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

Molan PC

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 review[2] 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."

Peter Molan BSc, PhD

Professor in Biological Sciences and Director of the Honey Research Unit, Department of Biological Sciences, University of Waikato, Private Bag 3105, Hamilton 3240, New Zealand
Tel +64 7 838 4325
Fax +64 7 838 4324
Email pmolan@waikato.ac.nz

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 compression[3]. 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

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 weeks[4]. 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 evidence[5-8]. 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.)

Leaper[9] 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 Campbell[10], 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 successfully[11]. A review published by Molan in 2006[12] of the evidence for the effectiveness of honey included 16 trials on wounds on experimental animals. There have been a further 11 such studies published[13-23] since the ones covered in that review.

The evidence supporting the use of honey in wound care

The review by Molan[12] 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 review[24] 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 honey[4]. 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 ulcers[3] 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 ago[25] 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 2009[26]. The number of reports published on the antibacterial activity of honey is very large, but honey varies greatly in its antibacterial potency[27] so the review by Molan[26] 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 anaerobes[26]. 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 baumanii* 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 detected[28]. 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 Molan[26] 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 ineffective[32].

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 debridement[33]. The evidence for the effectiveness of honey as a debriding agent was reviewed by Molan in 2009[34]. This evidence included an RCT with 108 participants[35], 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 sulfadiazine[36]. 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 scabs[13].

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 PAI[37], 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 malondialdehyde[46] and lipid peroxide[47], and histologically in observation of reduced numbers of inflammatory cells present in biopsy samples[36] 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 wounds[48]. 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 dyspepsia[53] and decreased the number of bleeding sites on gums in a trial of its use to treat gingivitis[54]. It was also found to be effective in relief of various ophthalmological inflammatory conditions[55], and in decreasing pain in non-healing leg ulcers[56] and after surgical removal of children's tonsils[57]. The results obtained in animal experiments have

also demonstrated the anti-inflammatory activity of honey: chemically induced colitis in rats was decreased[58-61] and prior dosage of honey to rats prevented gastritis being caused by subsequent dosage of ethanol[62-64]. 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 E2[65].

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 neutrophils[66], zymosan-activated neutrophils, monocytes and macrophages[69], thrombin-activated neutrophils[70] and zymosan-activated monocytes primed with lipopolysaccharide[71] 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 response[73], and this process can be blocked by phenolic antioxidants[74]. 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 activity[77]. Manuka honey, the type of honey most widely used in registered wound-care products, contains a very high level of phenolics[78]. One of these compounds present at a high level, methyl syringate, has been identified as a potent superoxide scavenger[79] 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-healing[80]. Also, by giving rise to ROS, which over-activate fibroblasts, inflammation causes fibrosis[81] 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 inactive[83-85] and the active forms of these digest the extracellular matrix and cell growth factors which are essential for tissue repair[86]. 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 sulfadiazine[36]. 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-1β and IL-6 from monocytes when compared with untreated cells, something known to play an important role in healing and tissue repair[88]. Keratinocytes, another type of cell involved in wound healing, have been found to have transcription of the genes for TNF-α, IL-1β 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%	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
			Proportion healed within 4 weeks: 100% vs 60% (Control 100% took 6 weeks)	Not given		
			Time required for pain to be relieved in all patients: 3 weeks vs 5 weeks	Not given		
Superficial & partial-thickness burns <50% TBSA	1% silver sulfadiazine cream	H: 37 C: 41	Average time taken for healing: 18.1 days vs 32.6 days	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	Proportion healed in 5–10 days: 56% vs 12%	p=0.002	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
			Proportion with pain relieved by 5 days: 36% vs 4%	p=0.01		
Superficial & partial-thickness burns <40% TBSA	Silver sulfadiazine cream	H and C on matched pair of burns on 150 patients	Average time taken for healing: 13.5 days vs 15.6 days	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
			7% had not healed within 19 days with honey vs 40% with control.			
Burns 10–60% TBSA	Silver sulfadiazine cream	H: 60 C: 60 Normal (not burnt): 25	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.	p<0.001		47
			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<0.001		

