Honey: A Biologic Wound Dressing

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Abstract: Honey has been used as a wound dressing for thousands of years, but only in more recent times has a scientific explanation become available for its effectiveness. It is now realized that honey is a biologic wound dressing with multiple bioactivities that work in concert to expedite the healing process. The physical properties of honey also expedite the healing process: its acidity increases the release of oxygen from hemoglobin thereby making the wound environment less favorable for the activity of destructive proteases, and the high osmolarity of honey draws fluid out of the wound bed to create an outflow of lymph as occurs with negative pressure wound therapy. Honey has a broad-spectrum antibacterial activity, but there is much variation in potency between different honeys. There are 2 types of antibacterial activity. In most honeys the activity is due to hydrogen peroxide, but much of this is inactivated by the enzyme catalase that is present in blood, serum, and wound tissues. In manuka honey, the activity is due to methylglyoxal which is not inactivated. The manuka honey used in wound-care products can withstand dilution with substantial amounts of wound exudate and still maintain enough activity to inhibit the growth of bacteria. There is good evidence for honey also having bioactivities that stimulate the immune response (thus promoting the growth of tissues for wound repair), suppress inflammation, and bring about rapid autolytic debridement. There is clinical evidence for these actions, and research is providing scientific explanations for them.

Key words: biology of wound healing, components of wound healing, honey, wound dressing

Honey has been in use as a wound dressing for thousands of years.[1,2] In the past few decades, there has been a large amount of clinical evidence has been accumulated that demonstrates the effectiveness of honey in this application.[3,4] However, it is only in more recent times that the science behind the efficacy has become available. It is now understood that honey is not just sugar syrup with certain physical properties that make it suitable as a wound dressing material, but that it is a biologic wound dressing with multiple bioactive components that can expedite the healing process.

The physical properties of honey alone will positively impact the wound healing environment and the healing process, specifically because honey is acidic and has a pH of around 3.2-4.5,[5] and it is well known that topical

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Keypoints
- Honey is a biologic wound dressing with multiple bioactive components that can expedite the healing process.
- The acidity of honey makes it less favorable for protease activity.
- The high osmolarity of honey is also beneficial to the healing process.

acidification of wounds promotes healing by increasing the release of oxygen from hemoglobin.[6] In addition, this pH is less favorable for protease activity, thus reducing the destruction of the matrix needed for tissue repair.[7] The high osmolarity of honey due to its high sugar content is also beneficial to the healing process, as substantiated in reports showing sugar pastes to be effective as wound dressings.[8] The osmotic effect of the sugar draws water out of the wound bed and, although it could be thought that this may potentially harm and dehydrate the wound tissue, this is not the case. If the circulation of blood underneath the wound is sufficient to replace fluid lost from cells, then the osmotic effect of sugar on the surface simply creates an outflow of lymph.[9] This outflow is beneficial to the healing process, as demonstrated by negative pressure wound therapy.

Sugar also draws water out of bacterial cells and, as long as the sugar does not become too diluted by the wound fluid, the growth of bacteria is inhibited.[10] The lowest concentration of sugar known to prevent the growth of *Staphylococcus aureus* has a water activity of 0.86.[9] Sucrose has this activity at a concentration of 67%; glucose at 55%; and fructose at 56%; however, it has been found that sucrose packed into an abdominal wound only maintains its activity for 4 hours before becoming sufficiently diluted by body fluids, allowing the water activity to increase to 0.897 and *S. aureus* to grow.[11] The additional bioactivity within the honey itself allows for continued inhibition of bacterial growth even when the osmolarity has been diluted below the point where it should cease to be inhibitory.

There has been only 1 clinical trial reported where honey was compared with sugar for its effectiveness,[12] in which honey was found to be more effective than sugar in reducing bacterial contamination and promoting wound healing. In addition to this 1 comparative clinical trial supporting the increased antimicrobial activity of honey, in vitro research has also been conducted[13] which has provided good scientific evidence for the presence of bioactivity in honey. This bioactivity would be expected to greatly augment the effects of the physical properties on healing of wounds.

