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Honey: A Potent Agent for Wound Healing?

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Although honey has been used as a traditional remedy for burns and wounds, the potential for its inclusion in mainstream medical care is not well recognized. Many studies have demonstrated that honey has antibacterial activity in vitro, and a small number of clinical case studies have shown that application of honey to severely infected cutaneous wounds is capable of clearing infection from the wound and improving tissue healing. The physicochemical properties (eg, osmotic effects and pH) of honey also aid in its antibacterial actions. Research has also indicated that honey may possess antiinflammatory activity and stimulate immune responses within a wound. The overall effect is to reduce infection and to enhance wound healing in burns, ulcers, and other cutaneous wounds. It is also known that honeys derived from particular floral sources in Australia and New Zealand (*Leptospermum* spp) have enhanced antibacterial activity, and these honeys have been approved for marketing as therapeutic honeys (Medihoney and Active Manuka honey). This review outlines what is known about the medical properties of honey and indicates the potential for honey to be incorporated into the management of a large number of wound types. (J WOCN 2002;29:295-300.)

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During the past decade there has been a worldwide increase in the use of traditional and complementary or natural systems of medicine.[1-3] Concomitant with this public interest has been a renewed interest in these therapies from both the scientific and medical communities. Whereas to date most research has focused on herbal and aromatherapy products, a number of other products show therapeutic promise. One such resource is honey.

Therapeutic honeys seem to offer considerable benefits in wound care, particularly for the treatment of chronic and infected wounds and for the treatment of burns. This review outlines what is known about clinical use of honey, particularly with respect to its possible role in improving wound management.

TRADITIONAL USES OF HONEY

Honey has a long tradition of use for wound healing and has been referred to extensively in the medical literature of Egypt, Greece, and in the Ayurvedic traditions of India.[4,5] The Koran also praises the virtues of honey.[6] Honey is described in a number of ancient texts as a wound healing agent either on its own or in combination with other ingredients. The Smith papyrus of 1700 BC describes a wound ointment that survived to be passed on to the Greek and later Roman civilizations. Honey was mixed with grease or fat, in the ratio of ⅓ honey to ⅔ fat, and then applied to a wound. The Greeks not only used honey in combination with vegetable or animal fat, but also as part of an ointment used to dry out wounds and prevent suppuration. These mixes, referred to as an enheme, typically contained white vinegar, honey, alum, sodium carbonate, and a little bile. Enhemes also would have had some antiseptic activity because of the astringent properties of the alum, the osmotic pressure of the honey, and the alkali pH created by the sodium carbonate and bile.[7]

Accounts of the use of honey as a wound dressing are not confined to ancient records. In recent years there have been a number of reports in the medical literature regarding the "rediscovery" of honey as a therapeutic agent, although many of these are clinical observations rather than randomized studies.[8-12]

THERAPEUTIC HONEYS

Therapeutic honeys are typically highly viscous honeys and are used "raw," that is, they do not undergo heat treatment as do culinary honeys. Currently 2 honeys are approved for therapeutic use, Medihoney (Capiliano, Australia[13]) and Active Manuka Honey (New Zealand), both of which are derived from *Leptospermum* spp (tea trees). (Manuka is the common name of *Leptospernum scoparium*, the floral source from which the honey is derived.) These honeys are thought to have additional therapeutic properties that have been derived from the floral source. Sterilization of therapeutic honeys is achieved via gamma irradiation, which destroys any bacterial spores while retaining biologic activity (the heat treatment used to produce "supermarket" honeys destroys the enzyme responsible for the production of hydrogen peroxide).[14] Variation exists in the effectiveness of honey as an antimicrobial treatment because of factors such as hydrogen peroxide levels and floral origin.

