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REVIEW ARTICLE

# Honey and Wound Healing: An Update

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**Abstract** For centuries, honey has been utilized for wound healing purposes. In recent times, this specific topic has become a field of interest, possibly due to the advent of antibiotic resistance in microbial pathogens. With constant technological advancement, the information regarding honey's mechanisms of action on wound healing has accumulated at a rapid pace. Similarly, clinical studies comparing honey with traditional wound care therapies are steadily emerging. As a follow-up to a previous review published in the journal in 2011, the current review article outlines publications regarding honey and wound healing that have been published between June 2010 and August 2016. Here we describe the most recent evidence regarding multiple types of honey and their mechanisms of action as antimicrobial agents, immunologic modulators, and physiologic mediators. In addition, outcomes of clinical studies involving a multitude of cutaneous wounds are also examined.

**Key Points**

Honey exerts its effects on wound healing through its antimicrobial properties and the alteration of physiologic and immunologic functions.

The successful use of honey has been reported for a multitude of wounds, including burns, surgical sites, infected surgical wounds, chronic ulcers, malignant wounds, and neonatal wounds, among others.

Systematic reviews have found "high quality evidence" and "unequivocal results" that honey is a superior dressing (relative to conventional dressings) and helps accelerate healing when treating partial thickness burns.

## 1 History and Background

The use of honey for medicinal purposes has been described since ancient times, with examples including the ancient Egyptians [1], Hippocrates and the ancient Greeks [2], Li Shizhen and the ancient Chinese [3], and religious texts including an Islamic Hadith, which is a saying of the Prophet Mohammed [4]. It has been most commonly used as a wound dressing [5] and is the oldest wound dressing material known to man [6]. As far back as 1500 BC, Ebers papyrus and Edwin Smith papyrus mention the use of honey for burn [7] and wound [8] treatment. Ayurveda (Indian medicine) records also demonstrate the use of honey in wound dressings to promote healing [7]. Ancient

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Greeks used honey in a treatment cocktail to desiccate their wounds and prevent suppuration, and the Roman army used honey for wound treatment [8]. Similarly, honey was used for wound care by Russian and Chinese soldiers during World War 1 [9, 10]. Other historical uses for honey include gastrointestinal ailments, pain relief, and defense from infections [8].

Honey, which is derived from nectar which is altered by honeybees [6], became a topic of scientific interest in the late 19th century, when its antimicrobial properties were noted by Van Ketel [11]. In the 1960s, honey was noted as a "worthless but harmless substance" [5]. Recently, however, the use of honey in the treatment of skin wounds, burns, and ulcers has experienced a revival [5, 8], becoming a focus of research, compared with its previous consideration as 'alternative.' One impetus for this interest may be the advent of antibiotic resistance to modern antibacterial medications [5]. Different kinds of honeys, such as Medihoney and Manuka honey, have been studied and found to have similar properties [6], yet honey types from different plants have been shown to have varying bactericidal abilities [5]. The majority of studies on honey for medicinal uses have been Manuka honey of the *Leptospermum* species, which is based in New Zealand and Australia [5, 12]. As our technology has advanced, clinical research and molecular biologic techniques have allowed for a greater exploration of the wound-healing properties of honey [12].

As a follow-up to the Lee et al. review titled "Honey and Wound Healing: An Overview" [12], this review outlines publications regarding honey and wound healing which have been published since May 2010. All clinical studies included in this review were not analyzed in the original 2011 Lee et al. review. PubMed MEDLINE (June 2010 to June 2016) and Cochrane Database of Systematic Reviews (2011 to June 2016) were searched using various combinations of the following terms: 'wound', 'wound healing', and 'honey'. The titles and abstracts from the initial literature search were appraised to identify articles for full review, and the references sections from each article were searched manually for relevant publications. We paid particular attention to articles describing the mechanism of action of honey or reporting the effects of honey on wound healing in vivo. We included both observation reports and randomized controlled trials in this review, as many of the wound types have not been formally examined in randomized trials. In addition to providing an update of the recently published literature, the objective of this review is to bring awareness to the possible uses of topical honey for enhancing wound care, which is a rapidly growing topic of research.

## 2 Honey Products

Given the renewed interest in honey use for wound healing purposes, many new products have been approved by the US Food and Drug Administration (FDA) since 2011 (see Table 1). *Leptospermum* honey, also known as Manuka honey, is utilized in a majority of these products. Usage instructions vary among these products, from single-use wound dressings to amorphous gels. In addition, depending on the product in question, the honey may be impregnated with other materials, including calcium alginate, which forms a gel as wound exudate is absorbed, assists in providing a moist environment, and supports autolytic debridement [13]. Some products contain irradiated honey. Irradiation is performed to protect the honey from insect and microbial contamination during storage (i.e. *Clostridium botulinum*). It has not been shown to significantly alter honey's physiochemical or mineral contents [14]. While the majority of products which have been approved by the FDA utilize Manuka honey, studies involving other types of honeys from around the world are also discussed within this review.

## 3 Mechanism of Action

### 3.1 Antimicrobial Agent

The antimicrobial effects of honey have been attributed to a multitude of factors, including high sugar content, which produces an osmotic effect leading to bacterial dehydration, and low pH (mean of 4.4) [5, 6, 15], among other factors. Honey has been shown to alter the size and shape of bacterial cells [5], with Lu et al. describing that *Staphylococcus aureus* and *Bacillus subtilis* become "significantly smaller" after treatment with sub-lethal doses of Manuka honey, in addition to having a higher likelihood of having condensed DNA in comparison with non-honey-treated bacteria [16]. When viewed under a scanning electron microscope, honey-treated *Pseudomonas aeruginosa* cultures demonstrated loss of structural integrity and changes in cell shape and surface. Under transmission electron microscopy, cell disruption and lysis was confirmed [17]. Even when honey is diluted with water, the ability to inhibit bacterial growth is still evident [5, 6]. One possible mechanism for this persistent effect is the production of hydrogen peroxide. Cooke et al. demonstrated that the antimicrobial activities of honey can be enhanced with concurrent increases in reactive oxygen species (ROS) peroxide activity [18]. The antimicrobial effect, however, is still present when catalase is neutralized. This is termed