Bioactivity of Honey

Antibacterial action. A number of reports have been published citing honey as having antibacterial action in vitro against a wide range of species of bacteria and fungi.[13] However, in many of these studies, the minimum inhibitory concentration (MIC) of honey was not determined, and the concentration of honey used was high enough that the inhibition of microbial growth could have just been due to the osmotic effect of the honey. Also, in many of the studies, where MIC values for honey were reported, the type of honey used had been arbitrarily chosen, yet it is well known that antibacterial potency can vary 100-fold between different honeys.[14]

The literature reporting MIC values for honey with a standardized level of antibacterial activity has been comprehensively reviewed by Molan[15] and, in these studies, the honeys used were selected to have antibacterial activity near the median level, mostly at a level equivalent to the standard reference antiseptic phenol at a concentration of 13% to 18% (weight/volume). Honey used in most products registered with the US Food and Drug Administration (FDA) for wound care is typically standardized to be equivalent to 12% to 16% phenol. The various studies conducted with these standardized honeys reported MIC values for a range of species of bacteria present in infected wounds: *S. aureus*, various coagulase-negative *Staphylococci*, various species of *Streptococci*, various species of *Enterococci*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella oxytoca*, and a range of anaerobes.

In all cases, the MIC values were found to be below 11%, which means even when honey is heavily diluted by wound exudate, it will still have more than enough potency of antibacterial activity to inhibit growth of bacteria. The various strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) tested were found to be as sensitive to the antibacterial activity of honey as the nonresistant strains of those species. Not included in the Molan[15] review, but covered by George and Cutting,[16] was a study of 130 clinical isolates of multiresistant gram-negative bacteria to determine their sensitivity to a standardized honey (antibacterial potency equivalent to 18% phenol).[16] Minimum inhibitory concentration values of 6% to 8% honey were reported for *Acinetobacter baumannii* (including 5 pan-resistant strains), for VRE and for

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extended-spectrum beta-lactamase (ESBL)-producing strains of *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species. The MIC values for isolates of *P. aeruginosa* were 12% to 14% honey.

There has been some concern that resistance to honey may develop in the bacteria exposed to it through wound care. However, in long-term "resistance training" experiments with 4 wound-infecting species of bacteria, no permanent decrease in susceptibility to honey could be created and no honey-resistant mutants could be detected.[17] It was concluded that the risk of bacteria acquiring resistance to honey is low as long as high concentrations of honey are maintained clinically. In a similar study conducted by other researchers, exposure to sublethal concentrations of the antibiotics tetracycline, oxacillin, and ciprofloxacilin rapidly induced a resistant phenotype in antibiotic-susceptible strains of *S. aureus* and *P. aeruginosa*, but constant exposure of these organisms to increasing sublethal concentrations of honey could not raise the level of resistance past the initial MIC of the honey.[18]

Honeys not only show variation in potency of their antibacterial activity but also in the nature of it. In most of the world's honeys, the antibacterial activity beyond that which is due to the osmolarity and acidity of the honey is due to hydrogen peroxide.[13] This antibacterial agent is generated by glucose oxidase, an enzyme that bees add to the collected nectar stored in honeycombs. The enzyme is inactive under the low level of free water present in honey, but becomes active if the honey becomes diluted, as with wound exudate.[19] Although honey diluted to 25% with water can still exhibit antibacterial activity equivalent to that of an 8% solution of phenol in laboratory testing, it will be much less active in a wound scenario because serum and wound tissue contain the enzyme catalase which rapidly breaks down hydrogen peroxide. Any visible antibacterial activity seen with the 25% solution of honey tested in the laboratory would be removed if blood at a concentration of 1% is added to the agar plates.

