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Honey and Wound Healing

An Overview

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Contents

Abstract

Honey has been used to treat wounds throughout the ages. This practice was rooted primarily in tradition and folklore until the late 19th century, when investigators began to characterize its biologic and clinical effects. This overview explores both historic and current insights into honey in its role in wound care. We describe the proposed antimicrobial, immunomodulatory, and physiologic mechanisms of action, and review the clinical evidence of the efficacy of honey in a variety of acute and chronic wound types. We also address additional considerations of safety, quality, and the cost effectiveness of medical-grade honeys. In summary, there is biologic evidence to support the use of honey in modern wound care, and the clinical evidence to date also suggests a benefit. However, further large, well designed, clinical trials are needed to confirm its therapeutic effects.

1. History and Background

Throughout history, the medicinal uses of honey have been well documented. The ancient Egyptians deemed bees to be sacred and used honey in a variety of remedies such as in surgical dressings to facilitate wound healing.[1] Judeo-Christian-Islamic traditions alike have revered honey as a gift from God and held the belief that honey invigorates both the mind and

soul. The Islamic Qur'an dedicates an entire chapter to the work of bees in the creation of honey,[2] and a Hadith, which is a saying of the Prophet Mohammed, acknowledges it as a "remedy for every illness."[3] Similarly, the ancient Greek physician Hippocrates favored the use of honey-based concoctions for fever, pain, and wound management.[4] Referring to honey, he wrote, "It causes heat, cleans sores and ulcers, softens hard ulcers of the lips, and heals carbuncles and running sores."[5] In the Far East, the Chinese used honey in various traditional remedies as documented in Li Shizhen's famed 16th century medical text, *Compendium of Materia Medica*.[6] Across the world in England, medieval physician Gilbertus Anglicus also incorporated honey into recipes in his own medical masterpiece, *Compendium Medicinae*.[7] In more recent history, Russian and Chinese soldiers in World War I commonly used honey to care for their battle wounds.[8]

It was not until the late 19th century that honey as a folk remedy became subject to scientific inquiry. Its antimicrobial properties were initially documented in 1892 by a Dutch scientist, B.A. Van Ketel,[9] and its efficacy in the management of infected wounds was first noted in Europe and the US in the mid-20th century.[10-12] However, with the advent of contemporary antibacterial agents in the 1920s, honey as a wound healing agent soon fell out of favor. It was not until the 1980s to the present time that investigators renewed their interest in these aspects of honey. One likely reason for this resurgence is the growing popularity of wound healing as a research discipline. Additionally, modern advances in clinical research methods and molecular biologic techniques have allowed for the wound-healing properties of honey to be revealed in greater detail. This review outlines historic and current insights into honey in its role in wound management.

MEDLINE (1947 to May 2010), Cochrane Database of Systematic Reviews (2005 to May 2010), and Google Scholar were searched using various combinations of the following terms: 'wound,' 'wound healing,' and 'honey.' The titles and abstracts from the initial literature search were appraised to identify articles for full review, and the references sections from each article were searched manually for relevant publications. We paid particular attention to articles describing the mechanism of action of honey or reporting the effects of honey on wound healing *in vivo*.

2. Honey Products

Numerous preparations of honey have been previously studied and categorized according to their floral source. Among these are honeys derived from the tree genus *Leptospermum*, which is native to Australia and New Zealand.[13] Common names of *Leptospermum*-derived honeys include manuka, jelly bush, goo bush, and tea tree. These particular species have been targeted for their bactericidal properties and marketed in the US as medical-grade honeys (MGHs) under various trade names and formulations (table I). Many of these MGHs are available as single-use dressings that contain honey in addition to complementary media such as sodium alginate or cross-linked sodium polyacrylic acid, which aid in moisturization and debridement of the wound. While *Leptospermum* honeys are perhaps the most widely studied, other less well characterized, local-regional honeys have been noted in the literature, which has presented a challenge in determining which features of honey are universal or unique.

