

The evidence and the rationale for the use of honey as a wound dressing

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Abstract

Although there are now several brands and types of honey wound-care products available as registered medical devices, there is little promotional advertising of honey products for wound care. The misconception that there is no evidence to support the use of honey, which seems to be quite common, may be due to this lack of advertising, and to the systematic reviews that have been published on honey concluding that the evidence is of low quality and/or there is a need for more evidence. However, the same lack of high-quality evidence exists with all the other options that clinicians have for dressing wounds. This places practitioners in a quandary. When clinical evidence of the highest level is not available, then decisions on modes of treatment need to be based on whatever evidence there is available. This review outlines the 16 randomised controlled trials (RCTs) of honey in wound care published since Molan reviewed the previous 17 in 2006, which bring the total of participants in the trials up from 1,965 to 3,556 and broadens the range of types of wounds on which trials with honey have been conducted. Another important factor influencing the choice by clinicians of which product to use on a wound is scientific rationale. This review covers the evidence and explanation of mode of action for various bioactivities in honey which aid wound healing: a very broad-spectrum antimicrobial activity that is effective on antibiotic-resistant strains; activation of autolytic debridement; anti-inflammatory activity; antioxidant activity; stimulation of growth of cells for tissue repair; and an osmotic action. The need for standardisation of these bioactivities is discussed.

Keywords: honey, review, clinical evidence, scientific rationale.

Introduction

With the move towards evidence-based practice, clinicians considering using honey will want to know what evidence there is to support it. There are now several brands and types of honey wound-care products available as registered medical devices (Table 1), but there is little promotional advertising of honey products for wound care. The misconception that there is no evidence to support the use of honey seems to be quite common and may be partly due to this lack of advertising. Also, anyone consulting the first of the two systematic reviews that have been published on the use of honey in wound care will get an impression of lack of evidence because it included

only seven randomised controlled trials (RCTs) conducted with honey and it was stated that “confidence in a conclusion that honey is a useful treatment for superficial wounds or burns is low”¹. Although a more recent review² included 19 RCTs (with a total of 2,554 participants) and concluded that “honey may improve healing times in mild to moderate superficial and partial thickness burns compared with some conventional dressings”, it was stated that “the poor quality of most of the trial reports means the results should be interpreted with caution”, and that “there is insufficient evidence to guide clinical practice in other areas.”

The one trial excepted from this opinion that the quality of evidence was low was one which compared honey dressings with usual care on venous ulcers under compression³. This trial found that there was no significant difference between honey and other dressings used as an adjuvant to compression. However, it was an example of a common shortcoming of RCTs conducted on dressing wounds with honey, where the number of participants is not large enough to give a conclusive result, even in this instance where there were 368 participants. To be able to conclude with confidence that honey was no better than any other treatment would have required much larger numbers. It was originally

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Table 1. Registered sterilised wound care products incorporating honey that are on sale.

Name of product	Description of product	Manufacturer
Algivon	Alginate fibre dressing pad impregnated with manuka honey	Advancis Medical
Activon Tulle	Non-adherent gauze dressing impregnated with manuka honey	Advancis Medical
Actilite	Non-adherent gauze dressing impregnated with manuka honey and manuka oil	Advancis Medical
Activon Tube	Manuka honey in a tube	Advancis Medical
HoneySoft	Polyvinylacetate dressing impregnated with Chilean multifloral honey	Taureon
Manuka Health Wound Dressing with Manuka Honey	Sheet of hydrogel sheet containing manuka honey	Manuka Health NZ
Manuka Health Breast Pad with Manuka Honey	Sheet of hydrogel containing manuka honey	Manuka Health NZ
Manuka Health Wound Gel	Manuka honey with gelling agents, in a tube	Manuka Health NZ
MANUKAhd	Super-absorbent polyacrylic fibre dressing pad impregnated with manuka honey, coated with a dry-touch absorbent hydrocolloid	ManukaMed
MANUKAtex	Non-adherent gauze dressing impregnated with manuka honey, coated with a dry-touch absorbent hydrocolloid	ManukaMed
MANUKApli	Manuka honey in a tube	ManukaMed
Medihoney Honeycolloid	Sheet of gelled manuka honey	Dermasciences
Medihoney Calcium Alginate	Alginate fibre dressing pad impregnated with manuka honey	Dermasciences
Medihoney	Manuka honey in a tube	Dermasciences
MelMax	Non-adherent wound dressing impregnated with a mixture of polyhydrated ionogens ointment and buckwheat honey	Dermagenics
MelDra	Open-weave acetate fabric impregnated with buckwheat honey	Dermagenics
L-Mesitran Soft	Mixture of honey (not manuka) with lanolin, polyethylene glycol and vitamins C and E	Triticum
L-Mesitran Hydro	Sheet of acrylic polymer hydrogel containing honey (not manuka)	Triticum
L-Mesitran Net	Open-weave polyester net impregnated with L-Mesitran Hydro	Triticum
L-Mesitran Ointment	Mixture of honey (not manuka), lanolin, cod liver oil, sunflower oil, calendula, aloe vera, zinc oxide and vitamins C and E	Triticum

