

The use of honey in diabetic foot ulcers

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Citation: Cooper R (2017) The use of honey in diabetic foot ulcers. *The Diabetic Foot Journal* 20(3): 154–9

Article points

1. Honey has antimicrobial properties and the potential to influence healing.
2. The use of honey in wound care has seen a resurgence with the availability of dressings containing modern medical grade honey.
3. Robust trials are still required to determine objectively the efficacy of medical grade honey for the management of diabetic foot ulcers

Key words

- Honey
- Ulceration
- Wound care

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The topical use of honey in treating wounds can be traced back to ancient civilisations, but it fell out of favour in modern medicine during the 1970s. Interest was rekindled at the start of this century with the development of medical devices incorporating medical grade honey and a range of formulations is now available. Therapeutic properties assigned to honey include antimicrobial effects and the ability to enhance wound healing. Honey is now being used in the management of both acute and chronic wounds. This review focuses on the role of honey in treating diabetic foot ulcers.

In the past, honey produced for human consumption was also used for medical purposes, and different honeys were selected for various conditions. However, honey now used for wound care in developed countries is distinct from table honey (Cooper and Jenkins, 2009). It is known as medical grade honey and is incorporated into gamma-irradiated wound care devices for use in conventional medicine. In less-developed countries, local, unsterile honeys may still be used to treat wounds.

Modern wound care products containing medical grade honey can be formulated in several ways, such as in tubes (as honey alone), or as gels, ointments or creams. Dressings can have the medical grade honey incorporated into non-adherent materials, alginates, hydrogels and hydrocolloids. They may be flexible sheets, ropes or meshes. Some require secondary, absorbent dressings, but others are non-sticky, with adhesive borders and are entire.

The floral origins of medical grade honey include buckwheat, chestnut, manuka and thyme, along with some unspecified multifloral honeys or bioengineered honey. The antibacterial activity of honey varies widely with honey type and is usually derived from several components (Table 1).

Antibacterial effects of honey

Honey has broad spectrum activity against most of the species capable of causing wound infections

(Blair, 2009; Carter et al, 2016). Importantly, both antibiotic-susceptible and antibiotic-resistant strains of the same species have been shown to be inhibited *in vitro* by honey. Moreover, exposing bacteria to low concentrations of honey has failed to select for honey-resistant strains to date.

The mode of action of medical grade manuka honey (which is largely produced in New Zealand) has been investigated. It was shown to prevent cell division in methicillin-resistant *Staphylococcus aureus* (MRSA) and reduce virulence of MRSA (Jenkins et al, 2011, 2014). It killed *Pseudomonas aeruginosa* by disrupting the cell wall; it also reduced virulence by decreasing motility and acquisition of iron via siderophores (Roberts et al, 2012, 2015; Kronka et al, 2013).

Antibiofilm properties of medical grade manuka honey have been demonstrated *in vitro*. Biofilm formation was prevented by down-regulating binding proteins normally used by *Streptococcus pyogenes*, *S. aureus* and *P. aeruginosa* to attach to human proteins (Maddocks et al, 2012; 2013). Established biofilms of *P. aeruginosa* were inhibited, but higher concentrations were required than those needed to inhibit suspensions of bacteria (Cooper et al, 2014).

Not all honeys inhibit bacteria in the same way (Kwakman et al, 2011). Buckwheat honey, for example, relies on free radicals generated from hydrogen peroxide to degrade bacterial DNA and to disrupt the cell wall (Brudzynski et al, 2011). Many

Table 1. Antimicrobial factors in medical grade honeys.

Antibacterial factor	Manuka	Multi-floral greenhouse sourced	Buckwheat	Chestnut	Thyme
High sugar content	√	√	√	√	√
Low water content	√	√	√	√	√
Acidity	√	√	√	√	√
Hydrogen peroxide	x	√	√	√	√
Methylglyoxal	√	x	-	-	-
Bee defensin-1	x	√	-	-	-

√ = detected; x = not detected; - = not tested

Table 2. Therapeutic claims attributed to honey pertinent to wound care.

Action	Mechanism
Antimicrobial activity and reduction of malodour	Antimicrobial factors
Provides a moist healing environment	Osmotic effect due to sugars
Debriding action	Inhibition of tissue plasminogen activator inhibitor
Anti-inflammatory action	Quenching of free radicals by anti-oxidants; modulation of cytokines
Angiogenesis	Not known (not due to sugars)
Promotes wound healing	Acidification of wound promotes release of oxygen from oxyhaemoglobin

honeys generate low levels of hydrogen peroxide on dilution, which might be degraded by catalase (an enzyme in human tissues). There is ambivalent evidence that honey sterilises wounds, so further clinical studies are needed. However, eradication of MRSA from colonised wounds following topical application of manuka honey has been demonstrated (Natarajan et al, 2001; Blaser et al, 2007; Gethin and Cowman, 2008).