3. Mechanism of Action

3.1 Antimicrobial Agent

The best characterized role of honey in wound healing is in the prevention and limitation of bacterial infection, thereby reducing the bioburden of the wound. Originally, this role was believed to derive from biochemical properties relating to peroxide generation via intrinsic glucose oxidase activity.[20] More recent research has suggested an ability to limit infection even in the presence of catalase,[21] promoting the theory of additional non-peroxide-mediated mechanisms. An electron microscopic analysis by Henriques et al.[22] revealed that manuka honey-treated *Staphylococcus aureus* colonies showed arrest at cell division, suggesting an ability of honey to impair bacterial cell cycle progression. Mechano-physical properties of honey are also believed to contribute to antimicrobial activity by hampering the development of biofilms[23,24] and limiting the amount of wound edema through its hygroscopic properties.[13] Among the specific microorganisms, honey has been shown to have activity against *Escherichia coli*, *Pseudomonas aeruginosa*,[21] *S. aureus*,[22] *Acinetobacter*, and *Stenotrophomonas*.[25] This activity has been shown to be directed against even antibacterial-resistant strains such as methicillin-resistant *S. aureus*[26] and vancomycin-resistant *Enterococcus*.[27] Interestingly, antiviral properties have also been attributed to honey. *In vitro*, anti-rubella activity has been observed,[28] and in humans it has been found to reduce the duration, crusting, and pain of labial and genital herpetic eruptions.[29] The exact manner in which honey interacts directly with microorganisms remains unclear.

3.2 Immunologic Modulator

A newer role for honey in wound healing involves immunomodulation. Seminal work by Tonks et al.[30] has revealed

Table I. US FDA-approved medical-grade honey products listed in chronologic order of FDA clearance (most recent listed first)[14-19]

Product (manufacturer; website)	Description	FDA-approved indications
Elasto-Gel™ manuka honey wound dressing (Southwest Technologies, Inc., N. Kansas City, MO, USA; http://www.elastogel.com) [product not yet available]	Sterile, single-use, cross-linked, polyacrylamide polymer dressing containing active manuka honey, glycerin, and water	Full- and partial-thickness wounds, pressure ulcers, venous stasis ulcers, diabetic ulcers, partial-thickness burns, acute wounds, abrasions, traumatic wounds healing by secondary intention, donor sites and other surface wounds, and surgical wounds
OTC API-MED, Medihoney® Primary, and Medihoney® 100% honey dressings with active manuka honey (Derma Sciences, Inc., Princeton, NJ, USA; http://www.dermasciences.com)	Three over-the-counter preparations of Medihoney®	Minor abrasions, lacerations, minor cuts, minor scalds and burns, diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), first- and second-degree partial-thickness burns, donor sites, and traumatic and surgical wounds
Medihoney® dressings with active manuka honey (Derma Sciences, Inc., Princeton, NJ, USA; http://www.dermasciences.com)	Sterile 100% w/w active manuka honey dispensed from a tube	Diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), first- and second-degree partial-thickness burns, donor sites, and traumatic and surgical wounds
Medihoney® Primary dressing with active manuka honey (Derma Sciences, Inc., Princeton, NJ, USA; http://www.dermasciences.com)	Sterile, single-use, wound care dressings containing 80% w/w active manuka honey and 20% sodium alginate	Minor abrasions, lacerations, minor cuts, minor scalds and burns, diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), first- and second-degree partial-thickness burns, donor sites, and traumatic and surgical wounds
L-Mesitran® Hydro, L-Mesitran® Border, L-Mesitran® Net, L-Mesitran® Active, and L-Mesitran® Soft[a] (Theo Manufacturing BV, Maastricht, Netherlands; http://www.l-mesitran.com)	**L-Mesitran® Hydro, L-Mesitran® Border, L-Mesitran® Active:** hydro-active, hydrogel-coated, polyurethane wound dressings containing honey **L-Mesitran® Net:** hydro-active, hydrogel-coated wound dressings containing honey on an open weave polyester net **L-Mesitran® Soft:** wound care gel containing honey, lanolin, polyethylene glycol, and vitamins A and E	**L-Mesitran® Hydro, L-Mesitran® Border:** bruises, cuts, bedsores, first- and second-degree burns and other traumatic wounds, venous, arterial, and diabetic ulcers, donor sites, and postoperative wounds **L-Mesitran® Active:** superficial cuts, lacerations, and abrasions, other small wounds, and minor burns **L-Mesitran® Net:** bruises, skin tears, and cuts, other external traumatic wounds, pressure ulcers, first- and second-degree burns, venous, arterial, and diabetic ulcers, donor sites, and postoperative wounds **L-Mesitran® Soft:** First- and second-degree burn wounds, oncologic wounds, decubitus wounds, varicose ulcers, postoperative wounds, diabetic foot ulcers, infected and necrotic wounds, other open wounds, foot and vaginal infections, preventive antibacterial treatment, grazes, bites and cuts
Derma Sciences API-MED active manuka honey absorbent dressing (Derma Sciences, Inc., Princeton, NJ, USA; http://www.dermasciences.com)	Sterile, single-use, wound care dressings containing 95% w/w active manuka honey and 5% sodium alginate	Minor abrasions, lacerations, minor cuts, minor scalds and burns, diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), first- and second-degree partial-thickness burns, donor sites, and traumatic and surgical wounds

