Honey for wound care in the 21st century

This review is written in memory of Professor Peter Molan, who published a paper in the *Journal of Wound Care* in 1999 describing the therapeutic properties of honey in relation to wound care. It provides an update to show how our understanding of the mode of action of honey has changed within the past 17 years.

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Using honey to treat wounds is an ancient global remedy that persisted in British hospitals until the 1970's. It was also used domestically by families in the UK who believed in the folklore of applying local honey to the surface of small cutaneous injuries. This practice seems to have been handed down through successive generations by word of mouth, but unlike ancient civilizations, careful selection of honey from differing floral origins for differing ailments seems to have been largely forgotten in recent times. The importance of honey for wound care in conventional medicine was diminished during the 1960s by the availability of effective antibiotics and by a letter that was published in *Nature* in which the need to create a moist environment for effective wound healing was advocated.[1] These events led to the development of occlusive wound dressings and subsequently to the introduction of more sophisticated, advanced dressings that ultimately caused the discontinuation of some traditional interventions that had long been used in managing wounds. The demise of honey was lamented in 1989,[2] but the lack of licensed wound care products restricted its use in conventional medicine at that time.

Peter Molan (1943–2015) made a significant contribution to modern medicine by reviving interest in the use of honey for wounds. Professor Molan was born and brought up in Cardiff, where he obtained a degree in biochemistry, before moving to Liverpool where he was awarded a PhD in dental science. In 1973, he migrated to New Zealand and lectured in the University of Waikato for 41 years. He heard, from Maori legends, of the medicinal properties of manuka honey and began to investigate its potential for wound care. He established a Honey Research Unit, methods to evaluate the antibacterial activity of honey the unique manuka factor (UMF) and Molan Gold Standard (MGS), and developed innovative ways of delivering honey to the surfaces of wounds, mouths and throats. He was awarded an MBE in the Queen's Birthday honours list in 1995. He researched and wrote extensively about honey and his first review of the evidence to support claims of the therapeutic potential of honey for wounds was published in the *Journal of Wound Care* in 1999.[3] In that paper, he described five actions of honey relevant to wounds: antibacterial, deodorising, debriding, anti-inflammatory and the stimulation of tissue growth. He illustrated these properties by reference to clinical observations and provided guidelines for clinical practice.[3] With the passing of Professor Molan in 2015, the aim of this review is to demonstrate how our knowledge of the relevance of honey to wound care has advanced since Professor Molan's initial review.[3] Where possible, the same headings will be used here. Although a search of PubMed (conducted on 19th July 2016) showed that much information has been published on honey (Table 1), this review will be largely confined to those honeys that have so far been used in licensed wound care products, and the microbial species that have the potential to infect wounds. As honey is now established in modern wound care, guidelines for clinical practice will not be covered here.

Modern wound care products containing honey

Despite the uninterrupted use of honey in developing countries,[2] it was reintroduced into conventional medicine in developed countries at the dawn of the 20th century. The first modern wound care product was Medihoney, which was developed in Australia and licensed by the Therapeutic Goods Authority as a complementary therapy in 1999. In the Netherlands two honey products were developed for wound care in 2001, one was a dressing impregnated with honey and the other was an ointment loosely based on a product that had been used in Germany during the 1930s. In 2004, honey was approved for clinical use in the UK and manuka honey that had been imported from New Zealand was employed in the manufacture of wound dressings. From this point onwards, a varied range of licensed wound care devices containing honey have been developed and are available throughout Europe, Australasia and North America. Formulations range from honey without additives, to honey mixed with waxes or oil, ointments containing honey and honey-impregnated dressings, ropes, meshes and gel sheets. Second generation products have also been developed. These

