer healing compared to basic wound contact dressings such as plain gauze in DFUs due to its ability to provide a moist environment for wound healing.

Some Malaysian local honey types include Tualang, Kelulut, Gelam, Pineapple, and Wild honey. Multiple animal and human studies conducted in Malaysia have proven the beneficial effects of honey produced by Tualang stinger honeybees in wound healing. For example, in USM in 2010, Nasir et al.[29] studied the antimicrobial effect of Tualang honey-impregnated Aquacel dressing on partial-thickness wounds in burn patients, which showed comparable results to Manuka-Aquacel against Gram-negative bacteria. In 2011, Sukur et al.[30] and Zaharil et al.[31] respectively studied the effect of Tualang honey on full-thickness wounds in Sprague Dawley rats. Sukur et al.[30] found that topical application of Tualang honey on burn wounds contaminated with organisms such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* led to the fastest healing rate compared with chitosan hydrogel and hydrofiber silver. Zaharil et al.[31] showed that Tualang honey-impregnated paraffin tulle was comparable to the commercially established wound dressing, such as silver-impregnated hydrofiber, in preventing dressing-wound adherence, ease of removal, and fluid accumulation. Another study by Imran et al.[32] in 2011 revealed that complete healing of split-thickness skin grafting donor site wounds in humans could be achieved with Tualang honey hydrogel with minimal pain and discomfort and pruritus.

However, the Tualang honey collection depends solely on local honey hunters because the Tualang stinger honeybees mostly set their nests in the deep jungles and high up from the ground. This unique characteristic restricts the ability to successfully farm these bees due to difficulty matching their original habitat. By contrast, the nest of stingless (Kelulut) bees exist in cavities or holes in trees, buildings, and hives. As these habitats can be replicated in controlled farm environments, Kelulut honey cultivation is made possible and more effortless; hence, the cost to acquire this honey is lower.[33] The invention of the commercial Meliponiculture Using a Split-able Throne within Air-jacketed palace For Amplification-Hive (MUSTAFA-Hive) by Dr. Zulkifli has led to the successful domestication of stingless bees and a faster large-scale harvest.[33,34]

Kelulut honey appeared to be at least as potent as gel in promoting wound healing, with no statistically significant difference was discerned between the honey and gel and their effects on the clinical progression of wounds over time. We observed a comparable trend of wound epithelialization percentage in both groups throughout the study period. The wound healing process might have been expedited by much faster cellular proliferation, epithelial cell migration rate, and removal of devitalized tissue via autolysis,[7] facilitated by the moisture content provided by both honey and gel to the wound beds.

Our study also revealed improvement of granulation tissue across all time points for those treated with both honey and gel. This observation may again be attributable to the moist environment provided by both dressings, which promote cellular proliferation, fibroplasia, and angiogenesis involved during granulation tissue formation.[7] As the granulation tissue functions as a temporary rudimentary tissue prior to wound epithelialization,[35] Kelulut honey could be a suitable alternative for wounds with exposed vital structures such as bone, tendon, or cartilage.

It is worth noting that the key feature shared by both honey and gel is the ability to provide an ideal microenvironment for wound healing, by transferring moisture to the wound bed, which serves as growth factors, nutrients and cytokines' transport medium, as well as facilitates cellular recruitment and migration during granulation tissue formation and wound epithelialization. It is well documented that desiccated and dry wounds often have impediments in wound contraction and healing.[36] However, there is a caveat to this additional advantage. Too much moisture in the wound bed can lead to excessive leaking of the exudative fluid, subsequently causing peri-wound skin maceration and excoriation. The breach of peri-wound skin in turn could lead to infection.[36] Thus, judicious usage of both gel and honey with close clinical monitoring of the peri-wound skin condition is warranted, especially in more superficial wounds. Despite utilizing semi-occlusive instead of absorbent dressings, we managed to avoid this issue by applying only a thin layer of either gel or honey during dressing change. We observed no visible skin excoriation or maceration in our subjects.

