Chapter 4
Honey Health Benefits and Uses in Medicine

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4.1 Antioxidant Capacity

The generation of reactive oxygen species (ROS) and other free radicals during metabolism is an essential and normal process that ideally is compensated through the antioxidant system. However, due to many environmental, lifestyle, and pathological situations, free radicals and oxidants can be produced in excess, resulting in oxidative damage of biomolecules (e.g., lipids, proteins, and DNA). This plays a major role in the development of chronic and degenerative illness such as cancer, autoimmune disorders, aging, cataract, rheumatoid arthritis, cardiovascular, and neurodegenerative diseases (Pham-Huy et al. 2008; Willcox et al. 2004). The human body has several mechanisms to counteract oxidative stress by producing

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antioxidants, which are either naturally synthetized *in situ*, or externally supplied through foods, and/or supplements (Pham-Huy et al. 2008).

Research indicates that foods rich in antioxidants such as honey can protect from the damaging effects of free radicals and ROS and thus exhibit beneficial effects on human health; such as cardiovascular protection by preventing ROS-induced low density lipoprotein (LDL) oxidation (Schramm et al. 2003); cell death in some cancer cell lines (Jaganathan et al. 2015); enhance the human antioxidant defense system (Schramm et al. 2003) among others (Ajibola 2015). For instance in animal models, honey showed a protective effect against damage and oxidative stress induced by cigarette smoke in rat testis (Mohamed et al. 2011); honey supplementation exhibited a hepatoprotective and nephroprotective effect in rats with experimental aflatoxicosis due to its antioxidant activity (Yaman et al. 2016).

The antioxidant capacity (or antioxidant activity) of honey is commonly attributed to its phenolic compounds. These compounds exhibit several preventive effects against different diseases like cancer, cardiovascular diseases, inflammatory disorders, neurological degeneration, wound healing, infectious diseases and aging (Khalil et al. 2010).

The main antioxidant phenolic compounds in honey are: (a) phenolic acids: gallic acid, caffeic, ellagic, ferulic and p-coumaric acids, syringic acid, benzoic acid, cinnamic acid; chlorogenic acid, and (b) flavonoids: apigenin, chrysin, galangin, hesperetin, kaempferol, pinocembrin and quercetin (Fig. 4.1) (Rao et al. 2016; Erejuwa et al. 2014). While some of these bioactive compounds are found in most honey samples, others such as hesperetin and naringenin are found in few honey varieties (Erejuwa et al. 2012).

The amount and type of the phenolic antioxidants depend largely upon the honey's floral source and/or variety of the honey (Gheldof et al. 2002). Generally, darker honeys have been shown to have a higher total phenolic content (TPC) and consequently a higher antioxidant capacity than lighter honeys (Eteraf-oskouei and Najafi 2013). Beside this, Ferreira et al. (2007) found that the dark honey contained the highest concentration of other antioxidants such flavonoids, ascorbic acid, and β-carotene compared to the light and amber honeys.

In addition, some *in vivo* studies have shown that the antioxidant compounds of honey are bioavailable to the human body. Schramm et al. (2003) observed that honey fed at 1.5 g/kg body weight increased both phenolic antioxidants and plasma antioxidant capacity inhealthy human subjects. These results supported the concept that phenolic antioxidants from honey are bioavailable and that these compounds may augment oxidative defense in the human body. Similar evidence has was observed by (Gheldof et al. 2003).

The antioxidant activity of phenolic compounds is related to a number of different mechanisms, such as free radical-scavenging, hydrogen-donation, singlet oxygen quenching and/or metal ion chelation (Eteraf-oskouei and Najafi 2013). Therefore, in order to obtain more accurate and representative results, the antioxidant capacity of honey is generally measured by use of various *in vitro* assays such as: in the form of antiradical activity using 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging assay; 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) assay; oxygen radical absorbance capacity (ORAC) assay; and commonly used ferric reducing antioxi-