Other therapeutic properties

The role of honey in promoting wound healing is well documented (Molan 1999, 2011; Cooper, 2016). Therapeutic claims include debriding, anti-inflammatory characteristics, ability to promote angiogenesis and the stimulation of healing (Table 2). Observations from laboratory experimentation, animal studies and clinical

practice provide some support for these claims (Molan, 2011; Cooper, 2016). However, robust clinical evidence from controlled, randomised clinical trials is limited at present (Jull et al, 2015; National Institute for Health and Care Excellence, 2016). Better designed clinical trials with larger cohorts, unbiased randomisation procedures and independent outcome assessment regimens are needed.

The problem of diabetic foot ulcers

The global prevalence of diabetic foot ulceration is estimated to be 6.3%; it is higher in men than women, and higher in type 2 diabetes than in type 1 (Zhang et al, 2017). This is a significant financial and social burden that is likely to increase during this century (Schreml and Berneburg, 2017). Diabetic foot ulcers (DFUs) also pose a complex clinical challenge because of their potential to develop persistent and recurrent infections that may result in delayed healing and/or amputation. Management by a multidisciplinary team involves assessing vascular and neurological impairment, determining the presence and severity of infection and selecting appropriate interventions, such as nutritional advice, surgery, antimicrobial interventions, adjunctive therapies and offloading.

Diagnosis of infection in DFUs

Diagnosis of wound infection requires assessment of the patient as a whole, as well as the affected limb and the wound itself (Lipsky et al, 2015). DFUs may be colonised by polymicrobial communities (Dowd et al, 2008). *S. aureus* has long been associated with DFUs, as have Gram-negative rods, anaerobes and fungi (Louie et al, 1976; Sapico et al, 1980; Jones et al, 1985; Wheat et al, 1986; Gardner et al, 2013).

More recently, the prevalence of multidrug-resistant bacteria, such as MRSA and extended spectrum beta-lactamase producing Gram-negative rods, has increased in DFUs (Uçkay et al, 2015). Conventionally, the routine investigation of the microbial flora of patients depended on the culture of organisms in the laboratory. However, the advent of molecular techniques has revealed an increasingly diverse range of microbial species (Dowd et al, 2008) and provided a means to

distinguish between colonisation and infection with *S. aureus* in DFUs (Sotto et al, 2012).

Molecular investigations of the microbial flora of chronic DFUs highlighted the presence of biofilms, confirmed by microscopic analysis (Dowd et al 2008; James et al, 2008; Neut et al, 2011; Oates et al, 2014). Microbial species within biofilm communities are markedly less susceptible to antimicrobial agents, making them recalcitrant to antimicrobial therapy and more difficult to eradicate (Stewart and Costerton 2001; Bridier et al, 2011).

Management of diabetic foot infection

Comprehensive guidelines for the diagnosis and management of foot infections in people with diabetes have been formulated and clearly indicate that wounds without signs of infection should not be treated with antimicrobial agents. Empiric antibiotic regimens for infected wounds based on likely or proven causative agents have been defined (Lipsky et al, 2015). However, infection caused by multidrug-resistant strains and the establishment of biofilms in DFUs often confound the management of infections. Hence, antimicrobial interventions other than antibiotics may be indicated for DFUs. Honey's broad spectrum of antimicrobial activity, its action against antibiotic-resistant bacteria and biofilm, and its ability to enhance wound healing, makes it an option worth considering in managing DFUs.

Safety issues using honey in diabetes

Honey is not cytotoxic and safety has been established by the treatment of wounds in neonatal and paediatric patients. Risks associated with honey include transient stinging sensations on application, which may not concern diabetic patients with neuropathy. Another perceived risk of using honey topically was that it would lead to increased blood glucose levels in people with diabetes. However, comparisons between pre- and post-honey dressing treatment of DFUs showed no statistically significant differences in glycaemic control (Jeffery 2008; Kirby et al, 2009) and sugar has been advocated for healing diabetic ulcers (Biswas et al, 2010).

Possible risks from methylglyoxal (an important antibacterial factor found in manuka honey)

have been raised (Majtan, 2010). It is capable of glycosylating proteins and contributing to advanced glycation end products that impair wound healing in diabetic animal models. However, clinical evidence to confirm this fear has not been reported. Advice of using honey on diabetic foot ulcers is published (Molan and Betts, 2008; Eddy et al, 2008). All medical honey in wound care needs to come with advice; to use an absorbent dressing, which locks in the exudate, and/or apply a good barrier cream around the wound edges.

