Resistance of pathogenic microorganisms to antibiotics is a serious global health concern. In this review, research investigating the antimicrobial properties of honeys from around the world against skin relevant microbes is evaluated. A plethora of in vitro studies have revealed that honeys from all over the world have potent microbicidal activity against dermatologically important microbes. Moreover, in vitro studies have shown that honey can reduce microbial pathogenicity as well as reverse antimicrobial resistance. Studies investigating the antimicrobial properties of honey in vivo have been more controversial. It is evident that innovative research is required to exploit the antimicrobial properties of honey for clinical use and to determine the efficacy of honey in the treatment of a range of skin disorders with a microbiological etiology.

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Introduction

In traditional medicine, honey has been recognized around the world for its skin-healing properties. The ancient Greeks and Egyptians, for example, used topical application of honey to treat skin wounds and burns, and Persian traditional medicine documented honey to be effective in the treatment of wounds, eczema, and inflammation.1,2

Microorganisms have been associated with the pathophysiology of a range of dermatological disorders. Wound infections, for example, are commonly caused by the microorganisms *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, and infection with *S. aureus* is common in atopic dermatitis.3,4 Another example is *Malassezia* yeasts, which have been associated with the skin conditions pityriasis versicolor, seborrheic dermatitis, atopic dermatitis, and psoriasis.5 Conventional treatments for some of these conditions are unsatisfactory, e.g.,
corticosteroids cause skin thinning and UV radiation therapy has been associated with the development of skin cancer.6

Scientists first reported the ability of honey to kill disease-causing microbes in the late 1800s, but with the advent of antibiotics in the early 1900s, scientific interest in honey waned.7 Today, with the emergence of antibiotic-resistant microbial strains, such as methicillin-resistant S. aureus (MRSA)—a cause of difficult-to-treat wound infections and a global health concern, honey has again caught the attention of medical researchers.7,8

In clinical practice today, Manuka honey produced by honey bees (Apis mellifera) collecting nectar from the Manuka tree (Leptospermum scoparium) is used topically in the management of wound infections.8 Products include gamma-irradiated honey in gels, ointments, and impregnated dressings. Revamil honey is another medical-grade honey commonly used in clinical practice for wound care.9 It is produced in greenhouses by manufacturers in The Netherlands, but further details about the origin of this honey have not been disclosed.

In this review, research findings on the antimicrobial activities of honeys from around the world, against skin relevant microbes, are evaluated. Furthermore, mechanisms of the antimicrobial properties of honey are explored. The principal aim was to understand more about the therapeutic potential of honey as a treatment option for skin diseases with a microbiological etiology.

Antimicrobial properties of Manuka honey against skin relevant microbes: in vitro studies

The most widely researched honey, to date, is Manuka honey from New Zealand. Studies have shown that Manuka honey has antimicrobial activity in vitro against the most common wound-infesting microorganisms, including MRSA, S. aureus, P. aeruginosa, and E. coli.11,12 Manuka honey can also inhibit the growth of Streptococcus pyogenes, a cause of cellulitis, impetigo, and necrotizing fasciitis, and the dermatophyte Trichophyton mentagrophyte, a cause of ringworm.15,16

Indeed, Manuka honey has been shown to inhibit the growth of a range of dermatophytes, including Epidermophyton floccosum, Microsporum canis, Microsporum gypseum, Trichophyton rubrum, and Trichophyton tonsurans, indicating that honey may be a therapeutic in the treatment of dermatophytosis (tinea infections).15 Studies have reported that Candida albicans is more resistant to Manuka honey than many other microbial species.14,15 Manuka honey has also been shown to have antiviral activity in vitro against varicella zoster virus, suggesting that honey may be a therapeutic for viral skin rashes.16 The antiviral properties of honey against other skin relevant viruses such as human papilloma virus may be worth investigating.

As the antimicrobial activity of honey varies not only between different types of honey but also between batches of the same type of honey, Manuka honey is often ascribed a unique Manuka factor (UMF). The UMF is a measure of the strength of the antibacterial activity of the honey against S. aureus and is calculated based on the concentration of a phenol solution that gives a similar zone of growth inhibition, in a radial diffusion assay, to the honey being tested. A criticism of the UMF classification is that it is a measure of activity against S. aureus only and not against other relevant microbes.

Antimicrobial activity of honeys from around the world against skin relevant microbes: in vitro studies

A plethora of scientific papers have reported in vitro antimicrobial activity of honeys from all over the world; some examples are discussed in this section.