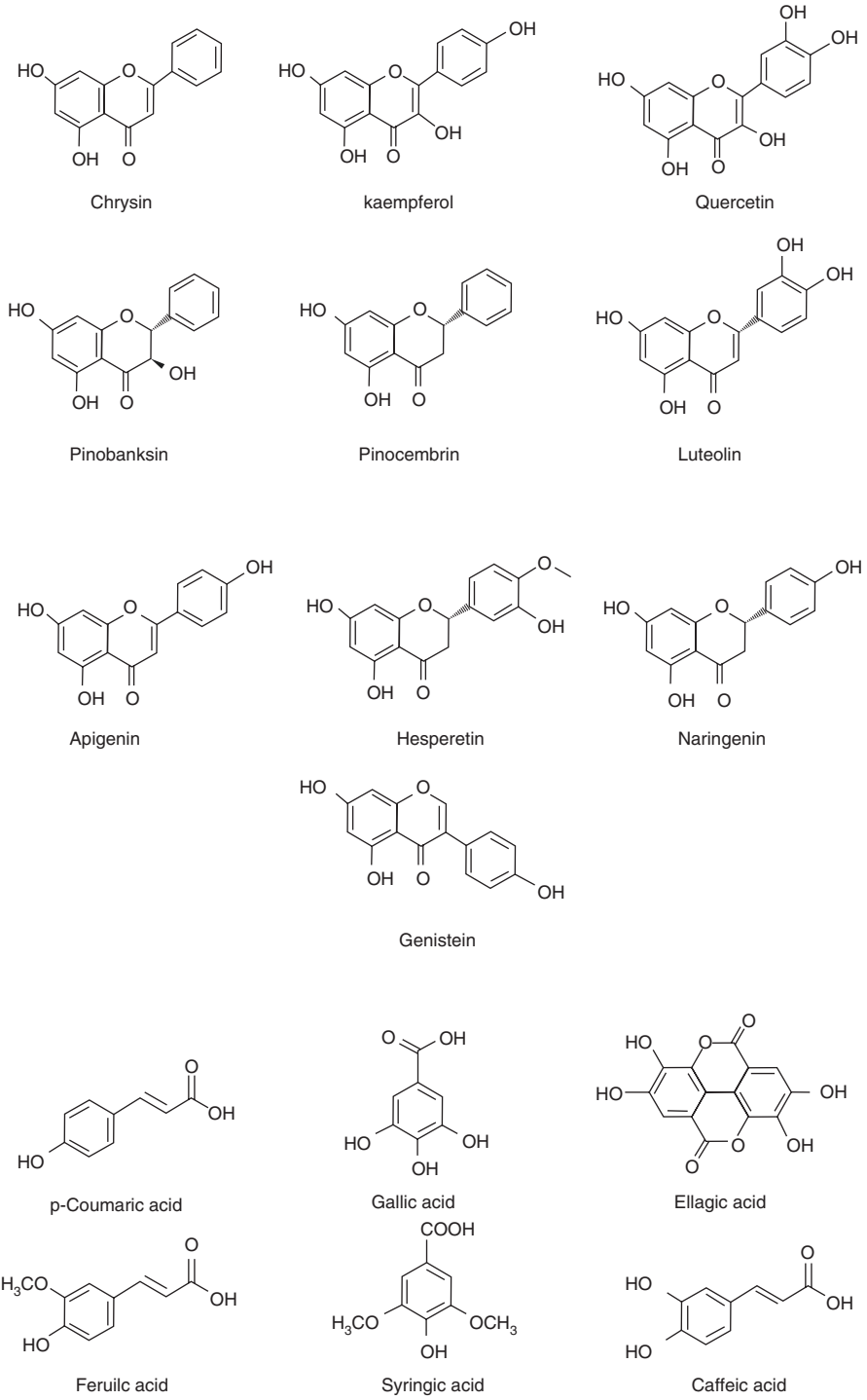

Fig. 4.1 Chemical structures of some flavonoids and phenolic acids in honey (Erejuwa et al. 2014)

dant power (FRAP) assay, that measures the conversion by antioxidants of the oxidized form of iron (Fe3+) to the reduced form (Fe2+) (Erejuwa et al. 2012). Several *in vitro* studies showed that the antioxidant capacity is strongly correlated with the content of the total phenolics in honey (Chua et al. 2013; Sagdic et al. 2013). For instance, a positive correlation was found between antioxidant capacity (ORAC assay) and TPC of various commercial honeys contributed to their antioxidant properties.

