Honey as a topical treatment for wounds (Review)

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[Intervention Review]

Honey as a topical treatment for wounds

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ABSTRACT

Background

Honey is a viscous, supersaturated sugar solution derived from nectar gathered and modified by the honeybee, *Apis mellifera*. Honey has been used since ancient times as a remedy in wound care. Evidence from animal studies and some trials has suggested honey may accelerate wound healing.

Objectives

The objective was to determine whether honey increases the rate of healing in acute wounds (burns, lacerations and other traumatic wounds) and chronic wounds (venous ulcers, arterial ulcers, diabetic ulcers, pressure ulcers, infected surgical wounds).

Search strategy

We searched the Cochrane Wounds Group Specialised Register (May 2008), CENTRAL (May 2008) and several other electronic databases (May 2008). Bibliographies were searched and manufacturers of dressing products were contacted for unpublished trials.

Selection criteria

Randomised and quasi randomised trials that evaluated honey as a treatment for any sort of acute or chronic wound were sought. There was no restriction in terms of source, date of publication or language. Wound healing was the primary endpoint.

Data collection and analysis

Data from eligible trials were extracted and summarised using a data extraction sheet by one author and independently verified by a second author.

Main results

19 trials (n=2554) were identified that met the inclusion criteria. In acute wounds, three trials evaluated the effect of honey in acute lacerations, abrasions or minor surgical wounds and nine trials evaluated the effect the honey in burns. In chronic wounds two trials evaluated the effect of honey in venous leg ulcers and one trial in pressure ulcers, infected post-operative wounds, and Fournier's gangrene respectively. Two trials recruited people with mixed groups of chronic or acute wounds. The poor quality of most of the trial reports means the results should be interpreted with caution, except in venous leg ulcers. In acute wounds, honey may reduce time to healing compared with some conventional dressings in partial thickness burns (WMD -4.68 days, 95%CI -4.28 to -5.09 days). All the included burns trials have originated from a single centre, which may have impact on replicability. In chronic wounds, honey in

addition to compression bandaging does not significantly increase healing in venous leg ulcers (RR 1.15, 95%CI 0.96 to 1.38). There is insufficient evidence to determine the effect of honey compared with other treatments for burns or in other acute or chronic wound types.

Authors' conclusions

Honey may improve healing times in mild to moderate superficial and partial thickness burns compared with some conventional dressings. Honey dressings as an adjuvant to compression do not significantly increase leg ulcer healing at 12 weeks. There is insufficient evidence to guide clinical practice in other areas.

PLAIN LANGUAGE SUMMARY

Honey as a topical treatment for acute and chronic wounds

Honey is a viscous, supersaturated sugar solution derived from nectar gathered and modified by the honeybee, *Apis mellifera*. Honey has been used since ancient times as a remedy in wound care. More recently trials have evaluated the effects of using honey to help wound healing in both acute wounds (for example burns, lacerations) and chronic wounds (for example venous leg ulcers, pressure ulcers). Although honey may improve healing times in mild to moderate superficial and partial thickness burns compared with some conventional dressings, it was found that honey dressings used alongside compression therapy do not significantly increase leg ulcer healing at 12 weeks. There is insufficient evidence to guide clinical practice for other wound types.

BACKGROUND

Description of the condition

Acute and chronic wounds are terms in regular use in clinical practice, yet definition of these terms has received little attention. Lazarus 1994 suggested acute wounds proceed through to healing "in an orderly and timely reparative process". Orderliness refers to the healing sequence of inflammation, angiogenesis, matrix deposition, wound contraction, epithelialisation, and scar remodeling. Timeliness is subjective, but refers to a healing time that could be reasonably expected. A chronic wound is therefore a wound where the orderly biological progression to healing has been disrupted and healing is delayed.

Description of the intervention

Honey is a viscous, supersaturated sugar solution derived from nectar gathered and modified by the honeybee, *Apis mellifera*. Honey contains approximately 30% glucose, 40% fructose, 5% sucrose, and 20% water, as well as many other substances, such as amino acids, vitamins, minerals and enzymes (Sato 2000). Honey has been used in wound care since ancient times and is frequently mentioned in early pharmacopeia, although more usually as an ingredient or carrier vehicle rather than a specific treatment. Dioscorides (40-80 CE) often mentioned honey as a vehicle for carrying therapeutic agents in *de materia medicis* (Riddle 1985) and Hippocrates (460-377 BCE), often cited as advocating honey for wound care, simply listed it as one of many ingredients in a multitude of unguents (Adams 1939). Probably the first deliberate advocacy of honey as a wound treatment was by the anonymous author of the Edwin Smith papyrus, an Egyptian surgical text written between 2600-2200 BCE (Breasted 1930). A dressing made from honey and plant material was also recommended for treating burns in the London Medical Papyrus written around 1325 BCE (Trevisanato 2006). Other early medical traditions, including Ayurvedic (Johnson 1992), Chinese (Fu 2001) and Roman traditions (Hajar 2002), also used honey in wound care.

How the intervention might work

Over the past decade there has been a resurgent interest in honey as a wound treatment, with 40 case reports or series in 875 patients published to December 2006 (Jull 2008). Recent research

has tended to concentrate on the antibacterial activity of the many different types of honey rather than its effect on wound healing (Molan 1999). Manuka honey, a monofloral honey derived from the leptospermum tree species in New Zealand and Australia, has been of particular interest as it has antibacterial activity independent of the effect of honey's peroxide activity and osmolarity (Molan 2001). The substance (or substances) responsible for this non-peroxide activity has not been definitively identified but has been termed Unique Manuka Factor (UMF). Manuka honey with a UMF rating has an antibacterial activity equivalent to a similar percentage of phenolic acid in solution. Recent research suggests methylglyoxal is the substance responsible for the non-peroxide activity (Mavric 2008).

There is evidence from different animal models (Bergman 1983; Oryan 1998; Postmes 1997) that honey may accelerate healing. Fifteen of the sixteen controlled trials in five different animal models (mice, rat, rabbit, pig, buffalo calf) found honey-treated incisional and excisional wounds and standard burns healed faster than control wounds (Jull 2008). In addition, a systematic review of honey as a wound dressing found seven randomised trials in humans, six in burns patients and one in infected post-operative wounds (Moore 2001). Although the poor quality of the trial reports prevented any recommendations, the findings did suggest an effect in favour of honey.

The microscopic actions of honey on wounds may be multiple. Honey appears to draw fluid from the underlying circulation, providing both a moist environment and topical nutrition that may enhance tissue growth (Molan 1999). Histologically, honey appears to stimulate tissue growth in animal and human controlled trials, with earlier tissue repair noted (Bergman 1983; Subrahmanyam 1998), fewer inflammatory changes (Oryan 1998; Postmes 1997), and improved epithelialisation (Oryan 1998). Macroscopically, reports have also noted the debriding action of honey (Blomfield 1973; Efem 1988; Ndayisaba 1993; Subrahmanyam 1991).

Why it is important to do this review

Communication with the authors of the earlier systematic review (Moore 2001) revealed the authors had no plans to update the review (personal communication: RA Moore) and at least three other trials had been completed since the review was published. Therefore an updated summary of the effect of honey on wound healing was warranted.

OBJECTIVES

The aim of this review was to assess whether the use of honey confers any benefit in wound healing. The objectives were to determine whether honey:

- increases the rate of healing in acute wounds (burns, lacerations and other traumatic wounds);
- increases the rate of healing in chronic wounds (venous ulcers, arterial ulcers, diabetic ulcers, pressure ulcers, infected surgical wounds).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi randomised controlled trials were included. A quasi-randomised controlled trial was any trial that used a quasi random allocation strategy, such as alternate days, date of birth, or hospital number.

Types of participants

Trials involving participants of any age with an acute or chronic wound were included. For the purposes of this review an acute wound was considered to be any of the following: burns, lacerations or other skin injuries resulting from minor trauma, and minor surgical wounds healing by primary or secondary intention. Chronic wounds were considered to be the following: skin ulcers of any type, pressure ulcers and infected wounds healing by secondary intention.

Types of interventions

The primary intervention was any honey topically applied by any means, alone or in combination with other dressings components, to an acute or chronic wound. Comparison interventions were dressings or other topical agents applied to the wound.

Types of outcome measures

Trials had to provide data on one of the primary outcomes:

Primary outcomes

- time to complete wound healing
- proportion of participants with completely healed wounds.

Secondary outcomes

- incidence of adverse events;
- hospital length of stay;
- change in wound size:
- incidence of infection;
- cost;
- quality of life.

Search methods for identification of studies

Electronic searches

Searches of the following electronic databases were undertaken:
Cochrane Wounds Group Specialised Register (Searched 27/5/08)
The Cochrane Central Register of Controlled Trials (CENTRAL) - The Cochrane Library Issue 2 2008
Ovid MEDLINE - 1950 to May Week 2 2008
Ovid EMBASE - 1980 to 2008 Week 21
Ovid CINAHL - 1982 to May Week 4 2008
The following search strategy was used in the CENTRAL and adapted where appropriate for other databases :
#1 MeSH descriptor Skin Ulcer explode all trees
#2 MeSH descriptor Pilonidal Sinus explode all trees
#3 MeSH descriptor Wounds, Penetrating explode all trees
#4 MeSH descriptor Lacerations explode all trees
#5 MeSH descriptor Burns explode all trees
#6 MeSH descriptor Wound Infection explode all trees
#7 MeSH descriptor Surgical Wound Dehiscence explode all trees
#8 MeSH descriptor Bites and Stings explode all trees
#9 MeSH descriptor Cicatrix explode all trees
#10 ((plantar or diabetic or heel* or foot or feet or ischaemic or ischemic or venous or varicose or stasis or arterial or decubitus or pressure or skin or leg or mixed or tropical or rheumatoid or sickle cell) NEAR/5 (wound* or ulcer*)):ti,ab,kw
#11 (bedsore* or (bed NEXT sore*)):ti,ab,kw
#12 (pilonidal sinus* or pilonidal cyst*):ti,ab,kw
#13 (cavity wound* or sinus wound*):ti,ab,kw
#14 (laceration* or gunshot stab or stabbing or stabbed or bite*):ti,ab,kw
#15 ("burn" or "burns" or "burned" or scald*):ti,ab,kw
#16 (surg* NEAR/5 infection*):ti,ab,kw
#17 (surg* NEAR/5 wound*):ti,ab,kw
#18 (wound* NEAR/5 infection*):ti,ab,kw
#19 (malignant wound* or experimental wound* or traumatic wound*):ti,ab,kw
#20 (infusion site* or donor site* or wound site* or surgical site*):ti,ab,kw
#21 (skin abscess* or skin abcess*):ti,ab,kw
#22 (hypertrophic scar* or keloid*):ti,ab,kw
#23 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR
#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24 MeSH descriptor Honey explode all trees
#25 honey:ti,ab,kw
#26 (#24 OR #25)
#27 (#23 AND #26)
The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format (Lefebvre 2008). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2008). Additionally, LILACS (1982 to October 2006), AMED (1985 to October 2006) and Google Scholar were searched using the text word "honey".

Searching other resources

Contact was made with experts in the field, authors of the included trials and manufacturers of honey products for wound care (Comvita NZ Ltd and MediHoney Australia Pty Ltd). The bibliographies of all obtained studies and review articles were searched for potentially eligible trials. No language or date restrictions were applied to the trials and both published and unpublished trials were sought.