Honey produced in South Gondar, Ethiopia, by the bee Apis mellipoda, a stingless bee, is used in traditional medicine in Ethiopia to treat a variety of diseases including skin infections.17 Using the method of agar well diffusion, Andualem17 demonstrated that this honey inhibited the growth of the wound-infesting microbes S. aureus and S. epidermidis and P. aeruginosa. The honey was shown to have inhibitory activity against 12.5% and 6.25%, respectively.

In a study by Pimentel et al.,18 honey samples collected from the stingless bee Melipona compressipes manosensis in Manaus, Amazonas, Brazil, were active against E. coli, S. aureus, Proteus vulgaris, and Klebsiella species. Using agar well diffusion assays, it was demonstrated that honey collected during the rainy season inhibited the growth of E. coli only in the undiluted form, while honey collected during the dry season inhibited the growth of E. coli, S. aureus, and a range of other microbes at much more diluted concentrations. These results clearly show the influence of seasonality on the antibacterial activity of honey. Plant-derived factors or entomological factors such as the health of the bee colonies can be affected by seasons, with consequences for the antimicrobial activity of the honey produced. Researchers also compared the ability of honey to inhibit microbial growth evaluated by agar well diffusion with that assessed by broth dilution assay, and found that the broth dilution assay was a more sensitive method, most likely due to better movement of the antimicrobial components of honey in liquid broth than in agar. Rutin, a flavonoid previously shown to have antibacterial activity, was identified in honey by high-performance liquid chromatography.

Kuncic et al19 reported that Slovenian honeys from diverse floral origins had antibacterial activity against E. coli, P. aeruginosa, and S. aureus. Slovenian chestnut and pasture honeys were found to be most active; for example, the MIC of the chestnut honey against S. aureus was found to be 2.5%. C. albicans was not inhibited by any of the Slovenian honeys tested, and Candida parapsilosis and Candida tropicalis were inhibited only by honey of concentrations higher than 50%.

In other studies, the growth of C. albicans was inhibited by Jujube honey, a honey obtained from bee keepers in Al-baha, Saudi Arabia, prepared by bees feeding on the plant Ziziphus jujuba, and by a mixture of honey, olive oil, and beeswax containing multifloral honey from the United Arab Emirates.20,21 Such findings indicate the potential of some honeys for use in the treatment of skin disorders caused by C. albicans such as cutaneous candidiasis.

Tualang honey, obtained from bees (Apis dorsata) feeding on Tualang trees (Koompassia excelsa) in the jungles of Malaysia, was found to inhibit the growth of MRSA, S.
Honey: An antimicrobial for skin disorders

Antimicrobial properties of honey: in vivo human studies

The majority of studies to date have demonstrated the antimicrobial activity of honey against a range of microbial strains including clinical isolates, using in vitro antimicrobial assays. Fewer studies have demonstrated the antimicrobial activity of honey in vivo; studies carried out so far have mainly investigated the antimicrobial activity of honey in relation to wound infections. In the 1st decade of the 21st century, several case studies involving wound patients produced optimistic findings. A brief report by Cooper et al.28 described how treatment of a *S. aureus*-infected, recalcitrant surgical wound in a 38-year-old female with Manuka honey-impregnated dressings and oral coamoxiclav resulted in significant healing of the wound and bacterial clearance 7 days after commencing the treatment. The wound was 3 years old, and had failed to respond to other conventional wound treatments and antibiotics during the 3-year period prior to commencing the honey/antibiotic combination therapy. Natarajan et al.29 treated an MRSA-infected leg ulcer of an immunosuppressed patient with topical application of Manuka honey; consequently, MRSA was eradicated and the wound successfully healed. Chambers30 described how treatment of a *S. aureus*-infected, recalcitrant surgical wound in a 38-year-old female with Manuka honey-impregnated dressings and oral coamoxiclav resulted in significant healing of the wound and bacterial clearance 7 days after commencing the treatment. The wound was 3 years old, and had failed to respond to other conventional wound treatments and antibiotics during the 3-year period prior to commencing the honey/antibiotic combination therapy. Natarajan et al.29 treated an MRSA-infected leg ulcer of an immunosuppressed patient with topical application of Manuka honey; consequently, MRSA was eradicated and the wound successfully healed. Chambers30 described how treatment of a

Table 1 Activity of some honeys from around the world against common skin relevant microbes