However, Gheldof et al. (2002) stated that the levels of single phenolic or other compounds in honey are too low to have a major individual antioxidant significance. Hence, the total antioxidant capacity of honey has been associated to the result of the combined activity and interactions of a wide range of compounds, including both enzymatic: catalase, glucose oxidase, peroxidase and non-enzymatic substances: ascorbic acid, α-tocopherol, carotenoids, amino acids, proteins, organic acids, Maillard reaction products, and other minor components (Nayik et al. 2016; Eteraf-oskouei and Najafi 2013; Ferreira et al. 2007).

Erejuwa et al. (2012) described the synergistic antioxidant effect of honey and thus considered the advantage of honey over other antioxidants, such as vitamins C and E. In fact, these vitamins in their antioxidant action do not end with scavenging or elimination of free radicals. Instead, they can become themselves pro-oxidants which can require other antioxidants for their regeneration into the active or antioxidant form. The advantage of honey is that it comprises several antioxidant constituents and if any of them exhibit pro-oxidant properties, there would be sufficient other antioxidants, which can protect the one against oxidative destruction, and thus lead to the regeneration into the antioxidant form. In fact, honey contains both aqueous and lipophilic antioxidants and thus can act at different cellular levels as an ideal natural antioxidant (Oryan et al. 2016).

Moreover, the quantity of honey consumed in the diet is low compared with the quantity of many of the food sources of antioxidants. According to (Erejuwa et al. 2012), if honey would be used instead of refined sugars as a sweetener for food and drinks it could make a substantial difference to the quantity of antioxidants consumed in the diet.

4.2 Antibacterial Activity

The treatment of bacterial infections is being increasingly complicated by the ability of bacteria to develop resistance to current available antimicrobial agents. This evidence leads to the need of less and better use of antibacterials and antifungals, improved infection control and research on new therapeutic compounds (Feás et al. 2013).

Antibacterial activity of honey is one of the most important findings that was first recognized in 1892 by the Dutch scientist Van Ketel (Eteraf-oskouei and Najafi 2013). The recent research indicates that the effectiveness of honey in many of its medical uses is due to its antibacterial activity that is capable of inhibiting Gram-positive and Gram-negative bacteria, including multidrug resistant strains (Kwakman et al. 2008), and some species of fungi and viruses (Irish et al. 2006; Naama 2009).

For instance, Junie et al. (2016) compared *in vitro* antibacterial activity of several types of honey of different origins against the bacterial resistant strains isolated from patients, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella enterica* serovar *Typhimurium*, *Bacillus cereus*, *Bacillus subtilis*, and *Listeria monocytogenes*. The results showed that all the honey samples presented antibacterial activity against the studied strains and that all the honey samples inhibited bacterial growth. This evidence was similar to other studies conducted elsewhere (Huttunen et al. 2013).

The quantitative determination of the reduction of microbial colonization against a representative panel of bacteria is generally analyzed by *in vitro* tests including (a) determination of minimum inhibitory concentration (MIC) using broth tube dilution methods through visual inspection and (b) by determination of minimum bactericidal concentration (MBC) by sub-culturing tubes showing no visible sign of growth/turbidity (Wasihun and Kasa 2016); these determinations allow a distinction between whether a honey is just stopping the bacteria from growing (bacteriostatic action) or is killing the bacteria (bactericidal action), respectively (Molan 1992). It has been stated that honey possessed a significant antibacterial activity against some bacteria which are resistant to antibiotics (Junie et al. 2016; Mohapatra et al. 2011).

