
# THERAPEUTIC REVIEW: MANUKA HONEY

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The complex nature of wound healing has been studied extensively in both humans and animals. Wound healing is typically categorized into 3 stages: an inflammatory phase, proliferative or repair phase, and wound maturation phase.[1] Although separate stages are observed, wound healing is a dynamic process with the 3 phases occurring simultaneously. Successful wound management involves the understanding of all stages of wound healing for one to properly use materials and pharmaceuticals in an effort to promote rapid healing with decreased risk for secondary infection and further damage.

Despite knowledge of wound care and treatment, soft tissue injuries can be a challenge to manage. Risk of nosocomial infection is always at the forefront when wounds are managed in the hospital setting. In addition, contamination of the wound bed can occur if it is not properly dressed or if bandage changes are infrequent. Proper bandage change is especially important during the earlier stages of wound healing. Antibiotic resistance is an increasing concern when managing soft tissue wounds, and thus necessitate the need for culture and sensitivity testing as well as products that can successfully treat resistant organisms. The time and materials used in wound care can be extensive, and this ultimately dictates the high cost associated with treatment. Medical professionals continuously search for an antimicrobial agent that is both inexpensive and effective in wound management. Manuka honey has been promoted as an inexpensive and effective means of treating soft tissue wounds for veterinary patients, and in particular, exotic animal species.

## HISTORICAL USE AND CLINICAL APPLICATION

The use of topical honey applied in wound care has been documented for several millennia, with records of use dating back to early Egyptian civilizations.[2] Across the globe, honeys from separate floral sources have been used to aid in wound treatment; however, it was not until the 20th century that evidence-based medicine supported the use of honey as a medicinal aid.[3] In human medicine, honey has been successfully used for the treatment of burns and ulcerated skin wounds with noted advantages over other topical treatments such as silver sulfadiazine.[4-7] In addition, honey has been considered a practical option for managing traumatic wounds created on the battlefield and is employed by military medical personnel.[5] In the veterinary world, honey is beginning to be accepted as a treatment option for soft tissue injuries. The agent is particularly useful for treating wounds that cannot undergo first-intention healing such as areas of increased skin tension. In standardbred horses with distal limb injuries, honey has been shown to decrease the healing time and increase wound contraction as compared with untreated controls.[6] More recently, peer-reviewed literature has focused on manuka honey as being superior to other sources of honey.

## MECHANISM OF ACTION

Manuka honey comes from the manuka tree (Leptospermum scoparium) that is native to New Zealand and southern Australia. Like other types of honey, manuka generates a favorable environment in the wound bed during the early stages of healing. Osmolarity, pH, hydrogen peroxide production, and nutrient content all contribute to the beneficial healing effects of honey.[3] However, unlike other honeys, manuka also contains a nonperoxide component that offers greater antibacterial activity. Although much of this activity has still yet to be elucidated, methylglyoxal (MGO) is the active ingredient in manuka honey that has been found to be effective against biofilm-producing *Staphylococcus aureus* (including

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methicillin-resistant *S. aureus*[8]) and *Psuedomonas aeurginosa* in an *in vivo* ovine model.[9] Other studies have also shown that MGO has activity against biofilm forming *Proteus mirabilis* and *Enterobacter cloacae*, common pathogens that are associated with the development of venous leg ulcers in people.[10] In addition to its antibacterial properties, manuka honey has also been found to increase production of inflammatory cytokines in leukocytes.[11] These proinflammatory cytokines create an environment conducive to angiogenesis and proliferation of fibroblasts and endothelial cells.[11,12] To this end, manuka honey is typically used when trying to promote a healthy bed of granulation tissue within a wound.

In addition to MGO, manuka honey has other properties beneficial to wound healing. As an agent with a high osmolarity, manuka is capable of decreasing wound edema and inflammation as lymphatic fluid is drawn out of the wound bed. During this process, the lymph carries nutrients that promote angiogenesis and regeneration of local tissues.[13-15] In addition to decreasing edema, the elevated osmolarity facilitates a concentrated environment that is detrimental to most bacteria because of osmotic dehydration.[13] Most notably, manuka honey contains glucose oxidase, an enzyme added to the substance by honey bees.[16] This enzyme, although present in honey, is only activated in the presence of water. Most honeys consist of approximately 40% glucose, 40% fructose, and 20% water.[3] When honey is applied topically, water is evacuated from the wound because of the high osmolarity of the therapeutic agent. This then dilutes the honey and activates glucose oxidase.[16] Gluconic acid, produced through glucose-oxidase activity, is responsible for the low pH of manuka honey. This contributes to both antibacterial effects as well as promotes wound healing through acidification.[17] The activation of glucose oxidase also results in the production of gluconic acid and hydrogen peroxide ($H_2O_2$) (Fig.). Commercial hydrogen peroxide (3% solution) is known to be detrimental to wound healing because of desiccation of the wound bed and damage from the development of oxygen-free radicals despite having antiseptic properties.[13-15] However, the concentration of hydrogen peroxide that accumulates in the diluted honey is approximately 1000 times less than that found in commercial solutions.[15] Although these concentrations have been found to possess antiseptic properties, it is believed that wound damage is not observed because of the high levels of naturally occurring antioxidants present in honey.[15] Lastly, the honey itself acts as a protective layer over the wound that maintains a moist environment favorable to wound healing. Other theories exist regarding additional mechanisms by which honey may benefit wound healing (such as contributions to wound debridement through enzymatic processes), but there is little scientific evidence to support these theories.[15]

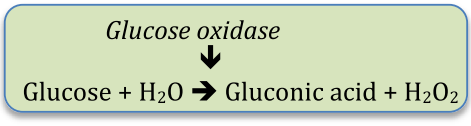


**FIGURE.** Constituents of honey yield gluconic acid and hydrogen peroxide in the presence of glucose oxidase.

## WOUND DRESSINGS

The dressing/bandage applied to the wound is critical for wound management success. A multitude of honey-impregnated dressings are now available (Table), although application of store-bought manuka honey is commonly practiced and equally effective. During the early stages of healing, excess exudate is produced from the wound, necessitating bandage changes anywhere from 1 to 3 times daily. Manuka honey can initially be applied to the primary layer; this may consist of gauze or another adherent material that helps aid in wound debridement when removed. During this time, an adsorbent or occlusive secondary layer is indicated to prevent the honey from oozing out of the bandage.[2] If the wound is not producing a large amount of exudate and is in the later stages of healing, a nonadherent layer can be used along with the manuka honey.[2] In human medicine, 30 mL of honey is used per $10 \times 10\ cm^2$ dressing.[15] As manuka honey promotes the formation of a healthy granulation bed, adherent dressings are contraindicated once granulation tissue is observed,[2] and further topical therapy is not indicated.

## EXOTIC ANIMAL APPLICATION

Soft tissue wounds are common among companion animal exotic, wildlife, and zoo animal species. Fight wounds from cage mates, thermal burns, pododermatitis, dental abscesses, and other traumatic injuries are just a few examples of representative wounds diagnosed in exotic animal medicine. The process of wound healing in reptilian and amphibian species is similar to other animals, with only minor