Journal of Microbiology, Immunology and Infection (2016) **49**, 161—167

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

REVIEW ARTICLE

Honey: A realistic antimicrobial for disorders of the skin

Pauline McLoone [a], Mary Warnock [b], Lorna Fyfe [b,*]

[a] *Department of Biomedical Sciences, School of Medicine, Nazarbayev University, Astana, Kazakhstan*
[b] *Dietetics, Nutrition, and Biological Sciences, Queen Margaret University, Musselburgh, East Lothian, Scotland, United Kingdom*

Received 24 November 2014; received in revised form 5 January 2015; accepted 19 January 2015
Available online 30 January 2015

KEYWORDS
Antimicrobial;
Dermatology;
Honey;
Wound infections

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.
Copyright © 2015, Taiwan Society of Microbiology. Published by Elsevier Taiwan LLC. All rights reserved.

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.,

* Corresponding author. Dietetics, Nutrition, and Biological Sciences, Queen Margaret University, Musselburgh, Queen Margaret Drive, EH21 6UU East Lothian, Scotland, United Kingdom.
E-mail address: lfyfe@qmu.ac.uk (L. Fyfe).

http://dx.doi.org/10.1016/j.jmii.2015.01.009
1684-1182/Copyright © 2015, Taiwan Society of Microbiology. Published by Elsevier Taiwan LLC. All rights reserved.

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.[9] 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.[10] 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-infecting 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.[11,13] 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).[13] 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 mellipodae*, 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, Andualem[17] demonstrated that this honey inhibited the growth of the wound-infecting microbes *E. coli* and *S. aureus* with minimal inhibitory concentrations (MICs) of 12.5% and 6.25%, respectively.

In a study by Pimentel et al,[18] honey samples collected from the stingless bee *Melipona compressipes manaosensis* 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 a 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 al[19] 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 Albaha, 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.*

aureus, *Streptococcus pyogenes*, *P. aeruginosa*, and *E. coli* in a broth dilution assay, with MICs comparable with those of Manuka honey.[11]

In 2013, researchers at Queen Margaret University, Edinburgh, Scotland, reported the antimicrobial activity of a Scottish honey, called Portobello honey.[22] Portobello honey was produced by honey bees in an apple orchard in Portobello, Edinburgh, Scotland. Five concentrations of the Portobello honey and medical-grade Manuka Honey (0%, 1%, 10%, 50%, and 70%) were tested against *S. aureus*, *P. aeruginosa*, and *E. Coli* using agar disc diffusion and a broth dilution assay. The agar disc diffusion method did not demonstrate any antimicrobial activity of the honeys tested; however, it was reported that the honey remained on the surface of the disc and did not diffuse into the agar. The broth dilution assay, by contrast, demonstrated antimicrobial activity of Portobello and Manuka honeys at concentrations of 50% and 70%, which were found to inhibit the majority of all the bacterial species tested. The MIC of Portobello honey was not calculated, but the authors concluded that honey is a superior antibacterial agent.

In a study by Carnwath et al,[23] the antimicrobial activities of a selection of 10 honeys against 10 microorganisms were tested at the Department of Veterinary Medicine, University of Glasgow, Scotland. The honeys tested included medical-grade and shop-bought Manuka honeys, Scottish heather honey (from a local bee keeper), blossom honey, Vipers bugloss honey, Inverness floral honey, and Glasgow floral honey. The microorganisms tested included MRSA, *S. aureus*, *E. coli*, *P. aeruginosa*, and *Acinetobacter baumannii*. Serial dilutions of the honeys were prepared in distilled water and mixed with equal volumes of nutrient agar, to produce final honey concentrations ranging from 2% to 16%. Plates were inoculated with the appropriate microorganism and incubated aerobically overnight. All the honeys tested demonstrated antimicrobial activity, but the Scottish heather honey was found to be most active, which inhibited the growth of all the microorganisms tested, with MICs ranging from <2% to 6%. The Scottish heather honey was even more active than all the Manuka honeys used in the study.