**Table 1** US FDA-approved medical-grade honey products listed in chronologic order of FDA clearance (most recent listed first)

| Product (manufacturer; website) | Description | FDA-approved indications |
|---|---|---|
| L-Mesitran® Soft and L-Mesitran® Tulle (L-Mesitran Dressing Family II) (Theo Manufacturing BV, Maastricht, The Netherlands, http://l-mesitran.com/) | L-Mesitran® Soft is a gel that contains 40% medical-grade honey, medical-grade hypoallergenic lanolin, propylene glycol, PEG 4000, and vitamins C and E<br>L-Mesitran® Tulle is a non-adherent polyethylene dressing impregnated with the patented L-Mesitran® Soft gel | L-Mesitran Soft and Tulle are to be used in conjunction with other secondary dressings<br>OTC: Indicated for light to moderately exuding wounds. May be used for minor abrasions, lacerations, minor cuts, and minor scalds and burns<br>Under healthcare professional supervision: indicated for light to moderately exuding wounds. Intended for the management of diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and leg ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), 1st and 2nd degree partial thickness burns, donor sites, and traumatic and surgical wounds |
| Medihoney Wound Gel (Derma Sciences Inc., Toronto, ON, Canada, http://www.dermasciences.com/) | Gel dressings containing active *Leptospermum* Manuka honey, myristyl myristate, Plantacare, and the preservative sodium benzoate which is then gamma irradiated at a 25–45 kGy dosage. This will reduce the product bioburden, but this product is not claimed to be sterile | OTC: Minor abrasions, lacerations, minor cuts, minor scalds, and burns<br>Under healthcare professional supervision: indicated for non-draining to moderately exuding wounds. Intended for the management of diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and leg ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), 1st and 2nd degree partial thickness burns, donor sites, and traumatic and surgical wounds |
| Medihoney Wound Dressings including the following:<br>- Calcium Alginate Dressing with Active *Leptospermum* Honey<br>- Adhesive/Non-Adhesive Honeycolloid Dressing with Active *Leptospermum* Honey<br>- Dressing with Active *Leptospermum* Honey<br>- Gel Dressing with Active *Leptospermum* Honey<br>- Adhesive/Non-Adhesive Hydrogel Colloidal Sheet with *Leptospermum* Honey<br>(Derma Sciences Inc., Toronto, ON, Canada, and Princeton, NJ, USA, http://www.dermasciences.com/) | Calcium Alginate Dressing with Active *Leptospermum* Honey: comprises 95% active Manuka honey and 5% calcium alginate. As wound exudate is absorbed, the alginate forms a gel, which assists in maintaining a moist environment that aids and supports the autolytic debridement<br>Adhesive/Non-Adhesive Honeycolloid Dressing with Active *Leptospermum* Honey: comprises 80% active Manuka honey and 20% sodium alginate powder (hydrocolloid sheet). As wound exudate is absorbed, the alginate forms a gel, which assists in maintaining a moist environment that aids and supports the autolytic debridement<br>Dressing with Active *Leptospermum* Honey: sterile wounds dressings comprise 100% active Manuka honey, which helps to maintain a moist environment<br>Gel Dressing with Active *Leptospermum* Honey: comprises 80% active Manuka honey, 15% myristyl myristate and 5% Plantacare 810. As wound exudate is absorbed, the dressing forms a gel, which assists in maintaining a moist environment that aids and supports autolytic debridement<br>Adhesive/Non-Adhesive Hydrogel Colloidal Sheet with *Leptospermum* Honey: comprises 63% *Leptospermum* honey and hydrogel both with and without an adhesive border. As wound exudate is absorbed, the dressing forms a gel, which assists in maintaining a moist environment that aids and supports autolytic debridement | Under healthcare professional supervision:<br>Calcium Alginate Dressing with Active *Leptospermum* Honey: indicated for management of moderate to heavily exuding wounds. Intended for management of diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and leg ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), 1st and 2nd degree partial thickness burns, donor sites, and traumatic and surgical wounds<br>Adhesive/Non-Adhesive Honeycolloid Dressing with Active *Leptospermum* Honey; Dressing with Active *Leptospermum* Honey; Gel Dressing with Active *Leptospermum* Honey: indicated for the management of light to moderately exuding wounds. Intended for the management of diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and leg ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), 1st and 2nd degree partial thickness burns, donor sites, and traumatic and surgical wounds<br>Adhesive/Non-Adhesive Hydrogel Colloidal Sheet with *Leptospermum* Honey: indicated for the management of non-draining to lightly exuding wounds. Intended for the management of diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and leg ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), 1st and 2nd degree partial thickness burns, donor sites, and traumatic and surgical wounds |

**Table 1** continued

| Product (manufacturer; website) | Description | FDA-approved indications |
|---|---|---|
| Wound Dressing with Manuka Honey (Manuka Health New Zealand Ltd, Bridgewater, NJ, USA, http://www.honeywoundcare.com/) | A single-use solid state wound dressing made with medical-grade New Zealand Manuka honey and glycerine gel (from website) | OTC: minor cuts, minor abrasions, minor scalds, and minor burns<br>Under healthcare professional supervision: full and partial thickness wounds, pressure ulcers (stages I–IV), venous stasis ulcers, diabetic ulcers, abrasions, surface wounds, traumatic wounds (healing by secondary intention), donor site wounds, and surgical wounds |
| MANUKA FOAM HC (Links Medical Products, Inc., Irvine, CA, USA, http://www.linksmed.com/) | Sterile, single-use wound care dressings consisting of 100% *Leptospermum scoparium* honey from New Zealand impregnated into an absorbent foam-fiber hybrid material. One version includes a polyurethane border with a silicone adhesive, while another version includes a polyurethane border with an acrylic adhesive | Under healthcare professional supervision: leg ulcers, pressure ulcers, 1st and 2nd degree burns, diabetic foot ulcers, surgical wounds, and trauma wounds |
| MANUKA FILL (Links Medical Products, Inc., Irvine, CA, USA, http://www.linksmed.com/) | Sterile, single-use wound care dressing which consists of 100% *Leptospermum scoparium* honey from New Zealand sealed in low-density polyethylene (LDPE) tubes and sterilized using gamma irradiation | OTC: minor abrasions, minor lacerations, minor cuts, minor scalds, and minor burns<br>Under healthcare professional supervision: leg ulcers, pressure ulcers, 1st and 2nd degree burns, diabetic foot ulcers, surgical wounds, and trauma wounds |
| MANUKA IG wounds dressings (Links Medical Products, Inc., Irvine, CA, USA, http://www.linksmed.com/) | Sterile, single-use wound care dressings with 100% *Leptospermum scoparium* honey from New Zealand impregnated into acetate gauze and coated with carboxymethyl cellulose (CMC) | OTC: minor abrasions, lacerations, minor cuts, minor scalds and burns<br>Under healthcare professional supervision: leg ulcers, pressure ulcers, 1st and 2nd degree burns (superficial and partial thickness), diabetic foot ulcers, surgical wounds, and traumatic wounds |
| MANUKA FILL wound dressings (Links Medical Products, Inc., Irvine, CA, USA, http://www.linksmed.com/) | Sterile, single-use wound care dressings with *Leptospermum scoparium* honey from New Zealand which is sealed into low density polyethylene tubes (LDPE) before sterilization using gamma irradiation | OTC: minor abrasions, lacerations, minor cuts, minor scalds and burns<br>Under healthcare professional supervision: leg ulcers, pressure ulcers, 1st and 2nd degree burns (superficial and partial thickness), diabetic foot ulcers, surgical wounds, and traumatic wounds |
| Derma Sciences Medihoney Hydrogel Sheet Dressings (adhesive and non-adhesive) with *Leptospermum* Honey (Derma Sciences Inc., Toronto, ON, Canada, http://www.dermasciences.com/) | Sterile, single-use wound care dressings comprising 63% *Leptospermum* honey and hydrogel both with and without an adhesive border | OTC: minor abrasions, minor cuts, minor scalds, minor burns<br>Under healthcare professional supervision: indicated for non-draining to lightly exuding wounds. Intended for management of: diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers, and leg ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), 1st and 2nd degree partial thickness burns, donor sites, and traumatic and surgical wounds |
| Activon Tube™ Sterile 100% Manuka Honey (Advancis Medical, Kirby in Ashfield, Nottinghamshire, England; http://www.advancis.co.uk/) | Wound care dressing containing 100% Manuka Honey which is sterilized by gamma radiation | OTC: normal skin, minor wounds, minor ulcerations, minor burns, minor abraded skin, minor irritated areas<br>Under healthcare professional supervision: diabetic foot and leg ulcers, leg ulcers (venous stasis ulcers, arterial ulcers and leg ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), 1st and 2nd degree partial thickness burns, grafted and donor sites, and traumatic and surgical wounds<br>Note: may be applied directly to the wound to fill the wound cavities or to a primary dressing |