Honey from manuka trees (and some other members of the *Leptospermum* genus) has a unique type of antibacterial activity not due to hydrogen peroxide, and as such, is not affected by the catalase enzyme activity in wounds. Its antibacterial activity is due to methylgloxal, which forms by spontaneous conversion in ripened honey from its precursor substance dihydroxyacetone that is found in manuka nectar.[20] Methylglyoxal on its own is a cytotoxic substance, and the possibility has been raised that the methylglyoxal in manuka honey may contribute to delayed wound healing in patients with diabetes.[21] It would seem however, that the combination and ratio with other components in the manuka honey counteracts the methylglyoxal component from exhibiting such toxicity, because no cytotoxicity is seen in the required testing for FDA registration of manuka honey wound-care products. In addition, clinical results obtained using manuka honey on patients with diabetes indicate that rapid healing is achieved—diabetic leg ulcers that had been nonhealing for long periods healed mostly within 3 months when dressed with manuka honey.[22]

The antibacterial component of manuka honey is a small water-soluble molecule that diffuses easily, which explains why manuka honey has also exhibited efficacy against bacteria contained in biofilms. Prolonged chronicity of wounds can be attributed to wound colonization that develops into a biofilm in which the bacteria stay protected by the matrix of the biofilm. These bacteria cannot be cleared by the host immune system and show resistance to both systemic and topical antimicrobial agents.[23] This may explain why antibiotics are of limited use in treating chronic wounds.[23] Manuka honey at a concentration of 40% has been found to give significantly reduced biofilm biomass with in vitro testing of clinical isolates of *P. aeruginosa* that had developed into a biofilm.[24] A similar finding was made in a comparable study conducted with *Streptococcus* pyogenes.[25] In another study conducted with biofilms developed from 11 isolates each of methicillin-sensitive *S. aureus* (MSSA),

Keypoints

- Honey used in most products registered with the US Food and Drug Administration for wound care is typically standardized to be equivalent to 12% to 16% phenol.
- The various studies conducted with these standardized honeys reported minimum inhibitory concentration (MIC) values for a range of species of bacteria present in infected wounds: *S. aureus*, various coagulase-negative *Staphylococci*, various species of *Streptococci*, various species of *Enterococci, Pseudomonas aeruginosa, Escherichia coli, Klebsiella oxytoca*, and a range of anaerobes.
- In all case, MIC values were found to be below 11%; even when honey is heavily diluted by wound exudate, it will still have potent enough antibacterial activity to inhibit growth of bacteria.

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MRSA, and *P. aeruginosa*, it was found that 50% manuka honey killed 9 out of 11, 7 out of 11, and 10 out of 11 of the isolates, respectively.[26] Greater sensitivity was found in another study on biofilms formed in vitro where the MIC for manuka honey was 6% honey for MRSA and methicillin-resistant *S. epidermidis*, and 12% honey for *P. aeruginosa* and ESBL *Klebsiella pneumoniae*.[27]

Clinically, there have been many reports[28-31] published of manuka honey being effective in achieving healing of chronic wounds. One of these was an observational study where 20 patients with spinal cord injuries who had chronic pressure ulcers (5 had grade IV ulcers and 15 had grade III ulcers) were treated with manuka honey.[28] After 1 week of treatment with manuka honey all swabs were void of bacterial growth, and after a period of 4 weeks, 18 patients showed complete wound healing. Another study[29] examined 40 patients with leg ulcers that had not responded to 12 weeks of compression therapy. Manuka honey dressings were applied to the ulcers for a 12-week study period. Overall, ulcer pain and size decreased significantly and odorous wounds were deodorized promptly. Average pain score as measured on the McGill Pain Index scale had decreased from 1.6 ± 1.22 to 1.08 ± 1.54 by the individual patients' endpoints. The average rate of reduction in wound area was 5.46%. At first assessment (after 2 weeks) the average score for odor had decreased from 1.58 ± 0.90 to 0.69 ± 0.79 (on a scale where 3 indicated severe odor), with 11/26 (42%) having no odor.[29] A further study[30] showed a group of 8 patients with nonhealing or recurrent venous leg ulcers treated with manuka honey healed with accelerated wound closure, and a study[31] of 11 cases involving only nonhealing venous ulcers that did not respond to a variety of usual treatment options showed that wounds treated with manuka honey dressings had complete closure in 3 to 6 weeks. There have also been many reports of single case studies where manuka honey resulted in healing of previously nonhealing wounds.[32-39]