planned to conduct the trial on patients who had had no healing of ulcers after six weeks of compression. Such cases usually stay as non-healing ulcers for a long time, but a pilot trial had shown that honey gave healing of these within 6–12 weeks⁴. However, to be able to get sufficient participants recruited there was no requirement that compression had been used, only that ulcers had been non-healing for six weeks. It can be expected that compression alone would give healing of venous ulcers in cases where there is no underlying complication, which would effectively decrease the number of participants in which honey would make a

difference. Over the total number of participants there was 5.9% more healing achieved at 12 weeks in the honey-treated group compared with those in the usual care group, the mean reduction from baseline ulcer area was 9.6% better and there were 23% fewer episodes of infection in the honey-treated group compared with those in the usual care group. With the number of participants in the trial it would have required a 30% difference in the rate of healing to be achieved for the difference to be statistically significant. The results of the pilot trial indicated that a larger difference than that would be obtained, but with rapid healing in the uncomplicated

ulcers (the more common ones) occurring anyway as a result of compression being used, the average difference was lower. To get statistical significance with a smaller difference would have required a larger sample size, for example, for a 10% difference 1,030 participants would have been required.

Other reviews of the published evidence for honey have also come to the conclusion that the evidence is of low quality and/or there is a need for more evidence⁵⁻⁸. However, the same lack of high-quality evidence exists with all the other options that clinicians have for dressing wounds. It is likely that people are less aware of this because of the very large volume of advertising of wound-care products: this author frequently hears of clinicians who will not consider using honey on wounds because of lack of evidence for it, implying that they think that there is better evidence for the products that they choose to use instead. Systematic reviews of the evidence for the products usually used to treat common types of wounds have shown that this is not the case. (The conclusions from these reviews are shown in Table 2.)

Leaper⁹ has discussed the inadequacy of evidence for wound dressings in general and the difficulties faced in ever obtaining high-quality evidence. He points out the quandary in which this places the inexperienced practitioner and questions where that practitioner can turn for help when making decisions. When clinical evidence of the highest level is not available, then decisions on modes of treatment of cases need to be based on whatever evidence there is available. There is a hierarchy of evidence. According to Campbell¹⁰, double-blind RCTs give the strongest evidence, with the next strongest evidence coming from single-blind RCTs, then from open RCTs, next from non-randomised studies, next from controlled case studies, then from case studies. It is almost impossible to conduct double-blind trials with honey on conscious patients because they will be able to detect the characteristic aroma of honey. Campbell does not mention animal studies, but the many studies that have been conducted using honey dressings on animals have been useful in this respect because they eliminate any

Table 2. Conclusions from systematic reviews of wound treatments.

Treatment	Conclusions	Ref. no.
Advanced dressings on pressure ulcers	Their generalised use for this treatment is not supported by high-quality evidence.	93
Dressings and topical agents for surgical wounds healing by secondary intention	Only small, poor-quality trials exist, rendering the evidence insufficient.	94
The various dressings in use to prevent infection in surgical wounds healing by primary intention	No evidence was found that any of the dressings were better than using no dressing at all.	95
Hydrogel dressings to promote the healing of diabetic foot ulcers	Uncertain findings of superiority over basic wound contact dressings have been reported and no RCTs comparing hydrogel with other advanced dressing types were found.	96
The many kinds of dressings used on venous ulcers	No evidence was found that any affected the rate of healing of the ulcers.	97
The many dressings available to treat superficial and partial-thickness burns	None had strong evidence to support their use and there was no evidence to support the use of silver sulfadiazine.	98
Silver dressings for treatment of infected or contaminated chronic wounds	There is insufficient evidence to recommend the use of these or silver-containing topical agents.	99
Silver-containing dressings and topical agents for the treatment of diabetic foot ulcers	No randomised or controlled trials were found for inclusion in a systematic review of their use, despite their widespread use for this treatment.	100
Silver-containing dressings and topical agents for the prevention of wound infection	No significant difference was found between these and the nine non-silver dressings they were compared with. There were significantly fewer infections with silver sulfadiazine/hydrocolloid in one trial and significantly more infections in one trial with silver sulfadiazine. Only one trial showed a significant reduction in healing time with a silver-containing dressing (hydrofibre, on diabetic foot ulcers).	101

placebo effect, which is likely to be large because there is so much public awareness of honey being used successfully¹¹. A review published by Molan in 2006¹² of the evidence for the effectiveness of honey included 16 trials on wounds on experimental animals. There have been a further 11 such studies published¹³⁻²³ since the ones covered in that review.

The evidence supporting the use of honey in wound care

The review by Molan¹² also included a lot of other evidence that got excluded from the other reviews that have been published. In total in this review, positive findings for honey in wound care were found to have been reported in all of the 17 RCTs involving a total of 1,965 participants, and in the five clinical trials of other forms involving 97 participants treated with honey. The benefit of honey in assisting wound healing was also found to have been demonstrated in four case studies where there were multiple wounds, allowing comparison of honey with other treatment. The review also summarised the details of 10 reports of studies of case series (totalling 276 cases). Honey gave good results in all but 14 of these cases. These case series were mostly chronic wounds. The clinical trials were on superficial and partial-thickness burns, infected surgical wounds, chronic leg ulcers, pressure ulcers, pyomyositis abscesses, donor sites from split-thickness skin grafts, Fournier's gangrene (a form of necrotising fasciitis) and exit sites for central vein catheters.

