A Critical Review and Perspective of Honey in Tissue Engineering and Clinical Wound Healing

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Significance: Historically, honey has been regarded as a potent agent in bacterial inhibition and wound healing. An increased prevalence of antibiotic resistant pathogens spurred an initial resurgence in honey's clinical popularity, with it quickly finding a place in wound care and regenerative medicine. However, this renewed usage demanded a need for improved delivery and overall research of its bioactive properties. This review provides an overview of the antibacterial properties and clinical use of honey.

Recent Advances: The past and present clinical use of honey is noted, focusing specifically on burns and ulcers, as these are the most common applications of the natural agent. While honey is often used without modification clinically, there are also commercially available products ranging from dressings to gels, which are discussed.

Critical Issues: Despite these products growing in popularity, the need for improved delivery and a structure to support wound healing could improve the treatment method.

Future Directions: Tissue engineering scaffolds can provide an alternative method of honey delivery with research focusing primarily on electrospun scaffolds, hydrogels, and cryogels. Current studies on these scaffolds are discussed with respect to their advantages and potential for future clinical work. Overall, this review provides a comprehensive overview of the properties of honey, its current use in wound healing, and the potential for future incorporation into tissue-engineered scaffolds to provide an innovative wound healing agent.

Keywords: honey, tissue engineering, scaffolds, wound healing, antibacterial properties

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Submitted for publication September 24, 2018. Accepted in revised form April 29, 2019.

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SCOPE AND SIGNIFICANCE

HONEY HAS BEEN previously utilized for its antibacterial and wound healing properties for centuries; however, the discovery of antibiotics dramatically decreased its application clinically. Due to the recent rise in antibiotic resistance, there has been an increased need for alternative treatment methods.^{1,2}

Honey offers a natural component that can be used directly in a clinical setting or incorporated into tissue-engineered scaffolds.² In this review, the overall properties of honey will be summarized, as well as its current use in wound healing and the potential of honey-based tissue-engineered products.

TRANSLATIONAL RELEVANCE

Recent research has focused on the development of tissue-engineered scaffolds to encourage wound healing. Various scaffold fabrication techniques, including electrospinning, hydrogels, and cryogels, have become popular as vehicles for additives to improve delivery during treatment. Specifically, honey has been incorporated into these scaffolds, and while this research is ongoing, this review focuses on the many *in vitro* and *in vivo* studies that have demonstrated the translational potential of these scaffolds for future clinical studies. Upcoming work should focus on identifying the overall bioactive properties and mechanisms in which tissue-engineered scaffolds incorporated with honey encourage healing.

CLINICAL RELEVANCE

Ongoing work has supported the use of honey in clinical applications, where numerous Food and Drug Administration-approved products are currently on the market. However, these products range greatly in their structure, honey release, and application. This review provides an overview of the clinical significance of honey compared with the currently available options for treatment.

BACKGROUND

Antibiotic resistance has emerged as a significant global health problem following their excessive use in managing infectious diseases. In response to this, alternative treatments have gained popularity, focusing on natural plant-based options.¹ Honey is produced from the nectar of flowers, which is collected by bees and mixed with a secreted enzyme. The hemolymph osmolarity of bees can greatly affect their health and depends on factors such as geographic region, age, and weather season.² Once collected, the deposited nectar mixture is slightly dried, reducing water content and increasing the concentration, producing the viscous honey.³

While honey composition can vary widely across varieties, it is generally considered to be primarily composed of sugar (40% fructose, 30% glucose, 5% sucrose, and other disaccharides in small quantities: maltose, isomaltose, nigerose, turanose, and maltulose) and water (up to 20%) with additional amino acids, enzymes, minerals, and vitamins.^{4,5} Its carbohydrate composition varies widely, depending on the floral source.⁵ Honey possesses both a high osmolarity and acidic pH, typically ranging between 3.2 and 4.5, which has been shown to inhibit bacteria.⁶ Additionally, the hy-

groscopic properties, the ability to draw moisture out of the environment and dehydrate bacteria, reduce water activity (free water) to 0.56–0.59, and while the pH change clears bacteria, it also stimulates macrophage activity, increases fibroblast proliferation, and promotes oxygenation.^{7,8} Additional antimicrobial activity and angiogenesis promotion are provided by the production of hydrogen peroxide during the degradation of glucose.^{6,9} However, some kinds of honey do not utilize hydrogen peroxide and thus most likely rely primarily on the pH change and osmolarity for bacterial clearance.⁶ One such example is Manuka honey, which is known to possess an additional source of antibacterial protection through the presence of methylglyoxal, also known as unique Manuka factor (UMF).⁷ In addition to these health and antibacterial properties, previous studies have identified honey's ability to accelerate healing in wounds stuck in a chronic inflammatory phase through the scavenging of reactive oxygen species (ROS) produced by neutrophils.^{6,10}