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non-sticky products no longer require secondary absorbent dressings or adhesive coverings and are easy to use. Most of these modern devices contain medical grade honey, which is distinct from table honey produced for human consumption;[4] it is sterilised by gamma irradiation without loss of antibacterial activity.[5] Some manufacturers disclose the floral source of their honey (chestnut, thyme or manuka honey), whereas others employ multifloral or unspecified honeys. Honey may be engineered to enhance its antimicrobial activity by generating reactive oxygen species (ROS) hydrogen peroxide,[6] standardised to ensure a consistent end-product by production in closed greenhouses,[7] and some are traceable to the hive of origin.[8]

Antibacterial action

The chemistry of honey is complex, and not all honeys are alike. Furthermore, it has been found that the chemistry of honey is known to be influenced by multiple environmental factors.[9–11] In 1999 our knowledge of the components in honey that contribute to its antibacterial activity was somewhat limited. The high sugar content, low water content and marked acidity that restricted microbial growth were known and were common to all honeys. Additionally the ability of many honeys to generate hydrogen peroxide on dilution was documented.[12] A laboratory test to determine the level of activity and to distinguish between peroxide-generating honeys and non-peroxide honeys (such as manuka) was developed in New Zealand, and later became the basis of UMF testing.[13] Whereas many unprocessed honeys possess the ability to generate hydrogen peroxide over 24 hours following dilution, manuka produces relatively low levels of hydrogen peroxide. Catalase, which is present in blood and human tissues, neutralises hydrogen peroxide but manuka honey retains antibacterial activity in the presence of catalase, hence it is known as non-peroxide activity.[13] Phytochemicals derived from the plant foraged by the bee were known to be involved in antibacterial activity,[14] but were relatively poorly characterised in medical grade honeys until 2008. A number of active components have now been identified (Table 2), and the inhibitory activity of honey can no longer be attributed to sugars alone.[15–21] It is likely that further bioactive components will be discovered.

Antibacterial action against planktonic organisms

The broad spectrum of antibacterial activity possessed by honey has been demonstrated by a multitude of laboratory studies, and at least 80 microbial species have been shown to be inhibited by honey.[14] However, many of those early studies used incompletely characterised samples of honey, reference strains of test organisms, and a diverse range of different methods.[14] Therefore, the relevance of many older studies to clinical practice is limited. More recently, with clinical isolates derived from wounds and medical grade honey, it has been demonstrated that antibiotic-resistant as well as antibiotic-sensitive strains are susceptible to honey.[22–30] The antibacterial activity of manuka honey against 59 bacteria has recently been collated.[31] Where antibiotics usually target a specific microbial intracellular site, molecular investigations have shown that honey exerts multiple lethal effects which depend on the species being tested and the type of honey.[27,32–36] This was first demonstrated by comparing the rates of inhibition of manuka honey and Revamil source honey on four bacteria *in vitro*.[37]

The precise mode of action of only a few honeys has been elucidated to date, and manuka honey features most prominently (Table 3).[38] The first detailed studies showed that cell division in *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) was prevented in the presence of manuka honey because the enzymes involved in cleaving the bacterial cell wall were inactivated so that cells accumulated with partially-completed cell cycles.[39,40] Conversely, manuka honey caused the down-regulation of a protein in the cell envelope that contributed to cell wall stability in *Pseudomonas aeruginosa*, hence structural abnormalities arose in the bacterial surface layers, which led to cell lysis and death.[41,42] Additional effects of manuka honey on bacterial virulence have recently been reported, for example, in MRSA the down-regulation of three of the four genes that comprise a global regulator explained the decrease in activity of several genes that code for biofilm formation and virulence determinants.[35] In *Pseudomonas*

Table 1. Publications relating to honey in PubMed on 19th July 2016

Search term(s) used	Number of items found	Publication dates
Honey	8604	1884–2016
Honey; bacteria	1250	1950–2016
Honey; wound healing	397	1952–2016
Honey; biofilm	51	2006–2016
Honey; biofilm; wounds	20	2006–2016

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5 Cooke, J., Dryden, M., Patton T,, Brennan. J., Barrett, J. The antimicrobial activity of prototype modified honeys that generate reactive oxygen