Box

Properties of honey that make it a useful therapeutic agent

- Osmotic activity: the high sugar content of honey inhibits bacterial growth
- pH: the acid pH of honey (3.2 to 4.2) inhibits growth of most pathogenic bacteria within wounds
- Production of hydrogen peroxide: slow, low level production of H_2O_2 within wounds kills bacteria without causing tissue damage; also aids in debridement of wounds
- Specific plant derived factors: floral sources such as *Leptospermum scoparium* (Manuka) and *L polygalifolium* (Medihoney) may contribute additional antibacterial, antioxidant, or other factors to the honey; as yet these factors have not been specifically identified
- Miscellaneous: therapeutic honeys also produce a moist wound environment

Honey is described in a number of ancient texts as a wound healing agent either on its own or in combination with other ingredients.

The susceptibility of bacterial species to honey also varies.[6] Honey may be bactericidal or bacteriostatic in its effects and may require a period of exposure before the bacteria succumb. However, whether the effects are bacteriostatic or bactericidal is not a major issue in terms of therapeutic use, because some of the antibiotics in common use in medical practice have only bacteriostatic effects. Complete bacteriostasis, maintained by regular application of honey, would be sufficient to allow the healing process to proceed normally. The suppression and resolution of infections that are found to occur under a dressing of honey may be a result of bactericidal action from prolonged exposure or a result of the natural defense system being more successful with multiplication of bacterial cells held in check.[6] Cooper et al[15] found that Manuka honey was highly effective against multiresistant *Burkholderia cepacia* implicated in nosocomial wound infections and respiratory infections of patients with cystic fibrosis. However, it was ineffective against *Pseudomonas aeruginosa* infections isolated from patients with cystic fibrosis. Manuka and other honeys have also been shown to possess antibacterial potency well in excess of that needed to stop the growth of clinically important organisms such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Escherichia coli*.[16]

HONEY AND WOUND HEALING: CLINICAL INFORMATION

Although the benefits of honey in wound and burns management have been clearly identified, the use of honey as a topical agent has yet to gain routine clinical status.[12,13,16,17] A summary of the benefits and disadvantages of honey are shown in Table 1; however, it should be noted that the disadvantages are relatively minor or largely theoretic in nature with no reports of, for example, allergy to honey or alteration of blood glucose in diabetic patients.

Clinical experience cites honey being used to treat a range of wounds, including surgical incisions, pressure ulcers, and catheter exit sites.[17,18] Observations are that infection is rapidly cleared; inflammation, swelling, and pain are quickly reduced; odor is reduced; sloughing of necrotic tissue is induced; granulation and reepithelialization are hastened; and healing occurs rapidly with minimal scarring.[18] The antibacterial properties of honey prevent microbial growth in the moist wound environment created, and unlike topical antiseptics, honey causes no tissue damage.[18]

Honey has also been used as a short-term storage medium for skin grafts. Subrahmanyam[10] reported that the search for a simple, cheap method of preservation of skin for grafting in the developing world had led to the trial of honey. It was found that skin grafts stored at room temperature or 4°C in honey for 7 to 12 weeks had 100% uptake when regrafted. Dunford et al[12] found that Manuka honey deodorized a wide range of acute and chronic wounds, such as abscesses, diabetic foot ulcers, and leg ulcers, and believed it to be a result of the antibacterial action of the honey against the infection causing the malodor. In some recent cases of fungating wounds, honey was the only effective agent in controlling the malodor.

CLINICAL TRIALS USING HONEY

Several clinical trials have been conducted that used honey for a variety of wounds. Efem[19] conducted one of the first clinical trials of honey (floral source not specified) as a wound dressing. Honey dressings were used to treat 59 patients with recalcitrant wounds and ulcers, 47 of which had been treated for what clinicians deemed a "sufficiently long time" (1 month to 2 years) with conventional treatments of commercial wound dressings or systemic and topical antibiotics. The wounds were of varied etiology, such as Fourniers gangrene, burns, cancrum oris, diabetic ulcers, traumatic ulcers, decubitus ulcers, sickle cell ulcers, and tropical ulcers, showed no signs of healing, and were increasing in size. Following topical application of honey, 58 of the 59 cases showed remarkable improvement. Microbial examination of swabs taken from the wounds showed that 51 wounds were infected at the beginning of treatment; however, following treatment, all were sterile within 1 week. Efem[19] observed that honey debrided wounds rapidly, replacing sloughed, gangrenous, and necrotic tissue with granulation tissue and advancing epithelialization. Under the honey, sloughs