Despite the multiple studies demonstrating honey's wound healing and overall health benefits, there remains a need for definitive clinical evidence of its success. However, the funding for this research is low and clinical trials are both costly and laborious.³ Additionally, the majority of clinical use involves the application of honey directly to the wound and cover with gauze. This method of application is incredibly inefficient as multiple applications and dressing changes are required to keep the honey in the wound site. Alternatively, clinical products and tissue-engineered scaffolds have become popular as alternative vehicles for the honey. This review will briefly discuss the antibacterial properties of honey, honey treatment of wounds (i.e., burns and pressure ulcers), and finally, honey in tissue-engineered scaffolds.

ANTIBACTERIAL PROPERTIES

There have been a wide array of honeys used for bacterial inhibition, with each having their own unique characteristics and impact on various bacterial strains (Table 1). However, it has been established that honey's antibacterial activity can be divided into five primary components: low water activity, low pH, the presence of hydrogen peroxide, immunostimulatory action, and the honey floral source. The inhibitory capability of honey depends on the concentration, potency, and strain of bacteria, with higher concentration and potency with a low virulence strain producing a greater inhibitory effect. Patton *et al.*¹¹ demonstrated via

Table 1. Inhibition of bacteria by various types of honey

Honey Type	Bacteria Inhibited	Reference
A. mellifera	<i>Staphylococcus aureus</i>	70,71
Bluegum	<i>Escherichia coli</i>	70
	<i>Staphylococcus aureus</i>	
	<i>Streptococcus mutans</i>	
Egyptian Clover	<i>Acinetobacter baumannii</i>	70,72–74
	<i>Aeromonas schubertii</i>	
	<i>Cellulosimicrobium cellulans</i>	
	<i>Escherichia coli</i>	
	<i>Haemophilus parahaemolyticus</i>	
	<i>Listonella anguillarum</i>	
	<i>Micrococcus luteus</i>	
	<i>Salmonella typhimurium</i>	
Fynbos	<i>Escherichia coli</i>	70
	<i>Staphylococcus aureus</i>	
	<i>Streptococcus mutans</i>	
Gelam	<i>Bacillus cereus</i>	75,76
	<i>Escherichia coli</i>	
	<i>Klebsiella pneumoniae</i>	
	<i>Staphylococcus epidermidis</i>	
	<i>Salmonella typhimurium</i>	
	<i>Staphylococcus aureus</i>	
	Vancomycin-resistant enterococci	
Hamadan	<i>Lactobacillus rhamnosus</i>	77
	<i>Streptococcus mutans</i>	
Heather	<i>Pseudomonas aeruginosa</i>	78
Khadikraft	<i>Pseudomonas aeruginosa</i>	78
Manuka	<i>Acinetobacter baumannii</i>	78,79,80
	<i>Actinomyces viscosus</i>	
	<i>Clostridium difficile</i>	
	Coagulase-negative Staphylococci	
	<i>Enterobacter aerogenes</i>	
	<i>Enterobacter cloacae</i>	
	<i>Escherichia coli</i>	
	<i>Helicobacter pylori</i>	
	<i>Lactobacillus rhamnosus</i>	
	Methicillin-resistant <i>Staphylococcus aureus</i>	
	<i>Proteus mirabilis</i>	
	<i>Pseudomonas aeruginosa</i>	
	<i>Salmonella typhimurium</i>	
	<i>Shigella flexneri</i>	
	<i>Staphylococcus aureus</i>	
	Staphylococci	
	<i>Stenotrophomonas maltophilia</i>	
	<i>Streptococcus agalactiae</i>	
	<i>Streptococcus mutans</i>	
	<i>Streptococcus pyogenes</i>	
Medihoney	<i>Acinetobacter calcoaceticus</i>	81,82
	<i>Citrobacter freundii</i>	
	<i>Escherichia coli</i>	
	<i>Enterobacter</i>	
	<i>Klebsiella pneumoniae</i>	
	<i>Serratia marcescens</i>	
	<i>Staphylococcus aureus</i>	
Nilgiri	<i>Escherichia coli</i>	83
	<i>Pseudomonas aeruginosa</i>	
	<i>Staphylococcus aureus</i>	
Pinecushion	<i>Escherichia coli</i>	70
	<i>Staphylococcus aureus</i>	
	<i>Streptococcus mutans</i>	
Tetragonisca angustula	<i>Staphylococcus aureus</i>	70,71
Tualang	<i>Pseudomonas aeruginosa</i>	70,80
	<i>Clostridium difficile</i>	
	<i>Staphylococcus aureus</i>	