Table 2. Active components discovered in honey since 2008

Active component	Biological origin	Citation
Methylglyoxal (MGO)	Formed from dihydroxyacetone which is found in the nectar of manuka flowers (*Leptospermum scoparium*)	14, 15
Bee defensin-1	An antimicrobial peptide derived from the honey bee (*Apis mellifera*)	16
Melanoidins	Maillard reaction-like products formed in honey as a result of the interaction between sugars and amino acids	17
Leptosperin (formerly called leptosin)	A glycoside of methyl syringate formed in manuka honey as a result of the Maillard reaction	18, 19
Jelleins	Antimicrobial peptides derived from the honey bee	20

Table 3. Mechanisms of action of honey against bacteria capable of causing wound infection

Bacteria	Type of honey	Target sites and/or mode of action	Reference
Escherichia coli	Buckwheat	DNA degradation	44
	Buckwheat; wild flower	Loss of cell wall integrity	46
	Non-peroxide honey	Inconsistent cell lengths	36
Pseudomonas aeruginosa	Manuka honey	Loss of cell wall integrity	41
	Manuka honey	Loss of cell wall integrity; down regulation of oprF	42
	Peroxide honey	Shortened cells; condensed DNA	36
	Non-peroxide honey	Inconsistent cell lengths; condensed DNA	36
	Manuka honey	Flagella; reduced motility	35
Staphylococcus aureus	Manuka honey	Cell division	39
	Peroxide honey	Shortened cells	36
	Non-peroxide honey	Shortened cells; condensed DNA	36
Methicillin-resistent *Staphylococcus aureus*	Buckwheat	DNA degradation	45
	Manuka honey	Cell division	40
	Manuka honey	Down regulation of genes conferring virulence and biofilm formation	34
Streptococcus pyogenes	Manuka honey	Siderophore production	43
	Manuka honey	Reduced adherence due to down regulation of fibronectin binding proteins	51
Vancomycin-resistant *Enterococcus* (VRE)	Buckwheat	DNA degradation	45

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6 Kwakman, P.H., Van den Akker, J.P., Güçlü, A. et al. Medical-grade honey kills antibiotic-resistant bacteria in vitro and eradicates skin colonization. Clin Infect Dis 2008; 46: 11, 1677–1682.
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aeruginosa, virulence has been shown to be diminished by manuka honey in two studies: motility was affected because flagella-associated genes were down-regulated,[35] and siderophore production was inhibited.[43]

Buckwheat honey is a hydrogen peroxide generating honey whose mode of action differs from manuka by depending on the oxidative effects of free radicals to degrade bacterial DNA. This effect was demonstrated in *Bacillus subtilis*, *Escherichia coli*, MRSA and vancomycin-resistant *Enterococcus faecium* (VRE);[44,45] in another study it was shown that the inhibition of *Escherichia coli* resembled the action of ampicillin by disrupting the cell wall.[46]

Antibacterial action against biofilms

Antibiofilm strategies were not seriously considered in wound management until 2008, when the association between wound chronicity and the presence of a biofilm was revealed.[47] The physiology of microbial cells within established biofilm communities is distinct from that of free-living cells, due to changes in gene expression. These are mainly controlled by intra- and intercellular communication (known as quorum sensing). Microorganisms within biofilms become increasingly tolerant to both antimicrobial agents and host immune responses as the biofilm matures,[48,49] and hence become increasingly difficult to eradicate. There are three strategies to control biofilm that can be identified:

- Preventing adherence of microbial cells during the initial stages of biofilm formation
- Interrupting quorum sensing during the maturation phase of biofilm formation
- Disrupting an established biofilm.

