Manuka honey in wound management: greater than the sum of its parts?

Few involved in wound care will have escaped the considerable interest which has been generated by the resurgence in honey. Equally, there will be many clinicians around the globe who are wondering why all the fuss, as they will have been using honey all along. However, even with the advent of 'medical-grade' honey, combined with considerable research into the numerous potential modes of action, there remains a lingering scepticism regarding the value of honey as a justified, modern intervention in wound care.
The purpose of this brief review is to summarise the ongoing chemical, biochemical and microbiological research and to correlate it with clinical outcomes. The purpose being to present the enquiring clinician with an evidence summary with which clinical choices may be made. While much of the early research was into generic honeys, one particular source, manuka, appears especially effective, and as such this has been the focus of recent studies.

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Honey has been used to treat wounds for millennia.[1,2] Indeed, until the modern age of evidence-based medicine, honey was so highly regarded as a treatment for wounds that it was accepted as a first-line intervention. It is, however, the scientific and clinical focus on honey which has come about in the past 30 years that has led to the classification of medical-grade honey and the commercial availability of highly regulated products.

Biological research into honey

The literature includes reports on numerous honeys, from different floral sources, for *in vitro* antimicrobial activity in particular. Due to the pioneering work of the late Peter Molan[3] in New Zealand over the past 25 years, it has emerged that of the range of honeys tested, those from one source, manuka, has particularly high antimicrobial activity.[4] Subsequently many other reports have supported and clarified this activity this is summarised in a review by Carter et al.[5] It is owing to a series of seminal articles by Molan[6] and colleagues[7,8] in 1999 that the modern approach to honey in wound can be traced. Until that time there had been debate as to the clinical effects of honey being largely osmotic.[9] Molan, based upon the considerable evidence available, identified a number of distinct actions of honey (primarily manuka) on the wound, namely:

- Antimicrobial
- Anti-inflammatory
- Debridement
- Exudate control.

In addition Molan[6] has listed the numerous advantages of honey based upon the available evidence:

- Provides a protective barrier to prevent cross-infection
- Creates an antibacterial moist healing environment
- Rapidly clears infecting bacteria including antibiotic-resistant strains
- Has a debriding effect
- Rapidly removes malodour
- Hastens healing through stimulation of tissue regeneration
- Prevents scarring and hypertrophication
- Minimises the need for skin grafting
- Is non-adherent and therefore minimises trauma and pain during dressing changes
- Anti-inflammatory action reduces oedema
- Has no adverse effect on wound tissues.
- Reduced costs of dressing materials and anti-bacterial agents
- More rapid healing
- Less need for surgical debridement
- Less need for skin grafting.

Given that this list is substantiated by numerous publications at the time of publication, and that numerous additional studies have been added since, it is evident that honey offers considerable advantages.

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Manuka honey

When considering which floral source honey to research and develop for commercial purposes, a number of important considerations must be made. Accepted that clinical and scientific evidence are essential, it is vital that the honey be available from a sustained, consistent source such that the specifications and quality assurance consistent with a regulated medical product be maintained.[10,11] It is important that all clinicians using honey, or any other medical device, be aware of the requirements demanded by current regulations. It is in this respect that manuka honey is the current 'standard' in wound care and thus the focus of this review.

Antimicrobial action

To some degree all honeys have an antimicrobial action as an evolutionary adaptation to prevent spoilage. In many honeys this is based on peroxidise activity. However, this has been attributed to the content of methyl glyoxal (MGO) in manuka honey.[12,13] The activity of manuka honey is not inhibited by catalase whereas peroxide activity is.[14] The evidence for all antimicrobial activity *in vitro* is extensive and well established. *In vivo*, in the wound itself, manuka has been shown to be clinically effective in reducing bioburden.[15–18] Additionally, manuka has been shown to be effective against organisms, which are known to be involved in malodour as well as those, in biofilm colonies.[19–23] The action of the honey on various organisms, including antibiotic resistant species[15,24,25] has been evaluated *in vitro*[14] and the extensive list of susceptible organisms published.[5] The mechanisms for this action, including a synergy, have also been reported.[13,26] This aspect of manuka action has recently been examined using 83 clinical isolates of six genera of wound pathogens.[3,27] The study involved measurement of both minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) and electron microscopy for evidence of cell lysis. The authors concluded that

> *'the findings provide optimism that topical manuka honey might have a role to play in limiting multidrug resistant Gram-negative bacteria'.*

Indeed, the action of antibiotics against wound pathogens has been shown to be enhanced by the presence of sub-lethal manuka).[28] The question whether or not resistance might become a problem has been addressed and dismissed at present.[29]

Clinical impact of manuka honey

Healing of chronic wounds

'Chronicity' has been attributed to an uncontrolled inflammation in the wound tissues and to pathogenic organisms. In order to redress the balance, some form of anti-inflammatory, or immunomodulatory action[30] is indicated in conjunction with an antimicrobial. The immunomodulatory effect is stimulation or inhibition of the release of cytokines TNFα, Il-1β and Il-6, from monocytes and macrophages depending on the condition of the wound. The combination of the anti-inflammatory, immunomodulatory and antimicrobial actions of manuka honey has proven effective in the kick-start of delayed healing wounds. The effective use of manuka honey in a range of chronic wounds has been reported in a number of reviews.[31–35] The clinical research in this area is growing, recent studies have shown that in diabetic foot ulcers manuka honey

> *'represents an effective treatment for NDFU [neuropathic diabetic foot ulcers] leading to a significant reduction in the time of healing and rapid disinfection of ulcers'.*[36]

Needless to say, further randomised controlled trials are required to provide substantive evidence. In the meantime there is substantial 'weak' evidence and sufficient support from expert clinicians to indicate the value of manuka honey in chronic wound management.