Data collection and analysis

Selection of studies

Two authors (AJ, NW) independently examined titles and abstracts of potentially relevant trials. Full text copies of all relevant trials, or trials that might be relevant to the review were obtained. The two authors independently selected the trials using the inclusion criteria (AJ, NW). Disagreements were resolved by discussion.

Data extraction and management

Data were extracted from included trials by one author (AJ) and recorded on a standardised form. The extracted data were independently reviewed for accuracy by the second author (NW) and disagreements resolved by discussion. If the data from the trial report were inadequate or ambiguous, additional information was sought from the trial authors. We collected data on the topics listed below:

1. Author
2. Title
3. Source of reference

4. Study setting
5. Study design
6. A priori sample size calculation
7. Sample size
8. Inclusion/exclusion criteria
9. Age of participants
10. Sex of participants
11. Wound type
12. Intervention and comparison
13. Outcomes
14. Withdrawals and reason for withdrawal
15. Funding source
16. Co-interventions

Assessment of risk of bias in included studies

The methodological quality of the trials was assessed for risk of bias. Data were extracted from included trials by one author (AJ) and recorded on a standardised form. The extracted data were independently reviewed for accuracy by the second author (NW) and disagreements resolved by discussion. If the data from the trial report were inadequate or ambiguous, additional information was sought from the trial authors. We appraised each study for the following items.

1. Randomisation method and allocation concealment - the sequence generation was clearly reported as using random number tables, computer random number generation, coin tossing, or shuffling. The allocation was concealed using a randomisation method described that would not allow an investigator/participant to know or influence an intervention group before an eligible participant entered the study, such as central randomisation; serially numbered, opaque, sealed envelopes.
2. Loss to follow up - extent of loss to follow up is reported and whether loss was differential between groups.
3. Use of blinding.
4. Use of intention to treat analysis: Defined in this review as analysis that included all participants in the groups to which they were randomised, regardless of whether they received the treatment, completed treatment or were found not to meet entry criteria after randomisation (Hollis 1999).
5. Baseline comparability for prognostic factors - table of baseline characteristics assessed for comparability.

Data synthesis

Where trials were sufficiently alike in terms of population and comparison interventions, results from the trials were combined. Weighted mean differences (WMD) and 95% confidence intervals (95%CI) were reported for continuous outcomes and relative risk (RR) and 95% confidence intervals (95%CI) were reported for dichotomous variables. Statistical heterogeneity was tested by comparing Cochran's Q statistic and the Chi-squared distribution. Heterogeneity was assumed with P values of less than 0.1 (Higgins & Green 2005). In addition, the I^2 statistic was used to determine the percentage of variation due to heterogeneity rather than chance (Higgins 2003) and any sources of heterogeneity were explored. Where significant statistical heterogeneity was present, a random effects model was used when combining trials (Ioannidis 2008).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Sixty seven citations or references were found. Three reports could not be obtained for assessment and three reports concerned ongoing studies obtained from one manufacturer (MediHoney Pty Ltd). Sixty one citations were reviewed and a further 33 were excluded, either because they were not trial reports, were animal model studies, did not use honey as an intervention, the participants did not have a wound, or had no interpretable data.

Four trials (five citations) that may have otherwise met the inclusion criteria did not provide sufficient data for inclusion in the analyses (Bangroo 2005; Gunes 2007; Memon 2005; Rucigaj 2006). These trials are included in the Table of Studies Awaiting Classification (Characteristics of studies awaiting classification). Efforts are still being made to contact the authors for further information.

Nineteen trials (24 citations) met the inclusion criteria and were available for analysis. Additional data were obtained from trials through contact with the investigators (personal communication: Georgina Gethin, Ron Ingle, Caroline McIntosh, and Mutya Subrahmanyam). Twelve of the trials recruited participants with acute wounds - nine with burns (Subrahmanyam 1991; Subrahmanyam 1993b; Subrahmanyam 1994;Subrahmanyam 1996a; Subrahmanyam 1996b; Subrahmanyam 1996c; Subrahmanyam 1998; Subrahmanyam 1999; Subrahmanyam 2001a) two with minor surgical excisions, (Marshall 2005; McIntosh 2006) and one with minor trauma (Ingle 2006 et al. 2006). Six of the trials recruited participants with chronic wounds - one with infected surgical wounds (Al Waili 1999), one with pressure ulcers (Weheida 1991), one with Fournier's gangrene (Subrahmanyam 2004) and two with leg ulcers (Jull 2008; Gethin 2007). Two trials recruited participants with mixed groups of chronic or acute wounds (Mphande 2007; Subrahmanyam 1993a).

Eleven trials were conducted by the same investigator (Subrahmanyam 1991; Subrahmanyam 1993a; Subrahmanyam 1993b; Subrahmanyam 1994; Subrahmanyam 1996a; Subrahmanyam 1996b; Subrahmanyam 1996c; Subrahmanyam 1998; Subrahmanyam

1999; Subrahmanyam 2001a; Subrahmanyam 2004). Four trials reported recruiting only adults (Al Waili 1999; Ingle 2006; Jull 2008; Subrahmanyam 2004). The remaining trials did not specify an age range (Gethin 2007; Marshall 2005; McIntosh 2006) or recruited both children and adults. Five trials were conducted in community settings or outpatient clinics (Gethin 2007; Ingle 2006; Jull 2008; Marshall 2005; McIntosh 2006) The remaining trials were conducted in hospital settings. Monofloral honey (aloe, jarrah, jambhul or manuka) was the intervention in seven trials (Gethin 2007; Ingle 2006; Jull 2008; Marshall 2005; McIntosh 2006; Subrahmanyam 2001a; Subrahmanyam 2004) and the floral type of honey was not specified in the remaining trials.

Fourteen trials reported either mean time to healing,(Al Waili 1999; Ingle 2006; Marshall 2005; McIntosh 2006; Subrahmanyam 1993a; Subrahmanyam 1994; Subrahmanyam 1996a; Subrahmanyam 1996c; Subrahmanyam 2001a) and/or time to healing events (Subrahmanyam 1991; Subrahmanyam 1993b; Subrahmanyam 1998; Subrahmanyam 2001a). In all of these trials, follow up appears to have been at least until complete healing. Mean hospital stay only was reported in two trials, but data on mean time to healing was provided for this review by the author (Subrahmanyam 1999; Subrahmanyam 2004). One trial reported median time to healing (Mphande 2007).

Four trials reported an *a priori* sample size calculation (Gethin 2007; Ingle 2006; Jull 2008; McIntosh 2006). In one of these trials, the difference the study was powered to detect was not reported, although the effect was stated to be "clinically significant" (McIntosh 2006).

Risk of bias in included studies

Overall, the methodological quality of the trials was variable, with most trials failing to adequately report on randomisation or allocation concealment, study design elements that are known to decrease the risk of bias (Schulz 1995; Moher 1998). Therefore, most trials must be considered to be at moderate to high risk of bias. A table of these characteristics is provided in Table 1.

Table 1. Quality characteristics of trial report

Study	Randomisation	Allocation concealed	Loss reported	Intention to t	Blinded assessment	Groups comparable	Power calculation
Al Waili	Not reported, but described as RCT	Not reported	Yes (0%)	Not reported	Not reported	Yes	Not reported
Gethin	Yes	Yes	Yes	Yes	No	Yes	Yes
Ingle	Yes	Not reported	Yes (6%)	No	Yes	Yes	Yes

Table 1. Quality characteristics of trial report (*Continued*)

Jull	Yes	Yes	Yes (2%)	Yes	No	Yes	Yes
Marshall	Yes	Yes	Yes (14%)	No	Yes	No	Not reported
McIntosh	Yes	Yes	Yes (0%)	No	Yes	Yes	Yes
Mphande	No; allocation on alternating basis at admission	Inadequate	Yes (0%)	Not reported	Not reported	Yes	Not reported
Subrahmanyam 1991	Yes*	Unclear	Yes (0%)	Not reported	Yes*	Yes	Not reported
Subrahmanyam 1993a	Yes*	Unclear	Yes (0%)	Not reported	Yes*	Yes*	Not reported
Subrahmanyam 1993a	Yes*	Unclear	Yes (0%)	Not reported	Yes*	Yes*	Not reported
Subrahmanyam 1994	Yes*	Unclear	Yes (0%)	Not reported	Yes*	Yes*	Not reported
Subrahmanyam 1996a	Yes*	Unclear	Not reported	Not reported	Yes*	Yes*	Not reported
Subrahmanyam 1996b	Yes*	Unclear	Not reported	Not reported	Yes*	Yes*	Not reported
Subrahmanyam 1996c	Yes*	Unclear	Yes (0%)	Not reported	Yes*	Yes*	Not reported
Subrahmanyam 1998	Yes*	Unclear	Yes (0%)	Not reported	Yes*	Yes*	Not reported
Subrahmanyam 1999	Yes*	Unclear	Yes (8%)	Not reported	Yes*	Yes*	Not reported
Subrahmanyam 2001a	Yes*	Unclear	Yes (0%)	Not reported	Yes*	Yes*	Not reported
Subrahmanyam 2004	Yes*	Unclear	Not reported	Not reported	Yes	Yes*	Not reported

Table 1. Quality characteristics of trial report (*Continued*)

Weheida	Not reported, but described as RCT	Not reported	Yes (0%)	Not reported	Not reported	No	Not reported
	* information provided by author						

Randomisation and allocation concealment:

Nineteen trials were described as randomised controlled trials, but only six trials reported how their allocation sequence was generated (Gethin 2007; Ingle 2006; Jull 2008; Marshall 2005; McIntosh 2006; Mphande 2007). One of these trials used the pseudo-randomised strategy of alternating admissions (Mphande 2007). Authors were approached for additional information about the generation of the allocation sequence. Information was supplied by one author for 11 trials. The method of randomisation was described as "by the chit method" (personal communication: M. Subrahmanyam),(Subrahmanyam 1991; Subrahmanyam 1993a; Subrahmanyam 1993b; Subrahmanyam 1994; Subrahmanyam 1996a; Subrahmanyam 1996b; Subrahmanyam 1996c; Subrahmanyam 1998; Subrahmanyam 1999; Subrahmanyam 2001a; Subrahmanyam 2004) but it is not known what this method involved.

Allocation concealment was reported in four trials (Gethin 2007; Jull 2008; Marshall 2005; McIntosh 2006) and allocation concealment (central telephone) was considered adequate in all. Additional information was supplied on 11 trials, where the method of allocation concealment was described as "sequential numbered envelopes" or "sequential numbered envelopes, which are sealed" (personal communication: M. Subrahmanyam) (Subrahmanyam 1991; Subrahmanyam 1993a; Subrahmanyam 1993b; Subrahmanyam 1994; Subrahmanyam 1996a; Subrahmanyam 1996b; Subrahmanyam 1996c; Subrahmanyam 1998; Subrahmanyam 1999; Subrahmanyam 2001a; Subrahmanyam 2004). It is not known whether the envelopes were opaque.

Loss to follow up:

Loss to follow up was reported by 14 trials. Loss ranged from 2 to 14% in five trials, (Gethin 2007; Ingle 2006; Jull 2008; Marshall 2005; Subrahmanyam 1999) with no loss in 11 trials.

Intention to treat analysis (ITT):

Three trials reported using ITT analysis (Gethin 2007; Jull 2008; McIntosh 2006), but in one trial participants were excluded after randomisation, thus failing to meet the criteria for ITT analysis (McIntosh 2006). In the remaining trials, it is unknown whether ITT analysis was used.