Antibiofilm activity by interference in bacterial attachment

Experimental evidence to support the role of honey in controlling biofilms is accumulating. Binding of *Pseudomonas aeruginosa* to human erythrocyte receptors was blocked when fructose (the most abundant sugar in honey) bound to the bacterial receptors.[50] Biofilm formation by *Streptococcus pyogenes, in vitro,* was inhibited by manuka honey down-regulating the expression of two genes that code for thesurface proteins required for binding to fibronectin.[51] Manuka honey has also been shown to prevent biofilm formation in *Streptococcus pyogenes*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* by blocking the binding to fibronectin, fibrinogen and collagen, as well as to keratinocytes *in vitro*. Additionally, invasion of *Streptococcus pyogenes* and a strain of *Staphylococcus aureus* with intermediate resistance to vancomycin (VISA) into keratinocytes was blocked by manuka honey.[52] Another study has demonstrated the ability of several honeys and dressings to prevent biofilm formation *in vitro*, but the mechanisms of action were not investigated.[53] Initiation of infection and biofilm formation is dependent on attachment of microbial cells to human cells or extracellular material, so it is possible that honey could be used prophylactically to block biofilm formation *in vivo*.

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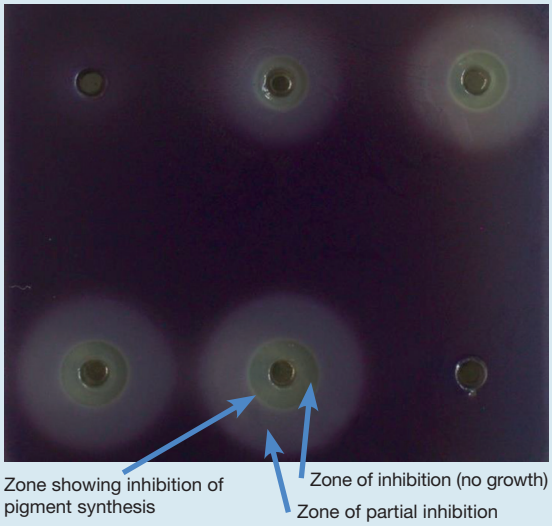
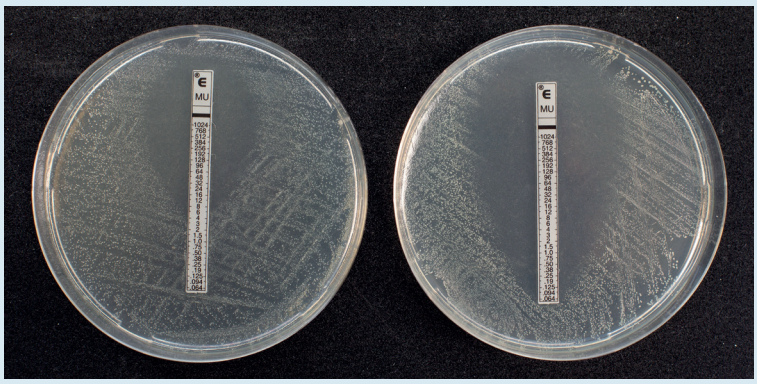
Fig 1. Assay for quorum sensing inhibition using *Chromobacterium violaceum*: clockwise from top left well, 10%(w/v) MH, 20%(w/v) MH, 30%(w/v) MH, no honey, 5-%(w/v) MH and 40%(w/v) MH.



Antibiofilm activity by interference in quorum sensing

When the ability of Spanish honeys to inhibit quorum sensing in bacteria was investigated, chestnut honey (which is now available in CE marked wound dressings in Slovenia) was found to be the most active of 29 samples tested.[54] Manuka honey has since been shown to inhibit quorum sensing inhibition in *Pseudomonas aeruginosa in vitro*.[55] Quorum sensing inhibition can be demonstrated with reporter bacteria whose purple pigment is not synthesised in the presence of a quorum sensing inhibitor (Fig 1). Siderophores are essential for the survival of pathogenic bacteria by acquiring iron from host molecules, and their production is regulated by quorum sensing. Hence the inhibition of siderophore production in *Pseudomonas aeruginosa*,[43] provides further evidence that quorum sensing was impaired by manuka honey.