a L-Mesitran® Soft has not yet been FDA approved.

w/w = weight in weight.

that manuka honey upregulates tumor necrosis factor-α, interleukin-1β, interleukin-6, and prostaglandin E_2 production from monocytes, the macrophage precursor cells. Macrophages, in turn, have numerous roles in wound healing, from the removal of debris to the formation of new blood vessels. This cytokine release has been proposed to be mediated by a

unique 5.8 kDa component in manuka honey that engages monocyte toll-like receptor 4,[31] although a subsequent report suggests that this proinflammatory activity is attributable to intrinsic endotoxins that can be isolated from ultra-filtrates of honey.[32] While this finding may suggest that honey extends the inflammatory phase of wound healing, it is believed that this immunomodulation further promotes the antimicrobial activity of honey. In addition, a recent study by Beretta et al.[33] demonstrated radical scavenging activity in honey. This finding supported earlier research that honey is able to reduce the release of reactive oxygen intermediates.[34,35] It should also be noted that recent *in vitro* studies have demonstrated limited cytotoxicity of honey to human keratinocytes and dermal fibroblasts when compared with conventional silver dressings.[36] Further research is required to identify the precise role of honey in the immunologic cascade, particularly to define modulation of transforming growth factor-β and peroxisome proliferator-activated receptor-γ, mediators that are at the center of current immunologic wound-healing research.

3.3 Physiologic Mediator

A review of the literature shows that honey improves the well defined physiology of wound healing. The three phases of wound healing are classically defined as inflammatory, proliferative, and remodeling.[37] The richest amount of data demonstrates the ability of honey to modulate the inflammatory phase. Initially, it was shown that honey had anti-inflammatory properties in guinea pigs.[38] While several mechanisms have been suggested to account for these properties as discussed in section 3.2, it is likely that an orchestra of events contributes simultaneously to limit inflammation and promote wound healing[39] (figure 1). Additionally, it has been shown that honey improves tissue granulation and epithelialization in the proliferative phase while decreasing total wound-healing time.[40] Subrahmanyam et al.[41] have reported decreased scarring and contractures with the use of honey on burn patients, suggesting enhancement of the remodeling phase. These effects can be attributed in part to upregulation of matrix