Immunostimulatory action. It is possible that the clearance of infection by the antibacterial activity of honey may be further augmented by its immunostimulatory action, although there will always be some attenuation of this by the anti-inflammatory activity of honey. Whether or not the stimulation of the immune response contributes to wound healing by helping suppress infection, it will definitely contribute to healing through the stimulation and growth of repair tissue. It is a commonly reported clinical observation that rapid healing is achieved when wounds are dressed with honey,[3,4] and similar observations have been made in numerous animal experiments.[40] These results could be considered a consequence of the honey suppressing infection; however, in experiments where dermal burn wounds were inflicted on pigs[41,42] and rats[43] under surgical conditions, the wounds created were free from bacteria and the rate of healing was still increased upon the application of honey.

Work in vitro has demonstrated that the immunostimulatory activity of honey on leukocytes causes the production of cytokines, which leads to the stimulation and growth of cells. Honey at a concentration of 1% was found to stimulate release of tumor necrosis factor alpha (TNF-α) by monocytes.[44] Although stimulation of inflammation is generally considered to be harmful, there is a modulation of this inflammatory response by the anti-inflammatory activity of honey. Thus, when 1% honey was added to inflamed macrophages formed by activation of monocytes by lipopolysaccharide and opsonized zymosan, there was no increase in the the release of TNF-α, and the honey suppressed the production of reactive oxygen intermediates formed in the respiratory burst.[44]

In a similar study, honey at a concentration of 1% was found to stimulate the release of TNF-α, interleukin-1 beta (IL-1β), and IL-6 from monocytes, cytokines known in vivo to play a role in tissue repair.[45] Keratinocytes have been found to have transcription of the genes for the cytokines TNF-α, IL-1β, and TGF-α upregulated by honey at a concentration of 1%.[46] In addition, honey upregulated the gene for matrix metallopeptidase 9 (MMP-9), which is a protease that detaches keratinocytes from the basement membrane to allow their migration in reepithelialization.[46] Reepithelialization would also be promoted by increased levels of TNF-α and IL-1β, which induce the production of the keratinocyte growth factor fibroblast growth factor 7.[46] Honey has also been demonstrated to stimulate angiogenesis in vitro[47] in a rat aortic ring assay, maximally at around a concentration of honey of 0.2%.

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This immunostimulatory activity of honey has been attributed to various components by different authors: major royal jelly protein-1 (MRJP-1), arabinogalactan, endotoxin contaminant in honey, and a substance of molecular weight 5.8 kDa.[48] Major royal jelly protein-1 was found to make only a minor contribution to the stimulation of keratinocytes, hence it was concluded that another component must be responsible.[46] In a study of stimulation of release of TNF-α by monocytes, it was found that the arabinogalactan-protein complex isolated from honey needed to be at a concentration of more than 25 µg/ml to give the amount of stimulation given by 0.5% honey but, upon calculation, the stated concentration of arabinogalactan-protein complex in the honey (10 µg/g) meant that 0.5% honey contained only 0.05 µg/ml of arabinogalactan.[49] The possibility that stimulation was due to endotoxin was ruled out, and so the major immunostimulatory factor was concluded to be an unidentified component of molecular weight 5.8 kDa that is not a protein.[50] This unidentified component has been found to work through stimulation of the toll-like receptor 4 on leukocytes.[50]