Fig 2. Synergistic inhibition of MRSA: Left plate showing inhibition of MRSA by mupirocin; right plate showing inhibition of MRSA by mupirocin in the presence of 5%(w/v) manuka honey



Antibiofilm activity by disruption of established biofilm

Whenever the disruption of established biofilms has been investigated, it has shown that higher concentrations of honey are required to disrupt biofilms than those effective in inhibiting planktonic bacteria or preventing biofilm formation.[51,56–62] Organisms tested include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, MRSA, *Proteus mirabilis*, *Enterobacter cloacae* and vancomycin-resistant *Enterococcus faecalis*. Methylglyoxal disrupted the individual biofilms of *Pseudomonas aeruginosa* and MRSA *in vitro*.[63]

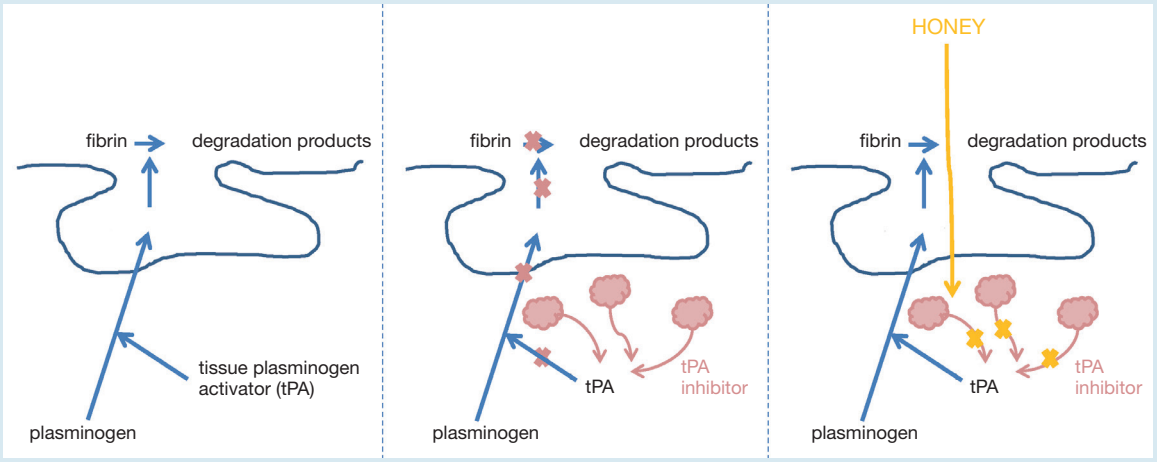
In a comprehensive study to evaluate the efficacy of antimicrobial dressings against mature biofilm of *Pseudomonas aeruginosa* established on porcine skin explants, products were found to differ in their ability to inhibit mature biofilm and two honey products were noticeably less effective than cadexomer iodine or time-release silver gel.[64] A chronic wound model with multispecies biofilm showed the persistence of *Enterococcus faecalis* to two different honeys and defensin-1.[65] Although laboratory models provide a valuable means of evaluating the efficacy of antimicrobial agents, they are limited because none precisely recreate the conditions that develop within a wound *in vivo*.[66] Only clinical studies yield appropriate evidence of efficacy, and in the case of biofilm a routine test to demonstrate their presence or absence, before and after antibiofilm interventions, is not yet available.

One approach to controlling biofilm in chronic wounds is biofilm-based wound care (BBWC) in which sharp debridement followed by topical application of a cocktail of appropriate antimicrobial agents to prevent biofilm regrowth and reformation has demonstrated significant cost savings in the US.[67] To date honey has not yet been employed in this context.