**Table 1** continued

| Product (manufacturer; website) | Description | FDA-approved indications |
|---|---|---|
| MANUKAtex wound dressings (Manuka Medical, Ltd., Mansfield, Nottinghamshire, England; http://manukamed.com) | Sterile, single-use wound care dressings which are coated with carboxymethyl cellulose (CMC) and incorporate 100% active *Leptospermum scoparium* medical-grade Manuka honey | OTC: minor abrasions, lacerations, minor cuts, minor scalds and burns<br>Under healthcare professional supervision: leg ulcers, pressure ulcers, 1st and 2nd degree burns (superficial and partial thickness), diabetic foot ulcers, surgical wounds, and traumatic wounds |
| Derma Sciences Medihoney Gel Dressings with Active Manuka Honey (Derma Sciences Inc., Toronto, ON, Canada, http://www.dermasciences.com/) | Sterile wound care dressings comprising 80% active Manuka honey, 15% myristyl myristate, and 5% Plantacare 810 | OTC: minor abrasions, lacerations, minor cuts, minor scalds and burns<br>Under healthcare professional supervision: diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers and leg ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), 1st and 2nd degree partial thickness burns, donor sites, and traumatic and surgical wounds |
| Activon Tulle (Advancis Medical, Kirby in Ashfield, Nottinghamshire, England; http://www.advancis.co.uk/) | Sterile, non-adherent, knitted viscose primary dressing impregnated with 100% Manuka honey | OTC: minor wounds, ulcerations and burns, abraded skin, and irritated areas<br>Under healthcare professional supervision: diabetic foot ulcers, leg ulcers (venous stasis ulcers, arterial ulcers and leg ulcers of mixed etiology), pressure ulcers/sores (partial and full thickness), 1st and 2nd degree partial thickness burns, grafted and donor sites, and traumatic and surgical wounds |
| MANUKAhd® wound dressings (Manuka Medical, Ltd., Mansfield, Nottinghamshire, England; http://manukamed.com) | Sterile, single-use wound care dressings containing a super absorbent polymer (SAP) fiber material impregnated with 100% medical Manuka honey and coated with carboxymethyl cellulose (CMC) | OTC: minor abrasions, lacerations, minor cuts, minor scalds and burns<br>Under healthcare professional supervision: leg ulcers, pressure ulcers, 1st and 2nd degree burns (superficial and partial thickness), diabetic foot ulcers, surgical wounds, and traumatic wounds |
| OTC Elasto-Gel Manuka Honey Wound Dressing (Southwest Technologies, Inc., N. Kansas City, MO, USA; http://www.elastogel.com) | Amorphous gel containing a mixture of a super absorbent crosslinked sodium polyacrylic acid, glycerine, honey, and water | OTC: minor cuts and abrasions, scrapes, surface wounds, minor scalds and burns |

*FDA* Food and Drug Administration, *OTC* over the counter

'non-peroxide activity' and is due to methylglyoxal (MGO), which can interact with DNA, RNA, and proteins [5]. MGO appears to be related to Manuka honey's ability to inhibit biofilm formation [5, 19]. Biofilms may persist in wounds and impair healing [19]. In fact, Manuka honey at 50% was shown to cause "significant partial detachment" of *Proteus* biofilms after 24 h [19]. Honey antimicrobial factors may be interacting or inter-regulating, as the treatment of defensin 1, a honey antimicrobial protein effective against Gram-positive bacteria, with MGO led to a time-dependent decrease in antimicrobial activity [20]. The level of another *Leptospermum* glycoside, Leptosin, correlates with honey potency and may affect its antimicrobial activity [21]. In *Pseudomonas aeruginosa*, treatment with Manuka honey led to downregulation of flagella-associated proteins [22], destabilization of the cell wall [22], and at sublethal concentrations, inhibition of siderophore production [23]. Inhibition of siderophore formation decreases the virulence of the bacteria, as siderophores allow *P. aeruginosa* to scavenge iron from the host environment [23]. In addition, Jenkins and Cooper demonstrated a downregulation of *mecR1*, a regulator of a penicillin-binding protein called mecA, in Manuka-treated methicillin-resistant staphylococcus aureus (MRSA), which resulted in a reversal of oxacillin resistance [24].