Debridement

This action has been reported over the past 20 years and is hypothesised to be owing to a stimulation of plasmin activity in the wound, so denaturing the fibrin which attaches slough to the wound bed. This theory is based upon the known effects of plasminogen activator inhibitor.[14] This mechanism is consistent with autolysis, where the creation of a moist wound environment at the appropriate pH leads to the removal of slough.

Anti-inflammatory action

By concentrating on the known inflammatory mediators active in wounds,[37–39] researchers have discovered that manuka honey is effective in reducing inflammation,[40,41] oedema,[6,42] and exudate levels via antimicrobial and anti-inflammatory actions. The clinical manifestations of these actions also include pain reduction, reported in many clinical studies.[43,44] In addition to overt anti-inflammatory action, manuka honey has been shown to exert an immunomodulatory effect, for example the stimulation of TNFα, IL-1β and TGFα a by monocytes.[30,45,46]

Exudate interaction

It is now known that honey is a biologic wound dressing,[14] which has been claimed by Molan and Rhodes to have:

> *'multiple bioactivities that work in concert to expedite the healing process. The physical properties of honey also expedite the healing process: its acidity increases the release of oxygen from haemoglobin thereby making the wound environment less favourable for the activity of destructive proteases, and the high osmolarity of honey draws fluid out of the wound bed to create an outflow of lymph as occurs with negative pressure wound therapy'.*

In some respects the chemical process of pH lowering attributed to manuka and other honeys is responsible for influencing the dissociation of oxygen from haemoglobin as Molan has stated. The reduction of the pH to an acid milieu also reduces the activity of MMPs: these have an alkalines pH optimum.

The secondary dressing effects

Needless to say, the activity of honey in the wound is dependent to a large degree to its duration in situ. This can be prolonged by having an impregnated dressing, or by use of an appropriate secondary dressing, the choice of which will vary according to the degree of exudate, location and projected wear time. Thus before selecting a honey-based wound treatment, it is essential that these considerations be acknowledged and the appropriate product or combination be used.

Characterisation of manuka honey

Pure manuka honey is produced by introduced European honey bees (*Apis mellifera*) from the manuka or tea tree (*Leptospermum scoparium*) which grows in New Zealand and southeastern Australia. Qualitative tests have been developed for the identification of honey which is claimed to be pure manuka. For example, MGO can be assayed to give a broad indication of identity of floral source.[47] More specifically, lepteridine can be isolated, characterised and quantified.[48] In his review of 2015, Molan points to the bee-derived protein apalbumin-1 (also known as MRJP-1) and its glycated form, make good candidates to develop a purity assay for manuka honey.[24,49] The quality and purity has been questioned,[50] it is thus necessary that medical products claiming to be 'manuka' be verified and certificated following valid assays. It is only then that clinicians can be assured that the products they are using will perform consistently, and be fit for purpose.

Systematic reviews

Clinical studies on honey in wound management have been subject to systematic reviews in recent years. The conclusions in the most recent[51] state that: 'It is difficult to draw overall conclusions regarding the effects of honey as a topical treatment for wounds due to the heterogeneous nature of the patient populations and comparators studied and the mostly low-quality of the evidence. The quality of the evidence was mainly downgraded for risk of bias and imprecision. Honey appears to heal partial-thickness burns more quickly than conventional treatment and infected postoperative wounds more quickly than antiseptics and gauze. Beyond these comparisons any evidence for differences in the effects of honey and comparators is of low or very low quality and does not form a robust basis for decision making'. However, these are the subject of considerable dispute, many of which are documented at the end of the report. As the reviews have included studies on all qualifying studies, and that the use of medical-grade honey has not been a prerequisite for selection, analyses and conclusions are based on generic honey. Given that we are now in the age of regulated, quality assured product which has been standardised, it is inappropriate (and not scientific) to include other honeys in such an analysis. These have not been standardised to any degree, are not at all quality-assured and not commercially available.

Discussion

Given that no single intervention provides a panacea for wound care, medical-grade manuka honey goes a considerable way towards that status. Equally, as no one dressing or topical application is suited to all wounds and all patients, honey must also be regarded as an option, to be targeted to the appropriate wound and patient. Given that systematic reviews have 'diluted' the manuka effect by the inclusion of other, non-specific or generic honeys, the clinical outcomes achieved in many indications are impressive. This is also complemented by the proven effects on multi-resistant bacteria, a feature which, in the post-antibiotic age, becomes priceless. For a natural product, used for millennia and now developed into a regulated medical device, honey has shown its real value. Given that research is still uncovering new aspects of the biological performance, it is extraordinary how subtly evolution has led to such an ex–quisite material. More that the sum of its parts, certainly, but what more remains to be discovered?

Conclusion

Honey is a valuable option in wound management. More specifically pure manuka honey, with its considerable evidence base, is pre-eminent among honeys for multifunctional activity in wound management. For something which has been long used to treat 'purulent' wounds, research has shown the further capacity to reduce inflammation, affect debridement, and promote healing. **JWC**

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