(continued)

Table 1. (Continued)

Honey Type	Bacteria Inhibited	Reference
	<i>Helicobacter pylori</i>	
	<i>Escherichia coli</i>	
	<i>Enterobacter aerogenes</i>	
	<i>Salmonella typhimurium</i>	
	Staphylococci	
	<i>Streptococcus agalactiae</i>	
	<i>Stenotrophomonas maltophilia</i>	
	<i>Acinetobacter baumannii</i>	
	<i>Proteus mirabilis</i>	
	<i>Shigella flexneri</i>	
	<i>Enterobacter cloacae</i>	
	<i>Streptococcus pyogenes</i>	
	Coagulase-negative Staphylococci	
	Methicillin-resistant <i>Staphylococcus aureus</i>	
Ulmo	Methicillin-resistant <i>Staphylococcus aureus</i>	84
	<i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i>	

spectrophotometric assay that the minimum inhibitory concentration (MIC)₀ (% v/v, the highest concentration of Comvita Manuka Care 18+, which results in no inhibition of growth) for *Staphylococcus aureus* (NCIMB 9518) was 0.05 and the MIC₁₀₀ (% v/v, the lowest concentration of Comvita Manuka Care 18+, which results in 100% inhibition of growth) was 6.25. Manuka honey is regarded as the consensus leader with regard to the antibacterial activity and is noteworthy for its unique antibacterial component, methylglyoxal.^{9,12–14} Methylglyoxal, the product of spontaneous conversion of its precursor substance dihydroxyacetone in ripened honey, was first isolated and characterized as a significant antibacterial component of Manuka honey by Adams *et al.* and Mavric *et al.*^{13,14}

The hygroscopic properties of honey mentioned previously derive from the high sugar content and, subsequently, high osmolarity of honey. When incorporated into a wound dressing, the osmotic effect of the sugar in honey results in water being drawn out of the wound bed. When combined with a sufficient circulation of blood beneath the wound to replace the lost fluid, this osmotic effect results in an outflow of lymph, and clearance of bacteria from the wound that may mimic the effects of negative pressure wound therapy.¹² However, honey osmolarity varies greatly and consequently, as do the antimicrobial benefits, where an increased water content decreases these effects.²

Honey is naturally acidic, generally possessing a pH ranging from 3.2 to 4.5.⁶ Furthermore, the unique presence of methylglyoxal and dihydroxyacetone in Manuka honey has been observed, *in vitro*, to inhibit urease derived from jack beans. This inhibition of urease suggests that Manuka honey may act to prevent urease-possessing bacteria

(*Helicobacter pylori* and other enteric tract colonizers) from breaking down urea into ammonium and carbon dioxide and thus alkalinizing their immediate environment.¹⁵

As the honey placed at a wound site is diluted with wound exudate, a typically inactive enzyme initially deposited within honey by bees becomes active. This enzyme, glucose oxidase, degrades glucose within the honey into gluconic acid and hydrogen peroxide, where the latter is antiseptic.^{12,16} Hydrogen peroxide has been observed to be an effective antimicrobial agent when present in a 3% concentration.¹⁷ However, when present in higher concentrations, hydrogen peroxide has also been observed to induce cellular and protein damage in tissue via the production of oxygen free radicals.¹⁸ Furthermore, hydrogen peroxide at the wound site may be subjected to degradation by tissue-produced catalase.¹²

Recently, honey has also been observed to possess immunomodulatory properties *in vitro*, which may contribute to its antibacterial activity. Specifically, honey has been observed to stimulate the release of proinflammatory cytokines, tumor necrosis factor- α , interleukin (IL)-1 β (IL-1 β), and interleukin 6 (IL-6), from human monocytes *in vitro*.¹⁹ Furthermore, Tonks *et al.*²⁰ successfully isolated a 5.8-kDa component of Manuka honey *in vitro*, which they concluded was responsible for the stimulating the release of these proinflammatory cytokines. This 5.8-kDa component was observed to stimulate human monocytes through interaction with toll-like-receptor 4, a fundamental pattern recognition receptor of the innate immune system. Additional studies are being conducted to characterize this 5.8-kDa component.²⁰