### 3.2 Immunologic Modulator

The immunomodulatory activity of honey involves many compounds with a variety of mechanisms. Studies have demonstrated that honey can alter cytokine release. According to Gannabathula et al., New Zealand honeys have been shown to release tumor necrosis factor alpha (TNF-α) from monocytic cell lines [25]. In addition, Majtan speculates that honey can stimulate the production of inflammatory cytokines in settings of low inflammation, while suppressing these same cytokines during the settings of infection, including TNF-α and interleukin-β [19].

Honey has also been shown to have anti-inflammatory properties, as Gelam honey has been shown to inhibit cyclo-oxygenase (COX)-2 and inducible nitric oxide (NO) synthase expression in rats [26]. In animal models, however, the anti-inflammatory effect was still present despite the absence of infection [6]. In addition, honey can have an antioxidant effect [27], secondary to alterations of neutrophil production of ROS, possibly secondary to the inhibition of neutrophilic respiratory burst [19]. New Zealand honey has been shown to decrease human neutrophil superoxide production without correlation with phenolic compounds, which are known free-radical scavengers in honey [28]. Fukuda et al., however, hypothesize that Jungle honey's antitumor activity is secondary to increased ROS via neutrophil activation [29], which exemplifies the need for more study to understand these mechanisms, especially when comparing differing types of honey. Finally, honey has been shown to alter immune cell function and movement. As Gannabathula et al. describe, Arabinogalactan proteins of New Zealand Kanuka honey can alter the immune system by activating monocytes [25]. In Jungle honey, a 261 Dalton compound was found to elicit chemotaxis in neutrophils [29]. In addition, honey may inhibit leukocyte infiltration [28]. Despite these advances in understanding honey's immunologic modulatory capabilities, further studies are warranted to fully elucidate these complex mechanisms of action.

### 3.3 Physiologic Mediator

Wound healing comprises the following stages: coagulation and hemostasis, inflammation, proliferation, and wound remodeling [30]. Honey has been shown to contribute to some of these stages, thus altering the natural physiology of wound healing. Honey reduces edema and exudate [31] from wounds. While Hussein et al. note that Gelam honey inhibits inducible NO synthase in rats [26], Al-Waili et al. note that local application of honey can alter inflammation via an increase in NO end products and a decrease of prostaglandin levels [32]. This statement was supported by previous studies (not involving Gelam honey) which demonstrated that honey contains NO end products [33] and that oral ingestion of honey could increase NO production in various body fluids, including saliva, blood, and urine [34]. This further strengthens the notion that differing honey types have different properties. In addition, honey's acidic pH can increase oxygen off-loading from hemoglobin, thus enhancing healing [6]. Honey has been shown to provide rapid autolytic debridement of wounds, stimulate granulation and epithelialization, and provide a moist environment which helps minimize scar formation [5, 31], including the formation of hypertrophic scars [35]. Fir honeydew honey has been shown to alter activity of matrix metalloproteinase-9 (MMP-9), a protease which is responsible for matrix degradation and cell-growth-promoting agents in chronic wound fluid in human keratinocytes [36], which may alter the wound proliferation and remodeling phases. Majtan speculated that in low inflammatory settings, honey stimulates inflammatory cytokines and MMP-9, but in high inflammatory settings, these factors are suppressed. This hypothesis also supports the notion of honey altering the inflammatory and wound remodeling phases of wound healing [19].

## 4 Clinical Uses of Honey

Honey has been used for medicinal purposes since antiquity. In 2011, Lee et al. noted that honey use for burn wounds has been documented in modern-day scientific journals since as early as 1933 [12]. In 1973, *JAMA* published an article discussing the use of honey for treatment of decubitus ulcers [37]. In 1980, the use of honey was documented for the treatment of infected wounds [38] and necrotic breast ulcers [39, 40]. The potential use of honey for infected wounds was again documented in 1982 [41]. In 1988, Efem noted honey's ability to sterilize infected wounds within 1 week of topical application, to rapidly debride wounds, and to promote epithelialization, among other properties [42]. As interest in honey for medical purposes grew, many FDA-approved products began emerging, including many in the last 5 years (see Table 1). With more interest came an increase in clinical studies examining honey for treatment of a variety of wounds, including randomized trials, case series, and cross-sectional studies from specialties ranging from dermatology and general surgery to ophthalmology. Many of these findings from the last 5 years have been summarized in the following sections and in Table 2 (see electronic supplementary material). Due to the multitude of available publications, our inclusion criteria for frequently studied wound types included the studies with the largest sample sizes and from the most reputable journals. Studies with smaller sample sizes and case reports were included for more rarely studied wound types.

### 4.1 Acute Wounds

#### *4.1.1 Burns*

Evidence supporting the benefit of honey application to burn sites has continued to accumulate in the past 5 years. The antimicrobial properties of honey (listed in section 3.1) are of interest, as bacterial contamination is a frequent concern in burn care [43]. Maghsoudi et al. [44] compared the application of honey dressings and mafenide

acetate in two randomized groups of 50 patients with fresh partial thickness burns. "Pure, unprocessed, undiluted honey obtained from hives" was utilized. A higher percentage of the honey-treated group experienced satisfactory epithelialization by days 7 and 21 in comparison with the mafenide acetate group (honey group: 84, 100%; mafenide acetate: 72, 84%). In addition to quicker wound healing, control of infection and inflammation was superior in the honey treatment-group [44]. When comparing honey ($n = 51$) to silver sulfadiazine ($n = 57$) in burn patients with first and second degree burns of <50% of total body surface area, the average healing time was shorter in the honey group (18.16 days vs 32.68 days, $p < 0.05$). For patients who reported within the first hour post-burn, all of the wounds treated with honey ($n = 8$) became sterile within 14 days, compared with two of 14 cases treated with silver sulfadiazine ($p < 0.05$). In addition to improving outcomes with regards to hypertrophic scars and contractures, complete recovery was seen in a higher percentage within the honey treatment group (78% vs 47%, $p < 0.002$) [45]. Multiple reviews of the available literature support these findings that honey has proven efficacious in the treatment of burn wounds [46, 47], specifically partial thickness burns [46]. Honey use for full thickness burns, however, appears to delay healing time when compared with surgical treatments [46].