Synergistic action of honey with antibiotics

Medical grade manuka honey has been shown to augment the action of antibiotics *in vitro* (Fig 2). Initially a sublethal concentration of manuka honey, in combination with a sublethal concentration of oxacillin, was found to reverse oxacillin-resistance in MRSA.[68] Testing a further 15 antibiotics with and without sublethal concentrations of manuka honey against each of MRSA and *Pseudomonas aeruginosa* using five methods discovered five synergistic combinations.[69] The findings for manuka honey and rifampicin against strains of *Staphylococcus aureus* and MRSA were confirmed,[70] and further honey and antibiotic combinations have been reported.[71] These observations suggest that low levels of manuka honey may potentiate the activity of antibiotics ,and that it has potential in the future control of antibiotic-resistant pathogens, although not all strains may be susceptible.[71] Clinical data is needed to substantiate claims and commercial products need to be developed.

Fig 3. Diagram to illustrate the role of honey in wound debridement



Deodorising action

Molan described the deodorising action of honey for malodourous wounds.[3] Volatile odours are generated during the anaerobic metabolism of bacteria such as *Bacteroides*, *Clostridium*, *Proteus*, *Klebsiella* and *Escherichia* due to the production of amines, short chain fatty acids, aromatic sulphides and hydrogen sulphide from proteins. Some common wound pathogens also produce unpleasant odours: *Pseudomonas aeruginosa* produces a rather fishy smell, and *Staphylococcus aureus* a slightly cheesy smell. The sugars contained in honey are able to drive bacteria towards fermentative metabolism which results in a less odorous mixture of organic acids and carbon dioxide. Despite anecdotal evidence to support the deodorising claim for honey in wounds,[72–74] there is still little objective clinical data available. One randomised clinical trial showed that dressings containing either manuka honey or nanocrystalline silver induced no statistically significant differences in exudate, odour or wound pain in malignant, fungating wounds.[75] Furthermore, a randomised feasibility study comparing medical grade honey with conventional dressings in reducing infection following reconstructive surgery for patients with head and neck cancer reported similar levels of satisfaction for controlling odour.[76]

Debriding action

Whereas the debriding action of honey had not been explained in 1999,[3] a mechanism was proposed in 2009.[77] Autolytic debridement depends on proteolytic enzymes slowly digesting devitalised tissue within the wound. One of the enzymes involved in this process is plasmin (formerly called fibrinolysin because of its ability to degrade fibrin). Plasmin is activated from an inactive precursor known as plasminogen by tissue plasminogen activator (tPA). It is important in tissue remodelling by contributing to the lysis of clots and several components of the extracellular matrix, as well as the mediation of inflammation. In wounds with chronic inflammation, tPA is blocked by tissue plasminogen activator inhibitor (tPAI). The osmotic potential of honey increases wound exudation, which facilitates the supply of plasminogen from tissue to the wound bed in lymph. By culturing macrophage cellsin the laboratory, it was suggested that honey increased levels of plasmin by inhibiting tPAI synthesis of macrophages.[78] A schematic illustration is given in Fig 3. Clinical observations to support the debriding action of honey were compiled by Professor Molan in 2009.[79] The safety and efficacy of manuka honey in neonatal and paediatric wounds requiring debridement has since been investigated.[80]

Anti-inflammatory action

The anti-inflammatory activity of honey has been investigated in a variety of human disorders, but only the studies directly relevant to wounds are included here. Simply, the antimicrobial action of honey assists in removing one of the stimuli that elicit inflammation in a wound. This, together with the osmolarity of honey which enhances wound exudation, could be described as anti-inflammatory activity since it reduces oedema and contributes to pain relief.[3] However, inflammation is a complex situation that demands detailed analysis. Monocytes, macrophages, neutrophils, platelets, leukocytes, fibroblasts and metalloproteinases are involved in the inflammatory process, and their responses following exposure to honey *in vitro* have been explored as a means to gain insight into mechanisms of anti-inflammatory action. Anti-inflammatory effects of honey have been attributed to an ability to inhibit complement activated by the classical pathway, the inactivation of ROS and the inhibition of ROS production.[77]

Immunomodulatory activity of honey was first demonstrated *in vitro* with a monocytic cell line. Production of ROS was significantly decreased by honey and the release of tumour necrosis factor (TNF-α) was increased.[81] Similarly, honey was shown to promote the production of proinflammatory cytokines

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such as IL-1β and IL-6 in this cell line, as well as in human peripheral monocytes.[82] TNF-α is a key modulator of many of the types of cells involved in tissue repair and wound healing.