<table>
<thead>
<tr>
<th>Type of honey</th>
<th>MRSA resistance</th>
<th>Staphylococcus aureus</th>
<th>Pseudomonas aeruginosa</th>
<th>Escherichia coli</th>
<th>Candida albicans</th>
<th>Dermatophytes</th>
<th>Malassezia species</th>
<th>HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuka honeya</td>
<td>+ (11)</td>
<td>+ (11)</td>
<td>+ (11,12)</td>
<td>+ (11,12)</td>
<td>+ (14,15)</td>
<td>+ (13)</td>
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<td>Scottish heather honeyb</td>
<td>$\bar{+}$ (C3)</td>
<td>+ (23)</td>
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<tr>
<td>Portobello honeyc</td>
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</tr>
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</table>

a New Zealand.
b Scotland.
c Malaysia.
Numbers in brackets are references.
HPV = human papilloma virus; MRSA = methicillin-resistant *S. aureus*; $+$ = active; $-$ = not active or low activity; $\bar{+}$ = unknown.
clinical experience, was now one of their first-line treatments for infected wounds at the Maxillofacial Unit at the Royal Surrey County Hospital, Guildford, Surrey.

Larger clinical studies have produced more controversial findings. Gethin and Cowman reported 108 patients with venous leg ulcers and treated them with either Manuka honey or hydrogel. In their study, Manuka honey successfully eliminated MRSA from 70% of MRSA-infected wounds; in comparison, hydrogel eradicated MRSA from only 16% of infected wounds. For P. aeruginosa-infected wounds, Manuka honey cleared infection in just 33% of wounds, whereas hydrogel cleared infection in 50% of wounds. Jull et al. in a randomized clinical trial of 368 participants, reported no significant difference in occurrence of infection in venous leg ulcers treated with either Manuka honey-impregnated dressings or usual care. Another clinical study showed no significant difference, in terms of development of peritoneal dialysis-related infections when patients undergoing peritoneal dialysis were treated with either Medihoney antibacterial wound gel (containing honey from Leptospermum species) or the topical antibiotic mupirocin applied to catheter exit sites. It is also important to consider that some honeys have been shown to be contaminated with bacteria and fungi, and therefore non-gamma-irradiated honeys may not be suitable for application on damaged skin. The production of medical-grade honeys, suitable for use in clinical practice, from local honeys would be economically advantageous and beneficial to local communities.

Effects of honey on microbial pathogenicity of skin relevant microbes: in vitro studies

Incredibly, recent research has shown that the antimicrobial properties of honey in vitro are more than bactericidal because honey has also been shown to reduce bacterial pathogenicity. The ability of pathogenic microbes to cause diseases is partly due to the production of pathogenicity factors. S. aureus, for example, produces a range of disease-causing proteins, including catalase, hemolysins (α, β, γ, and δ), epidermolytic toxins, and enterotoxins. Alpha-toxin (α-hemolysin) causes tissue damage during wound infections by creating pores in host cell membranes, allowing the discharge of low-molecular-weight compounds, and by inducing cytokine production and apoptosis.

Recently, Jenkins et al. reported that Manuka honey reduced the expression of α-toxin in MRSA. Expression of other virulence genes, quorum sensing genes, and genes associated with cell division was also reduced. Lee et al. reported that three types of honeys (Korean acacia, Korean polyfloral, and American clover honeys) at a concentration as low as 0.5% significantly inhibited pathogenic E. coli O157:H7 biofilm formation in vitro. Furthermore, low concentrations of the Korean acacia honey reduced the expression of curli genes (csgBAC), quorum sensing genes (AI-2 importer, indole biosynthesis), and virulence genes (LEE genes) in the bacterial strain. Kronda et al. reported that sublethal concentrations of Manuka honey reduced siderophore production, a virulence factor that scavenges iron for bacterial growth, in clinical and nonclinical strains of P. aeruginosa. Manuka honey has also been shown to alter the structure of P. aeruginosa; scanning and transmission electron microscopy revealed changes in cell shape and cell lysis following incubation with honey. A honey flavonoid extract was also found to alter membrane integrity and branching processes associated with virulence in C. albicans.

In addition to the more commonly investigated wound pathogens, subinhibitory concentrations of Manuka honey and Slovakian honeys (Hawthorn, honeydew, and acacia) significantly inhibited Proteus mirabilis and Enterobacter cloacae biofilm formation in vitro. In vivo studies investigating the efficacy of sublethal concentrations of honey against biofilms would advance our knowledge of the ability of honey to modulate bacterial pathogenicity.

Antimicrobial mode of action of honey

The antimicrobial properties of honey have been attributed to its multiple components, including high sugar concentrations, low pH, hydrogen peroxide (H₂O₂), methylglyoxal
(MGO), antimicrobial peptide bee defensin-1, and other compounds such as polyphenols that have not been fully elucidated.