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)%	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
			Proportion of patients fully recovered in 12 weeks: 74% vs 54%.	Not given		
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	p>0.05	A trend towards less pain, itching, irritation and patient satisfaction was seen in measurements of these on visual analogue scales.	107
			Mean time for closure: 11.9 days vs 13.9 days	p>0.05		
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	p<0.001		109
			Proportion of ulcers healed within 5 weeks: 20% vs 0%	p<0.05		
Venous leg ulcers	Usual care (Both groups received compression bandaging)	H: 187 C: 181	Proportion healed within 12 weeks: 55.6% vs 49.7%	p=0.258	25% reported pain with honey vs 10% with usual care (P = 0.001)	3
			Mean time for healing: 63.5 days vs 65.3 days	p=0.553		
			Mean reduction in ulcer area: 74.1% vs 65.5%	p=0.186		
			Proportion with incidents of infection: 17.1% vs 22.1%	p=0.228		
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%	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
			Mean reduction in wound size in 4 weeks: 67% vs 52.6%	p=0.001		
			Proportion healed in 12 weeks: 24% vs 18%	p=0.03		
			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		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	p=0.04	Mean post-operative pain (Visual Analogue Scale): 1.86 for H, 1.99 for C (P = 0.56)	111
			Mean healing time for total avulsion (16 cases H, 7 cases C):44 days vs 30 days	p=0.01		
			Mean healing time for partial avulsion (11 cases H, 17 cases C):44 days vs 30 days	p=0.16		

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	Mean post-operative pain (Visual Analogue Scale): 1.60 for H, 1.57 for C (p = 0.37) Mean pain on dressing changes (Visual Analogue Scale): 1.26 for H, 1.23 for C (p = 0.56)	112
			Mean healing time for total avulsion (41 cases H, 32 cases C):45.28 days vs 52.03 days	p=0.21		
			Mean healing time for partial avulsion (21 cases H, 20 cases C):31.76 days vs 19.62 days	p=0.01		
Wounds of various types, healing by secondary intention (mostly leg ulcers)	Most appropriate regular care for each wound	H: 52 C: 53	Median time for healing: 100 days vs 140 days.	p=0.134		11
			Proportion healed after 12 weeks: 46.2% vs 34.0%.	p=0.321		
			Median time for 50% reduction in wound surface area: 32 days vs 46 days.	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	Itching was experienced by 27% treated with honey and 31% with the control. Pain was experienced by 10% treated with honey but none asked for the treatment to be stopped.	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	Proportion of wounds with positive microbiological cultures decreased from 55% to 23% with honey treatment, and from 56% to 39% with the control treatment.	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%	Not given		
			Decrease in median ASEPSIS score over 3 weeks: 68% vs 67%	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	Patient responses in a questionnaire on satisfaction were generally more favourable for honey, but the difference was not significant.	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 honey[90]. 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 ulcers[35] 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 potency[27]. 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 honey[91]. 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. Twofold[70], threefold[69] and fourfold[66] 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 reported[66]. Differences between different samples of honey in the degree of stimulation of production of cytokines by leukocytes[71,88] and degree of stimulation of angiogenesis[90] 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 be 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 ago[92]. 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.

References

1. Moore OA, Smith LA, Campbell F, Seers K, McQuay HJ & Moore RA. Systematic review of the use of honey as a wound dressing. BMC Complement Altern Med 2001; 1(1):2.
2. Jull AB, Rodgers A & Walker N. Honey as a topical treatment for wounds. Cochrane Database Syst Rev 2008; 4:Art. No.: CD005083.
3. Jull A, Walker N, Parag V, Molan P & Rodgers A. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. Br J Surg 2008; 95(2):175–82.
4. Betts JA & Molan PC, editors. A pilot trial of honey as a wound dressing has shown the importance of the way that honey is applied to wounds. 11th Conference of the European Wound Management Association, 2001, Dublin, Ireland.
5. Fox C. Honey as a dressing for chronic wounds in adults. Br J Community Nurs 2002; 7(10):530–4.
6. Gethin G. Is there enough clinical evidence to use honey to manage wounds? J Wound Care 2004; 13(7):275–8.
7. Mwipatayi BP, Angel D, Norrish J, Hamilton MJ, Scott A & Sieunarine K. The use of honey in chronic leg ulcers: a literature review. Primary Intention 2004; 12(3):107–12.
8. Templeton S. A review of the use of honey on wounds. ACCNS J Community Nurs 2002; 7(1):13–4.