Anti-inflammatory action. Honey has a long history of use as an anti-inflammatory substance. The ancient Greek physician and pharmacologist Pedanius Dioscorides used honey to treat sunburn and spots on the face, as well as to heal inflammation of the throat and tonsils.[51] In the modern era, there have been numerous observations of honey applied to inflamed wounds and burns resulting in reduced edema and exudate, providing a soothing effect, and minimizing scarring.[52] In clinical trials on burns comparing honey with silver sulfadiazine, honey showed decreased levels of the marker for inflammation, decreased levels of malondialdehyde,[53] and a reduced number of inflammatory cells present in biopsy samples.[54] The numerous reports of anti-inflammatory activity in experimental wounds and burns of animal models, where there were few or no bacteria present (due to aseptically produced wounds),[52] indicate honey has a direct anti-inflammatory activity, the decrease in inflammation not simply being a secondary effect of the antibacterial activity of honey removing inflammation-causing bacteria.

The anti-inflammatory activity of honey has also been demonstrated in clinical trials to reduce the severity of mucositis in radiotherapy of the head and neck region,[55-58] and to treat gingivitis.[59] Anti-inflammatory activity has also been seen in clinical trials to treat dyspepsia[60] and found to be effective in the relief of various ophthalmological inflammatory conditions.[61] Honey has been found to decrease pain after surgical removal of children's tonsils,[62] and also to decrease pain in nonhealing leg ulcers.[29] In experiments with rats, honey demonstrated a highly significant reduction in peritoneal adhesions following surgery on the cecum,[63] efficacy as a treatment for chemically induced colitis,[64-67] and prevention of gastritis caused by administered dosage of ethanol.[68-70] Injection of 50% honey into rat paws prior to injecting lipopolysaccharide to cause inflammation resulted in less swelling, reduced sensitivity to pain, and a lower level of inflammatory markers.[71] In a study of carrageenan-induced edema in rat paws, pretreatment with oral doses of honey gave a dose-dependent reduction in the edema and a suppression in expression of the genes for inducible nitric oxide synthase, COX-2, TNF-α, and IL-6.[72]

This well-documented anti-inflammatory activity in honey has been attributed to the present plant phenolic compounds[73]; however, no correlation was found between the level of anti-inflammatory activity observed in various honeys and the known phenolic compounds present.[74] A wide range of varieties of honeys were tested for anti-inflammatory activity: pasture honey, clover honey, kanuka honey buttercup honey, and beech honeydew honey.[75] Phenolic components may well be involved, as they are as a class of compound known to inhibit the production of the inflammatory cytokine TNF-α,[76] but more recently, another major anti-inflammatory component of honey has been identified that is not a phenolic compound but rather a protein that works in a different way.[77] This bee-derived protein, apalbumin-1, was identified as the component of honey that inhibits phagocytosis by macrophages, the first

Keypoints

- Clinical observation shows rapid healing is achieved when wounds are dressed with honey,[3,4] and similar observations have been made in numerous animal experiments.[40]
- Work in vitro has demonstrated that the immunostimulatory activity of honey on leukocytes causes the production of cytokines, which lead to the stimulation and growth of cells.
- This immunostimulatory activity of honey has been attributed to various components: major royal jelly protein-1 (MRJP-1), arabinogalactan, endotoxin contaminant in honey, and a substance of molecular weight 5.8 kDa.[48]

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step in the sequence of an inflammatory response to necrotic tissue and/or microbial cells. It was found that manuka honey is a much stronger inhibitor of phagocytosis than other types of honey. It was determined that methylglyoxal, a substance found in significant quantities only in manuka honey, reacts with apalbumin-1 to glycate it, and this glycated apalbumin-1 is a much stronger inhibitor of phagocytosis than the unmodified apalbumin-1 generally found in other types of honey. A 0.5% solution of manuka honey gave 67% inhibition of phagocytosis. The mechanism of action of apalbumin-1, both the glycated and unmodified forms, is by blocking the mannose receptor on phagocytes which is the trigger for phagocytosis.[77]