Remarkably, *in vitro* research has also shown that honey can actually reverse antibiotic resistance, suggesting that honey used in combination with antibiotics may have additional therapeutic effects.[24] A suggested mechanism is via honey-induced downregulation of *mecR1* gene product, a transducer associated with antibiotic resistance in MRSA. Indeed, Muller et al[25] reported that Manuka honey worked synergistically with the antibiotic rifampicin to inhibit the growth of MRSA and clinical isolates of *S. aureus*.

The evidence is clear that, in a laboratory setting, honeys from all over the world have potent antimicrobial activity against skin relevant microbes (Table 1). Indeed, the antimicrobial activity of honey from Iran has been shown to be comparable with that of the sulfonamide family of antibiotics.[26] The microorganism *S. aureus* is clearly inhibited by honeys of different floral origins. In addition to wound infections, *S. aureus* is an important cause of furuncles, styes, and impetigo. Honey has broad-spectrum antimicrobial properties; it may also have therapeutic value in the treatment of other skin disorders, in which microbes have been associated with the etiology of the disease, as well as those disorders that are commonly treated with topical antibiotics, e.g., acne. Analysis of the antimicrobial activity of different types of honeys against other dermatologically relevant microbes should be encouraged.

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. Chambers[30] reported bacterial clearance in three cases of MRSA-infected leg ulcers following treatment with topical Manuka honey, while Visavadia et al[31] reported that Manuka honey, based on

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

Type of honey	MRSA	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Candida albicans*	Dermatophytes	*Malassezia* species	HPV
Manuka honey[a]	+ (12)	+ (11)	+ (11,12)	+ (11,12)	− (14,15)	+ (13)	†	†
Scottish heather honey[b]	+ (23)	+ (23)	+ (23)	+ (23)	†	†	†	†
Portobello honey[b]	†	+ (22)	+ (22)	+ (22)	†	†	†	†
Tualang honey[c]	+ (11)	+ (11,27)	+ (11,27)	+ (11,27)	†	†	†	†

[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; † = 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[32] recruited 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,[33] 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.[34]

Antimicrobial properties of honey: *in vivo* animal studies

Antimicrobial effects of honey have been observed in animal studies *in vivo*. Al-Waili[35] reported that application of a natural honey from the United Arab Emirates to *S. aureus* or *Klebsiella* species-inoculated surgical wounds induced in mice reduced the time for bacterial elimination to occur. Khoo et al[36] reported that Tualang honey was superior to hydrofiber and hydrofiber silver dressings in reducing the growth of bacteria in *P. aeruginosa*-inoculated burn wounds induced in Sprague Dawley rats. Conversely, hydrofiber and hydrofiber silver dressings were superior to Tualang honey in reducing bacterial growth in *A. baumannii*-inoculated wounds, while there was no significant difference between the three treatments in inhibiting the growth of bacteria in *Klebsiella pneumoniae*-inoculated wounds. Gunaldi et al[37] investigated the antimicrobial activity of Manuka honey in clearing MRSA infection in MRSA-inoculated spinal implants inserted in rats. The results showed that while Manuka honey significantly reduced MRSA growth on the implants, it did not eradicate the MRSA entirely. In the vertebral column of the rats, MRSA growth was also reduced more in the Manuka honey-treated group compared to the control group, but this was not statistically significant.

It could be said that the research findings for the antimicrobial activity of honey *in vivo* have not been as "outstanding" as those observed *in vitro*, and the reasons for this require investigation. Human and animal cells are known to contain the enzyme catalase, an enzyme that breaks down hydrogen peroxide (an important antimicrobial component of some honeys) into hydrogen and oxygen. If the antimicrobial properties of honey are due to hydrogen peroxide, the antimicrobial activity may be reduced when honey comes into contact with live cells.[38] Innovative research that can overcome obstacles associated with *in vivo* use of honey is urgently required.