An editorial commentary on this review²⁴ noted the importance of considering evidence lower down in the hierarchy and stated the opinion, "Every potential remedy that does no harm needs to be examined for its use and availability for the good of all." The evidence for honey doing no harm is to be seen in the absence of any adverse effects being reported in all of the trials covered in the above-mentioned review and in all the published trials and the many case studies cited below in the present article. It is frequently reported by patients that honey causes a stinging pain, but this is when wounds are inflamed and it has been found to be due to the acidity of honey⁴. The nociceptor nerve endings which detect acidity are sensitised by inflammation, which explains the clinical observation that the sensitivity to honey decreases in a few days if sufficient honey is kept on the wound bed to allow the anti-inflammatory activity of honey to suppress the inflammation. In a large RCT of honey dressings on venous ulcers³ 29 more participants in the honey group found the dressings more painful than did those in the regular care group, but only four of the 187 treated with honey found the pain sufficient to withdraw from the trial.

As well as this RCT the results of a further 16 clinical trials of honey in wound care have been published in the five years

since the review by Molan was published in 2006. The details of these are summarised in Table 3. These broaden the range of types of wounds on which trials with honey have been conducted and together bring the total of participants in RCTs on honey up from 1,965 to 3,556.

Rationale for use of honey in wound care

Another important factor influencing the choice by clinicians of which product to use on a wound is scientific rationale. Despite the modern mantra of 'evidence-based medicine', this factor is as important today as it was in days gone by. In a paper on acupuncture published by John Renton in the *Edinburgh Medical and Surgical Journal* nearly two centuries ago²⁵ he wrote:

And when, moreover, no satisfactory explanation can be afforded of the modus operandi of the reagent, professional persons, unhappily for the interests of medical science, are too apt to reason upon the authenticity of the facts averred, instead of adopting the more simple and direct method of determining their value by subjecting them to the test of farther experience.

To put this in modern language, he was saying that if medical professionals do not know how a product works they will dispute the evidence rather than try the product. The importance of rationale for products in clinical decisions is well illustrated by the huge size of the market that was built up for silver dressings based on advertising that silver was released and killed bacteria, when there was no high-quality clinical evidence for it doing so in wound infections. The rationale for the action of honey in bringing about clearance of infection in wounds and accelerating healing is well established but not well known, having not been advertised. Even less well known about honey by wound care practitioners are its other bioactivities which are also important in promoting wound healing: activation of autolytic debridement, anti-inflammatory activity, antioxidant activity, stimulation of growth of cells for tissue repair, and an osmotic action. There is good evidence from clinical studies, laboratory studies and studies with animal models for honey having these bioactivities. These are summarised in Table 4, and are discussed in more detail in the following sections.

Antibacterial activity of honey

The evidence for the antibacterial properties of honey relevant to wound care was reviewed by Molan in 2009²⁶. The number of reports published on the antibacterial activity of honey is very large, but honey varies greatly in its antibacterial potency²⁷ so the review by Molan²⁶ focused on studies which used large numbers of different samples of honey to get representative results, or used honeys with their antibacterial activity standardised against phenol as a reference antiseptic.

In these studies, the minimum inhibitory concentration of honey has been found for a broad range of bacterial species which infect wounds. This level is generally less than 10%, a concentration of honey that is usually well below that which would be present on a wound bed under a honey dressing. Fungal species are generally less susceptible to honey, with the minimum inhibitory concentration of honey being in the range of 10%–50%²⁶. Honey has been found to have a very broad spectrum of antibacterial activity, it being inhibitory to Gram-positive and Gram-negative species, and to both aerobes and anaerobes²⁶. Of particular interest to wound-care practitioners is its effectiveness against antibiotic-resistant strains of bacteria such as *Pseudomonads*, MRSA, coagulase-negative *Staphylococci*, VRE, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*. Also of clinical interest is the finding in long-term “resistance training” experiments with four wound-infecting species of bacteria that no permanent decrease in susceptibility to honey could be created and no honey-resistant mutants could be detected²⁸. It was concluded by the authors that the risk of bacteria acquiring resistance to honey is low as long as high concentrations of honey are maintained clinically. The review by Molan²⁶ also outlined the evidence from seven clinical trials, three case series studies and one case report for the effectiveness of honey dressings clearing infection in wounds. In many of the cases honey worked where other antibacterial therapy had failed. A possible explanation for this may be because honey has been found to be effective against bacteria in biofilms^{29–31}, a situation where antibiotics and silver wound dressings have been found to be ineffective³².