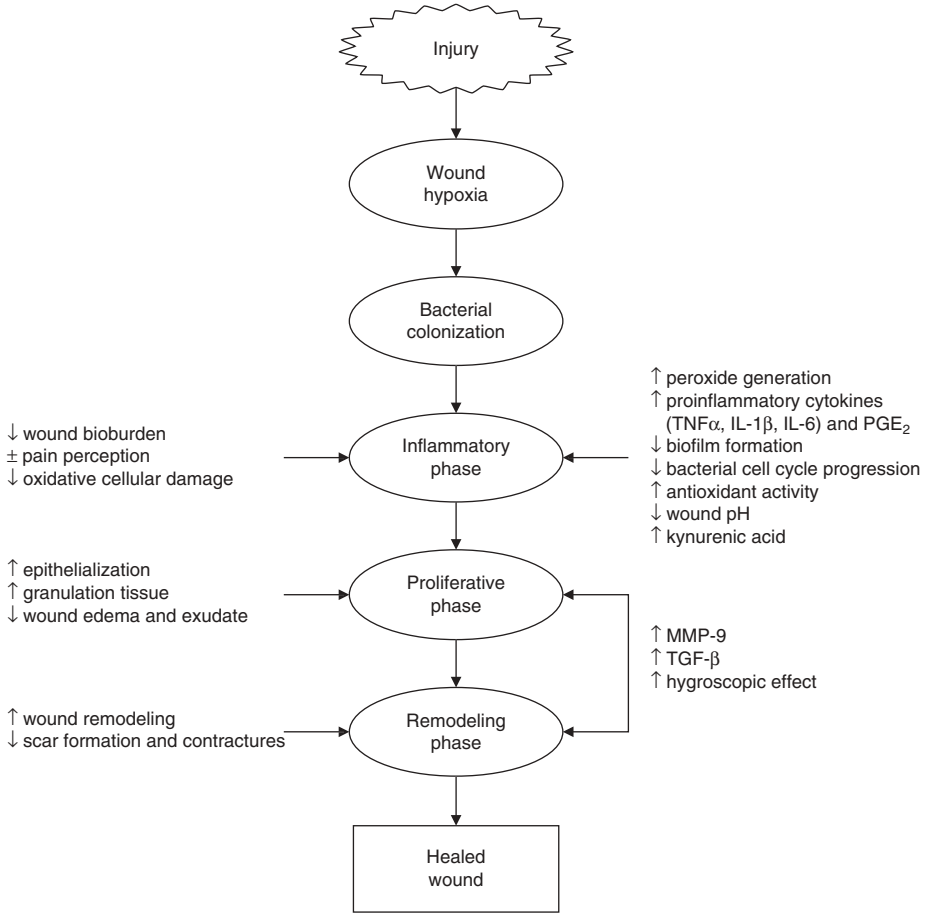

Fig. 1. Modulatory effects of honey on classical phases of wound healing. Clinical effects (left) and proposed mechanisms (right) are listed. **IL** = interleukin; **MMP-9** = matrix metalloproteinase-9; **PGE_2** = prostaglandin E_2; **TGF-β** = transforming growth factor-β; **TNFα** = tumor necrosis factor-α.

metalloproteinase-9 and transforming growth factor-β in epidermal keratinocytes, which are involved in extracellular matrix reorganization and fibroblast-mediated collagen deposition, respectively.[42]

Other roles of honey in the physiology of the wound have been proposed. It has been shown, for instance, that manuka honey dressings lower the alkaline pH of the chronic wound bed, which is associated with superior healing outcomes.[43,44] Neurophysiologically, certain honeys (such as chestnut honey) exhibit antinociceptive properties, which are thought to be mediated by its anti-inflammatory effects as well as antagonism of NMDA at peripheral GABA receptors by kynurenic acid, an endogenous tryptophan metabolite.[33] Clinically, however, *Leptospermum* honeys have been associated with both pain relief and heightened pain.[13,45] While the latter has been attributed to the relative acidity of honey, the final sensory input is likely regulated by the balance between these opposing properties. Overall, further studies are needed in larger subsets of patients, which may confirm that honey enhances the various stages of wound healing.

4. Clinical Uses of Honey

While honey has been suggested as a remedy for a variety of medical conditions, the US FDA has approved MGHs for a specific set of indications (table I). The scope of these indications is limited to the management of wounds, ranging from minor abrasions and ulcers to full-thickness burns and surgical wounds. The clinical use of honey in wound healing was initially documented in several case series beginning in the mid-20th century. In 1951, Seymour and West[46] observed the antiseptic effect of honey in refractory cervical ulcers, attributing its efficacy to its high sugar content. Following suit, Bulman[12] and Cavanagh et al.[47] reported improved outcomes when honey was applied to surgical wounds, and Hutton[48] advocated the use of honey in pressure sores. The potential benefits of honey in burn wounds were proposed as early as 1933,[49] and Burlando[50] later observed this clinically, reporting reduced inflammation and pain relief in honey-treated superficial burns. In the early 1990s, honey was first discussed as a treatment for chronic leg ulcers in a series of journal correspondences.[51-53] Early reports such as these set a precedent for larger case series, clinical trials, and systematic reviews that have ultimately brought honey into prominence as a promising component of modern wound care. Investigators from medical and surgical specialties alike have explored its efficacy in a variety of wound types, and many of their findings have been summarized below.

