Review Article

Honey as a promising treatment for diabetic foot ulcers (DFU)

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Abstract

Diabetic Foot Ulcers (DFUs) are complex, chronic wounds, which have a major long-term impact on the morbidity, mortality and quality of patients' lives. Individuals who develop a DFU are at greater risk of premature death, myocardial infarction, and fatal stroke than those without a history of DFU. Unlike other chronic wounds, the development and progression of DFU is often complicated by wide-ranging diabetic changes, such as neuropathy and vascular disease. These, along with the altered neutrophil function, diminished tissue perfusion, and defective protein synthesis that frequently accompany diabetes, present practitioners with specific and unique management challenges.Honey has been used for centuries in wound care. Its therapeutic properties are largely attributed to its antimicrobial and anti-inflammatory activities. This review provides an insight on the mechanisms by which honey affects wound healing. Honey is being used to treat many types of wound, including: traumatic wounds, surgical incision sites, burns, sloughy wounds, and pressure ulcers.The number of publications reporting the use of honey has increased. A great number of studies haves concluded that clinical evidence to support the use of honey in the treatment of superficial wounds and burns was of low quality. Other studies suggested that honey improved healing times in mild to moderate superficial and partial thickness burns when compared to conventional dressings.This was supported by a meta-analysis of systematic reviews of topical and systemic antimicrobial interventions for wounds. Of 109 evidence based conclusions, robust evidence was found to support the use of topical honey to reduce healing times in burns.Yet, there are many studies which did not indicate the positive result on using honey to treat DFU's. Therefore, more studies should be carried out in order to make a solid proof for using honey in treatment of DFU's.

Key Words: Burns, DFU's, Honey, Manuka, Neuropathy, Pressure ulcers, Wounds

INTRODUCTION

It is well-established that 25% of people diagnosed with diabetes will develop a Diabetic Foot Ulcers(DFU) during their lifetime.[1]DFUare complex, chronic wounds, which have a major long-term impact on the morbidity, mortality, and patients quality of life.[2,3] Individuals who develop a DFU are at greater risk of premature death, myocardial infarction and fatal stroke than those without a history of DFU.[4] Unlike other chronic wounds, the development and progression of a DFU is often complicated by wide-ranging diabetic changes, such as neuropathy and vascular disease. A DFU is a pivotal event in the life of a person with diabetes and a marker of serious disease and comorbidities. Without early and optimal intervention, the wound can rapidly deteriorate, leading to amputation of the affected limb.[5,6]

It has been estimated that every 20 seconds a lower limb is amputated due to complications of diabetes. http://bit.ly/Kcg0TU Globally, around 370 million people have diabetes and this number is increasing.[8]Successful diagnosis and treatment of patients with DFUs involves a holistic approach that includes:

- Diabetes management
- Effective local wound care
- Infection control
- Pressure relieving strategies
- Restoring pulsatile blood flow.

With regard to effective local wound care, honey has been for many years in different parts of the world a premiere options to treat DFUs.

It has been demonstrated in many studies that honey has antibacterial effects, attributed to its high osmolarity, low pH, hydrogen peroxide (H2O2) content, and content of other uncharacterized compounds.[1,2]

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The low water activity of honey is inhibitory to the growth of the majority of bacteria, but this is not the only explanation for its antimicrobial activity. Molan has studied sugar syrups of the same water activity as honey and found them to be less effective than honey at inhibiting microbial growth *in vitro*. Honey is mildly acidic, with a pH between 3.2-4.5. The low pH alone is inhibitory to many pathogenic bacteria and, in topical applications at least, could be sufficient to exert an inhibitory effect. When consumed orally, honey would be so diluted by body fluids that any effect of low pH is likely to be lost.[1,3] H2O2 was identified as the major source of antibacterial activity in honey. It is produced by the action of glucose oxidase on glucose, producing gluconic acid. This is inhibited by excessive heat and low water activity.[4] The H2O2 concentration produced in honey activated by dilution is typically about 1,000 times less than in the 3% solution commonly used as an antiseptic. More recently, a correlation has been established between the level of H2O2 and the degree of antimicrobial activity of honey. It was also suggested that H2O2 alone may not be sufficient to account for the antimicrobial activity.[5] There are a range of other, largely uncharacterized, substances present in some honeys that have antibacterial effects.[6] For example, Manuka honey from New Zealand with nonperoxidal antibacterial activity has been found to be effective at low concentrations.[7] Antibacterial aromatic acids[8] and 10-HDA, the main royal jelly acid with antibacterial properties[9] have also been found in honey, as well as defensin-1.[10] The strong antibacterial activity of Manuka honey is due to the presence of the antibacterial substance methylglyoxal.[11] The antifungal activity of honey against *Candida albicans*has been reported in many studies.[7,12] Although honey has been used for centuries in wound care, it is now being integrated into modern medical practice.Currently, honey is used to treat a range many types of wound, including: traumatic wounds, surgical incision sites, burns, wounds, and pressure ulcers.