CLINICAL WOUND HEALING

Honey has been used to target a wide range of wound types to clear bacteria, malodor, and necessary debridement. While this section will primarily focus on honey for burns and chronic ulcers, the two most common uses in wound healing, honey has been shown to treat the following wounds successfully: amputation wounds, burns, skin grafting sites, skin lesions, vulvectomy wounds, and skin ulcers including leg, varicose, diabetic, malignant, and sickle cell ulcers.²¹

Burns

The World Health Organization defines burns as "an injury to the skin or other organic tissue primarily caused by heat, radiation, radioactivity, electricity, friction or contact with chemicals."²² Generally, a burn results in the loss of skin, which

is imperative for infection prevention and moisture retention.²² Burns can range from superficial to partial thickness to full thickness with the former having damage solely to the epidermis and the two latter involving damage to structures within and beneath the skin, respectively. A burn leads to both a local and systemic response, depending on both the cause and severity.

Burns often require both excision and skin grafting; however, infections are often caused by pathogens such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*.³ As an alternative to skin grafts, the current gold standard of treatment involves a dressing typically composed of paraffin-impregnated gauze with a layer of cotton wool. The two layers prevent the wound from adhering to the dressing and absorb wound exudate, respectively. Additionally, the use of silver sulfadiazine has become increasingly common for preventing infection. Infection prevention often relies on a high osmolarity to both prevent bacterial growth and encourage wound healing.²³ Thus, honey has been identified as a potential alternative.

The use of honey as a treatment for burn wounds has become increasingly popular, despite its lack of supporting literature. The majority of studies focusing on honey for burn treatment have compared the effects of honey with various other treatments, often retrospectively. Recently, silver sulfadiazine has been compared with honey because it has the advantage of absorbing wound exudates and releasing the antimicrobial silver into the wound site.^{22,24–27} However, the anti-inflammatory properties of honey have proved superior in most comparative studies. Specifically, a study completed by Baghel *et al.*²⁴ demonstrated that honey was able to ensure greater sterility at the wound site, decrease scarring, and reduce necessary debridement. Another study treated superficial thermal burns of less than 40% of the body, with 52 patients receiving honey and the other 52 receiving silver sulfadiazine at the wound site daily for up to 60 days (Table 2).²⁷ As shown in the table, the patients treated with honey had accelerated epithelization and healthy granulation tissue in comparison to treatment with silver sulfadiazine. Overall, a systemic review of randomized controlled trials conducted by Aziz and Abdul Rasool Hassan²² found that published studies comparing the two treatments demonstrated that honey dressings had a statistically significant improved healing time and sterility.

Despite the demonstrated success of honey in a clinical setting for the treatment of burn wounds,

Table 2. An overview of the healing time for 104 patients with superficial thermal burns treated with either honey (group 1) or silver sulfadiazine (group 2)

Time Required for Healing (Days)	Group 1 (Patients Treated with Honey)	Group 2 (Patients Treated with Silver Sulfadiazine)
0–10	33	3
11–15	12	2
16–20	5	17
21–30	1	18
31–40	1	7
41–50	0	4
51–60	0	1
Total	52	52

Note that the honey led to the formation of healthy granulation tissue and expedited healing, with 33 of the patients experiencing wound healing within 10 days. Modified with permission from Subrahmanyam.²⁷

there remain many challenges. While clinical trials overall support the use of honey, none of the trials were double-blind to provide completely reliable data. It is challenging to conduct this type of study as patients can easily tell when their wound is being treated with honey due to color and aroma. Additionally, many of the studies listed previously did not specifically identify the honey type used for treatment. *In vitro* differences in the efficacy of honey based on origin and type have been identified and should be compared in clinical trials. This comparison would provide further information on the healing response based on the inclusion of honey, as well as the honey's process for healing. Table 3 provides a list of commercially available honey-based products for use in wound care, and each products specific indications.