Debriding action. Debridement of wounds using honey dressings has been observed in clinical trials on burns.[54,78,79] In one such trial,[54] honey was found to prevent the formation of eschar, whereas eschar formed in the cases treated with silver sulfadiazine. Seven case series and ten single case studies in which honey was reported to be effective in debriding wounds have been outlined in a review of the clinical evidence for the effectiveness of honey as a debriding agent.[80]

Clinical trials have also shown honey is a good alternative to surgical debridement for the treatment of necrotizing fasciitis in the genital region.[81-83] In a clinical trial comparing honey with hydrogel for debridement of wounds, it was found that better debridement was obtained with honey, although there was not a statistically significant difference.[84] The results were compared with those published from other studies, and it was concluded that in the desloughing of venous leg ulcers, manuka honey is slower than larval therapy or curettage but superior to some hydrogels, enzymatic agents, hydrocolloids, paraffin gauze, or cadexomer iodine. In a

Keypoints
- Seven case series and ten single case studies in which honey was reported to be effective in debriding wounds have been outlined in a review of the clinical evidence for the effectiveness of honey as a debriding agent.[80]
- It has been hypothesized that honey increases the activity of plasmin, an enzyme that specifically digests fibrin (fibrin attaches slough to the wound surface) but does not digest the collagen matrix needed for tissue repair.

trial on adjacent experimental rabbit wounds, wounds treated with honey-soaked gauze were kept clean while wounds treated with saline-soaked gauze formed thick dense scabs.[85]

A possible explanation for the mechanism by which honey brings about debridement of wounds has recently been discovered.[86] It was hypothesized that honey increases the activity of plasmin, an enzyme that specifically digests fibrin (fibrin attaches slough to the wound surface) but does not digest the collagen matrix needed for tissue repair. In work with cultures of inflamed macrophages it was demonstrated that honey increased plasmin activity in the culture medium, and that the plasmin activity increased because the honey inhibited the production of plasminogen activator inhibitor (PAI) by the macrophages. Plasminogen activator inhibitor normally blocks the conversion of plasminogen (the enzymically inactive precursor of plasmin) into active plasmin. Inflammation increases production of PAI,[87] so it is to be expected that honey would lead to a decrease in production of PAI because of the well-established anti-inflammatory activity of honey.

Conclusion

Honey is a biologic wound dressing with multiple bioactivities. Each of the healing-promoting activities can be found separately in pharmaceutical products, but in honey they are all present and work together synergistically to enhance the healing process. In addition, there is the added benefit from the physical properties of the honey creating a moist healing environment, one in which the antibacterial activity removes all likelihood of moist conditions favoring bacterial growth. Bacterial infection and critical colonization can inhibit healing, either through the direct effects of bacteria on wound tissue, or through the deleterious effects of excessive inflammation,[88] but the combination of antibacterial

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Keypoints
- Honey should always be sterilized by gamma-irradiation, not heat, which would destroy the antibacterial activity.
- From a clinical perspective, there is a vast amount of evidence to support the use of honey in wound care;[3,4] however, some reviews have still concluded there is a lack of true clinical evidence due to the absence of high quality controlled or comparative randomized studies.[94,95]

and anti-inflammatory activity within honey, along with the debriding action of detaching slough (which is a harbor for inflammation-causing bacteria), may explain why honey can so readily bring about the healing of chronic wounds. It should be noted that there are situations where a stagnated healing process can be re-started by inflammation, and research has been conducted that shows wound healing can be improved to a certain extent by inoculation of live staphylococci, but only by very low bacterial concentrations that promote a local inflammatory response but are not sufficient to slow healing.[89] It is believed that the immunostimulatory action of honey, modulated by the anti-inflammatory activity, gives a similar effect. This would account for the observations that honey kick-starts healing of chronic wounds that have remained nonhealing for long periods of time.[90-93]

It is necessary to keep the honey present at the wound bed interface for these bioactivities to work. This is achieved by the use of primary dressings in which the honey is impregnated in an absorbent material. An optimal primary dressing would be one that can absorb wound exudate and provide constant exposure and contact of the wound with honey. Three different types of such dressings are available: an alginate dressing (Algivon Dressings, Advancis Medical, Kirby in Ashfield, Nottingham, UK, and Medihoney Apinate Alginate Dressing, Derma Sciences, Princeton, NJ); a polyacrylate gel dressing (Manuka Health Wound Dressings, Manuka Health New Zealand Ltd, Auckland, NZ); and a dressing based on superabsorbent fibers (ManukaHD, Manuka-Med, Largo, FL).