Debriding action of honey

The debriding action of honey may also be useful clinically in combatting bacteria in biofilms in chronic wounds. A strategy (called biofilm-based wound care) has been designed to tackle the problem, of which a major component is aggressive debridement³³. The evidence for the effectiveness of honey as a debriding agent was reviewed by Molan in 2009³⁴. This evidence included an RCT with 108 participants³⁵, which demonstrated better debriding with honey than with hydrogel, the mean wound area covered in slough after four weeks being reduced to 29% with honey, compared with 43% with hydrogel; however, this difference was not statistically significant ($p=0.065$). The review also outlined other trials which have shown that honey is a good alternative to surgical debridement for the treatment of necrotising fasciitis in the genital region. Furthermore, it outlined seven case series and 10 single case studies in which the effectiveness of honey in debriding wounds was reported. In an RCT comparing honey with silver sulfadiazine for the treatment of burns, honey was found to prevent the formation of eschar, whereas

it was formed in the cases treated with silver sulfadiazine³⁶. Similarly, in a trial on adjacent experimental wounds on rabbits the wounds were kept clean with honey-soaked gauze but the ones treated with saline-soaked gauze formed thick dense scabs¹³.

A possible explanation for the mechanism by which honey brings about debridement of wounds has recently been found. Working with cultures of inflamed macrophages it was found that honey increased the activity of the enzyme plasmin in the culture medium (Harcourt and Molan: paper submitted for publication). Plasmin efficiently digests fibrin, which is what attaches slough to the wound surface, but does not digest the collagen matrix which is needed for tissue repair. The study found that the plasmin activity is increased by way of honey inhibiting the production of plasminogen activator inhibitor (PAI) by the macrophages, which otherwise would block enzymically inactive plasminogen from being converted to active plasmin by plasmin activator. Inflammation increases production of PAI³⁷, hence the decrease in production of PAI brought about by honey is to be expected because it is well-established that honey has anti-inflammatory activity.

Anti-inflammatory activity of honey

The large body of evidence for honey having anti-inflammatory activity comes from many sources. Clinically there have been numerous observations reported of honey reducing oedema and exudate, minimising scarring and having a soothing effect when applied to inflamed wounds and burns^{36,38–45}. Direct evidence of an anti-inflammatory activity in clinical settings has been obtained biochemically in the form of decreased levels of malondialdehyde⁴⁶ and lipid peroxide⁴⁷, and histologically in observation of reduced numbers of inflammatory cells present in biopsy samples³⁶ in clinical trials where burns were dressed with honey. Evidence that honey has a direct anti-inflammatory activity, and that it is not a secondary effect from the antibacterial activity of honey removing bacteria which are causing inflammation, is seen in the many reports of anti-inflammatory activity being observed in experimental wounds and burns in animal models, where there were few or no bacteria present in these aseptically produced wounds⁴⁸. The anti-inflammatory activity of honey has also been shown in various clinical trials where it decreased the severity of mucositis in radiotherapy of the head and neck region^{49–52}, decreased symptoms of dyspepsia⁵³ and decreased the number of bleeding sites on gums in a trial of its use to treat gingivitis⁵⁴. It was also found to be effective in relief of various ophthalmological inflammatory conditions⁵⁵, and in decreasing pain in non-healing leg ulcers⁵⁶ and after surgical removal of children's tonsils⁵⁷. The results obtained in animal experiments have

also demonstrated the anti-inflammatory activity of honey: chemically induced colitis in rats was decreased⁵⁸⁻⁶¹ and prior dosage of honey to rats prevented gastritis being caused by subsequent dosage of ethanol⁶²⁻⁶⁴. Injection of 500 µl of 50% honey into rat paws one hour prior to injection of lipopolysaccharide gave less swelling, reduced sensitivity to pain, and a lower level of nitric oxide and prostaglandin E2⁶⁵.

There are possibly several mechanisms of action by which honey gives an anti-inflammatory effect. It has been reported that honey inhibits complement that has been activated by the classical pathway, some honeys giving a 50% inhibition at a concentration of less than 1%⁶⁶. Inhibition of the production of nitric oxide by macrophages by solvent extracts of honey has also been reported, but to achieve 75% inhibition of production the concentration of extract required was equivalent to honey at a concentration of more than 50%⁶⁷. It has also been proposed that the anti-inflammatory action is also due to inactivation of reactive oxygen species (ROS) produced in the 'respiratory burst' of phagocytes, and to inhibition of their production^{66,68}. Inhibition by honey of production of ROS by zymosan-activated neutrophils⁶⁶, zymosan-activated neutrophils, monocytes and macrophages⁶⁹, thrombin-activated neutrophils⁷⁰ and zymosan-activated monocytes primed with lipopolysaccharide⁷¹ has been reported, there being inhibition of 50% or more obtained with a concentration of 1% or less with some honeys. Although a stimulation of the 'respiratory burst' of neutrophils has been reported to be brought about by honey, this stimulation was maximal at 0.1% honey, and at 0.8% honey (the highest concentration tested) there was 46% inhibition of the 'respiratory burst'⁷². The possibility that the decrease in production of ROS reported was due to the antioxidant components of honey scavenging the ROS and preventing them reacting with the reagents used to measure them, rather than honey directly inhibiting the 'respiratory burst' has been investigated, and this has been discounted by the finding that honey has an inhibitory action on the process of phagocytosis which is what activates the 'respiratory burst' (Bean, Cursons and Molan: paper submitted for publication).

