

Understanding how honey impacts on wounds: an update on recent research findings



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Honey is a topical antimicrobial agent that has been used for millennia in wound care. Licensed wound care products containing medical-grade honey first became available in 1999 and are now widely used. Honey's therapeutic properties are largely attributed to its antimicrobial and anti-inflammatory activities. This review provides an insight into the laboratory evidence published in the past 5 years that illustrate how the mechanisms by which honey impacts on wounds are beginning to be understood.

Although honey has been used for centuries in wound care, it is now being integrated into modern medical practice. The first modern wound care product to gain regulatory acceptance by the Australian Therapeutic Goods Administration was an irradiated tube of blended honeys. Currently, a range of products are available from several manufacturers (Table 1) and 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, yet systematic reviews have been critical of the design of some of those studies (Moore et al, 2001; Bardy et al, 2008; Jull et al, 2008). 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 randomised 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 (Jull et al, 2008). 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 five 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 (Brölmann et al, 2012).

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 generalised deductions about clinical efficacy.

Characterisation of the various bioactivities of honey is required if sound comparisons between products are to be made. To date, no RCT has randomised similar wounds to receive different types of honey to assess their relative efficacy.

THERAPEUTIC PROPERTIES OF HONEY

Much has been written about the bioactivities of honey (Molan, 1999; 2011), which can best be summarised thus: antimicrobial activity, deodorising 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 (Molan, 1992). However, all honeys are not equal (Allen et al, 1991; Cooper and Jenkins, 2009; Kwakman et al, 2011) and new bioactive components are still being discovered.

Methylglyoxal was shown to contribute to the antibacterial activity of manuka honey (Adams et al, 2008; Mavric et al, 2008), as well as leptosin (Kato et al, 2012). An antimicrobial

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peptide called bee defensin that is synthesised as part of the insect's innate immune system was found in the honey used in Revamil® (Bfactory Health Products BV; Kwakman et al, 2010). Many honeys generate hydrogen peroxide on dilution (Allen et al, 1991), but manuka honey does not produce detectable levels and, as such, has been called a non-peroxide honey (Kwakman et al, 2011).

Inhibition of planktonic bacteria

Honey has a broad spectrum of activity against bacteria and fungi (Molan, 1992; Blair and Carter, 2005). 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 (Cooper et al, 2002; Blair et al, 2009; Henriques et al, 2010), as have antibiotic resistant strains, such as methicillin-resistant *S. aureus* (MRSA), vancomycin-sensitive and vancomycin-resistant *Enterococci* (VSE and VRE, respectively) (Cooper et al, 2002; George and Cutting, 2007; Sherlock et al, 2010; Jenkins, et al, 2011), and coagulase negative *Staphylococci* (French et al, 2005). A recent study showed that the growth of 15 cultures of *Streptococcus* species isolated from wounds were inhibited by honey (Cooper et al, 2011a).

Of Gram-negative bacteria commonly implicated in wound infection, *Pseudomonas aeruginosa* (Cooper et al, 2002; Blair et al, 2009; Sherlock et al, 2010), enteric bacteria (Lin et al, 2011), *Stenotrophomonas* species (Majtan et al, 2011), and *Acinetobacter baumannii* (George

and Cutting, 2007; Blair et al, 2009) 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* (Henriques et al, 2010) and in MRSA (Jenkins et al, 2011) 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 (Packer et al, 2012)

Analysis of changes in *Escherichia coli* following exposure to manuka honey demonstrated multiple effects on the expression of genes (Blair et al, 2009). In *P. aeruginosa*, manuka honey caused changes in the bacterial cell wall that led to instabilities, resulting in cell lysis (Henriques et al, 2011; Roberts et al, 2012). 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 hydrogen peroxide on exposure (Bruzynski et al, 2012).

Patients with infected or highly exuding wounds may experience wound malodour. Honey has been shown to have a deodorising 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 (Molan and Betts, 2004; Gethin et al, 2008; Segovia, 2010).

Table 1: Honey dressing modalities (from Hewish [2012], with permission).

Dressing type	Definition
Honey gel or ointment	Packaged in tubes and useful for sinus or cavity wounds where alginate or fibrous dressings are difficult to place. Generally, more effective in wounds with low exudate levels.
Honey-impregnated tulle	A synthetic, fine-weave, non-adherent dressing; low absorbency, for use on superficial wounds with low to moderate exudate levels.
Honey gel sheet	Consists of a mix of honey and sodium alginate; conforms well to uneven wound surfaces and cavity wounds; generally effective at managing low-exuding wounds.
Honey-impregnated calcium alginate	Alginate dressing impregnated with honey; useful for cavity wounds with moderate- to high-exudate levels.

Inhibition of biofilms

Following reports that link the presence of biofilms in a wound to chronicity (Merckoll et al, 2009), 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 (Merckoll et al, 2009). Similarly, biofilms of *S. aureus* and *P. aeruginosa* exposed to honey were inhibited *in vitro* (Alandejani et al, 2009). Methylglyoxal has been implicated in the inhibition of biofilms (Jervis-Bardy et al, 2011). 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 (Cooper et al, 2011b). Honey has been shown to be effective in inhibiting six isolates of *P. aeruginosa* forming biofilms *in vitro* (Okhiria et al, 2009) and one reference strain of *Streptococcus pyogenes* (Maddocks et al, 2012).

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 (Maddocks et al, 2012).

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. For example, in healthcare settings where many patients are vulnerable to infection.

Antibiotic-resistant bacteria have become a worrying global public health issue. Antimicrobial resistance not only threatens to increase the cost of health care and jeopardise healthcare gains to society, but it may even damage trade and impact the economy (WHO, 2012). Experiments in which bacteria were exposed to low concentrations of manuka honey failed to select for honey-resistant strains (Blair et al, 2009; Cooper et al, 2010). 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 Molan (2009). In one RCT, Manuka honey was demonstrated to promote improved debridement, compared to a hydrogel (Gethin and Cowman, 2009).

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 (Tarnuzzer and Schultz, 1996). Proteases work optimally at an alkaline pH and manuka honey has been shown to reduce pH (Gethin et al, 2008); this is likely to modulate protease activity in chronic wounds.

The osmotic effect of honey has been thought to encourage lymphatic flow to devitalised tissue (Molan 2009), while reducing bacterial load (Gethin and Cowman, 2009). This promotes autolytic debridement by bringing plasminogen into the wound environment, which is normally activated into active plasmin by plasminogen activator. 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 (Molan, 2009).

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 characterised by excessive neutrophil infiltration (Menke et al, 2007). 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 (Henriques et al, 2006; van den Berg et al, 2008).

The antioxidant potential of honey has been attributed to its phenolic content (van den Berg et al, 2008; Kassim et al, 2010; Leong et al, 2012). Although the anti-inflammatory effects of antioxidants in honey have been demonstrated in animal models, clinical studies are scarce (Subrahmanyam et al, 2003), but it may be that these effects explain the benefits seen in treating burns with honey (Jull et al, 2008).

THE FUTURE

The use of honey in modern wound care is still met with some scepticism. 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.

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Medical devices (such as wound dressings) are not required to demonstrate the same level of evidence in order to become licensed for use, but high levels of evidence should be aimed for, and will widen use. However, carrying out meaningful RCTs is difficult in complex and chronic wounds.

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 of evidence is available for the use of honey in wound management, definitive RCTs remain to be undertaken. ■