#### *4.1.2 Surgical and Traumatic Wounds*

Literature on the use of honey for non-infected surgical and traumatic wounds has also continued to emerge. Subrahmanyam [48] described a randomized trial of 100 skin graft donors who were divided into an Indian *Syzygium cumini* honey-treated treatment group ($n = 50$) and a Vaseline gauze-treated treatment group ($n = 50$). On Day 7 of treatment, 48/50 of the honey group had experienced epithelialization, in comparison with 39/50 of the Vaseline gauze-treated group ($p < 0.05$). By Day 10, all wounds had healed in the honey treatment group, in comparison with 38/50 (76%) of the Vaseline gauze-treated group ($p < 0.05$) [48]. Similarly, Parmar et al. documented their successful use of honey as a wound dressing in split-thickness skin graft donors, subjectively observing that patients report less pain and concern than with previous standard dressings. They also subjectively noted earlier epithelialization and healing, and decreased incidence of infection [49]. In segmental mandibular resections resulting in wound dehiscence which could not be closed primarily, Anyanechi and Saheeb described a randomized trial with two groups consisting of Nigerian Obudu honey dressing ($n = 36$) and control ($n = 36$). At 5 weeks of treatment, the honey group had experienced more healing (19/36, 52.8%) in comparison with the control group (13/36, 36.1%). However, at 9 weeks the difference in healing was not statistically significant ($p = 0.23$) [50].

Nikpour et al. [51] described a triple-blind randomized prospective clinical trial comparing the use of 25% honey gel (containing coriander and Goat's thorn honey) ($n = 37$) and placebo gel ($n = 38$) on post-Cesarean section abdominal wounds, which utilized the REEDA scale (Redness, Edema, Ecchymosis, Discharge, Approximation of Wound Edges) to measure outcomes. On Day 7 and Day 14 of treatment, redness, edema, and hematoma formation was lower in the honey treatment group ($p = 0.002$) [51]. Dryden et al. examined the use of Surgihoney as a single-application wound dressing in post-Cesarean section wounds in a retrospective observational study. Surgihoney has been engineered to have three adjustable levels of antimicrobial potencies and has antimicrobial activity comparable to chemical antiseptics [52], while retaining the wound healing properties of natural honey [53]. In this study, Surgihoney 10 g was applied to the surgical wound using aseptic technique, with the patients subsequently monitored for 30 days for any signs of surgical site infection. Overall, a sample size of 186 patients was included in the 3-month study period. Four of 186 women experienced surgical site infections (2.15%) and one patient reported an adverse effect to the Surgihoney (wound irritation). In the prior 9 months (where Surgihoney was not utilized), 590 Cesarean sections were completed with an infection rate of 5.42% (32/590). This represents a 60% reduction in surgical site infections ($p = 0.042$). The timing of antibiotic doses was not uniform between patients in the pre-Surgihoney and Surgihoney time periods, which may be a confounding factor. In addition, the study was not randomized [53]. Heidari et al. [54] also examined the use of honey on post-Cesarean section wounds in a prospective randomized trial, with a sample size of 130 women divided into honey (Iranian *Astragalus gossypinus* honey) ($n = 44$), placebo ($n = 42$), and control ($n = 46$) groups. The REEDA scale was also used to assess the wounds in this study on the 10th and 40th post-operative day. A difference in REEDA scale findings on post-operative day 40 was found between honey and control groups ($p < 0.001$), but not between honey and placebo groups. The authors concluded that their findings did not support the use of Iranian *Astragalus gossypinus* honey for accelerated wound healing and prophylaxis of scar formation [54].

While many studies support the use of honey in surgical and/or traumatic wounds [51, 53], the contradiction with Heidari et al. validates the need for additional clinical trials, especially utilizing the same type of honey. In addition, some cases describing honey use in surgical wounds did not yield a significant difference. Johnson et al. [55] performed a randomized study comparing the combination of

Medihoney Antibacterial Wound Gel plus standard wound care ($n = 186$) with the combination of standard wound care plus intranasal mupirocin prophylaxis (in nasal *S. aureus* carriers only) ($n = 185$) in peritoneal dialysis wound sites with regards to infection prevention. No statistically significant difference in median infection-free times was found [55].

## 4.2 Chronic Wounds

### *4.2.1 Infected Surgical and Traumatic Wounds*

While sparse, literature on honey use in infected surgical and traumatic wounds has demonstrated efficacy of honey treatment. Jarjis et al. [56] described the use of topical Manuka honey in a post-bariatric abdominoplasty patient who developed wound infection and dehiscence. With the use of honey, healing was effective and resulted in 'significant' clinical improvement [56]. Majtanova et al. [57] described a case of a 23-year-old contact lens user who developed a corneal ulcer 7 days after swimming in a lake. Cultures from the corneal scraping grew numerous organisms, including *Stenotrophomonas maltophila*. A combination of topical levofloxacin and 25% irradiated honeydew honey solution was an effective treatment, and in vitro, the honeydew honey solution proved effective against the *S. maltophila* [57]. One 2005 study by Okeniyi et al. examined the use of honey-soaked gauze compared with Edinburgh University solution of lime (EUSOL)-soaked gauze in healing of pyomyositis abscesses excision sites ($n = 43$). The study spanned 3 weeks, with 20/23 (87%) patients in the honey group healed, in comparison with 11/20 (55%) in the EUSOL group (relative risk 1.58; confidence interval 1.03–2.42). In addition, the mean length of hospital stay was decreased in the honey group (mean difference $-2.50$ days, $p = 0.019$) [58]. While reports and studies of honey use in infected wounds are emerging, however, more clinical trials are still necessary.

### *4.2.2 Pressure Ulcers*

Biglari et al. [59] reported a prospective, observational study of Medihoney use for chronic pressure ulcers in 20 spinal-cord-injury patients. Five patients had grade IV ulcers, while the rest had grade III ulcers, with locations including sacral, leg, and ischial, among others. After week 1 of treatment, bacterial swabs from all patients did not result in growth, and after week 4, 18 patients (90%) showed complete wound healing with soft and elastic scars. No adverse effects were noted [59]. Khadanga et al. [60] compared the effectiveness of honey ($n = 20$) and povidone iodine ($n = 20$) dressings in decubitus ulcer healing in an observational, cross-sectional study. While the reduction in wound size and bacteriologic cultures were not significantly different, the subjective pain on a visual analog scale (VAS) was lower in the honey group ($p = 0.010$) [60]. Saha et al. [61] described a randomized study comparing treatment with honey plus metronidazole powder ($n = 20$) to metronidazole powder only ($n = 20$) in cancer patients with bedsore wounds. A standardized Bates Jensen Wound Assessment Tool and VAS were utilized to assess wound healing and subjective pain, respectively. Utilizing $F$ value statistical analysis, the authors declared a statistically significant increase in wound healing between days 1 and 10 of treatment and a decrease in subjective pain between days 1 and 7 in the treatment group [61].

