

## COMPARATIVE STUDY BETWEEN MALAYSIAN STINGLESS BEE KELULUT HONEY AND MEDICAL-GRADE MANUKA HONEY IN THE TREATMENT OF DIABETIC FOOT ULCER

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### ABSTRACT

Diabetes foot complications have emerged as a global threat, with 25% of diabetics with poor glycemic control developing a foot ulcer in their lifetime. Chronic diabetic foot ulcer (DFU) increased the risk of infection, gangrene, and lower limb amputation. With the rise in antibiotic-resistance, DFU becomes hard to heal and warrants alternatives. Due to its antibacterial properties, medical-grade manuka honey by *Apismeliiifera* has been sparingly used in wound healing. Despite higher antioxidant potency, honey from stingless bee has been under-researched. Thus, the study was aimed to compare the efficacy of kelulut honey by *Trigona itama* with medical-grade manuka honey in the treatment of DFU. Sixty adult diabetics with chronic DFU was randomized into two groups, one receiving kelulut honey and another medical-grade manuka honey dressing. All wounds were debrided with maggot therapy and wounds measured on day 7 and 14. The study showed a statistically significant healing outcome ( $p < 0.05$ ) with a percentage size reduction of 42% on day 14 with kelulut honey dressing as compared to 7.5% (day 14) with medical-grade manuka honey. Hence, the potential of kelulut honey dressing was shown to be greater than medical-grade manuka honey in the treatment of DFU.

**Keywords:** foot ulcer, healing, honey dressing, stingless bee

### INTRODUCTION

Diabetic foot ulcers (DFUs) are common complications of poor-controlled diabetes and a major cause of morbidity and mortality around the world. If left untreated, DFUs cause open sores on the feet and lower legs, which can lead to infection, gangrene, and amputation[1]. Up to 25% of diabetics will develop a DFU at some point in their lives, according to estimates. The foot complication due to poor controlled diabetes included infection with more than 50% of DFU prone for infection, resistant to antibiotics and ultimately ended up with lower limb amputation[2]. Lower limb amputation has become a devastating impact on the patients and the nation[3].

DFUs are caused by a combination of neuropathy, peripheral artery disease, and immune dysfunction. DFUs develop and persist as a result of the ischemia, neuropathy, and impaired wound healing[4]. DFUs are difficult to treat and frequently necessitate a multidisciplinary approach that includes glycemic control, wound debridement, off-loading, and antimicrobial therapy. Of late, antibiotic resistance had played a major role in the delay in chronic wound healing especially in DFU[5]. Hence, alternative therapy which involved modern, advanced dressing with antibacterial properties were highly sought for and one of the ancient remedies which has resurfaced was honey.

Honey has been used for centuries for medicinal purposes, and recent scientific studies have revealed that different types of honey have distinct therapeutic properties[6]. Manuka honey is the most popular medical-grade honey used in the wound treatment of burns and few chronic wounds[7]. Another type of honey which has been present but less common is honey produced by stingless bees known as kelulut honey in Malaysia[8]. Manuka

honey is produced in New Zealand by bees that feed on the nectar of the Manuka plant, whereas kelulut honey is produced in Southeast Asia, including Malaysia, by stingless bees of the *Trigona* species.

In recent years, kelulut honey has gained significant attention in scientific research due to its potential therapeutic properties, particularly for wound healing[9]. Studies have demonstrated the therapeutic efficacy of kelulut honey in promoting wound healing, reducing inflammation, and preventing infections making it a promising natural alternative to conventional wound care treatments[10]. Despite the growing interest in kelulut honey, there is still much to be learned about its potential benefits and underlying mechanism of actions.

Both manuka and kelulut honey have antimicrobial and wound-healing properties. Manuka honey is well-known for having high levels of methylglyoxal (MGO), a bioactive compound responsible for its antimicrobial activity. In clinical settings, medical-grade Manuka honey with a standardized level of MGO is used to treat various types of wounds, including diabetic foot ulcers and surgical wounds[11], [12]. Kelulut honey, on the other hand, has high levels of flavonoids, phenolics, and enzymes, which contribute to its antioxidant, anti-inflammatory, and wound-healing properties but less widespread in clinical research[13].