In a study by Wasihun and Kasa (2016) the antibacterial activity of honey was evaluated against multidrug resistant human pathogenic bacterial isolates (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, coagulase-negative *Staphylococcus*, *Streptococcus pyogenes* and *Klebsiella pneumoniae*). The MIC and MBC values indicated that the tested honeys had potential bacteriostatic and bactericidal activities against the tested bacteria. Unlike most conventional antibiotics, honey dose may not lead to development of antibiotic-resistant bacteria and it may be used continuously (Eteraf-oskouei and Najafi 2013). According to Alandejani et al. (2009), antibiotics tested (cefazolin, oxacillin, vancomycin, azithromycin, fusidic acid, gentamicin, and linezolid) were not bactericidal to methicillin-sensitive *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), or *Pseudomonas aeruginosa* (PA) biofilms. But the bactericidal rates for the Sidr and Manuka honeys were significantly higher than those seen with the single antibiotics. Thus, the use of honey in a medical setting is considered to be helpful in combating bacterial resistance (Kwakman et al. 2008).

The bacterial strains differ in their sensitivity to honeys. Due to the different floral source, locations, bee species, storage (time and temperature), and processing, the antibacterial potency of different honeys can vary (Grego et al. 2016; Sousa et al. 2016), for some by more than 100-fold (Lusby et al. 2005). Thus it is difficult to standardize honeys and assess their usefulness in a medical application (Sousa et al. 2016). In spite of this, there are medical grade honeys like Revamil source (RS) honey and Manuka (i.e., Medihoney). Having reproducible antibacterial activity, these honeys are produced under controlled conditions in greenhouses and each batch is analyzed individually to assess the Unique Manuka Factor (UMF) that gives a number based on its bactericidal activity (Knight 2013).

However, the mechanism by which honey exerts the activities against a broad spectrum of organisms is still under debate. There are some factors that are closely related to the antibacterial capacity of honey, including the level of hydrogen perox-

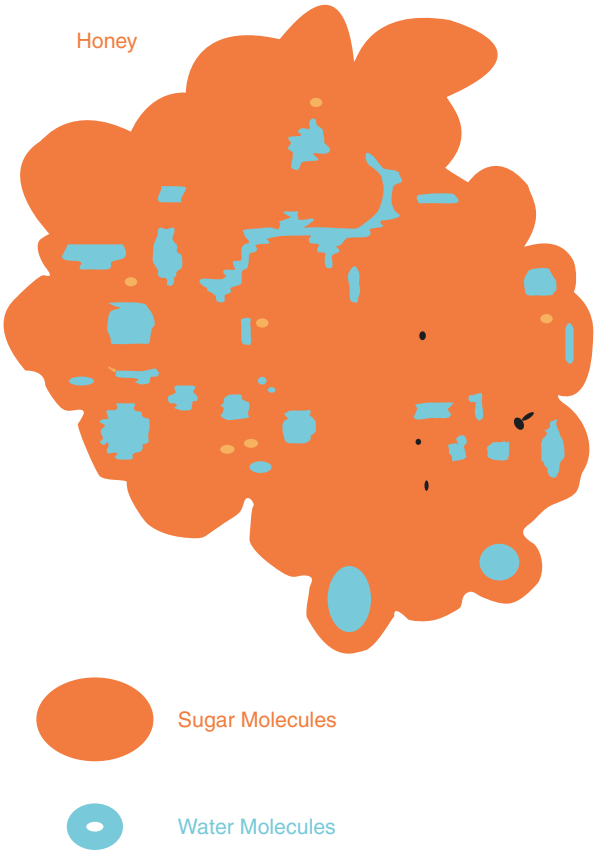

Fig. 4.2 Physical structure of honey (Hadagali and Chua 2014)

ide (H_2O_2), which is formed when honey is diluted (Knight 2013). According to Hadagali and Chua (2014), enzymes convert sucrose into a simple and soluble mixture of monosaccharides. The sugar molecules in the honey solution bind to free water molecules (Fig. 4.2), which means that there is no water available for microbes to use, preventing their survival. The enzyme glucose oxidase (produced by bees) converts glucose into gluconic acid, making the honey too acidic for microbes to grow and survive. The H_2O_2 produced as a by-product of this reaction acts as a sporicidal antiseptic that sterilizes the honey (Fig. 4.3).