Ulcers

Pressure ulcers are localized tissue injuries that are exposed to prolonged pressure, restricting blood flow into the area and causing tissue damage and tissue necrosis. Reperfusion of blood to the wound causes cellular edema, further tissue damage, and overproduction of ROS, causing further tissue damage.²⁸ If unrelieved, the affected area initially increases in redness, followed by a blister, open sore, and finally a deep crater. An ideal bio-active scaffold will allow for increased tissue regeneration by debriding of the necrotic tissue, preventing infection, and aiding in new tissue formation.²⁹ Honey is a favorable option due to its antimicrobial activity, deodorizing ability, debridement, osmotic effect, anti-inflammatory, antioxidative, and enhanced rate of healing. However, clinical confirmation has proven difficult due to the "low quality of evidence."^{4,30}

Jull *et al.*³¹ performed a systemic review of clinical trials in 2015, restricting the studies included to those with the lowest risk of bias. Al-

though the authors stated that honey increases the relative risk of healing of chronic ulcers compared with saline gauze (not the previously described gold standard), the evidence is of low quality and, as such, difficult to draw a definite conclusion throughout the articles. Gethin and Cowman³² found that at 12 weeks there was an increase in the healing of venous leg ulcers, whereas Jull *et al.*³¹ reported no significant difference between honey and the usual care (alginate, hydrofiber, hydrocolloid, foam, hydrogel, nonadherent, iodine or silver dressings available to nursing services at each study center). For diabetic foot ulcers, there was no significance between either the honey and saline gauze or the honey and povidone-iodine group.^{33,34} When compared with Clostridial collagenase ointment, medicinal honey had more revisits and outpatient visits. However, this study focused on debridement and not on wound healing.³⁵ Vandamme *et al.*³⁰ reported similar results to Jull *et al.*,⁴ although they concluded that honey stimulates wound healing in burns, ulcers, and other wounds and that it debrides, removes odor, has anti-inflammatory, and pain-reducing properties. The main discrepancy between these two reviews is that Vandamme *et al.* included more studies, since Jull *et al.*⁴ only observed to ones with the lowest risk of bias, yet both studies agreed that the quality evidence of the studies involved needs to be improved.

However, the variety of ways that honey is beneficial in general wound healing suggests that it has a role in chronic ulcers, as previous studies have shown that the use of honey expedites the complete healing of wounds.^{36,37} This expedited healing may in part be due to a honey-mediated decrease in microorganisms and bacteria, which is demonstrated in a study by Biglari *et al.*,³⁸ where an ankle ulcer (grade 3) was infected with methicillin-resistant *Staphylococcus aureus* (MRSA). Following treatment with Medihoney, the patient experienced complete wound closure by 4 weeks and full eradication of MRSA (Fig. 1).

The two main problems for all these clinical trials are the lack of consistent methodologies as well as biases during treatment. For instance, the type of honey is not always described, which can drastically change the biological properties. Additionally, non-medical nonsterile honey has been used, further increasing the likelihood of infection.³⁹ Further standardization, such as the frequency of changing the dressing as well as the method of incorporation, needs to be controlled to increase effectiveness.^{30,40} Although the clinical trials are generally inconclusive, *in vivo* experi-