Antioxidant activity of honey

The antioxidant activity of honey probably also contributes to its anti-inflammatory properties because ROS act as messengers to give feedback amplification of the inflammatory response⁷³, and this process can be blocked by phenolic antioxidants⁷⁴. It has been demonstrated that application of antioxidants to wounds decreases inflammation^{75,76}, and the main mechanism of action of honey in improving the healing of burns has been found to be through its antioxidant activity⁷⁷. Manuka honey, the type of honey most widely

used in registered wound-care products, contains a very high level of phenolics⁷⁸. One of these compounds present at a high level, methyl syringate, has been identified as a potent superoxide scavenger⁷⁹ and thus can be expected to remove one of the major ROS messengers amplifying inflammation.

Although there has been little reference to anti-inflammatory activity in promotion of wound-care products because anti-inflammatory pharmaceuticals are not compatible with wound healing (non-steroidal anti-inflammatory drugs are cytotoxic, and corticosteroids inhibit the growth of epithelial tissue), inflammation is a major factor in chronic wounds remaining non-healing⁸⁰. Also, by giving rise to ROS, which over-activate fibroblasts, inflammation causes fibrosis⁸¹ which in cutaneous wounds gives hypertrophic scars. This would explain why when honey, which has an anti-inflammatory activity, has been used in clinical trials to treat burns its usage results in less scarring^{44,82}. The ROS produced by phagocytes in inflamed tissue also activate proteases which are normally inactive⁸³⁻⁸⁵ and the active forms of these digest the extracellular matrix and cell growth factors which are essential for tissue repair⁸⁶. The anti-inflammatory action of honey suppressing this activation would explain why in a clinical trial of use of honey to treat superficial burns none of the burns became full-thickness with honey whilst four did that were treated with silver sulfadiazine³⁶. Another benefit of the anti-inflammatory action of honey is that it decreases oedema, thus decreasing the pressure on the microvasculature of wound tissue that otherwise restricts the availability of oxygen and nutrients required for growth of tissue for wound repair.

Increasing the rate of healing

The acidity of honey also helps provide oxygen to regenerating tissue, as it decreases the pH of the wound bed and thus makes more oxygen available from haemoglobin in the blood. A clinical trial to find the effect of honey dressings on the surface pH of chronic wounds demonstrated it to cause a significant $p < 0.001$ decrease in pH, a reduction in pH of 0.1 being significantly ($p < 0.001$) associated with a decrease in wound size of 8.1%⁸⁷. An additional action in speeding the growth of repair tissues is the stimulatory action of honey on growth of cells. Honey at a concentration of 1% has been found to significantly ($p < 0.001$) stimulate the release of the cytokines TNF- α , IL-1 β and IL-6 from monocytes when compared with untreated cells, something known to play an important role in healing and tissue repair⁸⁸. Keratinocytes, another type of cell involved in wound healing, have been found to have transcription of the genes for TNF- α , IL-1 β and TGF- β up-regulated by honey a concentration of 1%⁸⁹. Honey has also been demonstrated to stimulate angiogenesis

Table 3. Summary of recent randomised controlled clinical trials that have been carried out on honey as a wound dressing.

(Abbreviations: H = treated with honey; C= control treatment; TBSA = total body surface area)

Type of wound	Control treatment	No. in trial	Results honey vs control	Statistics	Other findings	Ref. no.
Superficial & partial thickness burns <15% TBSA	1% silver sulfadiazine cream	H: 25 C: 25	Healed within 2 weeks: 52% vs 20% Proportion healed within 4 weeks: 100% vs 60% (Control 100% took 6 weeks) Time required for pain to be relieved in all patients: 3 weeks vs 5 weeks Average time taken for healing: 18.1 days vs 32.6 days	Not given Not given Not given	Wounds giving positive swabs took 3 weeks to all become sterile with honey (20 positive at start); took 5 weeks with control (19 positive at start).	102
Superficial & partial-thickness burns <50% TBSA	1% silver sulfadiazine cream	H: 37 C: 41	Proportion healed in 5–10 days: 56% vs 12% Proportion with pain relieved by 5 days: 36% vs 4%	p<0.05	Significantly shorter time with honey for swabs to show burns were sterile (P from 0.01 to 0.04; varied depending on time to report for treatment). Proportion sterile after 7 days treatment: 65% vs 0%; after 14 days 92% vs 7%; after 21 days 100% vs 44%.	103
Superficial burns 5–40% TBSA	1% silver sulfadiazine cream	H: 25 C: 25	Average time taken for healing: 13.5 days vs 15.6 days 7% had not healed within 19 days with honey vs 40% with control.	p=0.002 p=0.01	Positive swabs → sterile for 17 patients took 1 week, 2 weeks for the remaining 3 with honey (20 positive at start); with control (22 positive at start) 11 were sterile by 1 week, 16 by 2 weeks, the remainder taking 3–6 weeks.	104
Superficial & partial-thickness burns <40% TBSA	Silver sulfadiazine cream	H and C on matched pair of burns on 150 patients	Elevation above normal of lipid peroxidation product (an indicator of inflammation): 125% vs 150% after 1 week; 69% vs 135% after 2 weeks; 53% vs 113% after 3 weeks. Elevation above normal of ceruloplasmin (an acute-phase protein, an indicator of inflammation): 77% vs 94% after 1 week; 106% vs 119% after 2 weeks; 138% vs 154% after 3 weeks.	p<0.0001	6 wounds failed to heal with honey (4 of these infected), 29 wounds failed to heal with control (all of these infected). 8 wounds required skin grafts with honey, 29 with control.	105
Burns 10–60% TBSA	Silver sulfadiazine cream	H: 60 C: 60 Normal (not burnt): 25		p<0.001 p<0.001		47