9. Leaper D. Are we close to developing the ultimate wound dressing? Wounds UK 2006; 2(2):94–5.
10. Campbell MJ. What is evidence? In: Mani R (ed). Chronic wound management – the evidence for change. London: Parthenon, 2003, pp. 11–22.
11. Robson V, Dodd S & Thomas S. Standardized antibacterial honey (Medihoney™) with standard therapy in wound care: randomized clinical trial. J Adv Nurs 2009; 65(3):565–75.
12. Molan PC. The evidence supporting the use of honey as a wound dressing. Int J Low Extrem Wounds 2006; 5(1):40–54.
13. Kundu S, Biswas TK, Das P, Kumar S & De DK. Turmeric (Curcuma longa) rhizome paste and honey show similar wound healing potential: a preclinical study in rabbits. Int J Low Extrem Wounds 2005; 4(4):205–13.
14. Lusby PE, Coombes AL & Wilkinson JM. A comparison of wound healing following treatment with Lavandula x allardii honey or essential oil. Phytother Res 2006; 20(9):755–7.
15. Jalali FSS, Saifzadeh S, Tajik H & Farshid AA. Experimental evaluation of repair process of burn-wounds treated with natural honey. J Anim Vet Adv 2007; 6(2):179–84.
16. Sukur SM, Halim AS & Singh KKB. Evaluations of bacterial contaminated full thickness burn wound healing in Sprague Dawley rats Treated with Tualang honey. Indian J Plast Surg 2011; 44(1):112–7.
17. Zohdi RM, Zakaria ZAB, Yusof N, Mustapha NM & Abdullah MNH. Gelam (Melaleuca spp.) honey-based hydrogel as burn wound dressing. Evid Based Complement Alternat Med 2012; in press: DOI:10.1155/2012/843025.
18. Gutiérrez Vega R, Ortiz Barranco I, Lazos Ochoa M, Amancio Chassín O & Rodríguez Báez A. Efecto de la miel aplicada tópicamente sobre la cicatrización en heridas infectadas. Modelo experimental / Effect of topical aplication of honey on healing process in infected wound. An experimental model. Rev méd Hosp Gen Méx 1995; 58(3):101–4.
19. Rozaini MZ, Zuki ABZ, Noordin MM, Norimah Y & Nazrul Hakim A. Macroscopic evaluation of burn wound healing progress treated with different types of honey. Pak J Biol Sci 2005; 8(5):672–8.
20. Rozaini MZ, Zuki ABZ, Noordin MM, Norimah Y & Nazrul Hakim A. The effects of different types of honey on tensile strength evaluation of burn wound tissue healing. Int J Appl Res Vet Med 2004; 2(4):290–6.
21. Aljady AM, Kamaruddin MY, Jamal AM & Mohd Yassim MY. Biochemical study on the efficacy of Malaysian honey on inflicted wounds: and animal model. Med J Islamic Acad Sci 2000; 13(3):125–32.
22. Schencke C, Salvo J, Veuthey C, Hidalgo A & del Sol M. Healing of burns type AB-B in guinea pig (Cavia porcellus) using ulmo honey associated with oral vitamin C. Int J Morphol 2011; 29(1):69–75.
23. Yusof N, Hafiza AHA, Zohdi RM & Bakar MZA. Development of honey hydrogel dressing for enhanced wound healing. Radiat Phys Chem 2007; 76(11–12):1767–70.
24. Mani R. Commentary on "the evidence supporting the use of honey as a wound dressing" by P. C. Molan. Int J Low Extrem Wounds 2006; 5(1):55.
25. Renton J. Observations on acupuncture. Edinb Med Surg J 1830; 34:100–7.
26. Molan PC. Honey: Antimicrobial actions and role in disease management. In: Ahmad I & Aqil F (eds). New Strategies Combating Bacterial Infection. Weinheim: Wiley VCH, 2009, pp. 229–53.
27. Molan PC. The antibacterial activity of honey. 2. Variation in the potency of the antibacterial activity. Bee World 1992; 73(2):59–76.
28. Cooper RA, Jenkins L, Henriques AFM, Duggan RS & Burton NF. Absence of bacterial resistance to medical-grade manuka honey. Eur J Microbiol Infect Dis 2010; 29(10):1237–41.
29. Alandejani T, Marsan J, Ferris W, Slinger R & Chan F. Effectiveness of honey on Staphylococcus aureus and Pseudomonas aeruginosa biofilms. Otolaryngol Head Neck Surg 2009; 141(1):114–8.
30. Merckoll P, Jonassen TØ, Vad ME, Jeansson SL & Melby KK. Bacteria, biofilm and honey: A study of the effects of honey on 'planktonic' and biofilm-embedded chronic wound bacteria. Scand J Infect Dis 2009; 41(5):341–7.