The number of publications reporting the use of honey has increased, yet systematic reviews have been critical of the design of some of those studies.[13-15] Moore *et al*., (2001) concluded that clinical evidence to support the use of honey in the treatment of superficial wounds and burns was of low quality. By contrast, a review of 19 randomized controlled trials (RCTs) with a total of 2554 participants suggested that honey improved healing times in mild to moderate superficial and partial thickness burns when compared to conventional dressings.[15] This was supported by a meta-analysis of systematic reviews of topical and systemic antimicrobial interventions for wounds. A total of 44 Cochrane reviews out of 149, which had been graded into 5 categories based on their size, homogeneity, and the effect size of outcome, were selected. Of 109 evidence based conclusions, robust evidence was found to support the use of topical honey to reduce healing times in burns.[16]

Another recent review (Molan, 2011) of 33 RCTs noted that participants using honey had increased from 1965 in 2006 to 3556 in 2011, with a broadening in the range of wound types included, the choice of dressings available to clinicians, and the types of honey employed. With such variations, it is difficult to make generalized deductions about clinical efficacy. Characterization of the various bioactivities of honey is required if sound comparisons between products are to be made. To date, no RCT has randomized similar wounds to receive different types of honey to assess their relative efficacy.[17]

Therapeutic properties of honey

Many articles have been written about the bioactivities of honey[17,18] which can best be summarized thus: Antimicrobial activity, deodorizing action, debriding action and osmotic effect, anti-inflammatory activity, antioxidant activity, and enhanced rate of healing. Essentially, honey can be regarded as an antimicrobial agent with the ability to promote wound healing. In chemical terms, honey is a complex substance whose antimicrobial components have been well established.[18]

However, all honeys are not equal[19-21]and new bioactive components are still being discovered. Methylglyoxal was shown to contribute to the antibacterial activity of Manukahoney[22,23] as well as leptosin.[24] Many honeys generate H2O2 on dilution but Manuka honey does not produce detectable levels and, as such, has been called a non-peroxide honey.[21]

Inhibition of planktonic bacteria

Honey has a broad spectrum of activity against bacteria and fungi.[25]A variety of bacteria capable of causing wound infection have now been tested under laboratory conditions for their susceptibility to honey. Gram-positive bacteria are often involved in wound infection. *Staphylococcus aureus*, the most common cause of wound infection has been shown to be inhibited by relatively low concentrations of honey[26-28] as have antibiotic resistant strains, such as methicillinresistant *S. aureus*(MRSA), vancomycinsensitive and vancomycinresistant *Enterococci* (VSE and VRE, respectively)[29-31] and coagulase negative *Staphylococci*.[32] A recent study showed that the growth of 15 cultures of Streptococcus species isolated from wounds were inhibited by honey.[33] Of Gram-negative bacteria commonly implicated in wound infection, *Pseudomonas aeruginosa*[30] enteric bacteria,[34]*Stenotrophomonas*species,[35] and *Acinetobacterbaumannii*[27] have been shown to be susceptible to honey *in vitro*. In recent years, laboratory studies have been designed to investigate the mode of action of Manuka honey at cellular and molecular levels, and have demonstrated that cell division in *S. aureus*

and in MRSA is interrupted by exposure to honey. Cells exposed to Manuka honey accumulated at the end of the cell cycle with fully formed cross walls, but did not separate into daughter cells. Without completing cell division, bacteria cannot establish a colony. Multiple changes in cellular proteins have also been observed in *S. aureus*exposed to Manuka honey.[36]

Analysis of changes in *Escherichia coli* following exposure to Manuka honey demonstrated multiple effects on the expression of genes. In *P. aeruginosa*, Manuka honey caused changes in the bacterial cell wall that led to instabilities, resulting in cell lysis.[37] Hence, Manuka honey has been shown to induce distinct cellular effects in Gram-positive bacteria, compared with Gram negatives. Buckwheat honey has been shown to inhibit MRSA, VRE, *E. coli* and *Bacillus subtilis*by extensive degradation of DNA elicited by the generation of H_2O_2 on exposure.[38] Patients with infected or highly exuding wounds may experience wound malodor. Honey has been shown to have a deodorizing effect in patients with malodorous wounds, which is probably due to the inhibition of bacteria. This trait is most notable within 24 hours of the application of honey to the wounds.[39]