Slovakian acacia honey stimulated TNF-α release from murine macrophages,[83] and secretion of elevated levels of TNF-α, IL-1β, TGF-β and MMP-9 in keratinocytes.[84] Enhanced levels of MMP-9 were also detected in healthy human foreskin incubated with honey, with increased degradation of collagen IV in basement membranes. Treatment of the cell line and human tissue with a glycoprotein major royal jelly protein 1 (MRJP 1) purified from the honey sample indicated a similar but diminished effect, hence MRJP 1 was implicated in this response.[84] Yet, research conducted in the same laboratory found that flavonoids isolated from fir honeydew honey inhibited TNF-α-induced MMP-9 expression in human keratinocytes.[85] French thyme honey stimulated murine macrophages to increase production of TNF-α and led to the over-expression of prostaglandin E_2 (PGE_2) and cycloxygenase-2 (COX-2) by activating two transcription factors.[86]

In two investigations into the immunomodulatory role of honey in wound healing differing modes of action were established in differing honeys. Using either a human keratinocyte cell line or a human fibroblast cell line, scratch wound and chemotaxis assays, differing efficacy and mechanisms of actions were established for each of acacia, buckwheat and manuka honey, respectively.[87,88] These observations suggest a role for honey in promoting re-epithelialisation.

One important category of anti-inflammatory components in honey is antioxidants. However, the antioxidants in honey (which include polyphenols, flavonoids and ascorbic acid) vary according to floral source.[89–91] Of the honeys used in modern wound care, the flavonoids in manuka have been the most extensively characterised.[92] Antioxidants, many of which also possess antibacterial activity, help to protect cells by quenching free radicals. Elevated levels of free radicals characterise wounds with chronic inflammation; they are released during oxidation and initiate a complex series of reactions that gives rise to ROS that ultimately result in tissue damage by multiple routes. The ability of manuka honey to scavenge free radicals *in vitro* was demonstrated using electron spin resonance.[93,94] Methyl syringate was implicated in this effect.[93] Also, American buckwheat honey scavenged superoxide ion, inhibited production of ROS by activated human polymorphonuclear neutrophils (PMNs), and inhibited human complement *in vitro*.[95] Phenolic extracts of two Cuban honeys with high antioxidant activity due largely to quercetin have been shown to protect erythrocytes against oxidative damage. Incorporation of honey flavonoids into erythrocyte membranes facilitated uptake of flavonoids to assist in defensive mechanisms against oxidative stress.[96] Four different types of New Zealand honey (manuka (*Leptospermum scoparium*), kanuka (*Kunzea ericoides*), clover (*Trifolium spp.*), and a manuka/kanuka blend) were used to explore the mechanisms by which anti-inflammatory effects are modulated in three human cell lines. A common mechanism was not found: only kanuka honey and manuka honey influenced a toll-like receptor signalling pathway (TLR1/TLR2). Phenolic content of honey was correlated to anti-inflammatory effectiveness, but specific compounds were not identified.[97]

The first study to propose a mechanism by which manuka honey might promote wound healing has recently been published. Up to 16 phenolic components were found to contribute to the total antioxidant capacity of manuka honey. Using primary human dermal fibroblasts (HDFa), unfractionated manuka honey was shown to protect fibroblasts against death by apoptosis, to promote cell proliferation and migration, to improve the antioxidant response by increasing the expression of two key antioxidant enzymes (superoxide dismutase and catalase), and to protect mitochondrial function in terms of oxygen consumption rate. AMPK phosphorylation via activation of the AMPK/Nrf2 signalling pathway was suggested as the mechanism.[98]