Radiation-induced burn following conservative surgery for breast cancer	Silver sulfadiazine cream (H and C each with antihistamine, pentoxifylline & analgesic also)	H: 50 C: 50	Decrease in cutaneous surface area of burn in 12 weeks: 76(±58)% vs 86(±34)% Proportion of patients fully recovered in 12 weeks: 74% vs 54%.	Not given	Significantly better decrease in pain (P=0.029) and in restriction of ipsilateral shoulder movement (P=0.027) with honey than with control	106
Grade 3 skin toxicity following radiotherapy for breast cancer	Paraffin gauze	H: 12 C: 12	Mean time for complete healing: 18.4 days vs 19.8 days Mean time for closure: 11.9 days vs 13.9 days	p>0.05 p>0.05	A trend towards less pain, itching, irritation and patient satisfaction was seen in measurements of these on visual analogue scales.	107
Skin lesions from leishmaniasis	No honey used (Both groups had lesions injected with meglumine antimoniate)	H: 45 C: 45	51.1% had complete cure with honey, 71.1% without honey	p=0.04		108
Pressure ulcers (stage II or stage III)	Ethoxy-diaminoacridine plus nitrofurazone	H: 25 ulcers (15 patients) C: 25 ulcers (11 patients)	Pressure Ulcer Scale for Healing score over a period of 5 weeks: 15.00 decreased to 6.55 vs 14.52 decreased to 12.62 Proportion of ulcers healed within 5 weeks: 20% vs 0%	p<0.001 p<0.05		109
Venous leg ulcers	Usual care (Both groups received compression bandaging)	H: 187 C: 181	Proportion healed within 12 weeks: 55.6% vs 49.7% Mean time for healing: 63.5 days vs 65.3 days Mean reduction in ulcer area: 74.1% vs 65.5% Proportion with incidents of infection: 17.1% vs 22.1%	p=0.258 p=0.553 p=0.186 p=0.228	25% reported pain with honey vs 10% with usual care (P = 0.001)	3
Sloughy venous leg ulcers	Hydrogel (Both groups received compression bandaging. H or C was for 4 weeks, then followed by usual treatment.)	H: 54 C: 54	Mean reduction in slough in 4 weeks: 34% vs 13% Mean reduction in wound size in 4 weeks: 67% vs 52.6% Proportion healed in 12 weeks: 24% vs 18% Mean reduction in wound pain (Visual Analogue Scale) in first week: 52% vs 34%. No statistically significant differences between treatments in wound pain were found in subsequent weeks.	p=0.05 p=0.001 p=0.03 p<0.05	Cases with MRSA in the wound decreased in 4 weeks from 10 to 3 with honey treatment and from 6 to 5 with control treatment; cases with Pseudomonas in the wound decreased from 6 to 4 with honey treatment and from 10 to 5 with control treatment.	35 110
Surgical wounds from toenail removal with matrix phenolisation	Povidone iodine	H: 27 C: 24	Mean healing time for all cases: 33 days vs 25 days Mean healing time for total avulsion (16 cases H, 7 cases C): 44 days vs 30 days Mean healing time for partial avulsion (11 cases H, 17 cases C): 44 days vs 30 days	p=0.04 p=0.01 p=0.16	Mean post-operative pain (Visual Analogue Scale): 1.86 for H, 1.99 for C (P = 0.56)	111

Table 3 continued). Summary of recent randomised controlled clinical trials that have been carried out on honey as a wound dressing. (Abbreviations: H = treated with honey; C= control treatment; TBSA = total body surface area)