Blinding:

Four trials used assessor blinding (Ingle 2006; Marshall 2005; McIntosh 2006; Subrahmanyam 2004) and two trials were open label (Jull 2008; Gethin 2007), although one of these used blinded review of photographs in a sensitivity analysis for the primary outcome (Jull 2008). The remaining trials did not report whether blinding was employed and so additional information about blinding was sought from authors of these trials. Information was supplied by one author on 10 trials, who stated the investigators and outcome assessors were blinded to participant allocation (Subrahmanyam 1991; Subrahmanyam 1993a; Subrahmanyam 1993b; Subrahmanyam 1994; Subrahmanyam 1996a; Subrahmanyam 1996b; Subrahmanyam 1996c; Subrahmanyam 1998; Subrahmanyam 1999; Subrahmanyam 2001a).

Baseline comparability:

Baseline equivalence was not reported in five trials (Subrahmanyam 1993a; Subrahmanyam 1993b; Subrahmanyam 1996a; Weheida 1991). The majority of trials reported baseline data, although the reported data were limited in many cases. Additional information was sought from authors. Information was supplied by one author for 11 trials (Subrahmanyam 1991; Subrahmanyam 1993a; Subrahmanyam 1993b; Subrahmanyam 1994; Subrahmanyam 1996a; Subrahmanyam 1996b; Subrahmanyam 1996c; Subrahmanyam 1998; Subrahmanyam 1999; Subrahmanyam 2001a; Subrahmanyam 2004). Baseline equivalence appeared to be present in these trials. One study did not have equivalent groups and in each instance this imbalance

appeared to favour the comparison treatment, potentially influencing the results (Marshall 2005).

Effects of interventions

19 trials including 2,554 participants were included in this review. The trials were generally small (median size 92, range 30 to 900) and there was very obvious clinical and methodological heterogeneity in the included trials. Therefore it was not appropriate to combine the trials in a meta-analysis to produce a summary statistic for honey overall, or even subgroup summary statistics for acute, chronic, mixed wounds. Within the subgroups (acute, mixed acute and chronic, and chronic wounds) trials have been combined in meta-analysis where appropriate. Otherwise the trials have been summarised narratively.

1. Acute wounds

1.1 Minor acute wounds

Three trials (n=213) recruited participants with minor acute wounds (Ingle 2006; Marshall 2005; McIntosh 2006). In two trials, the wounds were surgical wounds created following partial or total toe nail avulsions (Marshall 2005; McIntosh 2006) with the control group treated with paraffin gauze in one trial and an iodophor dressing in the second trial. The remaining trial recruited mine workers with lacerations or shallow abrasions and control participants were treated with a hydrogel (Ingle 2006) Combination of trial findings was undertaken using a fixed effect model. There was no statistically significant difference between treatments for mean days to healing (WMD 1.55 days, 95%CI -1.91 to 5.00 days) Analysis 1.1. Moderate heterogeneity was present (I^2 = 48%), although this was not statistically significant.

1.2 Burns

With the exception of one trial (Subrahmanyam 2001a), all the reports of burns trials were single author trials. All the reports originated from a single study centre. Two trials (n=154) recruited participants with superficial thickness burns (Subrahmanyam 1991; Subrahmanyam 1998) and five trials (n=1,240) recruited participants with partial thickness burns (Subrahmanyam 1993a; Subrahmanyam 1994; Subrahmanyam 1996a; Subrahmanyam 1996b; Subrahmanyam 1996c). Two trials (n=200) recruited participants with mixed depth (partial and full thickness) burns (Subrahmanyam 1999; Subrahmanyam 2001a). There were six comparison treatments, which have been grouped under the broad categories of conventional dressings, early excision, silver sulfadiazine and unconventional dressings for this review.

1.2.1 Honey compared with conventional dressings

Two trials (n=992) compared honey with conventional dressings for the treatment of partial thickness burns (Subrahmanyam 1993a; Subrahmanyam 1996a; Subrahmanyam 1999). In one trial (Subrahmanyam 1993a) the comparison was a polyurethane film dressing and in the other trial (Subrahmanyam 1996a) the control participants were treated with either a polyurethane film (n=90), Vaseline-impregnated gauze (n=90), sterile linen dressings (n=90), or a soframycin dressing (n=90). Mean days to healing were reported but not the standard deviations. This additional information was provided by the author (personal communication: M. Subrahmanyam), on pooling the WMD was -4.68 days (95%CI -5.09 to -4.28 days) in favour of honey (Analysis 2.1).

1.2.2 Honey compared with early excision

One trial (n=50) compared early tangential excision and skin grafting with honey dressings and delayed excision and skin grafting for the treatment of mixed partial and full thickness burns (Subrahmanyam 1999). Mean time to healing was not published, but was provided by the author (personal communication: M. Subrahmanyam). Mean time to healing was 32 days in the honey-treated group and 18.4 days in the comparison group (WMD 13.6 days, 95%CI 10.02 to 17.18 days)(Analysis 3.1), significantly favouring early excision and skin grafting.

1.2.3 Honey compared with silver sulfadiazine

Three trials (n=254) compared honey with silver sulfadiazine (Subrahmanyam 1991; Subrahmanyam 1998; Subrahmanyam 2001a). Two of the trials recruited participants with superficial burns (Subrahmanyam 1991; Subrahmanyam 1998), while the other trial did not report on the depth of the burns in recruited participants. One trial reported mean time to healing and time to healing data (Subrahmanyam 2001a) and the other two trials provided time to healing data only (Subrahmanyam 1991; Subrahmanyam 1998). Time to healing data in the two trials were reported using different schedules e.g. reporting complete healing at days 7, 14 and 21 compared with reporting complete healing at days 10, 15 and 20. Mean time to healing was provided by the author (personal communication: M. Subrahmanyam) and this was used as the outcome. The weighted mean difference between the trials was not significant (WMD -4.37 days, 95%CI -8.94 to 0.19)(Analysis 4.1). A random effects model was used as there was significant statistical heterogeneity (P<0.00001, I^2=95%) despite the apparent clinical and methodological similarities. Heterogeneity appears to have been contributed by one trial (Subrahmanyam 1991), but it was not possible to determine what it was about this trial that caused the heterogeneity.

1.2.4 Honey compared with unconventional dressings

Three trials (n=248) by the same investigator compared honey with unconventional dressings or materials (Subrahmanyam 1994; Subrahmanyam 1996b; Subrahmanyam 1996c). The interventions were too dissimilar to combine in a meta-analysis. Therefore the trials are summarised here in a narrative review.

One trial (n=100) recruited participants with partial thickness burns and compared honey to treatment with boiled potato peel dressings (Subrahmanyam 1996b). Mean days to healing was reported, but without the standard deviations. This additional information was supplied by the author (personal communication: M. Subrahmanyam). The findings clearly favoured the honey. Mean time to healing was 10.4 days in the honey-treated group and 16.2 days in the potato peel group (MD -5.8 days, 95%CI -6.88 to -4.92 days)(Analysis 5.1).

The remaining two trials both recruited participants with partial thickness burns. One trial (n=64) compared honey-impregnated gauze with treatment with amniotic membranes (Subrahmanyam 1994). Mean days to healing was reported, although without the standard deviations. This additional information was supplied by the author (personal communication: M. Subrahmanyam). Mean time to healing was 9.4 days in the honey-treated group and 7.5 days in the group treated with amniotic membranes, with a non-significant mean difference of 1.9 days (95%CI -0.88 to 4.68 days)(Analysis 5.1). Participant allocation was uneven in this trial at approximately 2:1 in favour of the honey-treated group (40 versus 24 participants allocated to honey or comparison, respectively). No rationale was provided for this imbalance. The second trial (n=84) compared honey to treatment with honey-plus (Subrahmanyam 1996c). Honey-plus consisted of unprocessed undiluted honey with added vitamins C and E, and polyethylene glycol. Mean days to healing was reported, but without the standard deviations. This additional information was supplied by the author (personal communication: M. Subrahmanyam). Mean time to healing was 8.3 days in the honey-treated group and 6.4 days in the comparison group, with a significant mean difference of 1.9 days (95%CI 0.59 to 3.21 days)(Analysis 5.1) in favour of the honey-plus.

2. Mixed acute and chronic wounds

One trial (n=100) recruited participants with either burns or leg ulcers (Subrahmanyam 1993b), and a second trial recruited a mix of acute and chronic wounds (Mphande 2007). In Subrahmanyam 1993b (n=100), the severity of the burns was not described. The participants with leg ulcers had traumatic ulcers, pressure ulcers, diabetic ulcers, venous ulcers or trophic ulcers. The comparison treatment was silver sulfadiazine. Information on overall mean time to healing was provided by the author (personal communication: M. Subrahmanyam). The mean difference was -13.0 days (95%CI -15.24 to -10.76)(Analysis 6.1) in favour of honey. In Mphande 2007 (n=40) participants had ulcers, chronic osteomyelitis, abscesses, post-surgical or traumatic wounds. The comparison treatment was sugar dressings. Median time to complete healing was 31.5 days in the honey-treated group and 56 days in the sugar-treated group. As only the central tendency and the range of values was was reported, it was not possible to estimate the median difference with a 95%CI.

3. Chronic Wounds

Five trials (n=596) recruited participants with chronic wounds (Al Waili 1999; Jull 2008; Gethin 2007; Subrahmanyam 2004; (Weheida 1991). Two trials recruited participants with venous leg ulcers (Gethin 2007; Jull 2008). One trial recruited women with infected post-caesarean or hysterectomy wounds (Al Waili 1999) and the remaining trial recruited adults with uninfected pressure ulcers (Weheida 1991). Two trials reported mean time to healing (Al Waili 1999; Weheida 1991) and two trials reported proportion of participants with completely healed ulcers (Gethin 2007; Jull 2008). Mean hospital stay only was reported in one trial, but data on mean time to healing was provided by the author (Subrahmanyam 2004). The comparison treatments saline soaked gauze (Weheida 1991), antiseptic washes (70% ethanol and povidone iodine) (Al Waili 1999), Edinburgh Solution of Lime (Subrahmanyam 2004), hydrogel (Gethin 2007) and usual care (Jull 2008). Given the clinical and methodological heterogeneity between the trials, it was not possible to combine all the trials to produce a summary statistic.

3.1 Leg ulcers

Two trials recruited participants with venous leg ulcers. One trial (n=368) recruited patients presenting to community-based nursing services for assessment and treatment of their venous ulcers. Participants were allocated to receive either manuka honey-impregnated calcium alginate dressings or usual care (Jull 2008). Participants allocated usual care could receive any clinically indicated dressing from the wide range normally available to community nurses (non-adherent, alginate, hydrogel, hydrofibre, hydrocolloid, silver or iodophor dressings). Both groups received compression bandaging as a standard background treatment. Participants were treated for 12 weeks. The second trial (n=108) recruited participants with uninfected venous ulcers which were 50% or more covered with slough (Gethin 2007). Participants were allocated to receive either manuka honey dressings or hydrogel dressings for 4 weeks and then standard care for the remaining 8 weeks of the 12 week follow up. Both groups received compression bandaging as a standard background treatment. The primary outcome was change in area of slough at 4 weeks with healing reported at 12 weeks as a secondary outcome. Although the duration of treatment was dissimilar, they were considered sufficiently alike to be

able to provide meaningful information when combined. The I^2 was 0% and combination of the two trials found no significant effect of honey on ulcer healing at 12 weeks (RR 1.15, 95%CI 0.96 to 1.38)(Analysis 7.1).