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.[23] 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[39] 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[40] 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:HA 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[41] 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.[42] A honey flavonoid extract was also found to alter membrane integrity and branching processes associated with virulence in *C. albicans*.[43]

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*.[44]

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 concentration, low pH, hydrogen peroxide (H_2O_2), 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 (H_2O_2) and gluconic acid. H_2O_2 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 $\pm$ 0.25 mM H_2O_2 in 40% (v/v) honey after 24 hours, but no H_2O_2 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 conversion 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 in Manuka honey, and its levels were found to correlate positively with the UMF.[47] Identification of phenolic compounds in honey may be important for the production of new antimicrobials, and therefore the analysis of the phenolic profile of active honeys should be encouraged. Combinations of polyphenols may be more effective, as they may act synergistically to inhibit microbial growth, or structural alteration of individual polyphenols can be employed to enhance antimicrobial activity.

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.

References

1. Eteraf-Oskouei T, Najafi M. Traditional and modern uses of natural honey in human diseases: a review. *Iran J Basic Med Sci* 2013;**16**:731—42.
2. Sepehr S. The most important medicinal uses of honey, and its side effects in the book of the Canon by Avicenna, and in the modern medical literature: a comparative study. *J ApiProd ApiMed Sci* 2010;**2**:43.
3. Collier M. *Recognition and management of wound infections*. World Wide Wounds. January 2004, http://www.worldwidewounds.com/2004/january/Collier/Management-of-Wound-infections.html [accessed October, 2014] [online].
4. Ong PY. Recurrent MRSA skin infections in atopic dermatitis. *J Allergy Clin Immunol Pract* 2014;**2**:396—9.
5. Gaitanis G, Magiatis P, Hantschke M, Bassukas ID, Velegraki A. The *Malassezia* genus in skin and systemic disease. *Clin Microbiol Rev* 2012;**25**:106—41.
6. Gasparro FP. The role of PUVA in the treatment of psoriasis. Photobiology issues related to skin cancer incidence. *Am J Clin Dermatol* 2000;**1**:337—48.
7. Molan PC. Potential of honey in the treatment of wounds and burns. *Am J Clin Dermatol* 2001;**2**:13—9.