### *4.2.3 Lower Extremity Ulcers*

Literature on the use of honey in lower extremity ulcers has emerged with differing conclusions based on the type of ulcer at hand. Imran et al. conducted a randomized, controlled trial examining the use of Pakistani Beri (*Ziziphus jujuba*)-honey-impregnated dressings in diabetic foot ulcers. These patients, with grade 1 and 2 Wagner graded ulcers, were randomized into a honey treatment group ($n = 179$) and a saline control group ($n = 169$). With a maximum follow-up of 120 days, 136/179 (75.97%) of the honey group healed completely, in comparison with 97/169 (57.39%) of the control group ($p = 0.001$). In addition, the application of honey decreased the median healing time (18.00 days vs 29.00 days, $p < 0.001$) [62]. Kamaratos et al. [63] conducted a prospective, randomized, double-blind study examining the use of Manuka-impregnated honey dressings (Medihoney Tulle) in Caucasian type 2 diabetes mellitus patients with neuropathic diabetic foot ulcers. These patients were divided into a honey treatment group ($n = 32$) and a saline-soaked gauze-dressing control group ($n = 31$), with follow-up for 16 weeks. A Perfusion, Extent/size, Depth/tissue loss, Infection, and Sensation (PEDIS) system was utilized for evaluating the wounds. While there was not a significant difference in the percent of ulcers which healed, the use of honey decreased mean healing time ($31 \pm 4$ days vs $43 \pm 3$ days, $p < 0.05$). In addition, 78.13% of the ulcers in the honey group became sterile after 1 week of treatment, in comparison with 35.5% of the control group. Overall, 0/32 (0%) patients in the honey group required antibiotic treatment, while 9/31 (29%) control group patients did, of whom four were hospitalized. This led to the authors to conclude that the Manuka honey-impregnated dressings "nullified the need for antibiotics and hospitalizations" in patients with neuropathic diabetic ulcers [63]. While these studies support clinical efficacy of honey use for diabetic neuropathic ulcers, Majtan noted that the MGO contained within

Manuka honey is a precursor of advanced glycation end products (AGEs) [64]. AGEs are involved in the pathophysiology of cardiovascular disease as they stimulate inflammation and affect vascular stiffness [65]. This relationship between MGO, AGEs, and vessel disease implies that honey may possibly delay clinical diabetic wound healing [64]. More study is necessary to further clarify the relationship between the noted clinical outcomes and Majtan's hypothesis.

Gulati et al. [66] performed a randomized study on clean, non-infected chronic wounds of ≥6 weeks' duration, the majority of which were of venous etiology. Forty of 42 wounds were on the lower extremity. Honey dressings ($n = 22$) were compared with povidone iodine dressings ($n = 20$). Seven of 22 (31.82%) patients in the honey group versus 0/20 (0%) in the povidone iodine group achieved complete healing at 6 weeks of treatment ($p < 0.05$). Decreases in wound surface area and pain scores (assessed via VAS) and increase in overall comfort score of dressings (assessed via VAS) were also seen in the honey treatment group ($p < 0.05$) [66]. Holland and Norris [67] conducted a review of the use of medical-grade honey in patients with chronic venous leg ulcers. Due to conflicting findings and lower grades of evidence, they concluded that inconclusive evidence was present to declare that honey use resulted in improved outcomes [67]. Ruttermann et al. recommended against the use of honey in wounds due to previous studies which showed that honey does not accelerate wound healing and may result in more pain in patients with venous leg ulcers [68]. Despite this lack of high-quality randomized controlled studies of honey use, one author still claims that treatment with honey is an efficient, cost-effective option in diabetic foot syndrome [69]. This dialogue signifies the importance of more high-quality randomized trials on the use of honey in both lower extremity venous ulcers and diabetic ulcers.

#### *4.2.4 Other Chronic Wounds*

Thomas et al. [70] completed a retrospective study investigating the effectiveness of topical Manuka honey for recurrent or chronic pilonidal sinus disease. Of the 17 patients in the study, 15 experienced complete wound healing, while one patient discontinued the honey treatment due to an adverse effect. The mean time to commencing honey therapy after surgery was 93 days (range 5–517 days; median 33 days) and mean time of healing was 65 days (range 14–262 days; median 49 days). Of the 17 patients, two experienced recurrences after completing the honey treatment [70]. Haidari et al. [71] reported on their retrospective study examining the use of topical honey, concurrent with other treatment options, in 17 patients with Fournier's gangrene. After treatment with Betadine, normal saline, and 2% oxygenated water, 30–50 cc of honey was used on the wounds. The mean hospitalization time was 12 ± 6 days, which the authors noted to be much shorter than in comparable studies which did not use honey as part of the treatment regimen. As there was not a control group in Haidari's study, however, the authors disclose the need for further studies, including placebo-controlled clinical trials [71].

### 4.3 Mixed Acute and Chronic Wounds

Biglari et al. [72] conducted a 5-week, prospective, observational, multicenter trial in ten hospitals examining the use of Medihoney™ in wounds of varying etiologies. Over a 2-year period, 104 patients were included in the analysis, with wound etiologies including post-operative ($n = 26$), decubitus ulcers ($n = 20$), soft tissue infections ($n = 8$), and "undergoing treatment for cancer" ($n = 32$), among others. In the honey treatment group, a significant decrease was seen in the wound size, perceived pain levels, and wound sloughing/necrosis ($p < 0.05$) [72].

Dryden et al. [73] described a prospective, multi-institutional evaluation of the efficacy of Surgihoney for treatment of acute and chronic wounds with established delayed healing. The sample size consisted of 104 patients (including 33 with leg ulcers, 18 with pressure ulcers, 14 with surgical wounds, five with diabetic ulcers, and 20 with traumatic/surgical wounds in the developing world) with a total of 114 wounds. The mean duration of wounds prior to treatment was 3.7 months, and the mean duration of Surgihoney treatment was 25.7 days. Twenty-one percent of wounds (24/114) healed completely after treatment, and the remaining 79% (90/114) improved, with no deterioration noted. Of the 37 leg ulcers, 68% (25/37) demonstrated a reduction in size while 92% (34/37) showed improvement in healing. Of the 19 pressure ulcers, 63% (12/19) demonstrated a reduction in wound size and 89% (17/19) showed improvement in healing. Reductions were also noted in patient pain levels, wound exudate, and devitalized tissue. While bacterial cultures were not performed on all wounds, 39 of the 40 swabbed cultures showed reduction in bacterial load when treated with Surgihoney [73].