Further, the osmolarity of honey, due to about 80% of its composition being sugars, is another important factor to prevent growth of bacteria (Kwakman and Zaat 2012). Different concentrations (or dilutions) of honey used in the *in vitro* tests have been associated with a different antibacterial response (Steinberg et al. 1996).

Beside the sugar content, the low pH (between 3.2 and 4.5 for undiluted honey) is inhibitory to many pathogenic bacteria. However, when consumed orally, the honey would be so diluted by body fluids that any effect of low pH is likely to be lost (Molan 1995). In spite, honeys have substantial antibacterial activity due to non-peroxide components including methylglyoxal and the antimicrobial peptide bee defensing-1. For instance, these compounds have been identified in Manuka and RS honey as antibacterial compounds (Kwakman and Zaat 2012). In addition, fac-

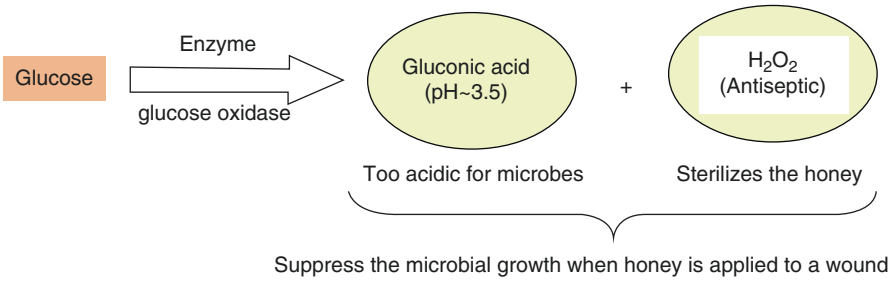

Fig. 4.3 Formation of gluconic acid and hydrogen peroxide (H_2O_2) (Hadagali and Chua 2014)

tors such as phenolic compounds (i.e. flavonoids and phenolic acids) (Kwakman and Zaat 2012; Sousa et al. 2016) and some unknown floral or bee components are being considered as contributing to the antibacterial activity of honey as well (Nishio et al. 2016).

4.3 Anti-inflammatory Capacity

Honey possesses quite a large number of therapeutic properties, including antioxidant and antimicrobial properties, as well as anti-inflammatory activity (Vallianou et al. 2014).

The anti-inflammatory property of honey is mainly related to its antiseptic nature that works by removing infectious bacteria stimulating the inflammatory response, and reduction of the amount of bacteria present in the wound (Hadagali and Chua 2014). In fact, that honey can remove bacteria that cause inflammation, a decrease in wound inflammation after applying honey gauze has been associated to its direct anti-inflammatory properties, such as antioxidant capacity (Yaghoobi et al. 2013). In particular, some of the antioxidant phenolic compounds (i.e. flavonoids) are deeply related to anti-inflammatory effects as previously reported in the literature (González et al. 2011). However, beside the wound inflammation (Tomblin et al. 2014), the correlation of antioxidant capacity of honey with its anti-inflammatory action has been observed in other inflammation models as well (Owoyele et al. 2011).

For instance, the potential protective effect of a honey flavonoid extract (HFE) has been studied on the production of pro-inflammatory mediators by lipopolysaccharide-stimulated N13 microglia. It has been shown that the HFE (containing luteolin, quercetin, apigenin, kaempferol, isorhamnetin, acacetin, tamarixetin, chrysin, and galangin) can inhibit microglial activation and thus be considered as a potential preventive–therapeutic agent for neurodegenerative diseases involving neuroinflammation (Candiracci et al. 2012). The main evidence that considers the antioxidant activity as the anti-inflammatory factor is the ability of antioxidants to inhibit ROS production during the inflammatory process. A number of drugs are available for the treatment of ulcerative colitis. Manuka honey has been shown to specifically decrease the inflammatory response associated with ulcerative colitis, an inflammatory bowel disease characterized by an over-expression of inflammatory cells, possibly by

increasing antioxidant activity (Prakash et al. 2008). In a study by Borsato et al. (2014), honey extract decreased edema, reduced leucocyte infiltration, and inhibited the production of ROS during the inflammatory process induced chemically in mice ear. The anti-inflammatory activity has been associated with a synergetic effect of the honey phenolic compounds, including kaempferol and caffeic acid.