4.1 Acute Wounds

4.1.1 Burns

The benefit of honey in treating acute burn wounds has been demonstrated clinically. Subrahmanyam[54,55] compared honey with other wound dressings, including polyurethane film, petrolatum-impregnated gauze, sterile linen dressings, boiled potato peel, and framycetin/gramicidin dressings in the treatment of 992 patients with partial-thickness burns. In these studies, mean days to healing was shown to decrease with the use of honey. The same author compared honey with silver sulfadiazine in 254 patients with burns and demonstrated decreased time to healing with the use of honey.[40,41,56] More recently, a systematic review and meta-analysis of randomized controlled trials including 624 subjects suggested greater efficacy of honey compared with other dressings in the treatment of burns.[57] The antimicrobial properties of honey have also been exploited in burn care; burns infected with various strains of *P. aeruginosa* were shown to have sensitivity and thus favorable response to honey treatment.[58] Medicinal honey has also been shown to be useful for the fixation of split-thickness skin grafts in burn patients due to its adhesive properties.[59]

4.1.2 Surgical and Traumatic Wounds

The use of honey for non-infected surgical and traumatic wounds is less understood; there have been few studies specifically addressing the safety or efficacy of honey in either of these settings. One non-randomized comparison trial of 81 patients who underwent skin grafting demonstrated the use of honey as an alternative to donor site treatment.[60] In the trial, donor sites treated with honey-impregnated gauzes were shown to have shorter epithelialization time and less subjective pain compared with paraffin gauzes and saline-soaked gauzes. Another elegant study employed a murine model for surgical wounds and demonstrated that tumor implantation was restricted with the application of honey both pre- and postoperatively.[61] This finding led to the suggestion of using honey to coat trochar sites during laparoscopic surgery to prevent tumor seeding. Despite these two fascinating studies, there is a need for further studies to assess the role of honey in the treatment of these acute wounds.

4.2 Chronic Wounds

4.2.1 Infected Surgical Wounds

Clinical evidence supporting honey in infected surgical wounds is also limited, though promising. A prospective case series involving nine neonates with surgical site infections refractory

to topical (povidone iodine or fusidic acid) and systemic antibacterials reported that all nine wounds demonstrated decreased edema and necrotic tissue after 5 days of adding or substituting unprocessed honey for the initial intervention.[62] By 21 days of treatment, all nine wounds, a majority of which initially grew *P. aeruginosa*, *S. aureus*, or *E. coli*, were deemed closed and sterile. In a trial of 50 patients with infected Caesarean or hysterectomy wounds, patients were randomly treated with either honey or washes with ethanol and povidone iodine.[63] Mean time to healing was shown to be over 11 days fewer in the honey-treated group.

4.2.2 Pressure Ulcers

Pressure sores in varying stages have been found to improve with honey-based dressings. Weheida et al.[64] compared honey with saline-soaked gauze dressings in a randomly assigned group of 40 patients with uninfected stage I or II pressure ulcers. Mean time to healing was lower in the honey-treated group by an average of 1.7 days. In a subsequent, randomized clinical trial, 36 patients with stage II or III ulcers were treated with either honey dressings or traditional ethoxy-diaminoacridine plus nitrofurazone (nitrofural) dressings, and Pressure Ulcer Scale for Healing (PUSH) scores[65] were determined for each ulcer at the onset and conclusion of the trial.[66] It was shown that pressure sores treated with honey had significantly improved PUSH scores compared with those treated with the control dressing ($p < 0.001$).

4.2.3 Lower Extremity Ulcers

Honey has been implicated for use in the primary dressing of chronic lower extremity ulcers, including venous, arterial, and diabetic ulcers. The most robust data are available on honey and venous ulcers, which is proportional to their higher prevalence. In addition to multiple small-scale reports suggesting efficacy in venous ulcers,[67-70] two large, randomized controlled trials have been conducted, revealing mixed results. A 12-week, multicenter trial by Gethin and Cowman[71] compared a 4-week regimen of manuka honey with hydrogel followed by 8 weeks of standard care in 108 patients with sloughy venous ulcers. The authors observed a 21% greater median reduction in wound size ($p = 0.001$) at 4 weeks and 11% more healed ulcers at 12 weeks ($p = 0.037$), both in favor of the honey group. At 4 weeks, greater desloughing was observed in the honey group, which was clinically but not statistically different ($p = 0.054$). The largest trial to date, entitled the HALT (Honey as Adjuvant Leg Ulcer Therapy) trial by Jull et al.[45] came to a separate conclusion. In this multicenter trial, 368 patients with venous ulcers of varying severity were subjected to calcium alginate dressings impregnated with manuka honey or to usual care as determined by individual providers. At 12 weeks of treatment, 55.6% of patients in the honey group were noted to have healed ulcers compared with 49.7% in the usual care group; however, these findings were not statistically significant ($p = 0.258$). Additionally, mean time to healing, mean reduction from baseline in ulcer area, and incidence of infection were not significantly different between the two groups. To account for these disparate findings, it has been proposed that honey may have a greater effect on larger and older venous ulcers such as those targeted in the Gethin and Cowman[71] trial.