3.2 Infected post-operative wounds

One trial (n=50) randomly allocated participants with infected Caesarean or hysterectomy wounds to twice daily applications of honey or antiseptic washes of 70% ethanol and povidone-iodine (Al Waili 1999) in addition to systemic antibiotics. There was very limited information on baseline comparability and no indication of the duration of treatment or length of follow up. Mean time to healing favoured the honey-treated group (MD -11.31 days, 95%CI -14.40 to -8.22 days)(Analysis 8.1).

3.3 Pressure ulcers

One trial (n=40) randomly allocated participants with uninfected grade I or grade II pressure ulcers greater than 2 cm in diameter to daily applications of honey or saline-soaked gauze dressings (Weheida 1991). There was very limited information on baseline comparability and no indication of the duration of treatment or length of follow up. Mean time to healing favoured the honey-treated group (MD -1.73 days, 95%CI -2.37 to -1.09 days)(Analysis 8.1).

3.4 Fournier's gangrene

One trial (n=30) of men with Fournier's gangrene randomly allocated participants to treatment with monofloral (jamun) honey-soaked gauze dressings or EUSOL-soaked gauze dressings (Subrahmanyam 2004). Fournier's gangrene is an infection of the scrotum that can also involve the perineum and abdominal wall. One participant died in the honey-treated group and two participants died in the EUSOL-treated group. Skin grafting was required in nine participants in each group. Only mean length of hospital stay was reported in the paper, but mean time to healing was supplied by the author (per. comm. M. Subrahmanyam). Mean time to healing significantly favoured the honey-treated group (MD -8.00 days, 95%CI -9.92 to -6.08 days)(Analysis 8.1).

4. Adverse events

One trial did not report adverse events (Weheida 1991) and three trials reported that no events occurred (Marshall 2005; McIntosh 2006; Subrahmanyam 1996b). One trial (Jull 2008) reported any adverse event, whereas the remaining trials appear to have limited reporting of events to specific types of events, rather than encouraging reports of any event. Adverse events are presented by wound type and the findings have been combined using a random effects model due to heterogeneity of results in the burns subgroup. Although only one trial reported frequency of events by participant (Jull 2008), it is assumed one event equals one participant in all other trials.

4.1 Minor acute wounds

Ingle and colleagues reported the frequency of itching, burning and pain (Ingle 2006). There was no significant difference between honey and hydrogel (RR 1.37, 95%CI 0.77 to 2.45)(Analysis 9.1).

4.2 Burns

Five trials reported the frequency of hypergranulation, contracture, hypertrophic scarring or minor scarring as adverse events (Subrahmanyam 1991; Subrahmanyam 1993a; Subrahmanyam 1994; Subrahmanyam 1996a; Subrahmanyam 1999; Subrahmanyam 2001a). There was no statistically significant difference between the honey and the control treatments (RR 0.85, 95%CI 0.29 to 2.51)(Analysis 9.1). The frequency of the different adverse events is presented in Table 2.

Table 2. Frequency of adverse events reported in burns trials (Subrahmanyam 1991, 1993a, 1994, 1996a, 1999, 2001a)

Adverse event	Honey	Control treatment	RR (95%CI)
Hypergranulation	8/548	17/548	0.47 (0.26 to 0.84)
Contracture	8/213	14/197	0.53 (0.30 to 0.93)
Minor scarring	28/450	87/450	0.32 (0.23 to 0.45)
Hypertrophic scarring	0/52	7/52	Not estimable

4.3 Infected post-operative wounds

Al Waili reported the frequency of wound dehiscence (Al Waili 1999). There was a statistically significant difference in favour of honey treatment (RR 0.31, 95%CI 0.11 to 0.82)(Analysis 9.1).

4.4 Venous leg ulcers

Jull and colleagues (Jull 2008) reported all adverse events, whether or not the event was believed to be related to the treatment, whereas Gethin (Gethin 2007) reported events that complied with the Irish Medicines Board criteria. There were statistically significantly more adverse event reports in the honey-treated group (RR 1.27, 95%CI 1.05 to 1.56)(Analysis 9.1). The frequency of the different adverse events in presented in Table 3.

Table 3. Frequency of adverse events reported in venous ulcer trial (Jull et al 2008)

Adverse event	Honey treatment	Control treatment	RR (95%CI)
Ulcer pain	47/187	18/181	2.53 (1.53 to 4.18)
Bleeding	3/187	3/181	0.97 (0.20 to 4.73)
Dermatitis	8/187	8/181	0.97 (0.37 to 2.52)
Deterioration of ulcer	19/187	9/181	2.04 (0.95 to 4.40)
Erythema	6/187	4/181	1.45 (0.42 to 5.06)
Oedema	4/187	1/181	3.87 (0.44 to 34.31)
Increased exudate	5/187	1/181	4.84 (0.57 to 41.02)
Deterioration of surrounding skin	5/187	3/181	1.61 (0.39 to 6.65)
New ulceration	16/187	15/181	1.03 (0.53 to 2.03)
Other	6/187	3/181	1.94 (0.49 to 7.62)
Cardiovascular	4/187	3/181	1.29 (0.29 to 5.69)
Cancer	2/187	2/181	0.97 (0.14 to 6.80)
Neurological	4/187	1/181	3.87 (0.44 to 34.31)
Gastrointestinal	4/187	2/181	1.94 (0.36 to 10.44)
Injury	10/187	9/181	1.08 (0.45 to 2.59)

Table 3. Frequency of adverse events reported in venous ulcer trial (Jull et al 2008) (*Continued*)

Musculoskeletal	13/187	9/181	1.40 (0.61 to 3.19)
Respiratory	6/187	3/181	1.94 (0.49 to 7.62)
Other	3/187	8/181	0.41 (0.11 to 1.58)

4.5 Fournier's gangrene

Subrahmanyam 2004 reported the frequency of mortality. There was no significant difference in patient deaths (RR 0.57, 95%CI 0.06 to 5.65)(Analysis 9.1).

5. Incidence of infection

Three trials reported the incidence of infection (Marshall 2005; McIntosh 2006; Jull 2008) and a fourth study reported withdrawals due to infection (Gethin 2007). Infection was operationally defined as clinical signs of infection or a positive swab result, and treatment with antibiotics in one trial (Jull 2008); in the other trials infection was described as clinically diagnosed and requiring referral for antibiotics. There was no significant difference in infection rates (RR 0.72, 95%CI 0.50 to 1.04)(Analysis 10.1).

Six burns trials (n=610) reported the proportion of patients with positive swab cultures at admission rendered sterile after 7 days treatment with honey compared with another non-honey treatment (Subrahmanyam 1991; Subrahmanyam 1993a; Subrahmanyam 1994; Subrahmanyam 1996b; Subrahmanyam 1998 Subrahmanyam 2001a). All six trials reported the number of patients with a positive swab at admission that were sterile after seven days treatment, rather than the number of patients overall that had a sterile wound. The relative risk of rendering a burn sterile after seven days treatment was 3.95 (95%CI 1.36 to 11.44)(Analysis 10.2) which was significantly in favour of honey. The trials were combined using a random effects model as significant heterogeneity was present (P<0.00001, I^2=96%).

6. Cost

Two trials reported cost information (Ingle 2006; Jull 2008); one was a trial of honey compared with hydrogel in participants with shallow wounds and abrasions (Ingle 2006) and the second was a trial of honey compared with usual care in venous leg ulceration (Jull 2008). Ingle 2006 found that honey was cheaper than hydrogel (ZAR 0.49 vs ZAR 12.06) per patient. However only the cost of the product was considered in this trial. Jull 2008 and colleagues conducted a full cost-effectiveness analysis using a health service perspective. Information was collected on dressings and related products, district nursing time, general practitioner and laboratory time, outpatient consultations, antibiotic use, and hospitalisation. In the base case analysis, the average cost of treatment with honey was NZ$917.00 per participant compared to NZ$972.68 per participant for usual care. This cost was driven by a small difference in hospitalisations that was considered likely to be due to chance variation (three participants in the honey group were hospitalised for ulcer-related reasons for 10 days as compared with six participants hospitalised for 40 days). A sensitivity analysis excluding the hospitalisations found the average cost of treatment was reversed with usual care being cheaper (NZ$811.12 per participant) than treatment with honey (NZ$877.90 per participant). Incremental cost effectiveness ratios were calculated, but are not reported here as effectiveness was not established and therefore cost-effectiveness ratios could be misleading.

7. Quality of life

One trial of honey for treating venous leg ulcers reported data on health-related quality of life (Jull 2008). Two generic instruments (SF-36, EQ5D) and one disease-specific instrument (Charing Cross Venous Ulcer Questionnaire) were used. A small but statistically significant improvement in the physical functioning domain of SF-36 was found in favour of honey (mean difference 4.6, 95%CI 0.5 to 8.7), but no differences were found in any of the other domains measured by the SF-36. In addition, there was no significant difference between the groups for either physical summary component score (mean difference 1.1, 95%CI -0.8 to 3.0) or the mental component summary score (mean difference 0.7, 95%CI -1.1 to 2.4). There were also no significant differences on any domain measured by EQ5D or the Charing Cross Venous Ulcer Questionnaire.

DISCUSSION

This is a complex review addressing a diverse range of wound types. Therefore, the findings with respect to specific wound types are discussed below. The results should be interpreted with caution as the 19 trials included in this review were of variable methodological quality, with most at moderate to high risk of bias. In addition, the high number of single author, single centre trials may have implications for replicability. Data from trials of higher quality found honey had no significant effect on healing rates (Gethin 2007; Ingle 2006; Jull 2008; McIntosh 2006) or had significantly slower rates of healing (Marshall 2005). The findings of this systematic review advance those of the previous review in the area (Moore 2001), which found seven trials compared with 19 here. The previous review was unable to make any recommendations due to the poor quality of the reports and the fact that six of the seven trials were conducted by the same sole researcher. The greater quality of recent reports and the provision of additional information by authors have facilitated analyses in this systematic review that were not possible in the previous review. However, the key findings remain couched in caution, especially given the number of reports from one investigator.

1. Acute wounds

1.1 Minor acute wounds

The evidence currently does not support the use of honey in acute wounds such as abrasions and lacerations, or on minor uncomplicated wounds left to heal by secondary intention following surgery. Further trials of honey may be justified in these types of wounds as the possibility of a modest effect in favour of honey cannot be ruled out.

1.2 Burns

The evidence with respect to the treatment of burns is mixed. Honey may be more effective than conventional dressings (such as impregnated gauze, saline soaks, or polyurethane film dressings) in treating mild to moderate partial thickness burns. However honey appears to delay healing in mixed depth burns (i.e. both partial and deep thickness burns) compared with early excision and skin grafting. These findings were derived from one small trial, but the effect was such that early excision and grafting must be considered the superior alternative.

The evidence for honey compared with other treatments in the treatment of burns is more uncertain. While amniotic membrane dressings performed better than honey dressings in one trial, honey dressings performed better than boiled potato dressings in another trial. Both trials were small and of uncertain quality and thus these results should only be used to inform future research efforts. The effect of honey compared with silver sulfadiazine in treating partial thickness burns has not been established, although the trend is towards honey. However, a trend towards honey may be as a consequence of the comparison treatment delaying healing rather than honey increasing healing. Use of silver sulfadiazine until healing has been found to impede healing times in comparison to inactive treatments, such as hydrocolloid dressings and silicone-impregnated dressings (Wasiak 2006). It is in recognition of this evidence that guidelines recommend silver sulfadiazine only be used for limited periods in the treatment of burns rather than for the entire treatment period (ACC 2007).

Further trials with superficial and partial thickness burns with current best practices as a comparator may be justified.