8. Fry DE, Barie PS. The changing face of *Staphylococcus aureus*; a continuing surgical challenge. *Surg Infect (Larchmt)* 2011;**12**:191—203.
9. Irish J, Blair S, Carter DA. The antibacterial activity of honey derived from Australian flora. *PLoS One* 2011;**6**:e18229.
10. Kwakman PH, teVelde AA, deBoer L, Vandenbroucke-Grauls CM, Zaat SA. Two major medicinal honeys have different mechanisms of bactericidal activity. *PLoS One* 2011;**6**:e17709.
11. Tan HT, Rahman RA, Gan SH, Halim AS, Hassan SA, Sulaiman SA, et al. The antibacterial properties of Malaysian tualang honey against wound and enteric microorganisms in comparison to manuka honey. *BMC Complement Altern Med* 2009;**9**:34. http://www.biomedcentral.com/1472-6882/9/34-34 [accessed September 2014], http://dx.doi.org/10.1186/1472-6882-9.
12. Sherlock O, Dolan A, Athman R, Power A, Gethin G, Cowman S, et al. Comparison of the antimicrobial activity of ulmo honey from Chile and manuka honey against methicillin resistant *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*. *BMC Complement Altern Med* 2010;**10**:47. http://www.biomedcentral.com/1472-6882/10/47 [accessed September, 2014], http://dx.doi.org/10.1186/1472-6882-10-47.
13. Brady NF, Molan PC, Harfoot CG. The sensitivity of dermatophytes to the antimicrobial activity of manuka honey and other honey. *Pharm Pharmacol Commun* 1996;**2**:471—3.
14. Basson NJ, Grobler SR. Antimicrobial activity of two South African honeys produced from indigenous *Leucospermum cordifolium* and Erica species on selected micro-organisms. *BMC Complement Altern Med* 2008;**8**:41. http://www.biomedcentral.com/1472-6882/8/41 [accessed September, 2014], http://dx.doi.org/10.1186/1472-6882-8-41.
15. Lusby PE, Coombes AL, Wilkinson JM. Bactericidal activity of different honeys against pathogenic bacteria. *Arch Med Res* 2005;**36**:464—7.
16. Shahzad A, Cohrs RJ. *In vitro* antiviral activity of honey against varicella zoster virus (VZV): a translational medicine study for potential remedy for shingles. *Transl Biomed* 2012;**3**. pii:2, http://dx.doi.org/10.3823/434.
17. Andualem B. Combined anti-bacterial activity of stingless bee (*Apis mellipodae*) honey and garlic (*Allium sativum*) extracts against standard and clinical pathogenic bacteria. *Asian Pac J Trop Biomed* 2013;**3**:725—31.
18. Pimentel RB, da Costa CA, Alburquerque PM, Junior SD. Antimicrobial activity and rutin identification of honey produced by the stingless bee *Melipona compressipes manaosensis* and commercial honey. *BMC Complement Altern Med* 2013;**13**:151. http://www.biomedcentral.com/1472-6882/13/151 [accessed September, 2014], http://dx.doi.org/10.1186/1472-6882-13-151.
19. Kuncic MK, Jaklic D, Lapanje A, Gunde-Cimerman N. Antibacterial and antimycotic activities of Slovenian honeys. *Br J Biomed Sci* 2012;**69**:154—8.
20. Ansari MJ, Al-Ghamdi A, Usmani S, Al-Waili NS, Sharma D, Nuru A, et al. Effect of jujube honey on *Candida albicans* growth and biofilm formation. *Arch Med Res* 2013;**44**:352—60.
21. Al-Waili NS. Mixture of honey, beeswax and olive oil inhibits growth of *Staphylococcus aureus* and *Candida albicans*. *Arch Med Res* 2005;**36**:10—3.
22. Schneider M, Coyle S, Warnock M, Gow I, Fyfe L. Anti-microbial activity and composition of manuka and Portobello honey. *Phytother Res* 2013;**27**:1162—8.
23. Carnwath R, Graham EM, Reynolds K, Pollock PJ. The antimicrobial activity of honey against common equine wound bacterial isolates. *Vet J* 2014;**199**:110—4.
24. Jenkins RE, Cooper R. Synergy between oxacillin and manuka honey sensitizes methicillin-resistant *Staphylococcus aureus* to oxacillin. *J Antimicrob Chemother* 2012;**67**:1405—7.
25. Muller P, Alber DG, Turnbull L, Schlothauer RC, Carter DA, Whitchurch CB, et al. Synergism between Medihoney and rifampicin against methicillin-resistant *Staphylococcus aureus* (MRSA). *PLoS One* 2013;**8**:e57679.
26. Tajik H, Jalali FSS. *In vitro* evaluation of antimicrobial efficacy of natural honey in comparison with sulfonamide derivatives. *J Anim Vet Adv* 2009;**8**:23—5.
27. Zainol MI, Mohd Yusoff K, Mohd Yusof MY. Antibacterial activity of selected Malaysian honey. *BMC Complement Altern Med* 2013;**13**:129. http://www.biomedcentral.com/1472-6882/13/129 [accessed September, 2014], http://dx.doi.org/10.1186/1472-6882-13-129.
28. Cooper RA, Molan PC, Krishnamoorthy L, Harding KG. Manuka honey used to heal a recalcitrant surgical wound. *Eur J Clin Microbiol Infect Dis* 2001;**20**:758—9.
29. Natarajan S, Williamson D, Grey J, Harding KG, Cooper RA. Healing of an MRSA-colonised, hydroxyurea-induced leg ulcer with honey. *J Dermatolog Treat* 2001;**12**:33—6.
30. Chambers J. Topical Manuka honey for MRSA contaminated ulcers [Letter to the editor]. *Palliat Med* 2006;**20**:557.
31. Visavadia BG, Honeysett J, Danford M. Manuka honey dressing an effective treatment for chronic wound infections. *Br J Oral Maxillofac Surg* 2008;**46**:55—6.
32. Gethin G, Cowman S. Bacteriological changes in sloughy venous leg ulcers treated with manuka honey or hydrogel: an RCT. *J Wound Care* 2008;**17**:241—7.
33. Jull A, Walker N, Parag V, Molan P, Rodgers A. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. *Br J Surg* 2008;**95**:175—82.
34. Johnson DW, Badve SV, Pascoe EM, Beller E, Cass A, Clark C, et al. Antibacterial honey for the prevention of peritoneal-dialysis-related infections (HONEYPOT): a randomised trial. *Lancet Infect Dis* 2014;**14**:23—30.
35. Al-Waili NS. Investigating the antimicrobial activity of natural honey and the effects on the pathogenic bacterial infections of surgical wounds and conjunctiva. *J Med Food* 2004;**7**:210—22.
36. Khoo YT, Halim AS, Sing KK, Mohamad NA. Wound contraction effects and anti-bacterial properties of tualang honey on full-thickness burn wounds in rats in comparison to hydrofibre. *BMC Complement Altern Med* 2010;**10**:48. http://www.biomedcentral.com/1472-6882/10/48 [accessed September 2014], http://dx.doi.org/10.1186/1472-6882-10-48.
37. Gunaldi O, Postalci L, Guclu G, Tugcu B, Kizilyildirim S, Daglioglu YK, et al. Assessment of the antimicrobial effect of manuka honey in implant-related spinal infections in rats. *J Neurol Sci* 2013;**30**:551—8.
38. Molan P. Manuka—not the best? *Bee Culture* 2013;**141**:7.
39. Jenkins R, Burton N, Cooper R. Proteomic and genomic analysis of methicillin resistant *Staphylococcus aureus* (MRSA) exposed to manuka honey *in vitro* demonstrated down regulation of virulence markers. *J Antimicrob Chemother* 2014;**69**:603—15.
40. Lee JH, Park JH, Kim JA, Neupane GP, Cho MH, Lee CS, et al. Low concentrations of honey reduce biofilm formation, quorum sensing, and virulence in *Escherichia coli* 0157:H7. *Biofouling* 2011;**27**:1095—104.
41. Kronda JM, Cooper RA, Maddocks SE. Manuka honey inhibits siderophore production in *Pseudomonas aeruginosa*. *J Appl Microbiol* 2013;**115**:86—90.
42. Henriques AF, Jenkins RE, Burton NF, Cooper RA. The effect of manuka honey on the structure of *Pseudomonas aeruginosa*. *Eur J Clin Microbiol Infect Dis* 2011;**30**:167—71.
43. Canonico B, Candiracci M, Citterio B, Curci R, Squarzoni S, Mazzoni A, et al. Honey flavonoids inhibit *Candida albicans* morphogenesis by affecting DNA behaviour and mitochondrial function. *Future Microbiol* 2014;**9**:445—56.
44. Majtan J, Bohova J, Horniackova M, Klaudiny J, Majtan V. Anti-biofilm effects of honey against wound pathogens *Proteus*