Inhibition of biofilms

Following reports that link the presence of biofilms in a wound to chronicity,[40] interest in the control of biofilms has increased. Unsurprisingly, research indicates that higher concentrations of honey are required to disrupt established biofilms than to prevent biofilm formation, and they also indicate that planktonic bacteria are more susceptible to honey than are biofilms. The adherence of bacteria to a wound is an important step in establishing initiation of infection and biofilm formation. In 2009, a study into the effects of honey on planktonic and biofilm-embedded bacteria suggested that honey has a bactericidal effect against the wound pathogens grown in the laboratory as biofilms.[40] Similarly, biofilms of *S. aureus*and *P. aeruginosa*exposed to honey were inhibited *in vitro*.[41]

Methylglyoxal has been implicated in the inhibition of biofilms.[42] Biofilms of methicillin-sensitive *S. aureus*(MSSA), MRSA, and VRE can be prevented from forming and established biofilms can be inhibited*in vitro* with varying concentrations of Manuka honey.[43] Honey has been shown to be effective in inhibiting six isolates of *P. aeruginosa*forming biofilms *in vitro*[44] and one reference strain of *Streptococcus pyogenes*. The downregulation of two genes coding for surface-binding proteins in *S. pyogenes*following exposure to Manuka honey was found to contribute to the prevention of biofilm formation.[45]These findings need to be validated by clinical studies once a reliable test for the presence of a biofilm has been developed.

Antimicrobial resistance to honey

With the introduction of new antimicrobials into clinical practice, the emergence of resistant strains of bacteria normally follows at some point. Resistant species tend to dominate in environments where antimicrobial agents are in common use. Antimicrobial resistance not only threatens to increase the cost of health care and jeopardize healthcare gains to society, but it may even damage trade and impact the economy.[46] Experiments in which bacteria were exposed to low concentrations of Manuka honey failed to select for honey-resistant strains. While these findings do not preclude the emergence of bacterial strains resistant to honey in the future, they do suggest that the possibility is slight.

Debriding action of honey and osmotic effect

The role of honey in wound debridement has been described by.[47] In one RCT, Manuka honey was demonstrated to promote improved debridement, compared to a hydrogel.[48] In chronic wounds, the increased level of proteases lead to the degradation of growth factors, cytokines, and extracellular matrix components and thereby contribute to the deposition of nonviable tissue.[49] Proteases work optimally at an alkaline pH and Manuka honey has been shown to reduce pH;[50] this is likely to modulate protease activity in chronic wounds. The osmotic effect of honey has been thought to encourage lymphatic flow to devitalized tissue while reducing bacterial load. This promotes autolytic debridement by bringing plasminogen into the wound environment, which is normally activated into active plasmin. In chronic wounds, the production of plasminogen activator inhibitor (PAI) by macrophages inactivates plasminogen activator and results in low levels of active plasmin. By inactivating PAI, honey allows plasminogen to become plasmin and, in turn, digest fibrin and so lower the quantity of nonviable tissue.[49]

Antioxidant and anti-inflammatory activity of honey

Wounds that do not progress through the usual phases of healing persist in a chronic inflammatory state that is characterized by excessive neutrophil infiltration.[51] Release of reactive oxygen species by neutrophils leads to damaging oxidation reactions within the wound, as well as the recruiting of more neutrophils to the wound. One way to interrupt this chronic inflammatory cycle is to remove free radicals with antioxidants and honey is known to contain antioxidants that scavenge free radicals.[52]The antioxidant potential of honey has been attributed to its phenolic content.[53,54] Although the anti inflammatory effects of antioxidants in honey have been demonstrated in animal models, clinical studies are limited, but it may be that these effects explain the benefits seen in treating burns with honey.[55]

FUTURE PERSPECTIVE

The use of honey in modern wound care is still met with some skepticism. Since the advent of evidence-based medicine, changing clinical practice depends on providing clinicians with appropriate levels of evidence of clinical efficacy. Although honey has become a first-line intervention in some wound care clinics, larger and better designed RCTs are needed to cement the role of honey in modern wound care.

CONCLUSION

In the context of the continued emergence of antibiotic-resistant pathogens, some alternative or "traditional" topical antimicrobials have been reintroduced into modern wound care, one such example being honey. While a range evidence is available for the use of honey in wound management, definitive RCTs remain to be undertaken.

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