While manuka honey has been extensively researched for its therapeutic properties, there is growing interest in Kelulut honey's potential health benefits. However, comparative studies which directly compare the therapeutic properties of medical-grade manuka honey and kelulut honey to date remains less common. As a result, the purpose of this research is to compare the efficacy of kelulut honey and medical-grade Manuka honey in the treatment of diabetic foot ulcer which will contribute to the existing body of knowledge on kelulut honey and its therapeutic properties in chronic wound healing. The study's findings could provide important insights into the potential clinical applications of kelulut honey in diabetic foot ulcers. The findings of this study also could provide the much-needed implication for the development of new natural wound dressing for the treatment of chronic wound such as diabetic foot ulcers to improve wound healing outcomes. Also, promote the sustainability of beekeeping practices in Malaysia.

## BACKGROUND

The stages of wound healing follow a complex biological process that includes haemostasis, inflammation, proliferation and tissue remodelling. However, a chronic wound does not follow the typical healing process. Chronic wound gets stuck in the inflammatory stage and takes a longer duration of time to heal with the standard treatments[14]–[16]. Poor healing can be contributed by many factors including underlying disease such as diabetes and immune system disorders. Treatment of chronic wound such as diabetic foot ulcers mostly rely on conventional therapies such as antibiotics, and surgical interventions[17], [18]. Despite being effective in the management of wounds, majority of the conventional treatments do have drawbacks and limitations especially when it involves infected wounds with antibiotic resistance.

Stingless bee kelulut honey, also known as “Malaysian honey” or “Trigona honey,” is a special variety of honey produced by stingless bees of the *Trigona* species. It has been used for centuries in traditional medicine in Southeast Asia, including Malaysia, for its various health benefits. Kelulut honey is well-known for its distinctive flavor, rich aroma and numerous health benefits[19]. Recent scientific studies have shown that kelulut honey has potent antioxidant, antimicrobial, and wound-healing properties, which make it a potential natural alternative to conventional therapies.

It has been discovered that kelulut honey possesses large concentrations of antioxidant substances like flavonoids, phenolics, and enzymes. These substances have been demonstrated to offer defense against oxidative damage, which plays a significant role in many diseases and ageing. Kelulut honey has a substantial antioxidant activity that is comparable to, or even greater than, that of other forms of honey, such manuka honey, according to in vitro research[20]–[22].

Broad-spectrum antibacterial activity against several bacterial, fungal, and viral infections has been documented for kelulut honey. Its antibacterial properties have been attributed to the presence of bioactive substances such bee defensin-1 and hydrogen peroxide. Kelulut honey has the potential to be a successful treatment for a number of infectious disorders, including *Staphylococcus aureus*, *Candida albicans*, and *Herpes simplex* virus, according to in vitro and in vivo investigations[23].

Due to its anti-inflammatory, antibacterial, and antioxidant qualities, kelulut honey has been proven to have effective wound-healing properties. It has been demonstrated that kelulut honey encourages the growth of fibroblasts and keratinocytes, two key cells in the healing of wounds. Studies conducted in both the lab and on animals have shown that kelulut honey can speed up the healing process, lessen swelling, and shield wounds from infection in a variety of wound types, including burn wounds and diabetic foot ulcers[24].

## **METHODOLOGY**

This is a quasi-experimental study conducted in a tertiary hospital in Malaysia on 60 diabetic patients with foot ulcers. Simple randomizations process was applied to recruit the participants. Adult diabetic above 18 years old with stage3 chronic diabetic foot ulcer were randomized into 2 group. Choice of debridement was maggot therapy which was done debridement of wounds prior to commencement of honey application. 30 participants in each group with the intervention group treated with kelulut honey and other 30 with medical-grade manuka honey. Size of wound was measured using NDKare™ application software at baseline (before honey application) and after honey application on day 14. Honey dressing for both groups were changed every other day. The honey dressing was applied upon aseptic cleansing technique with normal saline for all the 60 wounds. Exclusion criteria included patients requiring urgent amputation, osteomyelitis and ischaemia.