mirabilis and *Enterobacter cloacae*. *Phytother Res* 2014;**28**:69—75.

45. Cushnie TP, Lamb AJ. Antimicrobial activity of flavonoids. *Int J Antimicrob Agents* 2005;**13**:343—56.
46. Weston RJ, Brocklebank LK, Lu Y. Identification and quantitative levels of antibacterial components of some New Zealand honeys. *Food Chemistry* 2000;**70**:427—35.
47. Kato Y, Umeda N, Maeda A, Matsumoto D, Kitamoto N, Kikuzaki H. Identification of a novel glycoside, leptosin, as a chemical marker of manuka honey. *J Agric Food Chem* 2012;**60**:3418—23.
48. Kwakman PH, teVelde AA, deBoer L, Speijer D, Vandenbroucke-Grauls CM, Zaat SA. How honey kills bacteria. *FASEB J* 2010;**24**:2576—82.
49. Campos JF, dos Santos UP, Macorini LF, de Melo AM, Balestieri JB, Paredes-Gamero EJ, et al. Antimicrobial, antioxidant and cytotoxic activities of propolis from *Melipona orbignyi* (Hymenoptera, Apidae). *Food Chem Toxicol* 2014;**65**:374—80.
50. World Health Organisation. *Antimicrobial resistance: global report on surveillance*. http://www.who.int/drugresistance/documents/surveillancereport/en; 2014 [accessed October, 2014].