31. Okhiria OA, Henriques A, Burton NF, Peters A & Cooper RA. Honey modulates biofilms of Pseudomonas aeruginosa in a time and dose dependent manner. J ApiProduct ApiMed Sci 2009; 1(1):6–10.
32. Hill KE, Malic S, McKee R. An in vitro model of chronic wound biofilms to test wound dressings and assess antimicrobial susceptibilities. J Antimicrob Chemother 2010; 65(6):1195–206.
33. Thomson CH. Biofilms: do they affect wound healing? Int Wound J 2011; 8(1):63–7.
34. Molan PC. Debridement of wounds with honey. J Wound Technol 2009; 5:12–7.
35. Gethin G & Cowman S. Manuka honey vs hydrogel – a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. J Clin Nurs 2009; 18(3):466–74.
36. Subrahmanyam M. A prospective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. Burns 1998; 24(2):157–61.
37. Esmon CT. Crosstalk between inflammation and thrombosis. Maturitas 2004; 47(4):305–14.
38. Burlando F. Sull'azione terapeutica del miele nelle ustioni. Minerva Dermatol 1978; 113:699–706.
39. Dumronglert E. A follow-up study of chronic wound healing dressing with pure natural honey. J Nat Res Counc Thail 1983; 15(2):39–66.
40. Efem SEE. Clinical observations on the wound healing properties of honey. Br J Surg 1988; 75:679–81.
41. Efem SEE. Recent advances in the management of Fournier's gangrene: Preliminary observations. Surgery 1993; 113(2):200–4.
42. Hejase MJ, Simonin JE, Bihrle R & Coogan CL. Genital Fournier's gangrene: experience with 38 patients. Urology 1996; 47(5):734–9.
43. Keast-Butler J. Honey for necrotic malignant breast ulcers. Lancet 1980; ii(October 11):809.
44. Subrahmanyam M. Honey impregnated gauze versus polyurethane film (OpSite®) in the treatment of burns – a prospective randomised study. Br J Plast Surg 1993; 46(4):322–3.
45. Subrahmanyam M. Honey dressing versus boiled potato peel in the treatment of burns: a prospective randomized study. Burns 1996; 22(6):491–3.
46. Subrahmanyam M, Sahapure AG, Nagane NS, Bhagwat VR & Ganu JV. Effects of topical application of honey on burn wound healing. Ann Burns Fire Disasters 2001; XIV(3):143–5.
47. Nagane NS, Ganu JV, Bhagwat VR & Subramanium M. Efficacy of topical honey therapy against silver sulphadiazine treatment in burns: a biochemical study. Indian J Clin Biochem 2004; 19(2):173–6.
48. Molan PC. Re-introducing honey in the management of wounds and ulcers – theory and practice. Ostomy/Wound Manage 2002; 48(11):28–40.
49. Biswal BM, Zakaria A & Ahmad NM. Topical application of honey in the management of radiation mucositis: a preliminary study. Support Care Cancer 2003; 11:242–8.
50. Chiba M, Idobata K, Kobayashi N, Sato Y & Muramatsu Y. Use of honey to ease the pain of stomatitis during radiotherapy [in Japanese]. Kangogaku Zasshi 1985; 49(2):171–6.
51. Motallebnejad M, Akram S, Moghadamnia A, Moulana Z & Omidi S. The effect of topical application of pure honey on radiation-induced mucositis: A randomized clinical trial. J Contemp Dent Pract 2008; 9(3):040–7.
52. Rashad UM, Al-Gezawy SM, El-Gezawy E & Azzaz AN. Honey as topical prophylaxis against radiochemotherapy-induced mucositis in head and neck cancer. J Laryngol Otol 2009; 123(2):223–8.
53. Salem SN. Honey regimen in gastrointestinal disorders. Bull Islamic Med 1981; 1:358–62.
54. English HK, Pack AR & Molan PC. The effects of manuka honey on plaque and gingivitis: a pilot study. J Int Acad Periodontol 2004; 6(2):63–7.
55. Emarah MH. A clinical study of the topical use of bee honey in the treatment of some ocular diseases. Bull Islamic Med 1982; 2(5):422–5.
56. Dunford CE & Hanano R. Acceptability to patients of a honey dressing for non-healing venous leg ulcers. J Wound Care 2004; 13(5):193–7.
57. Ozlugedik S, Genc S, Unal A, Elhan AH, Tezer M & Titiz A. Can postoperative pains following tonsillectomy be relieved by honey? A prospective, randomized, placebo controlled preliminary study. Int J Pediatr Otorhinolaryngol 2006; 70(11):1929–34.