Table 3. Commercially available, honey-infused wound healing products

Product Name	Product Type	Manufacturer	Indications
Medihoney Wound Dressing	Wound dressing	Derma Sciences	Diabetic foot ulcers, leg ulcers, pressure ulcers/sores (partial and full thickness), first- and second-degree partial-thickness burns, and donor site coverage ⁸⁵
TheraHoney Sheet	Wound dressing	Medline	Wounds with any drainage level ⁸⁶
Honey Gauze Dressing	Wound dressing	Gentell	Partial- and full-thickness wounds, leg ulcers, pressure ulcers, first- and second-degree burns, diabetic foot ulcers, minor abrasions, and lacerations ⁸⁷
MANUKAtex	Wound dressing	ManukaMed	Leg ulcers, pressure ulcers, first- and second-degree burns, diabetic foot ulcers, surgical wounds, and traumatic wounds ⁸⁸
TheraHoney HD	Wound dressing	Medline	Wounds with any drainage level ⁸⁶
Medihoney Calcium Alginate Dressing	Gel composite	Derma Sciences	Moderate-to-heavy exuding wounds, diabetic foot ulcers, leg ulcers, pressure ulcers, burns, donor sites, traumatic wounds, and surgical wounds ⁸⁵
L-Mesitran Soft	Gel composite	Dynarex	Chronic wounds, pressure ulcers, venous stasis ulcers, fungating wounds, colonized acute wounds, surgical wounds, traumatic wounds, and burns (superficial and partial thickness) ⁸⁹
L-Mesitran Hydro	Gel composite	Dynarex	Wound rehydration, chronic wounds, pressure ulcers, venous stasis ulcers, fungating wounds, colonized acute wounds, surgical wounds, traumatic wounds, and burns (superficial and partial thickness) ⁸⁹
L-Mesitran Border	Gel composite	Dynarex	Wound rehydration, chronic wounds, pressure ulcers, venous stasis ulcers, fungating wounds, colonized acute wounds, surgical wounds, traumatic wounds, and burns (superficial and partial thickness) ⁸⁹
MANUKAhd	Gel composite	ManukaMed	Leg ulcers, pressure ulcers, burns, diabetic ulcers, surgical wounds, and traumatic wounds ⁸⁸
MANUKAhd lite	Gel composite	ManukaMed	Leg ulcers, pressure ulcers, burns, diabetic ulcers, surgical wounds, and traumatic wounds ⁸⁸
MANUKApli	Gel composite	ManukaMed	Leg ulcers, pressure ulcers, burns, diabetic ulcers, surgical wounds, and traumatic wounds ⁸⁸
Algivon Plus	Gel composite	Advancis Medical	Biofilm prevention, pressure ulcers, leg ulcers, diabetic ulcers, surgical wounds, burns, graft sites, and infected wounds ⁹⁰
Activon Tube	Gel	Advancis Medical	Minor wounds, ulcerations, burns, abraded skin, irritated areas, diabetic foot ulcers, pressure ulcers, first- and second-degree burns, and traumatic surgical wounds ⁹⁰
Medihoney Gel	Gel	Derma Sciences	Minor abrasions, lacerations, minor cuts, minor scalds and burns, diabetic foot ulcers, leg ulcers, pressure ulcers/sores (partial and full thickness), first- and second-degree partial thickness burns, and donor site coverage ⁸⁵
TheraHoney Gel	Gel	Medline	Wounds unamenable to traditional dressings ⁸⁶
Medihoney HCS	Highly absorbent dressing	Derma Sciences	Superficial to partial-thickness wounds and absorption of wound exudate ⁸⁵
TheraHoney Foam	Highly absorbent dressing	Medline	Substantial wound exudate reabsorption ⁸⁶
Medihoney Tulle	Tulle dressing	Derma Sciences	Leg/foot ulcers, pressure ulcers, infected wounds, sloughy wounds, necrotic wounds, malodorous wounds, donor and recipient graft sites, burns, surgical wounds, diabetic wounds, and abrasions ⁸⁵
L-Mesitran Tulle	Tulle dressing	Dynarex	Chronic wounds, pressure ulcers, venous stasis ulcers, fungating wounds, colonized acute wounds, surgical wounds, traumatic wounds, and burns (superficial and partial thickness) ⁸⁹
Activon Tulle	Tulle dressing	Advancis Medical	Granulating or shallow wounds, pressure ulcers, leg ulcers, diabetic ulcers, surgical wounds, burns, graft sites, infected wounds, cavity wounds, and sinuses ⁹⁰
L-Mesitran Net	Net dressing	Dynarex	Low to heavily exuding chronic wounds, pressure ulcers, superficial and partial-thickness burns, venous, arterial and diabetic ulcers, fungating wounds, donor sites, surgical wounds, cuts, and abrasions ⁸⁹
Actilite	Net dressing	Advancis Medical	Granulating or epithelializing wounds, cuts, abrasions, burns, surgical wounds, leg ulcers, pressure ulcers, diabetic ulcers, and infected wounds ⁹⁰

ments show promise for ulcer healing. Overall, the prospect of using honey for chronic ulcers appears promising, but the quality of clinical trials needs to be improved to draw accurate conclusions.

FUTURE PERSPECTIVES WITH TISSUE-ENGINEERED SCAFFOLDS

The use of honey in wound care first began with the application of 80–100% Manuka honey and a gelling agent, but its high osmolarity would cause it to absorb the wound exudate, causing the honey

to leak out of the wound bed.⁴¹ The solution to this problem was to incorporate honey into scaffolds to provide a vehicle for controllable release such that wound exudate absorption is maintained.⁴² The most common types of honey-infused scaffolds currently being researched are electrospun fibers, hydrogels, and cryogels.

Electrospinning utilizes a high voltage to draw a polymer solution in the form of a fiber onto a grounded target. The resulting nanofiber mesh provides a structure mimicking the native extracellular matrix while maintaining a high surface

Figure 1. Medihoney was applied clinically in a patient with an (a) ankle ulcer infected with methicillin-resistant *Staphylococcus aureus*. Following application, partial closure was observed at (b) 2 weeks, with complete closure and irradiation of the bacteria observed at (c) 4 weeks. Reproduced with permission from Biglari *et al.*³⁸

area to volume ratio.⁴³ Hydrogels are a well-characterized tissue-engineered scaffold produced through the cross-linking of a polymer solution at room temperature. This results in a nanoporous scaffold with high water retention and is often used

for drug delivery and cellular encapsulation.⁴⁴ In comparison, the original fabrication of cryogels is very similar to hydrogels in that a polymer solution is also cross-linked; however, this solution is then immediately frozen ultimately resulting in a macroporous structure that is mechanically durable and sponge-like.⁴⁵ Changing the scaffold fabrication method, as well as the chemical composition, plays a vital role in tailoring the properties of the scaffold to the ideal application. It should be noted that many research studies that compare their products to clinical wound management focus on saline gauze, and so on, rather than an updated standard of care (e.g., moist wound dressings).