Clinical use of honey on DFUs

Several case studies, cohort studies and randomised controlled trials (RCTs) illustrate the clinical use of honey in treating DFUs. Details of RCTs (which provide high level evidence) are summarised in *Table 3*. Some of this evidence has already been reviewed (Alam et al, 2014; Asamoah et al, 2014; Tian et al, 2014; Katel et al, 2016).

Generally, the quality of the evidence has been judged to be poor. Randomisation procedures were not always clearly described and the number of patients treated was small. None of the studies were double blinded due to the difficulty in masking the smell and texture of honey and finding an appropriate placebo. Furthermore, locally available honey was utilised in some studies which, unlike medical grade honey, may not be well characterised, sterilised by gamma irradiation or reproducible.

Whether the type of honey influences clinical outcomes is not yet determined, so comparative studies of efficacy are needed to ascertain whether evidence from studies using local honeys is pertinent to modern medical practice.

Nevertheless, deductions from RCTs indicate that honey is either better than comparators or there is no significant difference. Outcomes significantly worse than conventional dressings have not been reported; one inference is that honey is not harmful.

An evaluation of medical grade honey dressings on infected DFUs by five clinicians was conducted using questionnaires. Over 6 months, feedback was derived from 65 completed forms related to 38 wounds in 34 patients; high satisfaction rates (66–93%) were found for clinician ease of use, clinician overall satisfaction and patient comfort (Freeman et al, 2010).

“Robust randomised controlled trials are still required to determine objectively the efficacy of medical grade honey for the management of diabetic foot ulcers.”

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Table 3. A summary of RCTs in which honey was used on DFUs.

Type of honey	Country	Type of diabetes and wound	Comparators used	Total number of wounds	Randomisation process	Outcomes assessed	Observations recorded	Reference
Australian food honey soaked gauze (AH)	Malaysia	Type 2; Wagner grade II DFUs admitted for surgery	Povidone iodine and saline soaked gauze (PI)	30 (numbers in each group not stated)	Not stated (unclear risk of bias)	Mean healing time	Mean healing time 14.4 days AH group, 15.4 days PI group ($P>0.005$)	Shukrimi et al (2008)
Manuka honey impregnated dressings (MH)	Greece	Type 2; Wagner grade I and II neuropathic foot ulcers	Saline soaked dressing (SS)	63 (32 MH; 31 SS)	First patient to MH group, then to alternating SS and MH groups (high risk of bias)	Number of wounds healed; negative wound swab	97% healed in MH group, 90% healed in SS group ($P>0.005$); 78% ulcers sterile in 1 week in MH group versus 35.5% in SS group	Kamaratos et al (2014)
Beri honey impregnated dressing (BH)	Pakistan	Wagner grade I and II DFUs	Saline dressing (SS)	348 (179 BH; 169 SS)	Computer generated random numbers (low risk of bias)	Proportion of wounds healed; wound healing time	76% healed in BH group, 57% healed in SS group ($P=0.001$); median wound healing time 18 for BH, 29 for SS ($P=0.001$)	Imran et al (2015)
Indian food honey (IH) soaked gauze	India	Type 2; Wagner grade II DFUs admitted for surgery	Povidone iodine (PI) and saline soaked gauze	36 (numbers in each group not stated)	Not stated (unclear risk of bias)	Mean duration for surgical closure	Mean duration until surgical closure 14.2 days in IH, 15.5 days in PI	Agarwal et al (2015)
Manuka honey dressing	China	Type 2; DFUs	Nanocrystalline silver (NS); paraffin tulle (PT)	31 (10 MH; 11 NS; 10 PT)	Online randomisation software (low risk of bias)	Healing at 12 weeks; reduction in ulcer size, bacteriology and infection	Healing: 82% in NS, 50% in MH, 40% in PT ($P>0.005$); ulcer size reduction rate: 97% for NS, 86% for MH, 75% for PT	Tsang et al (2017)

AH = Australian food honey; BH = beri honey; IH = Indian food honey; MH = manuka honey; NS = nanocrystalline silver PI = povidone iodine; PT = paraffin tulle; SS = saline dressing

Conclusion

Honey is a versatile intervention for wounds because of its antimicrobial properties and its potential to influence healing. Being a natural product, honey is variable in chemical composition and activity. However, wound devices containing medical grade honey represent consistent products. This is because they contain traceable ingredients that have been chemically analysed and blended to a predetermined specification, and which are manufactured under defined conditions that are subject to quality assurance procedures. To date, adverse clinical observations following the use of honey for DFUs have not been reported, but robust RCTs are still required to determine objectively the efficacy of medical grade honey for the management of diabetic foot ulcers. ■

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