58. Bilsel Y, Bugra D, Yamaner S, Bulut T, Cevikbas U & Turkoglu U. Could honey have a place in colitis therapy? Effects of honey, prednisolone, and disulfiram on inflammation, nitric oxide, and free radical formation. Dig Surg 2002; 19:306–12.
59. Mahgoub AA, el-Medany AH, Hagar HH & Sabah DM. Protective effect of natural honey against acetic acid-induced colitis in rats. Trop Gastroenterol 2002; 23(2):82–7.
60. Medhi B, Prakash A, Avti PK, Saikia UN, Pandhi P & Khanduja KL. Effect of Manuka honey and sulfasalazine in combination to promote antioxidant defense system in experimentally induced ulcerative colitis model in rats. Indian J Exp Biol 2008; 46(8):583–90.
61. Prakash A, Medhi B, Avti PK, Saikia UN, Pandhi P & Khanduja KL. Effect of different doses of manuka honey in experimentally induced inflammatory bowel disease in rats. Phytother Res 2008; 22(11):1511–9.
62. Ali ATMM. Prevention of ethanol-induced gastric lesions in rats by natural honey, and its possible mechanism of action. Scand J Gastroenterol 1991; 26:281–8.
63. Ali ATMM, Al-Humayyd MS & Madan BR. Natural honey prevents indomethacin- and ethanol-induced gastric lesions in rats. Saudi Med J 1990; 11(4):275–9.
64. Ali ATMM & Al-Swayeh OA. Natural honey prevents ethanol-induced increased vascular permeability changes in the rat stomach. J Ethnopharmacol 1997; 55(3):231–8.
65. Kassim M, Achoui M, Mansor M & Yusoff KM. The inhibitory effects of Gelam honey and its extracts on nitric oxide and prostaglandin E_2 in inflammatory tissues. Fitoterapia 2010; 81(8):1196–201.
66. van den Berg AJ, van den Worm E, van Ufford HC, Halkes SB, Hoekstra MJ & Beukelman CJ. An in vitro examination of the antioxidant and anti-inflammatory properties of buckwheat honey. J Wound Care 2008; 17(4):172–8.
67. Kassim M, Achoui M, Mustafa MR, Mohd MA & Yusoff KM. Ellagic acid, phenolic acids, and flavonoids in Malaysian honey extracts demonstrate in vitro anti-inflammatory activity. Nutr Res 2010; 30(9):650–9.
68. Henriques A, Jackson S, Cooper R & Burton N. Free radical production and quenching in honeys with wound healing potential. J Antimicrob Chemother 2006; 58(4):773–7.
69. Mesaik MA, Azim MK & Mohiuddin S. Honey modulates oxidative burst of professional phagocytes. Phytother Res 2008; 22(10):1404–8.
70. Ahmad A, Khan RA & Mesaik MA. Anti inflammatory effect of natural honey on bovine thrombin-induced oxidative burst in phagocytes. Phytother Res 2009; 23(6):801–8.
71. Tonks A, Cooper RA, Price AJ, Molan PC & Jones KP. Stimulation of TNF-a release in monocytes by honey. Cytokine 2001; 14(4):240–2.
72. Abuharfeil N, Al-Oran R & Abo-Shehada M. The effect of bee honey on proliferative activity of human B- and T-lymphocytes and the activity of phagocytes. Food Agric Immunol 1999; 11:169–77.
73. Iles KE & Forman HJ. Macrophage signaling and respiratory burst. Immunol Res 2002; 26(1-3):95–105.
74. Ma Q, Kinneer K, Ye JP & Chen BJ. Inhibition of nuclear factor kappa B by phenolic antioxidants: interplay between antioxidant signaling and inflammatory cytokine expression. Mol Pharmacol 2003; 64(2):211–9.
75. Martin A. The use of antioxidants in healing. Dermatol Surg 1996; 22(2):156–60.
76. Tanaka H, Hanumadass M, Matsuda H, Shimazaki S, Walter RJ & Matsuda T. Hemodynamic effects of delayed initiation of antioxidant therapy (beginning two hours after burn) in extensive third-degree burns. J Burn Care Rehabil 1995; 16(6):610–5.
77. Subrahmanyam M, Sahapure AG, Nagane NS, Bhagwat VR & Ganu JV. Free radical control – the main mechanism of the action of honey in burns. Ann Burns Fire Disasters 2003; 16(3):135–8.