Surgical wounds from toenail removal with matrix phenolisation	Paraffin-impregnated tulle gras	H: 52 C: 48	Mean healing time for all cases: 40.30 days vs 39.98 days	p=0.32	112
Wounds of various types, healing by secondary intention (mostly leg ulcers)	Most appropriate regular care for each wound	H: 52 C: 53	Mean healing time for total avulsion (41 cases H, 32 cases C):45.28 days vs 52.03 days	p=0.21	11
			Mean healing time for partial avulsion (21 cases H, 20 cases C):31.76 days vs 19.62 days	p=0.01	
			Median time for healing: 100 days vs 140 days. Proportion healed after 12 weeks: 46.2% vs 34.0%. Median time for 50% reduction in wound surface area: 32 days vs 46 days.	p=0.134 p=0.321 p=0.266	
Shallow wounds (< 2 cm deep), including partial thickness burns, abrasions and skin graft donor sites, all smaller than 100 cm ²	Hydrogel	H: 40 C: 42	Mean time for healing of shallow wounds (25 in each treatment group): 16.08 days vs 17.12 days.	p=0.28	113
			Mean time for healing of abrasions: 17.13 days vs 16.53 days.	p=0.94	
			Proportion of patients satisfied with dressing: 22% vs 29% Proportion of patients very satisfied with dressing:78% vs 71%	Stated "no significant difference"	
Open or infected wounds (chronic osteomyelitis, post-surgical wounds, ulcers, trauma wounds, abscesses)	Sugar	H: 22 C: 18	Median reduction in wound size in 2 weeks: 57% vs 31%	Not given	114
			Median time for healing: 31.5 days vs 56 days	Not given	
			Severe pain experienced on application of dressing: 36% vs 56%	Not given	
			Severe pain experienced on mobilising: 27% vs 56% Decrease in median ASEPSIS score over 3 weeks: 68% vs 67%	Not given Not given	
Microvascular free tissue reconstruction surgery	Conventional dressings	H: 25 C: 24	Proportion with positive wound swabs 7 days after surgery: 20% vs 13%	p=0.70	115
			Mean duration of stay in hospital: 16 days vs 21 days	p=0.047	

Table 4. Summary of the actions of honey promoting wound healing.

Antibacterial activity:

- Very broad spectrum of activity (antifungal as well)
- Effective against antibiotic-resistant species
- Effective against bacteria in biofilms
- The minimum inhibitory concentration with bacteria is generally less than 10% honey
- Development of resistance to honey is unlikely

Debriding action:

- Acts to activate plasminogen which lyses fibrin attaching slough
- Prevents formation of eschar and scabs

Anti-inflammatory activity:

- Many reports of clinical observation of decrease in symptoms of inflammation
- Biochemical and histological studies have demonstrated decreased inflammation
- The action is direct, not secondary to clearing infection causing inflammation
- Demonstrated in many studies on inflammation in sites other than wounds
- Acts to inhibit phagocytosis, the start of the inflammatory response

Antioxidant activity of honey:

- Contains plant phenolics from the nectar source
- Scavenges reactive oxygen species which act as messengers between cells to increase the inflammatory process and cause hypertrophic scarring
- Decreases oxidative activation of proteases which destroy the matrix and growth factors

Increasing the rate of healing:

- Stimulates leukocytes to release cytokines and growth factors that activate tissue repair
- Acidity of honey makes more oxygen available from the circulation for tissue repair
- Osmotic action causes outflow of lymph like in VAC therapy

in vitro in a rat aortic ring assay, maximally at around a 0.2% concentration of honey⁹⁰. The osmotic action, resulting from honey consisting of approximately 80% sugars, also helps with increasing the availability of oxygen and nutrients for growth of repair tissues, in the same way as VAC therapy does. Another advantage of the osmotic action is that it creates a liquid layer between the dressing and the wound bed, thus not only giving painless removal of dressings but also avoiding damage to newly grown tissue, which, if it adhered to the dressing, could be torn off the wound during removal of dressings. The sugar content of this liquid layer makes it hypertonic and this along with decreased protease activity resulting from suppression of inflammation accounts for why maceration is not seen when wounds are dressed with honey.

Challenges posed by variation in composition of honey

There is a major challenge faced both in providing honey wound dressings with the best functionality and in obtaining

clinical evidence for the use of honey as a wound dressing. This challenge is to take into account the large degree of variation in potency of each of the bioactivities of honey relevant to achieving optimal wound healing. It is a challenge faced with all natural products used medically. Unless the component(s) responsible for any therapeutic action(s) are known and the level of these components are standardised then the results obtained clinically may vary, and any results obtained from use of the products are applicable only to the particular batch used and cannot be attributed to the product in general. What also needs to be considered is that more than one bioactivity may be involved in achieving the clinical results obtained, so there needs to be careful choice of wound types on which clinical trials are conducted so that only the bioactivities that have been standardised in the honey used are likely to be involved in achieving the outcomes recorded. As an example of these points, the RCT that was conducted to compare manuka honey with hydrogel for desloughing efficacy in venous ulcers³⁵ gave results that demonstrated only that the particular batch of honey used had the relative efficacy found. A different batch of honey, even of the same

product from the same manufacturer, may have shown less (or greater) efficacy because only the antibacterial activity had been standardised in the product yet it would be expected that the unstandardised components of the honey responsible for increasing plasmin activity and suppressing inflammation would also be involved in achieving desloughing.