## **RESULT**

The study population consisted of poorly controlled adult diabetics (HbA1c 8.0mmol) with no age limit and gender profile. Size of ulcer was not limited. The ulcers were categorized according to SINBAD grading and majority of the ulcer fell into Grade 3. The gender profile of male to female(%) was 60:40. The wound size measured between the two groups were significantly different with intervention group showing a reduction of 42 % in wound size after 14 days as compared to 7.5% in the wounds treated with medical-grade manuka honey. The wounds treated with medical grade manuka honey had higher exudate as compared to wounds treated with kelulut honey. Patients with medical-grade manuka experienced mild pain upon application and it lasted for 30 mins the soonest medical-grade manuka honey was applied with average pain score 5, whereas no pain documented in the intervention group treated with kelulut honey.

## **DISCUSSION**

Both kelulut honey and medical-grade manuka honey has the antioxidant capacity but they differ in their respective specific antioxidant compositions. Manuka honey's main antioxidant is a compound found in high concentrations in the nectar of the manuka plant. Manuka honey also contains other antioxidants such as flavonoids and phenolic acids which had been shown to be lower than kelulut honey. In contrast, kelulut honey contains a range of antioxidants, including flavonoids, phenolic acids, and enzymes such as glucose oxidase. Some of the specific antioxidants found in kelulut honey include pinobanksin, pinocembrin, quercetin, kaempferol, epigenin, and chrysin, which are all flavonoids with potent antioxidant activity[25]–[27]. Moreover, the high flavonoids content in kelulut honey have been indicated to show potent free radical scavenging activity to defend cells against oxidative stress. Gallic acid, caffeic acid and p-coumaric acid are among the phenolic acids found in kelulut honey[28]. These compounds have been shown to have anti-inflammatory and antioxidant properties as well. Kelulut honey also contains ascorbic acid, a powerful antioxidant that aids in the protection of cells from oxidative damage similar to flavonoids. Similarly, carotenoids found in kelulut honey such as beta-carotene, lutein, and zeaxanthin have been shown to have anti-inflammatory and antioxidant properties. Certain enzymes in kelulut honey are part of the body's antioxidant defense mechanism such as glucose oxidase, catalase, and peroxidase which are indicated for protection of cells from oxidative stress as well[29][30], [31]. Overall, kelulut honey has a high antioxidant capacity due to its high concentration of bioactive compounds such as flavonoids, phenolic acid, ascorbic acid, carotenoids, and enzymes. Therefore, the compounds combined to provide a powerful anti-oxidant and anti-inflammatory effects making kelulut honey a potential therapeutic tool to bring health benefits and also improve wound healing outcomes especially in chronic wound such as DFU.

In summary, the use of honey in wound healing including medical-grade manuka honey and kelulut honey is

quite promising based on previous findings and the outcome demonstrated in this study. In view of the superiority of healing outcome based on the highest reduction of wound size with kelulut honey in this study, the potential of kelulut honey as wound dressing cannot be under-estimated. As mentioned, the potency of anti-oxidant in kelulut honey based on previous studies had shown its promising benefit in the reduction of wound size within two weeks as compared to medical-grade manuka honey. Further studies should include exploration on dosing, combination with other therapies for the treatment of DFUs. The body of evidence presented in this study should initiate more research on its anti-bacterial activities on biofilm and other resistant bugs. The use of kelulut honey in a randomized controlled studies and comparative studies with conventional and modern dressing should be warranted.

According to the existing research, kelulut honey has strong anti-oxidant potency and wound-healing capabilities, making it a possible natural remedy in place of conventional treatments. To completely comprehend the kelulut honey's therapeutic efficiency and methods of action, more research is nonetheless required. The potential application of kelulut honey dressing as demonstrated in this study could initiate randomized controlled trial in the treatment of DFU for further study. With the findings displayed in this study may reduce the dependency on medical-grade manuka honey as wound dressing for chronic wounds and turn the direction towards the commercialization of locally produced kelulut honey as a potential wound dressing in wound management. Furthermore, the findings in the study could further establish and sustain the bee keepings activities for kelulut honey in Malaysia.

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