78. Tan ST, Holland PT, Wilkins AL & Molan PC. Extractives from New Zealand honeys. 1. White clover, manuka and kanuka unifloral honeys. J Agric Food Chem 1988; 36(3):453–60.

79. Inoue K, Murayama S, Seshimo F, Takeba K, Yoshimura Y & Nakazawa H. Identification of phenolic compound in manuka honey as specific superoxide anion radical scavenger using electron spin resonance (ESR) and liquid chromatography with coulometric array detection. J Sci Food Agric 2005; 85(5):872–8.

80. Mulder GD & Vande Berg JS. Cellular senescence and matrix metalloproteinase activity in chronic wounds. Relevance to debridement and new technologies. J Am Podiat Med Assoc 2002; 92(1):34–7.

81. Murrell GAC, Francis MJO & Bromley L. Modulation of fibroblast proliferation by oxygen free radicals. Biochem J 1990; 265:659–65.

82. Subrahmanyam M. Honey-impregnated gauze versus amniotic membrane in the treatment of burns. Burns 1994; 20(4):331–3.

83. Ossanna PJ, Test ST, Matheson NR, Regiani S & Weiss SJ. Oxidative regulation of neutrophil elastase-alpha-1-proteinase inhibitor interactions. J Clin Invest 1986; 77:1939–51.

84. Peppin GJ & Weiss SJ. Activation of the endogenous metalloproteinase, gelatinase, by triggered human neutrophils. Proc Nat Acad Sci USA 1986; 83:4322–6.

85. Weiss SJ, Peppin G, Ortiz X, Ragsdale C & Test ST. Oxidative autoactivation of latent collagenase by human neutrophils. Science 1985; 227:747–9.

86. Toriseva M & Kahari VM. Proteinases in cutaneous wound healing. Cell Mol Life Sci 2009; 66(2):203–24.

87. Gethin GT, Cowman S & Conroy RM. The impact of Manuka honey dressings on surface pH of chronic wounds. Int Wound J 2008; 5(2):185–94.

88. Tonks AJ, Cooper RA, Jones KP, Blair S, Parton J & Tonks A. Honey stimulates inflammatory cytokine production from monocytes. Cytokine 2003; 21(5):242–7.

89. Majtan J, Kumar P, Majtan T, Walls AF & Klaudiny J. Effect of honey and its major royal jelly protein 1 on cytokine and MMP-9 mRNA transcripts in human keratinocytes. Exp Dermatol 2009; 19(8):E73–E9.

90. Rossiter K, Cooper AJ, Voegeli D & Lwaleed BA. Honey promotes angiogenic activity in the rat aortic ring assay. J Wound Care 2010; 19(10):440–6.

91. Allen KL, Molan PC & Reid GM. A survey of the antibacterial activity of some New Zealand honeys. J Pharm Pharmacol 1991; 43(12):817–22.

92. Forrest RD. Development of wound therapy from the Dark Ages to the present. J R Soc Med 1982; 75:268–73.

93. Bouza C, Saz Z, Muñoz A & Amate JM. Efficacy of advanced dressings in the treatment of pressure ulcers: a systematic review. J Wound Care 2005; 14(5):193–9.

94. Vermeulen H, Ubbink DT, Goossens A, de Vos R & Legemate DA. Systematic review of dressings and topical agents for surgical wounds healing by secondary intention. Br J Surg 2005; 92(6):665–72.

95. Dumville JC, Walter CJ, Sharp CA & Page T. Dressings for the prevention of surgical site infection. Cochrane Database Syst Rev 2011; 7:Art. No.: CD003091.