Antioxidants and proteins in honey appear to be central to the modulation of human cells. Some investigators have suggested that lipopolysaccharide (an endotoxin derived from bacteria) in honey may be responsible for the stimulatory effects observed in cell cultures,[99] others have excluded it.[81,82,86] A 5.8kDa component was isolated from manuka honey that induced TNF-α production from monocytes via activation of a toll-like receptor (TLR4), but its identity was not determined.[100] Arabinogalactans derived from plants were shown to be involved in the immunostimulatory properties of New Zealand honeys,[101] and recently the effects of plant arabinogalactans on monocytes were found to be augmented by proteins derived from the bee.[102]

In summary, observations from *in vitro* cellular studies indicate that the multiple anti-inflammatory and wound healing effects of honey are related to components associated with the floral source of the honey sample and to components derived from the bee. Also, more than one component is involved in the regulatory processes and honeys probably contain bioactive agents that exert both positive and negative influences at the same time. A more detailed review of the immunomodulatory properties of honey[103] and further evidence from animal and human studies are available.[3,104]

Stimulation of tissue growth

Apart from the evidence provided above, the role of honey in stimulating tissue growth is mainly supported by observations of healing rates obtained from either animal or clinical studies which were described in reviews by Professor Molan over the years.[3,79,104,105] Mechanisms by which honey influences wound healing need further investigation; antibacterial activity alone would not appear to be responsible.

Clinical experience

With the increased use of honey since 1999, there are systematic reviews to inform practitioners on the clinical efficacy of honey in treating wounds. Randomised controlled trials began in 1991 and have been conducted in many countries with a wide variety of wounds and different types of honey. A recent Cochrane review concluded that honey appeared to promote healing in partial-thickness wounds more quickly than conventional treatments, and infected post-operative wounds more quickly than antiseptics and gauze.[106] However, much of the evidence reviewed was considered to be of low quality due to limitations in blinding during treatment and assessment, and poor design of studies. Larger cohorts are required and a broader range of outcomes should be defined in future. Similar concerns were raised in another review.[107] Within the past year the efficacy of manuka honey in eyelid wound healing[108] and partial-thickness facial burns[109] has been studied. Following the development of licenced wound care products employing medical grade honey, there is an argument that systematic reviews should be limited to the clinical efficacy of these products, rather than including local honeys that are neither easily reproducible nor widely available.

Future developments

One of the factors that may limit uptake of honey in treating wounds is the messiness of using sterile honey directly. Some formulations now present honey in more manageable ways either by lowering the concentration of honey within the dressing, or by combining honey with other agents to produce non-sticky sheets which do not require secondary absorbent dressings. One suggestion has been to impregnate polyvinyl alcohol fibres with methylglyoxal (one of the antibacterial factor associated with manuka honey).[110] Another innovative approach has been to use the lactic acid bacteria (LAB) from the stomach of the honey bee to treat chronic wounds.[111] These bacteria are thought to be important in producing some of the components that contribute to the antimicrobial and therapeutic characteristics of honey.[112] In India a biodegradable hydrogel sponge containing chitosan, alginate, Indian honey and curcumin has been formulated.[113] Curcumin is derived from tumeric powder which has traditionally been applied to wounds in India. The potential of other herbs and spices for wound care may yet provide more interest.

Conclusions

This update illustrates how much information about honey has become available within the last 17 years and it emphasises the debt owed to Professor Molan. Ultrastructural and molecular studies have provided more detailed information on the mode of action of honey against wound pathogens than for any other topical agent. Knowledge of the effects of honey on the cells intimately involved in wound healing has expanded, but it demonstrates the complexity of the situation. No single constituent of honey seems to elicit a specific effect and some act synergistically. At present it is logical to continue to use whole honey for wound care, rather than try to isolate any component to use in isolation, or try to create an artificial preparation. Maybe medical grade honeys could be assessed in terms of anti-inflammatory and/or wound healing activity, in addition to antibacterial activity in the future? **JWC**

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