Studies of honey use in radiation-induced mucositis (RIM) have also emerged in the past 5 years. Maiti et al. [74] performed a prospective study examining the use of "pure natural honey" in 55 patients with head and neck cancer which required radiation therapy. The treatment group consisted of the combination of chemoradiation and topical honey application ($n = 28$), compared with chemoradiation only ($n = 27$). A significant decrease in symptomatic grade 3 (18 vs 41%) and grade 4 (4 vs 22%) mucositis was seen in the treatment group [74]. In contrast, Hawley et al. [75] performed a double-blind, randomized,

placebo-controlled trial comparing irradiated Manuka honey ($n = 54$) with placebo gel ($n = 52$), which the cancer patients were told to "swish, hold, and swallow" four times daily during radiation treatment, and 7 days' post-radiation treatment. Eighty-one patients who underwent at least one mucositis assessment were included in the analysis, which revealed no statistically significant difference in any outcome indicators. In addition, the Manuka honey was not tolerated very well by the patients [75]. Bardy et al. [76] also compared the use of Manuka honey ($n = 64$) with a golden syrup placebo ($n = 63$) in a double-blind, placebo-controlled, randomized trial in patients with head and neck cancer undergoing radiation therapy, and noted no difference in their effects on mucositis [76].

### 4.4 Malignant Wounds

Malignant wounds occur in 5–10% of cancer patients, with the most common side effects being malodor and exudation [77]. Lund-Nielsen et al. conducted a randomized study comparing the use of Manuka honey-coated bandages ($n = 34$) with silver-coated bandages ($n = 35$) in patients with malignant wounds and advanced cancer. While the median decrease in wound size did vary by treatment group (honey group 15 $cm^2$, silver group 8 $cm^2$), the difference was not statistically significant ($p = 0.63$). Utilizing the VAS score, however, significant differences in malodor ($p = 0.007$) and exudation ($p < 0.0001$) were noted [77]. This palliative use of honey has also been described in a patient struggling with the malignant odors of oral squamous cell carcinoma, where the application of Manuka honey decreased the odor and inflammation which the patient experienced [78]. In a prospective, randomized, single-blind study, Lund-Nielsen et al. compared the effect of Manuka honey ($n = 34$) with silver coating ($n = 33$) on the bacteriology of malignant wounds. The type and variety of wound pathogens between the groups did not demonstrate significant differences [79]. However, as Kamaratos et al. point out, this study did not perform quantitative analyses, thus overlooking possible antimicrobial differences between the treatments [63]. In addition, 81% of the patients in Lund-Nielsen's study were undergoing chemotherapeutic treatment regimens. Kamaratos et al. hypothesize that honey penetration in this study population may have been low, as wound debridement was not completed and the antineoplastic treatment could result in more necrosis and wound debris [63].

### 4.5 Systematic Reviews

As studies examining honey use for wound healing increase, so have the number of systematic reviews. Jull et al. [80] completed a Cochrane systematic review and found 'high quality evidence' that honey dressings, in comparison with conventional dressings, heal partial thickness wounds more quickly (two trials, $n = 992$). The evidence is unclear, however, on honey's effects on adverse effect rates ('very low quality evidence') and infection ('low quality evidence'). 'High quality evidence' was found (six trials, $n = 462$) that no difference in overall healing within 6 weeks was present when comparing honey with silver sulfadiazine, while a decrease in the overall risk of adverse effects with honey treatment was found. One trial ($n = 50$) was found showing 'moderate quality evidence' that honey healed infected post-operative wounds more rapidly than antiseptic washes and gauze, with fewer adverse effects. The authors concluded that the rest of the evidence was not suitable for determining other conclusions on honey as a topical wound treatment [80].

Lindberg et al. completed a systematic review of the literature which compared honey with silver on burns. Six randomized control trials ($n = 512$) were found, and confirmed honey's effectiveness as an antibacterial dressing in burns, deeming the results "unequivocal" that honey was superior to silver. They found that application of honey resulted in quicker healing, increased number of wounds which healed, and better antimicrobial effects [81]. In 2013, Vandamme et al. [82] reached a similar verdict to Lindberg et al., stating that randomized studies on burns show a clear link between antimicrobial effect and faster wound healing with honey treatment. With other wound types, the authors state that such a link is "not always obvious". The authors point out that even the antimicrobial properties of honey in burns should be further examined, as five of seven randomized controlled trials are by the same investigator, and in six trials, "pure, undiluted" honey is used without composition specifications [82].

Norman et al. completed a Cochrane systematic review on surgical wounds healing by secondary intention, and noted the Okeniyi et al. study examining the use of honey-soaked gauze compared with EUSOL-soaked gauze in healing of pyomyositis abscess excision sites to be 'moderate quality evidence' due to the small sample size ($n = 43$) [83].

### 4.6 Ongoing Trials

Continued investigation of honey use in wound healing is underway. One phase II study is currently recruiting participants to compare the use of New Mexico honey with standard-of-care sulfamethoxazole/trimethoprim antibiotics on wounds infected with community-acquired MRSA [84]. Multiple studies involving pressure ulcers are currently recruiting participants. One New York-based phase IV study is currently recruiting participants to compare *Leptospermum scoparium* honey with standard therapies

and determine if it will reduce site inflammation, site pain, and costs of treatment [85], while a French study is currently recruiting participants to examine wound surface evolution with the use of honey-impregnated dressings (Hyalumel) [86]. An Illinois-based phase IV study is currently recruiting participants to investigate the use of TheraHoney HD as a sacral pressure ulcer debridement product to determine efficacy on wound healing, as well as product safety [87]. A New York-based phase IV study is currently recruiting participants to compare the use of Manuka honey with standard wound care therapies in patients undergoing reconstructive surgery, assessing split-thickness skin graft and free tissue transfer donor sites to evaluate the honey's effect on scar scales (utilizing the Modified Vancouver Scar Scale) and patient pain scores [88]. Similarly, a Pennsylvania-based study is currently recruiting participants to compare MediHoney gel with active *Leptospermum* honey dressing versus a collagenase ointment (Santyl®) with regards to healing time, change in wound appearance, bacterial growth, patient satisfaction, and treatment costs in patients with partial thickness burns [89]. A French phase IV study is examining how sterile honey dressings (Melectis G) change healing time after pilonidal cyst excisions [90]. An Israel-based phase IV study is currently recruiting participants to examine the use of Medihoney dressings in comparison with paraffin gauze with saline (control group) and Polymem dressing (comparison group) for healing in split-thickness skin-graft donor sites [91]. While all of the studies mentioned to this point are actively recruiting participants, a University of Missouri-Columbia-based study is recruiting renal failure patients by invitation only to enroll in a study examining MediHoney use to facilitate catheter exit-site surgical wound healing, assessing the time from catheter wound implantation to first exit-site infection (up to 2 years, whichever comes first) [92].