Table 1. Advantages and disadvantages of use of honey as a topical wound dressing

Advantages	Disadvantages
Very effective means of quickly rendering heavily infected wounds sterile, without the adverse effects of antibiotics	Preparation of impregnated dressings is difficult and nonsterile
Effective against antibiotic-resistant strains of bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Escherichia coli*	In some patients a "drawing" or stinging sensation can cause some discomfort
Ideal first-aid dressing for patients in remote areas where there could be time for infection to set in before medical treatment is obtained	Becomes more fluid at high temperatures, which means it may liquefy at ambient wound temperature
Promotes healing through stimulus of tissue regeneration	Risk of liquefaction restricts body site usage, because dependent leakage is a possibility
Prevents/reduces scarring and hypertrophy	Bacterial inoculation of the wound from unsterilized honey
Antibacterial moist environment	When used on large wounds of diabetics, the blood glucose levels may rise to dangerous levels
No adverse effects on the healing wound tissues	
Minimizes the need for grafting	
Barrier to cross-infection of wounds	
Nonadherent wound dressing	

Data from references 12, 13, 16, and 18.

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and necrotic tissue separated so that they could be lifted off painlessly. Honey promoted rapid re-epithelialization; in addition, surrounding edema subsided, weeping ulcers dehydrated, and offensive-smelling wounds were rendered odorless within 1 week.

Subrahmanyam has conducted prospective randomized clinical trials investigating the effectiveness of honey as a topical agent for burns compared with other traditional remedies, such as boiled potato peelings or amniotic membrane,[5] and current pharmacologic and surgical methods, such as silver sulfadiazine (SSD)[20] and tangential excision with skin grafts.[21] In a study comparing boiled potato peel dressings and honey for partial-thickness burns, it was found that the wounds treated with honey had healthy granulation tissue after an average of 6.8 days, with the majority fully healed by 10.4 days. In comparison, the burns treated with boiled potato peel dressings had healthy granulation tissue by 9.2 days and were fully healed by 16.2 days. Rapid absorption of edema from soggy wounds was observed, as was an apparent chemical debridement by the honey that prevented the need for surgical debridement. The antibacterial activity of the honey caused the wounds to heal faster by preventing infection. It was concluded that honey dressings for burns were nonirritating, nontoxic, easily available, and cheap.

A randomized controlled clinical trial compared SSD, a topical antimicrobial agent used commonly in the treatment of partial-thickness burns, to an unidentified honey.[20] Subrahmanyam found that in the burn wounds treated with honey dressings, no adhesion of the dressing to the wound occurred, preventing pain for the patient and damage to the granulating surface of the wound. Eighty-four percent of patients treated with honey showed satisfactory epithelialization after 7 days, with 100% by 21 days. Of the patients treated with SSD, 72% were showing satisfactory healing by day 7, with 84% by day 21. Histologic studies showed early decrease in inflammation, better infection control, and faster healing. It was found that honey was as effective as or more effective than SSD, one of the most common topical burn treatments used.[20]

Subrahmanyam has conducted a number of studies comparing honey to conventional treatments in treating burns.[21,22] In a study of 900 patients with partial-thickness burns (injury extent 5% to 40%), 450 patients received honey dressings while the remainder were treated with conventional dressings.[22] Honey (15 to 30 mL) was applied on alternate days directly to the burns and then covered with sterile dressings. At the conclusion of the study, the burns treated with honey were found to have healed faster with less depigmentation and scarring (residual scarring occurred in 6.2% of burns treated with honey vs 19.7% of conventionally treated burns) than those treated with conventional dressings. Subrahmanyam has concluded that whereas honey was found to be superior for the treatment of superficial burns, full-thickness burns responded better to tangential excision and skin grafting.[21]