Unlike the results with venous ulcers, evidence to support the use of honey in diabetic neuropathic ulcers or arterial ulcers is meager. While several anecdotal accounts of the benefit of honey in diabetic ulcers have been documented,[72,73] only one randomized controlled trial, which studied 30 patients with Wagner grade II ulcers, has been performed to date.[74] The investigators of this study found no significant difference between honey and povidone iodine. Likewise, very few cases of pure arterial ulcers treated with honey have been noted in the literature, and no randomized clinical trials have been performed.

4.2.4 Other Chronic Wounds

Topical honey has been explored in other chronic wounds such as Fournier gangrene and pyoderma gangrenosum. Several reports have described the efficacy of honey in managing Fournier gangrene, a subset of necrotizing fasciitis involving the perineum and genitalia. A case series by Efem[75] involving 41 cases of Fournier gangrene compared outcomes of medical (topical honey and intravenous antibacterials) with surgical management. While patients who underwent surgical debridement had a shorter mean hospital stay, those who were initially treated conservatively had lower overall morbidity, requiring fewer total operations. A comparable case-control study by Tahmaz et al.[76] involving 33 cases of Fournier gangrene came to a similar conclusion, associating conservative therapy with fewer total surgical debridements and superior cosmetic results when compared with surgical management ($p < 0.05$).

Subrahmanyam and Ugane[77] compared honey with Eusol (chlorinated lime and boracic acid)-soaked gauze dressings in the treatment of Fournier gangrene in 30 patients. Mean time to healing was found to be 8 days fewer in the honey-treated group. Documentation of honey in the treatment of pyoderma gangrenosum remains sparse, though a single case report in 2008 described a patient whose ulcerative colitis-associated pyoderma gangrenosum ulcers responded favorably to a regimen of honey dressings, oral prednisone, and dapsone.[78]

4.3 Mixed Acute and Chronic Wounds

Multiple studies have simultaneously investigated honey in the treatment of both acute and chronic wounds. In 1993, a study of 100 patients with traumatic ulcers, pressure ulcers, diabetic ulcers, venous ulcers, or trophic ulcers was performed to determine if wound healing was superior with honey compared with silver sulfadiazine.[79] The mean difference in time to healing was 13 days in favor of patients treated with honey. More recently, Mphande et al.[80] studied a group of 100 patients with ulcers, chronic osteomyelitis, abscesses, and post-surgical or traumatic wounds. These results demonstrated time to complete healing of 31.5 days in the honey-treated group compared with 56 days in the sugar-treated group. Another investigator compared the efficacy of Medihoney® *Leptospermum* honey with that of conventional wound dressings (as determined by individual practitioners) in the management of acute and chronic wound healing by secondary intention.[81] In this open-label, randomized clinical trial involving 105 subjects, the median time to heal was 100 days in the experimental honey group and 140 days in the control arm, but the sample size was not large enough to establish statistical significance.

The use of honey in split-thickness skin grafts (STSGs) has been addressed by two case series: the first report observed the effect of topical honey in six cases of STSGs for chronic venous ulcers,[82] and the second examined the use of honey as a skin graft fixation agent in 11 cases of both acute and chronic wounds.[59] Both studies reported equivocal outcomes, observing no complications such as infection, graft loss, or rejection.