96. Dumville JC, O'Meara S, Deshpande S & Speak K. Hydrogel dressings for healing diabetic foot ulcers. Cochrane Database Syst Rev 2011; 9:Art. No.: CD009101.

97. Palfreyman SJ, Nelson EA, Lochiel R & Michaels JA. Dressings for healing venous leg ulcers. Cochrane Database Syst Rev 2006; 3:Art. No.: CD001103.

98. Wasiak J, Cleland H & Campbell F. Dressings for superficial and partial thickness burns. Cochrane Database Syst Rev 2008; 4:Art. No.: CD002106.

99. Vermeulen H, Van Hattem JM, Storm-Versloot MN & Ubbink DT. Topical silver for treating infected wounds. Cochrane Database Syst Rev 2007; 1:Art. No.: CD005486.

100. Bergin SM & Wraight P. Silver based wound dressings and topical agents for treating diabetic foot ulcers. Cochrane Database Syst Rev 2006; 1:Art. No.: CD005082.

101. Storm-Versloot MN, Vos CG, Ubbink DT & Vermeulen H. Topical silver for preventing wound infection. Cochrane Database Syst Rev 2010; 3:Art. No.: CD006478.

102. Mashhood AA, Khan TA & Sami AN. Honey compared with 1% silver sulfadiazine cream in the treatment of superficial and partial thickness burns. J Pak Assoc Dermatologists 2006; 16(1):14–9.

103. Baghel PS, Shukla S, Mathur RK & Randa R. A comparative study to evaluate the effect of honey dressing and silver sulfadiazine dressing on wound healing in burn patients. Indian J Plast Surg 2009; 42(2):176–81.

104. Sami AN, Mehmood N, Qureshi MA, Zeeshan HK, A MI & Khan MI. A comparative study to evaluate the effect of honey dressing and silver sulfadiazine dressing on wound healing in burn patients. Ann Pak Inst Med Sci 2011; 7(1):22–5.

105. Malik KI, Malik MAN & Aslam A. Honey compared with silver sulphadiazine in the treatment of superficial partial-thickness burns. Int Wound J 2010; 7(5):413–7.

106. Shoma A, Eldars W & Noman N. Pentoxifylline and local honey for radiation-induced burn following breast conservative surgery. Curr Clin Pharmacol 2010; 5(4):251–6.

107. Moolenaar M, Poorter RL, van der Toorn PP, Lenderink AW, Poortmans P & Egberts AC. The effect of honey compared to conventional treatment on healing of radiotherapy-induced skin toxicity in breast cancer patients. Acta Oncol 2006; 45(5):623–4.

108. Nilforoushzadeh MA, Jaffary F, Moradi S, Derakhshan R & Haftbaradaran E. Effect of topical honey application along with intralesional injection of glucantime in the treatment of the cutaneous leishmaniasis. BMC Complement Altern Med 2007; 7(1):13–7.

109. GüneşÜY & Eşer I. Effectiveness of a honey dressing for healing pressure ulcers. J Wound Ostomy Continence Nurs 2007; 34(2):184–90.

110. Gethin G & Cowman S. Bacteriological changes in sloughy venous leg ulcers treated with manuka honey or hydrogel: an RCT. J Wound Care 2008; 17(6):241–4, 6-7.

111. Marshall C, Queen J & Manjooran J. Honey vs povidone iodine following toenail surgery. Wounds UK 2005; 1(1):10, 4, 6–8.

112. McIntosh CD & Thomson CE. Honey dressing versus paraffin tulle gras following toenail surgery. J Wound Care 2006; 15(3):133–6.

113. Ingle R, Levin J & Polinder K. Wound healing with honey – a randomised controlled trial. S Afr Med J 2006; 96(9):831–5.

114. Mphande ANG, Killowe C, Phalira S, Wynn Jones H & Harrison WJ. Effects of honey and sugar dressings on wound healing. J Wound Care 2007; 16(7):317–9.

115. Robson V, Yorke J, Sen RA, Lowe D & Rogers SN. Randomised controlled feasibility trial on the use of medical grade honey following microvascular free tissue transfer to reduce the incidence of wound infection. Br J Oral Maxillofac Surg 2011; in press: DOI 10.1016/j.bjoms.2011.07.014.

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.