The high sugar concentration and low moisture content of honey cause osmotic stress to microbial cells, and low pH is unfavorable for the growth of many microorganisms. However, if a sugar solution with identical sugar components and pH to that of honey is prepared, the antimicrobial activity of the sugar solution is often considerably lower than that of honey, suggesting that other factors in the honey are responsible for its antimicrobial activity.23

Honey bees add an enzyme, called glucose oxidase, to the collected nectar during the honey-making process, which converts the glucose in the honey into hydrogen peroxide (H₂O₂) and gluconic acid. H₂O₂ is toxic to many microbes. During the ripening of honey, glucose oxidase is inactivated but regains its activity if the honey is diluted. In a study by Kwakman et al.,10 it was found that Revamil honey produced 3.47 ± 0.25 mM H₂O₂ in 40% (v/v) honey after 24 hours, but no H₂O₂ was detectable in the Manuka honey they tested, suggesting that nonperoxide factors are responsible for the antimicrobial activity of Manuka honey.

Manuka honey has been shown to contain high levels of MGO, 44-fold higher than Revamil honey. MGO in Manuka honey is produced by the nonenzymatic reduction of dihydroxyacetone present at high concentrations in the nectar of L. scoparium flowers. The change occurs slowly during honey storage. Kwakman et al.10 reported that neutralization of MGO in Manuka honey abolished the antimicrobial activity of the honey against S. aureus, but did not abolish the antimicrobial activity against E. coli and P. aeruginosa. The authors concluded that MGO is not fully responsible for Manuka honey’s nonperoxide antimicrobial activity and that other components, possibly polyphenols, may be responsible.

Polyphenols derived from plant nectar are natural organic chemicals characterized by the presence of multiple phenol structural units. Many are antioxidants, e.g., flavonoids. The antibacterial properties of flavonoids have been attributed to the inhibition of bacterial energy metabolism, bacterial DNA gyrase, and cytoplasmic membrane function.45 Researchers in New Zealand identified the polyphenol methyl syringate as the major component of the phenolic fraction of Manuka honey.46 A novel glycoside of methyl syringate, named leptosin, was recently identified. Researchers in New Zealand identified the polyphenol methyl syringate as the major component of the phenolic fraction of Manuka honey.46 A novel glycoside of methyl syringate, named leptosin, was recently identified.

(Bee defensin-1) is an antimicrobial peptide that is part of the honey bee innate immune system. It is secreted by the hypopharyngeal gland of honey bees and can enter honey via bee saliva during the regurgitation process of honey making. Bee defensin-1 has a strong activity against Gram-positive bacteria including S. aureus. Kwakman et al.48 identified bee defensin-1 in Revamil honey but not in Manuka honey.

Raw honey may also contain propolis, a substance composed of plant resins and used by bees to seal the hive. Scientific research has shown that propolis has antimicrobial properties.49

The research of Kwakman et al.48 demonstrates the diversity and complexity of the antimicrobial components of different types of honeys. Analysis of the antimicrobial components of other active honeys will be important for a fuller understanding of their applicability in medicine.

It can be concluded from in vitro studies that honey has powerful antimicrobial activity against dermatologically relevant microbes. These findings are particularly promising in current times when the problem of antimicrobial drug resistance is considered a global crisis and the World Health Organization (2014)50 has acknowledged the possibility of a postantibiotic era in which common infections can kill. Even more exciting are the in vitro findings that honey can reverse antimicrobial resistance and reduce microbial pathogenicity. Despite these optimistic findings in vitro, the use of honey in clinical practice today as an antimicrobial agent does not appear to have yet reached its full potential. Innovative research that can maximally exploit the antimicrobial properties of this natural substance and overcome obstacles associated with in vivo use may, in the future, lead to the production of an antimicrobial agent that is highly valued in clinical practice. Interestingly, no honey-resistant microbial strains have emerged to date, and this may be unlikely because of the multifactorial nature of the antimicrobial properties of honey. As honeys from diverse floral origins have been shown to have antimicrobial activity against a range of skin relevant microbes, research should continue to investigate the efficacy of honey in the treatment of other types of skin disorders where microbes have been implicated in the pathophysiology of the disease. There are countless varieties of honeys being produced worldwide, and some may have superior antimicrobial activities that are yet to be discovered.

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Please cite this article in press as: McLoone P, et al., Honey: A realistic antimicrobial for disorders of the skin, Journal of Microbiology, Immunology and Infection (2015), http://dx.doi.org/10.1016/j.jmii.2015.01.009


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