4.4 Systematic Reviews

With a growing body of literature available on honey-based wound care, several systematic reviews and meta-analyses have been performed to appraise the quality of studies and synthesize the available data. The earliest of these reviews was published in 2001 by Moore et al.,[83] who identified seven randomized controlled trials involving the management of burns and infected postoperative wounds. In a number needed to treat (NNT) analysis comparing honey with control dressings, the NNT to produce one patient with a healed burn wound at 7 days of treatment was 2.6 (95% CI 2.1, 2.4). In patients with infected wounds, the NNT to produce one infection-free patient at 7 days of treatment was 1.8 (95% CI 1.5, 2.2). Despite these favorable findings, the authors concluded that the studies were poor in quality due to their lack of blinding, limited sample sizes, poor reporting quality, and poor trial validity. Bardy et al.[84] arrived at a similar conclusion in their 2008 systematic review, reporting Jadad quality scores[85] of 1 or lower in 36 of the 43 studies appraised. An additional systematic review and meta-analysis published by Jull et al.[86] addressed the use of honey in both acute and chronic wounds. In the 19 trials (n = 2554) reviewed, honey was found to reduce healing times in acute, partial-thickness burns by an average of 4.68 days (weighted mean difference –4.68 days, 95% CI –4.08, –5.09) when compared with conventional dressings. This benefit in burn wounds was supported by the previously described meta-analysis by Wijesinghe et al.[57] Conversely, Jull et al.[86] reported that honey in conjunction with compression stockings did not significantly accelerate healing in chronic venous leg ulcers (relative risk 1.15, 95% CI 0.96, 1.38). The reviewers determined that there was insufficient data to satisfactorily assess the effects of honey on other subsets of acute and chronic wounds.

4.5 Ongoing Trials

Investigators continue to explore the range of therapeutic effects of honey through ongoing trials. One group of the British Columbia Cancer Agency is conducting a randomized controlled trial comparing manuka honey with placebo in the treatment of radiation therapy-induced oral mucositis.[87] Two other groups are investigating honey as a cough suppressant, though it is unclear whether any of the proposed wound-healing mechanisms translate to the cough reflex.[88,89]

5. Additional Considerations

In addition to the proposed benefits of honey, several clinical and practical implications should be considered. While topical honey is largely considered safe, a rare but serious potential complication is wound botulism, a toxin-mediated paralysis that has been previously associated with intravenous drug abuse.[90] While there are no formally documented cases linking honey to wound botulism, analyses of honeys from various regions have revealed that up to 26% of unprocessed honeys and 5% of commercial honeys are contaminated with *Clostridium botulinum*, the soil-borne organism implicated in botulism.[91-93] As such, producers of MGHs have incorporated γ-irradiation into the manufacturing process, which has been shown to effectively sterilize honey without attenuating its antibacterial effects.[94]

Another safety concern is the regulation and standardization of honey products that are used in the clinical setting. Numerous studies, including some that have been reported in this review, have investigated honeys of undetermined quality and potency. As stated previously, only select honey preparations have been cleared by the FDA for clinical use (table I). Likewise,

Table II. Summary of the proposed mechanisms of action and clinical uses of honey

Mechanisms of action
Antimicrobial
Antioxidant
Peroxide generator
Induces proinflammatory cytokine production
Decreases biofilm formation
Inhibits bacterial cell cycle progression
Decreases wound pH
Modulates pain perception
Clinical uses
Burns
Surgical/traumatic wounds
Pressure ulcers
Venous ulcers
Diabetic arterial ulcers
Fournier gangrene
Pyoderma gangrenosum
Infected surgical wounds
Lower extremity ulcers

the EU has designated the 'CE' mark for honey products suitable for use as sterile medical devices (products not listed).[95] While honey has been promoted as an affordable alternative to conventional wound dressings, the emergence of MGHs combining honey with other advanced wound dressings in addition to stricter manufacturing practices have probably driven up the cost of quality honey products.[13] In the HALT trial, a cost-effectiveness analysis accounting for the overall cost of utilized health services (including MGHs) concluded that honey-based care for venous ulcers was likely more expensive than the standard of care.[45] This finding, however, may not be generalizable to the management of other wound types or to the care provided in nations other than New Zealand where the trial was conducted.

One final and important consideration is the need to identify specific interactions or potential synergy between honeys and the various non-honey agents (such as alginates or polymeric dressings) that comprise commercially available MGHs. Understanding these interactions will enable manufacturers to optimize future honey-based formulations for better outcomes.

6. Conclusions

Honey has been used for millennia as an adjuvant to wound healing. Every year new studies further elucidate the precise action of honey in wound healing and demonstrate its efficacy in treating various wounds (table II). While many modern-day physicians are likely to remain skeptical of the benefits of honey until larger, randomized controlled trials support its use, one cannot deny the great body of literature that associates honey with remarkable wound healing.

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