The antibacterial activity of honey can vary up to 100-fold in potency²⁷. There is also the issue of whether the antibacterial activity is due to hydrogen peroxide (which could be to a large degree inactivated by catalase activity in the wound bed) or to non-peroxide factors as occur in some (but not all) honey described as manuka honey⁹¹. In research work investigating the mechanism of action of the debriding properties of honey, the increase in plasmin activity stimulated by samples of different honeys (tested at a concentration of 1%) was found to range from 21% to 103% (Harcourt and Molan: paper in preparation). In research work investigating the mechanism of action of the anti-inflammatory activity of honey (Bean, Cursons and Molan: paper submitted for publication) the degree of suppression of phagocytosis by samples of different honeys (tested at a concentration of 0.25%) was found to range from zero to 50% inhibition. Twofold⁷⁰, threefold⁶⁹ and fourfold⁶⁶ differences between different samples of honey in inhibition of the formation of ROS by leukocytes have been reported. Also, a fourfold difference between different samples of honey in inhibition of complement has been reported⁶⁶. Differences between different samples of honey in the degree of stimulation of production of cytokines by leukocytes^{71,88} and degree of stimulation of angiogenesis⁹⁰ have also been reported.

Some, maybe all, of the registered honey wound-care products on sale have the antibacterial activity standardised, thus there can be confidence that results from trials where clearance of infection has been reported with these products are likely to be achieved in clinical practice. The level of the antibacterial activity in the registered products is usually not stated because this could be construed as a therapeutic claim, something not allowed for products in the 'medical device' class in which they are registered. The public can purchase honey on which the level of antibacterial activity is stated; however, it is very much a case of *caveat emptor* because many marketers do not make clear whether the activity that is rated is non-peroxide (that is, not inactivated by catalase in wounds) or is due to hydrogen peroxide which could be inactivated. It is the author's view that it needs to be taken into account in clinical practice that the registered honey wound dressings on sale also differ from manufacturer to manufacturer in which type of antibacterial activity the honey has. Although there has been no clinical trial to compare the efficacy of the two types of activity there is a rationale to

support choosing honey with non-peroxide activity where the best antibacterial activity is wanted.

In vitro assays for the ability of samples of honey to stimulate production of cytokines and growth factors which stimulate tissue repair have already been published. These could be used to ensure that honey for wound-care products is standardised for this therapeutic activity. With research from the author's laboratory expected to be published soon describing *in vitro* assays for bioactivities involved in debriding of wounds and decreasing inflammation, it should be possible to have honey products standardised for these actions as well. Research in the author's laboratory is near completion developing an *in vitro* assay for the efficacy of antioxidants inside cells, which is much more relevant to wound care than the standard antioxidant assays used by the food industry. (Many antioxidants do not cross cell membranes efficiently.)

Concluding comments

Honey may be considered by some clinicians to be an "alternative medicine" or a "complementary medicine", and its reputation as a cure-all in the health food market may well cause clinicians to not give it due consideration for use in wound care. But honey is no more "alternative" or "complementary" than tulle gras, sutures, elasticated compression bandages and silver which, like honey, were commonly used in wound care about a century ago⁹². Like silver did, honey went out of common usage when antibiotics came into use in the early 1940s, and like silver it is coming back into use now that the problem of bacterial resistance to antibiotics is becoming widespread. The clinical and scientific evidence from modern research outlined in this review should make it clear that, at least in its use in wound care, honey should be considered alongside modern pharmaceutical products with regard to its effectiveness and therapeutic actions. However, other than in its physical properties and in its antibacterial activity in brands of honey wound-care products where this is standardised, there is an inherent weakness with respect to the variation in the level of bioactivities that occurs in all natural products used in medicine. It is next a matter of persuading manufacturers of honey products for wound care to standardise their products for all of the therapeutic activities that honey has, so that clinicians can use honey products with the confidence of knowing that they should have the same efficacy as when used on previous cases.

It is only with all of the relevant therapeutic activities standardised can conclusive clinical trials be conducted. At present there is insufficient high-quality evidence from trials of conventional treatments to establish, for each type of wound, what is the best treatment against which honey

should be compared in clinical trials, so in the meantime any trials should have as the control what is generally accepted as the standard treatment in modern wound-care practice. The control treatment, and the type of honey dressing used, will need to be selected to suit the type of wound being studied. Pilot trials may be needed to find the best type of honey dressing to use, rather than having the choice directed by sponsorship by manufacturers. In order to get statistically significant conclusions on which of the two treatments compared (honey or standard best practice) gives the best results the number of patients recruited into trials needs to be large enough to allow for the degree of variation that occurs between individuals in rate of healing for each type of wound, and for the expected (from pilot trials) degree of difference in effectiveness between honey and standard treatment.

Statement of conflicts of interest

The author has no financial interests in honey or wound-care products, nor receives any payments for consultancy. As an inventor on a patent (for a honey wound dressing) sold by the University of Waikato, the author stands to receive a share of the net income of the University of Waikato from royalty payments. Occasional sponsorship of travel and accommodation costs to attend wound-care conferences has

been received from several companies selling honey products for wound care. Some funding of the author's research work on honey has been received in the past from companies producing honey wound dressings. The writing of this review was unfunded.

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The AWMA Annual General Meeting will be held in accordance with the AWMA Constitution (2005) during the 9th National AWMA Conference at the Sydney Convention and Exhibition Centre on 19 March 2012 at 1730. At this meeting all positions are declared vacant and the election will occur. The Notification of the AGM and Call for Items of Special Business, The Call for Nominations form for the AWMA Committee, the Proxy Voting Form and the Call for Nominations for the Journal Editor (s) and Website Manager are available in the journal or PDF via the AWMA website.