Electrospinning

Incorporating honey into electrospun nanofibers is currently the most prevalent method for utilizing honey in tissue-engineered scaffolds. This is primarily because of the high surface area to volume ratio, ability to bioresorb, and permeable structure. Generally, the amount of honey added is 10–70%, but as little as 0.1% has been tested. Overall, adding honey has been shown to affect the morphology of the fibers, but the results are inconsistent where the addition of honey water-based solutions appears to prevent fiber drying, generally resulting in a flattened or beaded morphology. This is demonstrated in a study by Maleki *et al.*,⁴⁶ where scanning electron microscopy images were obtained of poly(vinyl alcohol) (PVA) electrospun scaffolds with varying amounts of Iran-Tabriz honey (100/0, 80/20, and 60/40) (Fig. 2). When the honey content was increased to 40%, beads within the nanofiber web can be observed (Fig. 2c) in comparison to plain PVA (Fig. 2a).

During electrospinning, complex factors affect the resultant fiber morphology, including viscosity, surface tension, conductivity, and chain entanglement.⁴⁷ While the electrospinning parameters alter the size and shape of the fibers, adding honey further changes the solution conductivity, surface tension, and viscosity. When honey is added, the honey molecules are dispersed, which increases the number of organic ions and ionic movement in the solution. Incorporating honey into the scaffolds allows for controlled release rates so that the honey is held within the wound to promote infiltration, proliferation, and adhesion. The antimicrobial capabilities of the scaffold depend on the incorporated honey type as well as the concentration. As previously discussed, the different types of honey change the antimicrobial affinity, as well as the amount of honey applied to the bacteria. As the scaffolds release honey at a rate based on the fiber

Figure 2. Scanning electron microscopy images of electrospun PVA with (a) 0%, (b) 20%, and (c) 40% Iran–Tabriz honey. Note that with increasing wt% of honey, there appeared to be beading within the fibers, as shown in (c). Reproduced with permission from Maleki *et al.*⁴⁶ PVA, poly(vinyl alcohol).

diameter and polymer concentration, the released honey will be less than the amount of honey added at a given time. Honey concentrations greater than 10% successfully inhibited bacteria, demonstrating appropriate amounts of honey elution.^{48–52} Instead of using a culture dish, Sarkar *et al.* used a 24-well plate and thus less liquid to demonstrate that 0.5% honey was sufficient to elute enough honey for antimicrobial properties.⁵³ This study raises the question of how much honey is ideal for incorporation into an electrospun scaffold. The ideal concentration of honey will depend on the specific polymer chosen, which will dictate the maximum amount of incorporated honey, as well as the release rate.

Hydrogels

Hydrogels are composed of polymer solutions cross-linked at room temperature, forming a solid gel-like structure. Similar to electrospinning, a wide range of polymers and types of honey have been used to fabricate the hydrogel scaffolds. Overall, antibacterial inhibition was increased with the addition of honey.^{54–60} Specifically, in a study by Lahooti *et al.*,⁵⁹ chitosan–poly(vinyl alcohol)–gelatin–thyme honey hydrogel films were created and tested for their clearance capacity. Figure 3 displays the inhibition zones against both *P. aeruginosa* and *S. aureus*, gram-positive and gram-negative bacteria, respectively. Although it was generally observed that increased honey con-

Figure 3. The inhibition zone of (a, b) *Pseudomonas aeruginosa* and (c, d) *Staphylococcus aureus* by chitosan–poly(vinyl alcohol)–gelatin–thyme honey hydrogel films. Note that the film on the left side of the petri dish in (a, b) as well as the right side of (c, d) are films composed of 0.03, 0.04, 0.03, and 0.03 g/mL of chitosan, PVA, gelatin, and honey, respectively. The right film in (a, b) and the top film in (c, d) is composed of 0.05, 0.02, 0.03, and 0.03 g/mL. Finally, the left film in (c, d) is composed of 0.05, 0.04, 0.03, and 0.03 g/mL of chitosan, PVA, gelatin, and honey, respectively. Reprinted with permission from Lahooti *et al.*⁵⁹

centration led to increased inhibition, the honey elution ultimately leads to the inhibition. The base materials affect the microstructure and hydrophilicity of the hydrogel, which in turn alters the honey elution after the initial burst-release and thus the bacterial inhibition.⁵⁶