In general, the transcription factor nuclear factor-kappa beta (NF-KB) plays a key role in pathogenesis of inflammation, being known as marker of inflammation (Vallianou et al. 2014). It enhances pro-inflammatory activity, thereby contributing to an amplified inflammatory response, and activates genes encoding pro-inflammatory cytokines – interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNF-α). These pro-inflammatory cytokines stimulate nitric oxide production (NO), an important mediator of inflammation (Tomblin et al. 2014).

The anti-inflammatory effect of honey has been observed in numerous reports, stating that honey can inhibit the release of pro-inflammatory cytokines, expression of nitric oxide synthase (iNOS), production of ROS (Candiracci et al. 2012), and can decreases prostaglandin levels, one of the major players in the process of inflammation (Al-Waili and Boni 2003). According to an *in vivo* study by Owoyele et al. (2011), honey caused inhibition of NO release in acute and chronic inflammation. Further, Gelam honey has been investigated in an acute inflammation model system showing the reduction of edema in inflamed rat paws. The mechanism was associated with the inhibition of cyclo-oxygenase (COX-2) and iNOS, which resulted in suppressed levels of pro-inflammatory mediators such as NO, PGE2, TNF-α, and IL-6 (Hussein et al. 2012).

In general, acute inflammation is the body's primary response to injurious stimuli, and some of the body's responses are characterized by pains (Hadagali and Chua 2014). Side effects of the available drugs for the treatment of inflammatory pain can sometimes limit the use of these drugs (e.g., NSAID, Indomethacin) (Owoyele et al. 2014). It has been shown that honey significantly decreased production of pro-inflammatory cytokines, which was similar to the effect of the anti-inflammatory drug Indomethacin (NSAID) (Hussein et al. 2012), and also could modulate muscarinic receptors to produce its analgesic effect (Owoyele et al. 2014), thus being potentially useful for treatment of inflammation.

4.4 Wound Healing Activity

Several animal studies and clinical trials have examined the application of honey for acute and chronic wounds (Moore et al. 2001) including burn injuries (Bangroo et al. 2005), and have demonstrated that it limits the amount of edema, improves granulation and epithelization in the proliferative phase while decreasing total wound healing time, reduces scarring and contractures in patients with burn wounds (Mohamed et al. 2015), without adverse effect (allergy or toxicity) at all (Yaghoobi et al. 2013). Due to its low adherence in wound surface, honey causes minimal pain