Subrahmanyam's prospective randomized controlled trials are well designed and adequately described. The statistically significant results from the large numbers of patients provide convincing evidence that dressing with honey is a safe and effective treatment for superficial burns. Whereas these clinical observations provide, in isolation, the lowest level of evidence on which to base a clinical decision when compared with more commonly used dressings, such as SSD, they indicate that honey has the potential to be a very useful wound dressing material.[18]

HONEY AND WOUND HEALING: MECHANISMS

Honey is a super-saturated sugar solution produced by honey bees from the nectar of plants, as well as from honeydew, a substance produced by insects who ingest the sap of the plant and then excrete it as droplets onto the trunk and leaves of the plant, which is then harvested by the bees.[23-25] Some of the components of honey (carbohydrates, water, traces of organic acids, enzymes, amino acids, pigments, pollen, and wax) are a result of either the maturation process of the honey, are added by the bees, or are derived from the plants.[25,26] The percentage of the various components may vary depending on the plant of origin, the geographic location, the season the honey was collected, its treatment since harvest, and its age.

Honey may be bactericidal or bacteriostatic in its effects and may require a period of exposure before the bacteria succumb.

The antibacterial properties of honey are well known. The physicochemical properties (eg, pH and viscosity) of honey not only contribute to its antibacterial properties but also to its wound-healing capabilities.

The benefits of a moist wound environment are well established: it protects the wound, reduces infection rates, reduces pain, debrides necrotic tissue, and promotes granulation tissue formation.[5,27] Moist wound dressings enable epithelialization to occur along the top surface of the wound, rather than underneath the scab, as occurs in dry wounds, resulting in a pitted scar. The physical properties of honey make it an ideal moist wound dressing. The high viscosity of honey (which varies from floral source to floral source) provides a protective barrier to prevent wounds from becoming infected, effectively sealing the wound.[5,13]

The layer of diluted honey and fluid also prevents the dressing from adhering to the wound, enabling the dressing to be changed without disrupting the partially healed wound or causing pain to the patient. It has been observed that chemical debridement by the action of honey is effective and there is no need for surgical debridement. It is thought that the generation of hydrogen peroxide aids in the debridement of the wound because of the Fenton reaction, where hydrogen peroxide reacts with ferrous ions, yielding the hydroxyl radical.[5,28] However, the debridement action is yet to be fully explained. The nutrient content of the honey, such as levulose and fructose, improves the local nutrition in the wound and promotes rapid epithelialization.[5]

Honey also aids in the deodorization of infected wounds, which is achieved by providing an alternative to the amino acids from the serum and dead cells that are metabolized by bacteria. This process gives rise to lactic acid rather than ammonia, amines, and sulfur compounds that are the cause of malodor in wounds.[17,18]

The pH of honey may help to create and maintain optimal conditions for fibroblast activity (migration, proliferation, and organization of collagen), which requires mildly acidic wound conditions.[29] It has been observed that the high osmolarity of honey causes rapid absorption of edema fluid from weeping burns.[5] The low water activity of the honey could be expected to dry out the wound; however, the osmotic pressure draws out fluid from the plasma or lymph in the underlying tissues. This mechanism dilutes the honey, activating glucose oxidase to produce continuous low levels of hydrogen peroxide, which inhibits bacterial growth.

Although hydrogen peroxide can be harmful to wounds when added as a rinse solution, honey continuously provides hydrogen peroxide at a consistent level that is antibacterial and physiologically nontoxic. Levels produced by diluted honey are approximately 1000 times lower than in rinse solutions. At this concentration hydrogen peroxide may act as a novel intracellular and intercellular "messenger" capable of promoting growth responses and stimulating expression of early growth genes important in wound healing.[12,30] Hydrogen peroxide generated by immune cells is likely to be physiologically important in contributing to the growth modulation of adjacent noninflammatory cells such as fibroblasts at the site of inflammation.[30] This may be one of the major mechanisms by which honey stimulates wound healing; however, further research is needed to confirm this theory.