We utilized FBG as a surrogate for HbA1c level to gauge glycemic control upon selection.[37] In previous studies, there was a clear correlation between HbA1c and average blood glucose levels in diabetic patients with HbA1C more than 6.5%.[38,39] For instance, HbA1c of 8% corresponds with a blood glucose level of 10.2 mmol/L, 9% with 11.8 mmol/L, and 10% with 13.4 mmol/L.[38,39] As HbA1c value of more than 8% is considered poorly controlled DM, this value correlates with our study's selection FBG criteria of 10 mmol/L.

HbA1c level was assessed at the baseline of our study, providing an assessment of long-term control of hyperglycemia. We believe that FBG or mean daily capillary glucose gave us a more accurate picture of current diabetic control during the wounding' acute event. By contrast, the HbA1c only reflects the control of diabetic status within the past 90–120 days.[40] Given our short study duration, as all participants were only followed up for 30 days, baseline HbA1c alone might not have provided a true reflection of glycemic control during the study, as no HbA1c at the end of the trial was available for comparative analysis. Nonetheless, this presumption was not subjected to further analysis as this was not the scope of our study.

As Kelulut honey has beneficial effects on the healing of diabetic wounds, it could be considered an alternative wound dressing material. Unlike Tualang honey, which can only be collected from wild honeybees' hives on the Tualang trees, Kelulut honey has been successfully farmed locally, which translates to a lower cost for its use in diabetic wounds.[33] This cost reduction would lower the financial burden on local healthcare institutions and the health ministry to manage such wounds. The patient's morbidity from diabetic wounds would be significantly reduced due to the shorter healing time and better wound healing. Unfavorable outcomes such as amputation in the case of DFUs could be avoided as well.

The strength of this study was the blinding and objectivity of the analysis. Despite the single-blind nature of our trial, we believe that the observed treatment effect of Kelulut honey was neither under nor overestimated by bias. We minimized the selection bias during recruitment and by allocation concealment and during data collection and analysis by blinding the assessors and analysts. Due to the physical property of the honey and gel, it was difficult to mask the subjects from the intervention. Nonetheless, we feel that it did not significantly impact our study as only objective measurements were recorded and analyzed, with no contribution of subjective patient self-reported outcomes such as the alleviation of pain, odor, or comfort during dressing in our analysis. Our main study limitation was that we only analyzed the wounds in two rather than three dimensions: the wound volume. Multiple attempts to measure the wound volume failed due to the difficulty of accurate depth measurement with a simple ruler, as most wound cavities were not even or crater-like. As granulation tissues grow and expand in all three dimensions, we might have understated the actual granulation tissue formation rate due to our inability to capture the vertical growth once the granulation tissue had fully covered the wound base.

Conclusion

In conclusion, this study showed that Kelulut honey is comparable to and as effective as conventional gel dressing in treating diabetic wounds in terms of promoting wound epithelialization and granulation tissue formation. Thus, Kelulut honey may be an option for wound management due to the postulated high benefit-to-cost ratio and the feasibility of a large-scale harvest and mass production. A future study with a larger sample size, longer follow-up period, and use of a three-dimensional scanner to measure the wound volume rather than the surface area is warranted to determine the actual effect of Kelulut honey and further confirm the beneficial effects of Kelulut honey.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethical approval

Ethical approval was granted by the Human Research Ethics Committee of Universiti Sains Malaysia (USM) (Code: USM/JEPeM/21020186), and the study was registered at ClinicalTrials.gov, Identifier: NCT04849143.

Authors contributions

MAR: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing. **NAMN:** Conceptualization, Methodology, Validation, Formal analysis, Writing - Review & Editing, Supervision, Project administration. **MZM**: Conceptualization, Methodology, Validation, Resources, Writing - Review & Editing, Visualization, Supervision, Funding acquisition. **MAO**: Formal analysis, Investigation, Data Curation, Writing - Original Draft. **ZZ**: Resources, Data Curation, Writing - Review & Editing, Supervision, Project administration. **ASH**: Conceptualization, Methodology, Validation, Data Curation, Writing - Review & Editing, Visualization, Supervision. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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