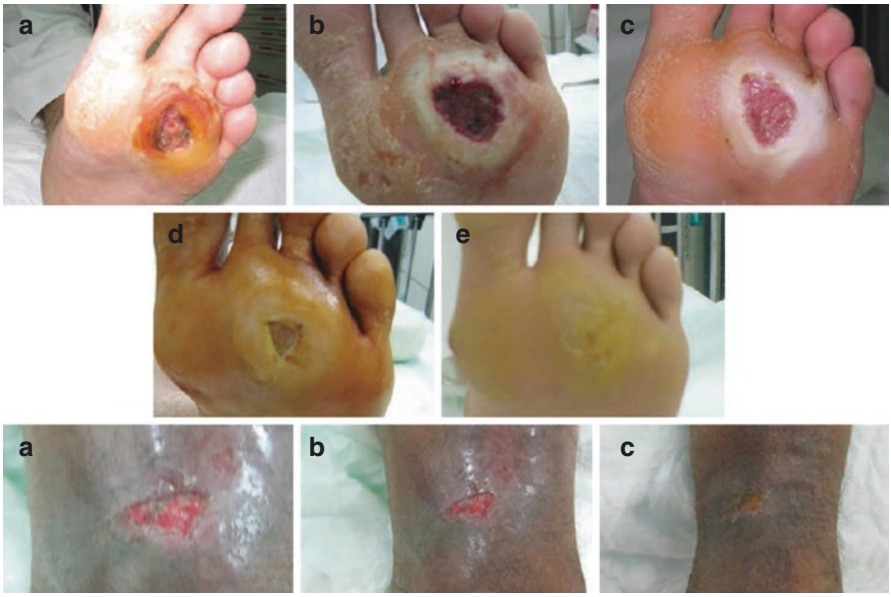

Fig. 4.4 Wound healing activity of honey. Case 1 (**a**–**e**): Diabetic neuropathic ulcer with 3 weeks time to healing. Case 2: (**a**–**c**): Varicose ulcer with 6 weeks time to healing (Mohamed et al. 2015)

during application and upon removal preserving the newly forming granulation tissue (Mohamed et al. 2015).

There is evidence that honey can heal partial thickness burns more quickly (around 4–5 days) than conventional dressings; and post-operative infected wounds can be treated by honey more effectively than by use of antiseptic or gauze (Jull et al. 2008). In a study by (Mohamed et al. 2015), a total of 12 patients with chronic foot ulcers utilized natural honey as an effective alternative to more expensive, advanced wound products. After the wound rinsing with normal saline, natural honey was applied and the wound was covered by glycerin-impregnated gauze. Patients were followed on a daily basis for an average of 4 weeks (Fig. 4.4). The results showed that all ulcers healed with no contractures or scars with a mean healing time of 3 weeks. Moreover, there was a 75% reduction in the dressing budget of the health center and a high level of satisfaction among both health professionals and patients. Also, patients' pain levels were reduced significantly after using natural honey. Similar evidence has been observed when Manuka honey gel was used for treatment of partial-thickness facial burns. The healing time was congruent with or better than what would been expected with standard treatment. No abnormal bacterial growth was reported and the patients reported overall satisfaction with the treatment and cost of the treatment. It has been suggested that Manuka honey is a clinically and economically valuable treatment for partial-thickness facial burns

(Duncan et al. 2016). In addition, a recent study by Aziz et al. (2017) showed that honey dressings can promote better results for burn wounds than the silver-based dressings (i.e., silver sulfadiazine), the currently extensively used method used to treat a variety of acute and chronic wounds.

The presence of antibiotic resistant *S. aureus* in wounds is a cause for concern due to its capacity to acquire resistance to multiple antibiotics that make the treatment of wounds difficult. Jenkins et al. (Jenkins et al. 2012) showed that Manuka honey effectively inhibited the strains of vancomycin-intermediate *S. aureus* (hVISA, VISA) and the clinical strains of vancomycin-sensitive *S. aureus* (VSSA) in the clinical setting. It has been indicated that Manuka honey at low concentration (≤6% (w/v)) can inhibit the growth of clinical isolates of *S. aureus* and thus can be used as a treatment option to help decontaminate wounds infected with antibiotic-resistant organisms like *S. aureus*. Besides that, clinical and laboratory data indicate that natural honey is effective against a variety of common pathogens (see Sect. 4.2).