2. Mixed acute and chronic wounds

The rationale for conducting trials in which the participants have either burns or a mix of chronic wounds (pressure ulcers, diabetic ulcers, varicose ulcers and trophic ulcers) is unclear. The aetiologies are so different that no matter whether the results are positive, negative or inconclusive, the findings are unlikely to influence clinical practice as practitioners will struggle with application of the evidence. Therefore trials with such broad inclusion criteria should be discouraged.

3. Chronic wounds

The effect of honey in the treatment of chronic wounds, with the exception of venous leg ulcers, cannot be established based on current evidence. Most trials were small, with inappropriate comparators and generally of poor quality.

3.1 Leg ulcers

Combination of two trials at low risk of bias found no significant effect for honey when used as an adjuvant to compression bandaging. The two trials did recruit different populations with one trial recruiting all comers (Jull 2008) and the other trial restricted participants that had ulcers with an area >50% covered in slough (Gethin 2007). Such differences may account for the difference in effect estimates for each trial, although trial size may also account for this difference. However, the key message is that the evidence does not currently support use of honey dressings as an adjuvant to compression, although the possibility of a modest effect cannot be ruled out. Further trials could be justified to quantify such an effect.

3.2 Infected post-operative wounds

The effect of honey as an adjuvant to systemic antibiotics cannot be determined from the single trial recruiting infected post-operative wounds. In addition to the small number of participants in this trial, and the lack of detail enabling an assessment of trial quality, the comparator was also an antiseptic that may impair wound healing (Leaper 1986). Such comparators are inappropriate when trying to estimate the effect of a therapeutic agent on wound healing. Further trials are justified.

3.3 Pressure ulcers

The effect of honey on pressure ulcers cannot be determined from the single trial. The trial lacked detail that would enable a quality assessment and did not report appropriate baseline data to deter-

mine whether the groups were comparable. An additional trial has been published (Gunes 2007) but lacked data that would have enabled combination with the included trial. Efforts to contact the author for additional information have not yet been successful and thus this trial has not been included in the review.

3.4 Fournier's gangrene

The effect of honey on Fournier's gangrene cannot be determined from this single trial. In addition to the small number of participants, and the lack of detail enabling an assessment of trial quality (although the authors provided information on request), the comparator was EUSOL, an antiseptic that has been demonstrated in animal model studies to impair wound healing (Brennan 1985). Such comparators are inappropriate when trying to estimate the effect of a therapeutic agent on wound healing. Further trials are justified.

4. Adverse events

The reporting of adverse events was poor in most trials, and non-existent in a few trials. This makes accurate assessment of the risk of adverse events associated with honey dressings difficult. Two trials reported treatment withdrawals, but without specifying the reasons for withdrawal beyond non-compliance with treatment (Marshall 2005; McIntosh 2006). In both these trials, the author stated there were no adverse events, but given that adherence with a treatment regimen is likely to be strongly correlated with the treatment itself, it is possible that adverse events were missed. In the trials recruiting participants with burns, information on the types of adverse events appears to have been pre-specified, as several trials reported zero events across both groups for particular adverse events e.g. allergy and renal failure. The International Conference on Harmonization's Guideline for Good Clinical Practice (ICH GCP) defines an adverse event as any untoward medical occurrence in a trial subject who has been administered an intervention, whether related to the intervention or not. With the exception of Jull and colleagues (Jull 2008), no trial reported all adverse events as required by ICH GCP. Therefore the adverse event findings should be interpreted very cautiously as most trials would not have complied with ICH GCP and thus the full adverse event profile of honey in different wounds is unknown.

5. Incidence of infection

The use of honey did not significantly decrease infection rates in other types of wounds. The accurate identification of wound infection is a difficult clinical issue in other types of wounds, particularly chronic wounds. Clinical presentation is an important indicator, but presentation may vary with wound type (Cutting 2005). Therefore trialists should operationalise their definition of infection to ensure that combination of trials in meta-analyses is both feasible and sensible.

Infection is a significant and threatening sequelae in burns. Wound sterility after a burn is maintained by careful attention to asepsis during wound care and the use of preventive agents. Honey dressings appear to increase the likelihood a burn will remain sterile compared with a range of control treatments. However, these findings are based on censored data. The denominator in all the trials was not the number of participants randomised to the treatment group, but the number of participants with a positive wound swab at baseline. Any future trials of honey dressings for burns should report wound sterility for all participants at baseline, operationally define infection and report the incidence of infection.

6. Cost

Only two trials have evaluated the cost of honey as a wound care option. Ingle and colleagues only considered the direct cost of treatment, which will be influenced by purchase price, but the source of the honey was not specified (Ingle 2006). Jull and colleagues conducted a full cost-effectiveness analysis using a health services perspective (Jull 2008). This perspective provides an estimate of the incremental cost-effectiveness ratio from a health service funders vantage point, but will not capture indirect costs such as loss of productivity. Although the base case analysis suggested honey was the cheaper treatment when the full costs were considered, the effectiveness of honey was not established by the trial and thus honey was not the dominant strategy.

7. Quality of life

The use of honey in the treatment of venous ulcers had little or no impact on health-related quality of life when measured using SF-36, EQ5D or the Charing Cross Venous Ulcer Questionnaire in an open label trial (Jull 2008).

8. Limitations of this review

This review is subject to a number of limitations. First, the use of mean time to healing is not the most appropriate method of analysing time to event data. Survival analysis would be more appropriate. However, we were limited to using a common metric provided by the majority of trials, which was mean time to event. Second, we have attempted to contact all authors where the original publication did not provide sufficient data. Where authors did not respond, we have retained the reports in Studies Awaiting Classification, but have not attempted to incorporate their data in the current review. We will continue in our endeavours to contact the authors for future updates. Third, we have retained two analyses where data was combined despite being highly heterogenous (Analysis 4.1 and Analysis 10.2). A priori decisions to pool trials was made on grounds of clinical and methodological similarity.

Our protocol stated that where significant statistical heterogeneity was present, combination of the trials would be by a random effects model and the I^2 used to explore sources of heterogeneity. While the above two analyses both had highly significant heterogeneity and an I^2 of 95%, there were clinical and methodological grounds for combining the trials and to do otherwise would have breached our protocol post hoc (Ioannidis 2008). Fourth, it was not possible to evaluate the overall possibility of publication bias, not all trials reported the same outcome and overall the trials were too heterogenous to combine. Combining similar trials only, and separately, was rejected as power of such analysis would be too low to distinguish real asymmetry from chance asymmetry.

AUTHORS' CONCLUSIONS

Implications for practice

Honey may improve healing times in mild to moderate superficial and partial thickness burns compared with conventional dressings. Honey dressings do not significantly increase rates of healing of venous leg ulcers at 12 weeks when used as an adjuvant to compression. There is insufficient evidence to guide clinical practice in other areas and purchasers should refrain from providing honey dressings for routine use until sufficient evidence of effect is available.

Implications for research

Based on our assessment of the included trials, we make the following recommendations:

1. Trials should be conducted in single conditions, or if multiple aetiologies are recruited, then results should be reported for each aetiology, and there should be sufficient statistical power for each aetiology.

2. Trials should identify a primary outcome and calculate a sample size using that outcome. The assumptions underpinning the calculations should be incorporated into the trial publications.

3. Trials should use true randomisation strategies and report the means of generating the allocation sequence and maintaining allocation concealment to the point of randomisation.

4. Every effort should be made to ensure follow up is as close to 100% as possible.

5. Analysis would use the intention-to-treat principle and include all participants in the denominator. Where participants have been have been lost to follow up, the report should identify how missing data from those participants was managed i.e. regarded as treatment failures, last value carried forward.

6. To ensure that the above elements of trial quality are adequately reported journals should require that trial are reported consistent with the Consolidated Statement on Reporting of Trials (Altman 2001).

7. All trials should be registered with a trials register that meets the WHO criteria and principal investigators should update their contact details on the register.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al Waili 1999

Methods	Single centre, two arm parallel group RCT. Allocation concealment not reported
Participants	50 participants who had had Caesarean sections or hysterectomies. Setting: hospital. Country: United Arab Emirates. Inclusion criteria: acute post-operative bacterial wound infections confirmed by MC & S. Exclusion criteria: not reported.
Interventions	Group 1 (n=26): Yemeni honey Group 2 (n=24): 70% ethanol with povidone iodine Treatment duration: Not reported, dressing changed 12 hourly
Outcomes	Complete healing Group 1: 22/26 (84.6%) Group 2: 12/24 (50.0%)
Notes	All participants received systemic antibiotics.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gethin 2007

Methods	Multi-centre RCT, open label. Allocation by "shuffling" method - sealed opaque envelopes containing allocation code shuffled by independent person and then sequentially numbered. Allocation concealment: central telephone.
Participants	108 participants in two arms. Setting: Hospital and community leg ulcer clinics. Country: Ireland. Inclusion criteria: Aged 18+ years, wound area < 100cm2, greater than 50% of wound covered by slough, able to provide written informed consent. Exclusion criteria: Current wound infection. medicated with antibiotics or steriods for any reason, cavity or malignant lesion.
Interventions	Group 1 (n=54): Monofloral (manuka) honey (Woundcare 18+) + compression Group 2 (n=54): Hydrogel (IntraSite) + compression Treatment duration: 4 weeks, dressing changed with compression

Gethin 2007 (*Continued*)

Outcomes	Complete healing at 12 weeks 1: 24/54 (44.4%) 2: 18/54 (33.3%)
Notes	Primary outcome - change in area of slough at 4 weeks (no significant difference)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ingle 2006

Methods	Single centre, two arm double blind, parallel group RCT; allocation by block randomisation (random permuted blocks of 10), stratified by wound type, HIV status and presence of slough.
Participants	87 participants with shallow wounds. Setting: community. Country: South Africa. Inclusion criteria: Wounds <2cm deep, abrasions between 10 cm2 and 100 cm2 (including donor sites for skin grafting and partial thickness burns). Exclusion criteria: Patients with wounds >100cm2, unwilling to have an HIV test, infected wound, genital or malignant ulcers, wounds on legs, perineum, fingers or toes which would make measurement difficult, systemic disease, chronic alcoholism.
Interventions	Group 1 (n=40): Monofloral (aloe vera) honey applied daily Group 2 (n=42): Hydrogel (IntraSite) applied daily Treatment duration: Until complete healing (abrasion) or wound <3cm2 (shallow wound)
Outcomes	Mean time to healing (all wounds) - supplied by authors Group 1: 16.48 days (SD 8.40) Group 2: 16.88 days (SD 11.31)
Notes	Diet supplemented with zinc sulphate and vitamins A, B and C for all participants. 5 participants excluded from analysis after randomisation

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Not reported

Jull 2008

Methods	Two arm parallel group, multi-centre RCT, allocation by dynamic randomisation (minimisation) stratified by study centre, ulcer size and duration, open label. Allocation concealment: central telephone.
Participants	368 participants with venous or mixed venous/arterial leg ulcers. Setting: community nursing services. Country, New Zealand. Inclusion criteria: Venous ulcer (clinical presentation + ABI>0.8) or mixed venous/arterial ulcer (clinical presentation + ABI>0.7), receiving compression, able to provide informed consent, residing in one of four study regions. Exclusion criteria: Diagnosis of diabetes, rheumatoid arthritis or significant peripheral arterial disease, allergy to honey or calcium alginate, currently using honey treatment.
Interventions	Group 1 (n=187): Monofloral (manuka) honey-impregnated calcium alginate dressing (ApiNate) + compression bandaging system normally available at study centre. Group 2 (n=181): Usual care: choice of any dressing clinically indicated + compression system normally available at study centre. Treatment duration: until healing or 12 weeks, dressing changed with compression
Outcomes	Complete healing at 12 weeks 1: 104/187 (55.6%) 2: 90/181 (49.7%)
Notes	No difference between groups on time to healing, change in ulcer area, incidence of infection or health related quality of life.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Marshall 2005

Methods	Single centre, two arm single blind, parallel group RCT. Allocation by random tables, allocation concealment by central telephone.
Participants	51 participants. Setting: outpatient clinic. Country, England. Inclusion criteria: Patients suitable for toenail removal (unilateral or bilateral, partial or total) with matrix phenolisation. Exclusion criteria: Unable to give informed consent, unable to attend follow up clinics, peripheral vascular disease, peripheral neuropathy.
Interventions	Group 1(n=27): Monofloral (Jarrah) honey dressing daily. Group 2 (n=24): Iodine (Inadine) dressing daily. Treatment duration: until complete epithelialisation of nail bed.