One has honey impregnated into an alginate fiber dressing which converts to a gel when exposed to wound fluid, but has a relatively limited capacity to absorb fluid. Another has the honey incorporated in a polyacrylate gel that has the capacity to absorb wound fluid and swell. The third type has honey impregnated

Keypoints
- The inadequacy of comparative randomized trials for wound dressings in general, and the difficulties faced in obtaining high quality evidence, has been discussed.
- Leaper[98] noted when clinical evidence of the highest level is not available, decisions on modes of treatment need to be based on whatever evidence is available.
- Although the criticism of the quality of the available studies is well taken, there have been at least 35 randomized controlled trials published on the use of honey in a wide range of wound types, with a total of 3,655 participants.[3,4,99,100]

into the interstitial spaces of a dressing composed of superabsorbent fibers. These fibers have a high capacity to absorb wound fluid and expand without losing structure while simultaneously absorbing the mixture of honey and wound fluid from the interstitial spaces and allowing continued diffusion of honey into the wound bed.

Honey can be used on any type of wound at any stage of healing, but certain precautions should be noted. The honey should always be sterilized since, although vegetative bacterial cells in honey are killed by the honey itself, bacterial spores are not. Spores of *Clostridium* may sometimes occur in honey and could theoretically germinate in necrotic tissue if left there once honey has been diluted to a subinhibitory concentration by wound exudate. Sterilization should be done by gamma-irradiation, not heat, which would destroy the antibacterial activity. In addition, much of the manuka honey available for purchase, other than that which is registered as a wound-care product, has little or no methylglyoxal in it. There are even some wound-care products made with non-manuka honey that do not contain any methylglyoxal. The antibacterial activity of non-manuka honey products would be due to the sugar content and hydrogen peroxide. The inhibitory action of the sugar would be lost as the honey is diluted by wound exudate, and the hydrogen peroxide would be destroyed by the activity of catalase which is present in serum and wound tissues. On inflamed wounds, honey may cause mild transient pain. This is because inflammation sensitizes the nocioceptor nerve endings which may then respond to the acidity of honey. The use of honey dressings in which the honey is gelled or provides for slow release reduces the impact of acidity

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in the wound, resulting in less pain than if plain honey or honey-impregnated gauze dressings are applied.

From a clinical perspective, there is a vast amount of evidence to support the use of honey in wound care;[3,4] however, some reviews have still concluded there is a lack of true clinical evidence due to the absence of high quality controlled or comparative randomized studies.[94,95] Campbell[96] has referred to the hierarchy of evidence ranging from double-blind randomized controlled trials giving the strongest evidence, through other forms of randomized controlled trials, non-randomized studies, controlled case studies, then case studies. It is important to note the US FDA does not require such high level evidence-based trials to be conducted and, therefore, there is a similar lack of high-quality studies for any of the dressings currently used in standard modern wound care.[4,97] The inadequacy of comparative randomized trials for wound dressings in general, and the difficulties faced in obtaining high quality evidence, has been discussed by Leaper[98] who made the point that when clinical evidence of the highest level is not available, then decisions on modes of treatment need to be based on whatever evidence is available. Although the criticism of the quality of the available studies is well taken, there have been at least 35 randomized controlled trials published on the use of honey in a wide range of wound types, with a total of 3,655 participants.[3,4,99,100] This is in addition to the large number of case studies and small trials that are published and continue to be published. Therefore, the authors conclude that the available evidence supports honey, and manuka honey specifically, as an important tool for wound care.

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