The antiinflammatory action of honey has been investigated in histologic studies and clinical observations, but no definite mechanism has been identified.[17] Honey provides a glucose supply for leukocytes, essential for the respiratory burst that produces hydrogen peroxide. It also provides substrates for glycolysis, which is the major mechanism for energy production in the macrophage and thus allows them to function in damaged tissues with low oxygen supply.[18,31] Preliminary data from in vitro studies have indicated that honey may be able to modulate the activation state of immunocompetent cells (eg, monocytes) within the wound.[32,33] These studies suggest that honey may have a number of effects on the molecular mechanisms of wound healing.

KEY POINTS

- Honey has a long history of traditional use in healing of burns and other wounds.
- In vitro studies demonstrate that many raw honeys possess antibacterial properties by virtue of their physicochemical properties.
- Some honeys, derived from specific floral sources such as *Leptospermum* spp, may offer additional benefits in wound healing and are referred to as therapeutic honeys.
- A number of clinical studies have shown that honey can reduce infection, accelerate overall healing, and also may reduce wound inflammation in a variety of wound types.
- More research is required to determine the types of wounds that respond best to honey and the optimal means of application, as well as research into understanding the mechanism of action of honey.

THE FUTURE FOR HONEY AND WOUND MANAGEMENT

In modern health care, few wounds require intensive treatment or hospitalization; patients with such wounds are often immunocompromised, immunosuppressed, or diabetic. In addition, wounds such as surgical incisions that become infected with nosocomial infections that are resistant to most conventional treatments are becoming an increasingly important problem. For persons with these wounds and those managing their care, the search for improved ways to treat wounds is ongoing. Perhaps we need to revisit the use of honey. The antibacterial properties of honey are well established, and these mechanisms most likely aid in the wound healing process by preventing infection while maintaining a moist wound environment. The work of Blair et al[32] and Jones et al[33] also demonstrates that honey may affect wound-healing processes at a molecular level to reduce inflammation. Honey has an obvious potential for use in a variety of clinical settings, and although a few clinics and individuals are using honey therapeutically, further research is needed to determine whether the benefits of honey can be realized in general clinical use.

One final area that will need to be addressed prior to the widespread use of honey in wound management is the practicality of applying honey to wounds, burns, and other cutaneous injuries. No consensus exists on the best mode of application of honey. In most studies, honey is applied either daily or every 2 days directly to the wound surface following irrigation with sterile saline solution, and then the wound is covered with sterile gauze.[18] However, others have used gauze soaked in honey or occlusive dressings to stop honey leakage, or they have left dressings in place for extended periods.[18,34] These practical issues will need to be addressed if honey is to be a routine addition to clinical care. This scenario will only occur with further well-constructed clinical trials into the use of honey for wound management so that nursing and other medical staff have clear, evidence-based guidelines for the use of this product in clinical settings.

A final limitation to the widespread use of honey is the availability of appropriately sterilized (ie, gamma-irradiated), unprocessed honey. At present only 2 honeys are approved for therapeutic use, and although these products are available from pharmacies and/or health food stores in Australia and New Zealand, the international availability of clinical quantities of these products is uncertain.

CONCLUSION

Therapeutic honeys, as distinct from culinary honeys, have the potential to be an excellent addition to wound treatment protocols. The recent interest in this ancient cure has shown that it is able to clear infection from chronically infected wounds and accelerate healing, particularly in wounds resistant to conventional treatments. Evidence also exists that honey may reduce inflammation, reduce scarring, and aid in the processes of cellular regeneration. However, further research is required to understand the mechanisms of action of honey and to investigate the best means for the application of honey to various wound types (eg, ulcers, burns, and surgical incisions). Honey has enormous potential to be a potent, nontoxic treatment for wounds, and once the practical issues have been addressed, there is little doubt that honey could be a valuable tool for all medical staff involved in the management of wounds.

Honey has enormous potential to be a potent, nontoxic treatment for wounds, and once the practical issues have been addressed, there is little doubt that honey will be a valuable tool for all medical staff involved in the management of wounds.

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