Marshall 2005 (*Continued*)

Outcomes	Mean time to healing Group 1: 33.4 days (SD 15.71) Group 2: 25.3 days (SD 8.70)
Notes	Imbalance in numbers of diabetics in honey group compared to comparison treatment (9 v 4) and in total avulsions (16 v 7) both of which favoured the comparison treatment.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

McIntosh 2006

Methods	Single centre, two arm double blind, parallel group RCT. Allocation by random tables, allocation concealment by central telephone.
Participants	100 participants. Setting: outpatient clinic. Country: England. Inclusion criteria: Patients suitable for toenail surgery (unilateral or bilateral, partial or total) with matrix phenolisation. Exclusion criteria: Aged <16 years, unable to give informed consent, unable to attend follow up clinics, communication barriers, not suitable for toenail surgery (patients with peripheral vascular disease, unstable diabetes, or where local anaesthetic contra-indicated.
Interventions	Group 1 (n=52): Monofloral (manuka) honey-impregnated calcium alginate (ApiNate) twice weekly. Group 2 (n=48): Paraffin-impregnated gauze (Jelonet), twice weekly. Treatment duration: until healed.
Outcomes	Mean time to healing Group 1: 40.30 days (SD 18.21) Group 2: 39.98 days (SD 25.42)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mphande 2007

Methods	Single centre, two arm quasi-randomised controlled trial; allocation by alternate admission
Participants	40 participants with open or infected wounds (chronic osteomyletis n=7, post-surgical n=14, ulcer n=8, trauma n=9, abscess n=2). Setting: Hospital with outpatient follow up Country: Malawi Inclusion criteria: Not reported. Exclusion criteria: Lived too far from hospital for follow up.
Interventions	Group 1 (n=22): Honey-soaked gauze daily with frequency reduced after one week if wound healing progressing. Group 2 (n=18): Sugar covered with gauze dressing with frequency reduced after one week if wound healing progressing. Treatment duration: Not reported Follow up duration: Not reported
Outcomes	Median time to complete healing Group 1: 31.5 days (range 14-98 days) Group 2: 56 days (range 21-133 days)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	Although described as a randomised controlled trial, allocation was by alternate admission.

Subrahmanyam 1991

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered envelopes.
Participants	104 participants with burns over <40% of total body surface area recruited between July 1988 and December 1989 Setting: hospital. Country: India. Inclusion criteria: Superficial burns Exclusion criteria: Not reported
Interventions	Group 1 (n=52): Unprocessed undiluted honey dressings daily. Group 2 (n=52): Silver sulfadiazine impregnated gauze daily. Treatment duration: until healed
Outcomes	Mean time to healing Group 1: 9.4 days (SD 2.3) Group 2: 17.2 days (SD 3.2)

Subrahmanyam 1991 (*Continued*)

Notes	Information on allocation method, allocation concealment, blinding, mean time to healing and standard deviation for mean time to healing provided by author.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 1993a

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered envelopes.
Participants	92 participants with burns over <40% of total body surface area recruited between January 1990 and January 1991 Setting: hospital. Country: India. Inclusion criteria: Treated within 6 hours of injury, partial thickness burns Exclusion criteria: Not reported
Interventions	Group 1 (n=46): Unprocessed undiluted honey-impregnated gauze daily. Group 2 (n=46): Polyurethane film (OpSite) left intact until day, unless evidence of infection, excessive exudate or leakage. Treatment duration: until healed
Outcomes	Mean time to healing Group 1: 10.8 days (SD 3.93) Group 2: 15.3 days (SD 2.98)
Notes	Information on allocation method, allocation concealment, blinding, mean time to healing and standard deviation for mean time to healing provided by author.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 1993b

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered envelopes.
Participants	100 participants with burns or ulcers recruited between January 1989 and January 1990 Setting: hospital. Country: India.

Subrahmanyam 1993b (*Continued*)

	Inclusion criteria: Not reported Exclusion criteria: Not reported
Interventions	Group 1 (n=50): Unprocessed undiluted honey-impregnated gauze daily. Group 2 (n=50): Silver sulfadiazine impregnated gauze daily. Treatment duration: until healed
Outcomes	Mean time to healing Group 1: 9.5 days (SD 6.2) Group 2: 22.5 days (SD 5.2)
Notes	Information on allocation method, allocation concealment, blinding, mean time to healing and standard deviation for mean time to healing provided by author.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 1994

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered envelopes.
Participants	100 participants with partial thickness burns recruited between June 1991 and July 1992. Setting: hospital. Country: India. Inclusion criteria: Treated within 6 hours of injury, Total body surface area burnt <40%. Exclusion criteria: Not reported
Interventions	Group 1 (n=50): Unprocessed undiluted honey-impregnated gauze every second day. Group 2 (n=50): Amniotic membrane left intact until day 8 and then every second day. Treatment duration: until healed
Outcomes	Mean time to healing Group 1: 9.4 days (SD 2.52) Group 2: 17.5 days (SD 6.66)
Notes	Information on allocation method, allocation concealment, blinding, and standard deviation for mean time to healing provided by author.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 1996a

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered sealed envelopes.
Participants	900 participants with partial thickness burns recruited between July 1987 and December 1993. Setting: hospital. Country: India. Inclusion criteria: Total body surface area burnt <40%. Exclusion criteria: Not reported
Interventions	Group 1 (n=450): Pure unprocessed undiluted honey-impregnated gauze every second day. Group 2 (n=450): Soframycin (90 participants), vaseline-impregnated gauze (90 participants), OpSite (90 participants), sterile gauze (90 participants) or left exposed (90 participants). Treatment duration: until healed
Outcomes	Mean time to healing Group 1: 8.8 days (SD 2.1) Group 2: 13.5 days (SD 4.1)
Notes	Information on allocation method, allocation concealment, blinding, and standard deviation for mean time to healing provided by author.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 1996b

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered sealed envelopes.
Participants	100 participants with partial thickness burns recruited between July 1992 and December 1993. Setting: hospital. Country: India. Inclusion criteria: Treated within 6 hours of injury, total body surface area burnt <40%. Exclusion criteria: Not reported
Interventions	Group 1 (n=50): Pure unprocessed undiluted honey every second day. Group 2 (n=50): Potato peel bandages every second day. Treatment duration: until healed
Outcomes	Mean time to healing Group 1: 10.4 days (SD 2.2) Group 2: 16.2 days (SD 2.3)
Notes	Information on allocation method, allocation concealment, blinding, and standard deviation for mean time to healing provided by author.

Subrahmanyam 1996b (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 1996c

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered sealed envelopes.
Participants	84 participants with partial thickness burns recruited between January 1993 and June 1994. Setting: hospital. Country: India. Inclusion criteria: Treated within 6 hours of injury, total body surface area burnt <40%. Exclusion criteria: Not reported
Interventions	Group 1 (n=42): Pure unprocessed undiluted honey every second day. Group 2 (n=42): Pure unprocessed undiluted honey with added vitamins C and E, and polethylene glycol 4000. Treatment duration: until healed
Outcomes	Mean time to healing Group 1: 8.3 days (SD 2.4) Group 2: 6.4 days (SD 3.6)
Notes	Information on allocation method, allocation concealment, blinding and standard deviation for mean time to healing provided by author.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 1998

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered sealed envelopes.
Participants	50 participants with superficial thermal burns recruited between June 1995 and December 1996 Setting: hospital. Country: India. Inclusion criteria: Present within 6 hours of injury, total body surface area burnt <40%. Exclusion criteria: Not reported

Subrahmanyam 1998 (*Continued*)

Interventions	Group 1 (n=25): Pure unprocessed undiluted honey every second day. Group 2 (n=25): Silver sulfadizine impregnated gauze daily Treatment duration: until healed
Outcomes	Mean time to healing Group 1: 4.92 days (SD 3.61) Group 2: 8.22 days (SD 8.31)
Notes	Information on allocation method, allocation concealment, blinding, mean time to healing and standard deviation for mean time to healing provided by author.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 1999

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered sealed envelopes.
Participants	50 participants with mixed depth (partial and full thickness) burns recruited between January 1996 and December 1997. Setting: hospital. Country: India. Inclusion criteria: Aged 10-40 years, haemodynamically stable, no systemic illness or smoke inhalation injury, total body surface area burnt <30%. Exclusion criteria: Not reported
Interventions	Group 1 (n=25): Unprocessed honey every second day, with autologous skin grafting as required. Group 2 (n=25): Tangential excision and skin grafting between days 3 and 6 after admission Treatment duration: Until healed
Outcomes	Mean time to healing Group 1: 32.0 days (SD 8.1) Group 2: 18.4 days (SD 4.2)
Notes	Information on allocation method, allocation concealment, blinding, mean time to healing and standard deviation for mean time to healing provided by author. Three participants died in honey treated group and one in the early tangential excision group.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 2001a

Methods	Single centre, two arm, blinded (investigators and outcome assessors), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered sealed envelopes.
Participants	100 participants with mixed depth (partial and full thickness) burns recruited between June 1998 and December 1999. Setting: hospital. Country: India. Inclusion criteria: Treated within 6 hours of injury, total body surface area burnt <40%. Exclusion criteria: Not reported
Interventions	Group 1 (n=50): Unprocessed undiluted monofloral (Jambhul) honey every second day. Group 2 (n=50): Silver sulfadiazine impregnated gauze every second day. Treatment duration: Until healed.
Outcomes	Mean time to healing Group 1: 15.4 days (SD 3.2) Group 2: 17.2 days (SD 4.3)
Notes	Information on allocation method, allocation concealment, blinding, and standard deviation for mean time to healing provided by author.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Subrahmanyam 2004

Methods	Single centre, two arm, blinded (outcome assessor), parallel group RCT; allocation by "chit method". Allocation concealment: sequentially numbered envelopes.
Participants	30 consecutive males with Fournier's gangrene recruited between April 2001 and May 2003 Setting: hospital. Country: India. Inclusion criteria: Not reported Exclusion criteria: Not reported
Interventions	Group 1 (n=14): Unprocessed undiluted monofloral (Jamun) honey daily. Group 2 (n=16): Edinburgh Solution of Lime (EUSOL) soaked gauze daily. Treatment duration: Until healed
Outcomes	Mean time to healing Group 1: 18.5 days (SD 2.1) Group 2: 26.5 days (SD 3.2)
Notes	Information on allocation method, allocation concealment, blinding, mean time to healing and standard deviation for mean time to healing provided by author.