The addition of honey into hydrogels had positive *in vivo* results for all studies, which is demonstrated by the increased wound closure.^{54,56,57,60–65} Other studies demonstrated that the incorporation of honey hydrogel scaffolds increased re-epithelialization, angiogenesis, and granulation tissue formation.^{54,56,57,64–66} Finally, due to the anti-inflammatory ability of honey, its incorporation into hydrogels decreased the expression of proinflammatory cytokines, IL-1 α , IL-1 β , and IL-6, attributing to the beneficial healing.⁶⁵

Cryogels

Cryogel fabrication is achieved through the freezing of a polymer solution immediately after cross-linking, resulting in ice crystals surrounded by the formation of gel-like matrices in this frozen environment. When thawed, the ice crystals melt out, leaving a mechanically durable, spongy, and a macroporous structure with interconnected pores.^{45,67} Although cryogels as tissue engineering templates have become increasingly popular in recent years, the incorporation of honey is restricted to a few articles. As of this article, the current materials that have been used are silk fibrin,^{8,67} gelatin,^{8,68} PVA/chitosan,⁶¹ and PVP/PVA/Keratin/PEG.⁶⁹ Note that a hybrid chitosan–gelatin–honey-incorporated cryogel showed promising *in vivo* wound healing; however, the scaffold contained an

Figure 4. The infiltration of MG-63 (osteoblast-like) cells in silk fibroin cryogels with 1%, 5%, and 10% MH, noted as 1H, 5H, and 10H, respectively. Note that the gray scale bar denotes 100 μ m and the white scale bar denotes 40 μ m. Reproduced with permission from Hixon *et al.*⁸

array of active ingredients, making it impossible to discern the effects of honey alone.⁶⁸

With respect to antibacterial properties, the incorporation of different concentrations of honey or variations of Manuka honey UMF had no effect on the bacterial clearance by the scaffold. Cryogels exhibit a sustained release honey, which provides clearance over an extended period of time, as demonstrated by glucose assays.^{8,67}

The glucose assay also demonstrated that silk fibroin cryogels released more glucose over time than the gelatin cryogels.⁸ Interestingly, it was also demonstrated that by increasing the concentration of honey, cellular infiltration was improved, as shown in Fig. 4. Specifically, silk fibroin had more cell proliferation than gelatin, but the proliferation was less than the tissue culture plastic control; however, the addition of pure honey was cytotoxic, signifying the importance of using a vehicle, such as a cryogel, for sustained honey release.⁸

SUMMARY

The use of honey in medicine is not unexpected as its application dates back for centuries. Despite its decrease in popularity with the discovery of antibiotics over 100 years ago, the recent need for an alternative to treat infections and promote wound healing with a rise in antibiotic resistance has researchers turning back to this natural material. Not only does honey possess potent bacterial clearance but also provides many nutrition benefits, encourages angiogenesis, and accelerates wound healing. Despite these benefits, more research must be conducted to achieve a better understanding of honey's role in wound healing. Additionally, while many studies have successfully incorporated honey into tissue-engineered scaffolds, further *in vivo* work should examine the release of honey within the wound site. While there are benefits to different types of honey, there should be some type of standardization to ensure that the same bioactivity is achieved with every use. However, current research, both *in vitro* and *in vivo*, have demonstrated the potential of honey to revolutionize medical treatment and wound healing.

TAKE-HOME MESSAGES

- Honey is a potent agent in bacterial inhibition and wound healing and has recently regained popularity due to increased antibiotic resistance.
- There is currently quite a large clinical application of honey, where primarily burns and ulcers have been targeted for this treatment method.
- Unique tissue-engineered scaffolds provide a novel mode of delivery of honey to the wound site, and various studies have explored its use both *in vivo* and *in vitro*.

ACKNOWLEDGMENTS AND FUNDING SOURCES

None declared.

AUTHOR DISCLOSURE AND GHOSTWRITING

No competing financial interests exist. The content of this article was expressly written by the authors listed. No ghostwriters were used to write this article.

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Abbreviations and Acronyms

IL = interleukin
 MIC = minimum inhibitory concentration
 PVA = poly(vinyl alcohol)
 ROS = reactive oxygen species
 UMF = unique Manuka factor