Honey facilitates wound healing by its ability to create an effective viscous barrier on the wound surface, thus preventing the invasion of microorganisms (Aziz et al. 2017) present in the wounds and can remove any dead tissue that may provide a favourable environment for the growth of microorganisms (Zbuchea 2014). The acidic pH of honey (3.2 to 4.5) inhibits growth of most pathogenic bacteria within wounds, and increases production of hydrogen peroxide from the enzyme glucose oxidase at 1:1000 concentration. This is less than the conventional rinse solutions but enough to inhibit bacterial growth without compromising the new granulation tissue (Mohamed et al. 2015). Thus, when applied topically, honey is capable of cleaning infection from a wound and improving healing (Al-waili et al. 2011). Nevertheless, the wound healing capacity of honey is not only through its antiseptic nature, but also through its immunomodulatory effects, which boost the immune system to fight infection (Fig.4.4). The components in honey related to its immunomodulatory properties have not been yet fully identified, but are being attributed to lipopolysaccharide (LPS), a 5.8 kDa component, major royal jelly protein 1, arabinogalactants, polyphenols, and antioxidants (McLoone et al. 2016). Different types of honey have been shown to act with different mechanisms, and moreover that some of these mechanisms are more efficient than others (Ranzato et al. 2013). For instance, buckwheat honey is used in wound healing products because of its high-polyphenolic content, which make this honey effective in reducing ROS levels causing cell damage and inhibition of wound healing; Manuka honey has notable antibacterial and healing activities, which directly originate from the methylglyoxal it contains, and make this honey useful for treating problematic wounds (Ranzato et al. 2013). The Manuka honey has been claimed to have therapeutic advantages over other honeys and is thus the type of honey most often studied in controlled wound healing studies (Majtan 2011) (Fig. 4.5).

The honey for wound healing is being commonly used as a base for ointments, gels, and in surgical dressings (Shenoy et al. 2012) and some studies successfully demonstrated its healing effect when applied directly in a raw form (Mohamed et al. 2015).

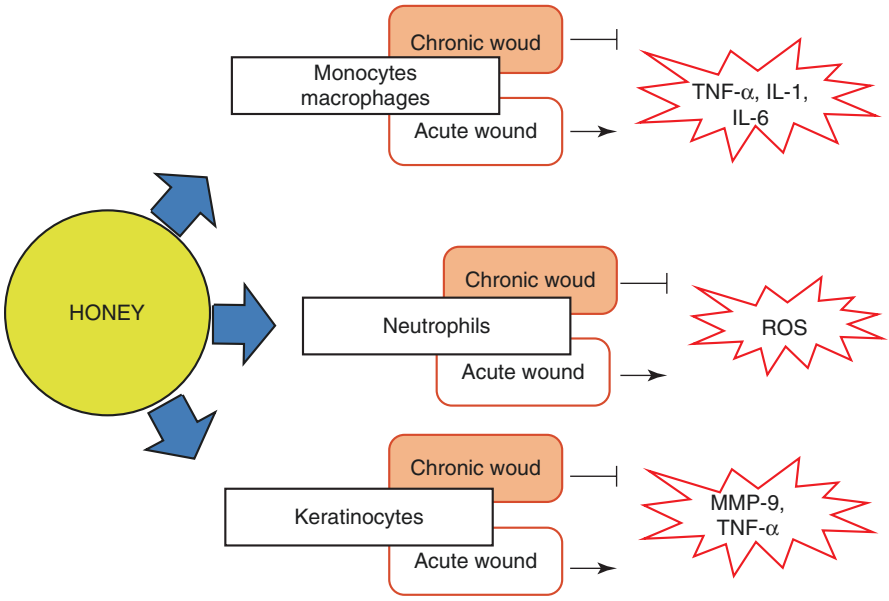

Fig. 4.5 The immunomodulatory action of honey on immune and cutaneous cells involved in wound healing. According to Majtan (2014), honey is able to either stimulate or inhibit the release of certain factors (i.e., cytokines; the MMP-9 protein that plays an important role in normal wound healing through its involvement in re-epithelialisation and extra-cellular matrix remodeling; and ROS) from immune and cutaneous cells depending on wound condition. Honey induces secretion of pro-inflammatory cytokines and MMP-9 during the inflammatory and proliferative wound healing phase, respectively. On the other hand, when the wound inflammation is uncontrolled, honey abrogates prolonged wound inflammation and reduces the elevated levels of pro-inflammatory cytokines, ROS, and MMP-9 (Majtan 2014)

However, natural honey from the comb is not medical grade and should not be used in wound care. Medical grade honey is filtered; gamma irradiated to kill *Clostridium* spores, and produced under exacting standards of hygiene. There are some commercially available sterile honey products like Revamil source (RS) and Manuka honey, the two major medical-grade honeys.

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