## 5 Additional Considerations

Honey has also shown potential uses in other aspects of medicine. In addition to Medihoney successfully treating multi-drug-resistant bacteria (specifically MRSA and *A. baumannii*) in vitro [93], combining honey with other treatments, specifically antimicrobials, has shown some benefit of synergism, where the combined activity is greater than the sum of the individual drug activities [5]. Jenkins and Cooper have demonstrated in vitro synergism between Manuka honey and numerous antimicrobials, including oxacillin [24], tetracycline, imipenem and mupirocin for MRSA [94], and additivity for Manuka honey with rifampicin, tetracycline, and colistin in treating *P. aeruginosa* [94]. Synergism has also been demonstrated between Medihoney and rifampicin for MRSA, in addition to halting the appearance of rifampicin-resistant *S. aureus* in vitro [95], which is clinically relevant because the development of resistance to rifampicin is often rapid [5]. Liu et al. also confirmed a frequent in vitro synergistic effect between Manuka-type honey and rifampicin, oxacillin, gentamicin, and clindamycin in the treatment of *S. aureus*. In cases where synergism was not present, a significant enhancement in susceptibility to the antimicrobial was seen, and in some highly resistant strains, a return of antimicrobial susceptibility [96]. On a related note, while clinical trials are still necessary, honey has been shown to be an effective anti-varicella zoster virus treatment in vitro [97]. Concurrent honey-gel use with silver dressings resulted in an increased osmolarity and did not decrease the in vitro antibacterial barrier activity of silver dressings, even increasing it in some cases [98]. Despite all of these in vitro relationships between honey and other treatments, clinical trials are still necessary.

Many factors predispose infants and neonates to skin injuries, including the presence of multiple devices on the skin during hospitalization [99]. While wound care in neonatal and pediatric populations is difficult due to a lack of standardization [100], recent literature has shown that honey is safe in this population. Amaya conducted a multicenter, retrospective, chart review of the use of active *Leptospermum* honey in 115 neonatal and pediatric patients, with a total of 121 wounds. Only two (1.7%) of the patients reported an adverse effect, which involved a "transient stinging sensation on application", which led the authors to deem this topical treatment safe and effective in this age group [100]. Mohr et al. described a case series where active *Leptospermum* honey was used in three neonates with wounds of varying etiologies, including ischemia and intravenous solution extravasation, further confirming the efficacy of honey treatment, as well as expanding on potential uses for wounds of differing etiologies [101]. Boyar et al. confirm Mohr et al.'s finding, as they describe a case series of successful Medihoney (containing *Leptospermum* honey) use in the treatment of a neonatal stage 3 pressure ulcer, a dehiscent and infected sternal wound, and a full-thickness wound from an extravasation injury [99]. In addition, Surgihoney honey has been shown to be effective in the treatment of a neonatal surgical site infected with MRSA [102].

Honey has also been shown to be of other possible utility. In six patients with wounds requiring debridement, after 9–20 days of treatment with active *Leptospermum* honey, the wounds were completely (or almost completely) debrided, with a 75% average increase in wound bed granulation tissue [103]. Stewart et al. suggested that honey's non-perishable food status and low risks may make it suitable for use in wilderness wound care or in resource-

poor environments, where its renewable nature is of vast importance [104].

In addition, varying honey types from around the world may have differing or similar antimicrobial effects in wound settings. Malaysian Tualang honey has proven more effective than Manuka honey against Gram-negative bacterial strains in burn wounds [105]. In addition, Dryden et al. advocate for the use of Surgihoney instead of Manuka honey for infection prevention, given its activity against Gram-positive, Gram-negative, and multi-drug-resistant bacteria [102]. Boateng and Diunase demonstrated that Cameroonian honeys possess antibacterial activity similar to that of medical-grade Manuka honey when examining minimum inhibitory concentrations in vitro against *E. coli*, *P. aeruginosa*, and *S. aureus* [106]. In addition, the Cameroonian honeys were shown to exhibit non-peroxide antimicrobial activity. Gomes et al. compared five commercial Portuguese honeys and noted that yeast growth (*Z. rouxii* ESA23, *Z. mellis* ESA35) did not vary with differing honey concentrations or with type of honey used. The effect of these Portuguese honeys on bacteria or comparisons with medical-grade Manuka honey were not examined [107]. These reports support the notion that studies further examining the clinical use of honey for skin disease of microbiological etiology are still needed [108].

As honey is classified as an emollient/humectant/moisturizing product by the International Nomenclature of Cosmetic Ingredients, and the fact that it is a natural product, honey derivative use in cosmetic agents is increasing. While honey allergies are not common, products containing honey-based derivatives may contain pollen and bee proteins, which may act as sensitizers and result in adverse reactions [109].

Given the many types of honey, each with their own chemical compositions and properties, there is no uniform honey formulation and application procedure as it pertains to research studies. Also, non-medical-grade honeys may contain compounds which affect the outcomes of studies. Additional study regarding honey products is still needed, specifically with a uniform combination of honey and treatment application, in addition to comparisons between differing types of honeys to better elucidate which type is most efficacious for certain wound types. Additional basic science research on honey and its properties is also needed to correlate clinical study findings.

Within this narrative review, we have summarized and organized the most recent literature within a rapidly growing field (see Table 2, electronic supplementary material). One limitation of a narrative review is the restriction to summarizing data. By definition, randomized controlled trials result in higher levels of evidence than observational studies. As some wound types have not been examined in randomized control trials, however, this presents a challenge when comparing studies. Overall, our review of the latest literature has demonstrated that honey has some proven clinical uses in wound healing (i.e., more rapid healing in partial thickness burns), while also bringing awareness to the possibility and need for randomized controlled studies for certain wound types (i.e., pilonidal cyst disease). Clinically, medical-grade honey may be an affordable wound dressing for those who cannot afford other dressings or those in rural settings.

## 6 Conclusions

The use of honey in wound healing has been described since antiquity. As our technology improves, the mechanisms of honey's antibacterial and healing effects are slowly becoming understood. While unbiased, large randomized clinical trials are still necessary to elucidate precise scientific wound healing outcomes involved with honey use, the majority of the literature that has accumulated throughout the past 5 years supports the notion that honey is efficacious in improving healing in a variety of cutaneous wounds.

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