Subrahmanyam 2004 (*Continued*)

	One participant in the honey-treated group and two participants in the EUSOL-treated group died.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Weheida 1991

Methods	Single centre, two arm parallel group RCT.
Participants	40 participants with grade I or II pressure ulcers. Setting: hospital. Country: Egypt. Inclusion criteria: Orthopaedic patients aged 21 or more years, ulcer > or = 2 cm in diameter, ulcer uninfected, haemoglobin > or = 10g/dL, oral temperature < or = 37.5 degrees, restricted to bed or wheelchair for at least two weeks Exclusion criteria: Debilitatory co-morbidities eg diabetes, cancer.
Interventions	Group 1 (n=20): Honey dressing daily. Group 2 (n=20): Saline soaked gauze daily. Treatment duration: 10 days. Follow up duration: three months
Outcomes	Mean time to healing Group 1: 8.20 days (SD 1.44) Group 2: 9.93 days (SD 0.27)
Notes	Grade I ulcer defined as moist irregular partial thickness ulcer confined to epidermis and dermis. Grade II ulcer defined as full thickness ulcer descending into subcutaneous tissue

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Ahmed 2003	Not a randomised or controlled clinical trial
Al Waili 2003	Participants did not have wounds; trial of honey mixture for atopic dermatitis or psoriasis.
Al Waili 2004a	Animal model study
Al Waili 2004b	Animal model study
Al Waili 2004c	Not a randomised or quasi-randomised controlled trial
Al Waili 2005	Not a randomised or quasi-randomised controlled trial
Albietz 2006	Participants did not have wounds
Berchtold 1992	Did not use honey
Biswal 2003	Participants did not have wounds; trial of honey for radiation-induced mucositis.
Bose 1982	Not a randomised or quasi-randomised controlled trial
Calderon Espina 1989	Could not be obtained for assessment
Chokotho 2005	No information on healing. No response to attempts to contact investigator.
Dunford 2004	Not a randomised or quasi-randomised controlled trial
Gad 1988	No information on healing. No response to attempts to contact investigator.
Gethin 2005	Not a randomised or quasi-randomised controlled trial
Johnson 2005	Participants did not have wounds; trial of honey to prevent catheter associated infections in haemodialysis patients
Lusby 2002	Not a randomised or quasi-randomised controlled trial
Marshall 2002	Not a randomised or quasi-randomised controlled trial
Mashood 2006	No information on healing. No response to attempts to contact investigator.
Misirligou 2003	Not a randomised or quasi-randomised controlled trial
Molan 2002	Not a randomised or quasi-randomised controlled trial
Molan 2006	Not a randomised or quasi-randomised controlled trial
Muller 1985	Did not use honey

(*Continued*)

Mwipatayi 2004	Not a randomised or controlled clinical trial
Nagane 2004	Not a randomised or quasi-randomised controlled trial
Okeniyi 2005	Wounds randomised, not participants. 32 participants had 43 wounds and individual participants may have been treated by both honey and the comparator (EUSOL). Healing rate provided by wound not by participant.
Oluwatosin 2000	No information on healing.
Quadri 1998	Participants did not have wounds; trial of honey to prevent catheter associated infections in haemodialysis patients. Duplicate study
Quadri 1999	Participants did not have wounds; trial of honey to prevent catheter associated infections in haemodialysis patients
Rivero Varona 1999	Could not be obtained
Robson 2002	Not a randomised or controlled clinical trial
Schumacher 2004	Not a randomised or quasi-randomised controlled trial
Subrahmanyam 1993	Not a randomised or quasi-randomised controlled trial
Subrahmanyam 2001b	Animal model study
Subrahmanyam 2003	No data on healing - biochemical data only
Thurnheer 1983	Not a randomised or quasi-randomised controlled trial
Tostes 1994	Not a randomised or quasi-randomised controlled trial
Visscher 1996	Not a randomised or quasi-randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bangroo 2005

Methods	Single centre, two arm, parallel group RCT; method of allocation not reported beyond being random; allocation concealment not reported.
Participants	64 participants with superficial thermal burns. Setting: Hospital. Country: India. Inclusion criteria: Aged < 12 years, total body surface area burnt < 50% with 2 or more months life expectancy.

Bangroo 2005 (*Continued*)

	Exclusion criteria: Not reported.
Interventions	Group 1 (n=32): Twice daily dressing with honey. Group 2 (n=32): Twice daily dressing with silver sulfadiazine. Treatment duration: Until healing Follow up duration: Not reported
Outcomes	Number healed: Group 1: 10 days (n=26), 2 or more weeks (n=6). Group 2: 3 or more weeks (n=19)
Notes	Recruitment period January 2001 to December 2003. Outcome data inadeqautly reported. Additional outcome information being sought. No response from authors to date.

Gunes 2007

Methods	Single centre, two arm, open label, parallel group RCT; allocation by computer-generated randomisation stratified for age, sex, and ulcer surface area; allocation concealment not reported.
Participants	27 participants with stage 2 or stage 3 pressure ulcers. Setting: Hospital. Country: Turkey. Inclusion criteria: Aged 18 or more years with 2 or more months life expectancy. Exclusion criteria: Not reported.
Interventions	Group 1 (n=15): Unprocessed honey daily or when the wound was contaminated by urine or faeces. Group 2 (n=12): ethoxydiaminoacridine and nitrofurazone dressing after cleaning with ethoxydiaminoacridine (0.1%). Dressing changed daily or when the wound was contaminated by urine or faeces. Treatment duration: 5 weeks Follow up duration: 5 weeks
Outcomes	Proportion of ulcers healed at 5 weeks Group 1: 5 (20%) Group 2: 0 (0%)
Notes	One participant in the control group died and was excluded from the analysis. Outcome reported by ulcer, not by participant. Additional outcome information by participant being sought. No response from authors to date.

Memon 2005

Methods	Single centre, two arm, parallel group RCT; method of allocation not reported beyond being random; allocation concealment not reported.
Participants	80 participants with superficial dermal, mid-dermal or deep dermal burns. Setting: Hospital. Country: Pakistan. Inclusion criteria: Aged 4 to 62 years, total body surface area burnt 10% to 40%.

Memon 2005 (*Continued*)

	Exclusion criteria: Patients with chemical or electrical burns, full thickness burns or burns involving more than 40% of body surface area.
Interventions	Group 1 (n=40): Natural unprocessed honey-gauze dressings every alternate day. Group 2 (n=40): Silver sulfadiazine-gauze dressings every alternate day. Treatment duration: Not reported. Follow up duration: Until healed.
Outcomes	Number healed: Group 1: By day 16 (n=20), by day 26 (n=12), by day 30 (n=8). Mean 15.3 days Group 2: By day 20 (n=16), by day 36 (n=18), by day 46 (n=6). Mean 20 days
Notes	Recruitment period January 2002 to January 2003. Outcome data inadequately reported. Additional outcome information (at least standard deviation) being sought. No response from authors to date.

Rucigaj 2006

Methods	Single centre, two arm, parallel group RCT; method of allocation not reported beyond being random; allocation concealment by sealed numbered envelopes.
Participants	60 participants with venous ulcers. Setting: Hospital. Country: Slovenia. Inclusion criteria: Aged 4 to 62 years, total body surface area burnt 10% to 40%. Exclusion criteria: Severe disease (cardiac decompensation, rheumatoid arthritis, uncontrollable hypertension, insulin dependent diabetes, carcinoma) and immobility.
Interventions	Group 1 (n=30): Honey dressings (Melmax) and long stretch compression bandages. Group 2 (n=30): Silver charcoal dressings and long stretch compression bandages. Treatment duration: Mean group 1 was 44 days; mean group 2 was 42 days. Follow up duration: Eight weeks.
Outcomes	Not reported.
Notes	Conference abstract. Author unwilling to provide additional information until study published. Publication date not provided.

DATA AND ANALYSES

Comparison 1. Minor acute wounds

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to healing	3	213	Mean Difference (IV, Fixed, 95% CI)	1.55 [-1.91, 5.00]

Comparison 2. Partial thickness burns - honey vs conventional dressings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to healing (days)	2	992	Mean Difference (IV, Fixed, 95% CI)	-4.68 [-5.09, -4.28]

Comparison 3. Burns - honey vs early excision

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Early excision	1	50	Mean Difference (IV, Fixed, 95% CI)	13.60 [10.02, 17.18]

Comparison 4. Burns - honey vs silver sulfadiazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to healing (days)	3	254	Mean Difference (IV, Random, 95% CI)	-4.37 [-8.94, 0.19]

Comparison 5. Burns - honey vs unconventional dressings

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to healing (days)	3		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 6. Mixed acute and chronic wounds

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to healing (days)	1	100	Mean Difference (IV, Fixed, 95% CI)	-13.0 [-15.24, -10.76]

Comparison 7. Venous leg ulcers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing	2	476	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.96, 1.38]

Comparison 8. Chronic wounds

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to healing (days)	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Infected postoperative wounds	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 Pressure ulcers	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Fournier's gangrene	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 9. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All adverse events	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Minor acute wounds	1	82	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.77, 2.45]
1.2 Burns	6	1310	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.29, 2.51]
1.3 Infected post-operative wounds	1	50	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.11, 0.82]
1.4 Venous leg ulcers	2	476	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.05, 1.55]
1.5 Fournier's gangrene	1	30	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.06, 5.65]

Comparison 10. Incidence of infection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of clinically diagnosed infection	4	627	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.50, 1.04]
2 Burns patients with positive swab cultures at admission rendered sterile after 7 days treatment	6	444	Risk Ratio (M-H, Random, 95% CI)	3.95 [1.36, 11.44]

Analysis 1.1. Comparison 1 Minor acute wounds, Outcome 1 Time to healing.

Review: Honey as a topical treatment for wounds

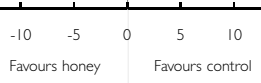
Comparison: 1 Minor acute wounds

Outcome: 1 Time to healing

Study or subgroup	Honey N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ingle 2006	40	16.5 (8.4)	42	16.9 (11.3)		64.8 %	-0.40 [-4.70, 3.90]
Marshall 2005	23	33.4 (15.7)	21	25.3 (8.7)		21.7 %	8.10 [0.68, 15.52]
McIntosh 2006	47	40.3 (18.21)	40	39.98 (25.42)		13.4 %	0.32 [-9.12, 9.76]
Total (95% CI)	**110**		**103**			**100.0 %**	**1.55 [-1.91, 5.00]**

Heterogeneity: Chi² = 3.85, df = 2 (P = 0.15); I² =48%

Test for overall effect: Z = 0.88 (P = 0.38)



Analysis 2.1. Comparison 2 Partial thickness burns - honey vs conventional dressings, Outcome 1 Time to healing (days).

Review: Honey as a topical treatment for wounds

Comparison: 2 Partial thickness burns - honey vs conventional dressings

Outcome: 1 Time to healing (days)

Study or subgroup	Honey N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subrahmanyam 1993a	46	10.8 (3.93)	46	15.3 (2.98)		8.2 %	-4.50 [-5.93, -3.07]
Subrahmanyam 1996a	450	8.8 (2.1)	450	13.5 (4.1)		91.8 %	-4.70 [-5.13, -4.27]
Total (95% CI)	**496**		**496**			**100.0 %**	**-4.68 [-5.09, -4.28]**

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0%

Test for overall effect: Z = 22.51 (P < 0.00001)

Analysis 3.1. Comparison 3 Burns - honey vs early excision, Outcome 1 Early excision.

Review: Honey as a topical treatment for wounds

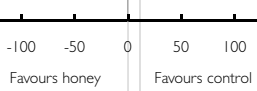
Comparison: 3 Burns - honey vs early excision

Outcome: 1 Early excision

Study or subgroup	Honey N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subrahmanyam 1999	25	32 (8.1)	25	18.4 (4.2)		100.0 %	13.60 [10.02, 17.18]
Total (95% CI)	**25**		**25**			**100.0 %**	**13.60 [10.02, 17.18]**

Heterogeneity: not applicable

Test for overall effect: Z = 7.45 (P < 0.00001)



Analysis 4.1. Comparison 4 Burns - honey vs silver sulfadiazine, Outcome 1 Time to healing (days).

Review: Honey as a topical treatment for wounds

Comparison: 4 Burns - honey vs silver sulfadiazine

Outcome: 1 Time to healing (days)

Study or subgroup	Honey N	Mean(SD)	Silver sulfadiazine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subrahmanyam 1991	52	9.4 (2.3)	52	17.2 (3.2)		35.5 %	-7.80 [-8.87, -6.73]
Subrahmanyam 1998	25	4.92 (3.61)	25	8.22 (8.31)		29.7 %	-3.30 [-6.85, 0.25]
Subrahmanyam 2001a	50	15.4 (3.2)	50	17.2 (4.3)		34.8 %	-1.80 [-3.29, -0.31]
Total (95% CI)	**127**		**127**			**100.0 %**	**-4.37 [-8.94, 0.19]**

Heterogeneity: Tau^2 = 14.97; Chi^2 = 42.95, df = 2 (P<0.00001); I^2 =95%

Test for overall effect: Z = 1.88 (P = 0.060)

Analysis 5.1. Comparison 5 Burns - honey vs unconventional dressings, Outcome 1 Time to healing (days).

Review: Honey as a topical treatment for wounds

Comparison: 5 Burns - honey vs unconventional dressings

Outcome: 1 Time to healing (days)

Study or subgroup	Honey N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Subrahmanyam 1994	40	9.4 (2.52)	24	7.5 (6.66)		1.90 [-0.88, 4.68]
Subrahmanyam 1996b	50	10.4 (2.2)	50	16.2 (2.3)		-5.80 [-6.68, -4.92]
Subrahmanyam 1996c	42	8.3 (2.4)	42	6.4 (3.61)		1.90 [0.59, 3.21]

Analysis 6.1. Comparison 6 Mixed acute and chronic wounds, Outcome 1 Time to healing (days).

Review: Honey as a topical treatment for wounds

Comparison: 6 Mixed acute and chronic wounds

Outcome: 1 Time to healing (days)

Study or subgroup	Honey N	Mean(SD)	Silver sulfadiazine N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subrahmanyam 1993b	50	9.5 (6.2)	50	22.5 (5.2)		100.0 %	-13.00 [-15.24, -10.76]
Total (95% CI)	**50**		**50**			**100.0 %**	**-13.00 [-15.24, -10.76]**

Heterogeneity: not applicable

Test for overall effect: Z = 11.36 (P < 0.00001)

Analysis 7.1. Comparison 7 Venous leg ulcers, Outcome 1 Complete healing.

Review: Honey as a topical treatment for wounds

Comparison: 7 Venous leg ulcers

Outcome: 1 Complete healing

Study or subgroup	Honey n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gethin 2007	24/54	18/54		16.4 %	1.33 [0.82, 2.16]
Jull 2008	104/187	90/181		83.6 %	1.12 [0.92, 1.36]
Total (95% CI)	**241**	**235**		**100.0 %**	**1.15 [0.96, 1.38]**

Total events: 128 (Honey), 108 (Control)

Heterogeneity: Chi^2 = 0.45, df = 1 (P = 0.50); I^2 =0.0%

Test for overall effect: Z = 1.55 (P = 0.12)

Analysis 8.1. Comparison 8 Chronic wounds, Outcome 1 Time to healing (days).

Review: Honey as a topical treatment for wounds

Comparison: 8 Chronic wounds

Outcome: 1 Time to healing (days)

Study or subgroup	Honey N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Infected postoperative wounds						
Al Waili 1999	26	10.73 (2.5)	24	22.04 (7.33)		-11.31 [-14.40, -8.22]
2 Pressure ulcers						
Weheida 1991	20	8.2 (1.44)	20	9.93 (0.27)		-1.73 [-2.37, -1.09]
3 Fournier's gangrene						
Subrahmanyam 2004	14	18.5 (2.1)	16	26.5 (3.2)		-8.00 [-9.92, -6.08]

Analysis 9.1. Comparison 9 Adverse events, Outcome 1 All adverse events.

Review: Honey as a topical treatment for wounds

Comparison: 9 Adverse events

Outcome: 1 All adverse events

Study or subgroup	Honey n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Minor acute wounds					
Ingle 2006	17/40	13/42		100.0 %	1.37 [0.77, 2.45]
Subtotal (95% CI)	**40**	**42**		**100.0 %**	**1.37 [0.77, 2.45]**
Total events: 17 (Honey), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.08 (P = 0.28)					
2 Burns					
Subrahmanyam 1991	20/52	9/52		26.1 %	2.22 [1.12, 4.41]
Subrahmanyam 1993a	4/46	3/46		16.4 %	1.33 [0.32, 5.63]
Subrahmanyam 1994	1/40	1/24		7.3 %	0.60 [0.04, 9.16]
Subrahmanyam 1996a	33/450	99/450		29.7 %	0.33 [0.23, 0.48]

(*Continued* . . .)

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Study or subgroup	Honey n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subrahmanyam 1999	3/25	1/25		10.0 %	3.00 [0.33, 26.92]
Subrahmanyam 2001a	1/50	5/50		10.5 %	0.20 [0.02, 1.65]
Subtotal (95% CI)	**663**	**647**		**100.0 %**	**0.85 [0.29, 2.51]**
Total events: 62 (Honey), 118 (Control)					
Heterogeneity: Tau^2 = 1.20; Chi^2 = 27.57, df = 5 (P = 0.00004); I^2 =82%					
Test for overall effect: Z = 0.29 (P = 0.78)					
3 Infected post-operative wounds					
Al Waili 1999	4/26	12/24		100.0 %	0.31 [0.11, 0.82]
Subtotal (95% CI)	**26**	**24**		**100.0 %**	**0.31 [0.11, 0.82]**
Total events: 4 (Honey), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.34 (P = 0.019)					
4 Venous leg ulcers					
Gethin 2007	0/54	1/54		15.5 %	0.33 [0.01, 8.01]
Jull 2008	111/187	84/181		84.5 %	1.28 [1.05, 1.56]
Subtotal (95% CI)	**241**	**235**		**100.0 %**	**1.27 [1.05, 1.55]**
Total events: 111 (Honey), 85 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.69, df = 1 (P = 0.41); I^2 =0.0%					
Test for overall effect: Z = 2.41 (P = 0.016)					
5 Fournier's gangrene					
Subrahmanyam 2004	1/14	2/16		100.0 %	0.57 [0.06, 5.65]
Subtotal (95% CI)	**14**	**16**		**100.0 %**	**0.57 [0.06, 5.65]**
Total events: 1 (Honey), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					

Analysis 10.1. Comparison 10 Incidence of infection, Outcome 1 Incidence of clinically diagnosed infection.

Review: Honey as a topical treatment for wounds

Comparison: 10 Incidence of infection

Outcome: 1 Incidence of clinically diagnosed infection

Study or subgroup	Honey n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gethin 2007	6/54	12/54		21.9 %	0.50 [0.20, 1.24]
Jull 2008	32/187	40/181		74.3 %	0.77 [0.51, 1.18]
Marshall 2005	1/27	0/24		1.0 %	2.68 [0.11, 62.81]
McIntosh 2006	0/52	1/48		2.8 %	0.31 [0.01, 7.39]
Total (95% CI)	**320**	**307**		**100.0 %**	**0.72 [0.50, 1.04]**

Total events: 39 (Honey), 53 (Control)

Heterogeneity: Chi^2 = 1.68, df = 3 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 1.74 (P = 0.082)

Analysis 10.2. Comparison 10 Incidence of infection, Outcome 2 Burns patients with positive swab cultures at admission rendered sterile after 7 days treatment.

Review: Honey as a topical treatment for wounds

Comparison: 10 Incidence of infection

Outcome: 2 Burns patients with positive swab cultures at admission rendered sterile after 7 days treatment

Study or subgroup	Honey n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subrahmanyam 1991	39/43	3/41		17.8 %	12.40 [4.15, 37.00]
Subrahmanyam 1993a	38/46	29/46		21.7 %	1.31 [1.01, 1.70]
Subrahmanyam 1994	24/28	13/24		21.3 %	1.58 [1.06, 2.36]
Subrahmanyam 1996b	38/40	0/42		8.9 %	80.76 [5.13, 1271.79]
Subrahmanyam 1998	17/23	19/25		21.5 %	0.97 [0.70, 1.35]
Subrahmanyam 2001a	40/44	0/42		8.9 %	77.40 [4.91, 1219.69]
Total (95% CI)	**224**	**220**		**100.0 %**	**3.95 [1.36, 11.44]**

Total events: 196 (Honey), 64 (Control)

Heterogeneity: Tau^2 = 1.34; Chi^2 = 111.29, df = 5 (P<0.00001); I^2 =96%

Test for overall effect: Z = 2.53 (P = 0.011)

WHAT'S NEW

Last assessed as up-to-date: 26 May 2008.

11 August 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 4, 2008

13 May 2009	Amended	Contact details updated.
28 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Andrew Jull:

Designed and coordinated the review. Extracted data and undertook quality assessment. Analysed or interpreted data and performed statistical analysis. Wrote to study author/experts/companies. Completed first draft of the review and approved final review prior to submission. Guarantor of the review.

Anthony Rodgers:

Designed the review and performed part of writing or editing of the review. Made an intellectual contribution to the review. Approved final review prior to submission.

Natalie Walker:

Designed the review and checked quality of data extraction. Checked quality assessment and the quality of statistical analysis. Performed part of writing or editing of the review. Approved final review prior to submission.

Contributions of editorial base:

Nicky Cullum:
Edited the review, advised on methodology, interpretation and review content.
Approved the final review prior to submission.
Sally Bell-Syer:
Coordinated the editorial process.
Advised on methodology, interpretation and content.
Edited and copy edited the review.
Ruth Foxlee:
Designed the search strategy and edited the search methods section.

DECLARATIONS OF INTEREST

Andrew Jull, Natalie Walker and Anthony Rodgers were investigators in the Honey as Adjuvant Leg ulcer Treatment (HALT) trial (ISRCTN 06161544), one of the trials included in this review. The Clinical Trials Research Unit, which employs Andrew Jull, Natalie Walker and Antony Rodgers received a small unconditional cash contribution from a manufacturer of honey dressings for the conduct of the HALT trial.

SOURCES OF SUPPORT

Internal sources

- Senior Health Research Scholarship, University of Auckland, New Zealand.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Two trials that compared active interventions allocated wounds to the interventions rather than participants (Oluwatosin 2000; Okeniyi 2005). The participants had multiple wounds in many cases and some participants would have received both interventions. The data in these trials was presented by wound and thus could not be combined (if possible) with trials where data was presented by participant. Such a scenario was not foreseen in the protocol where it was assumed data would be presented by participant. Presenting data by wound rather than by participant inappropriately increases the power of a study. These trials were excluded from this review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Honey; *Wound Healing; Burns [therapy]; Leg Ulcer [therapy]; Pressure Ulcer [therapy]; Randomized Controlled Trials as Topic; Surgical Wound Infection [therapy]; Varicose Ulcer [therapy]; Wounds and Injuries [*therapy]

MeSH check words

Humans