Honey Products and Their Potential in Wound Healing

18

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Abstract

Honey dressings attract attention as a therapeutic alternative for wound care due to its antibacterial, antioxidant, and immunomodulatory action. To obtain better medicinal properties, the formulation of honey requires the characterization of physicochemical and mechanical properties. This chapter aims to provide an in-depth account of the value of characterizing the honey dressing. Physical tests, such as swelling capacity, water vapor transmission rate, and thermal studies, are described. Therapeutic testings of honey wound dressings and their clinical applications have been covered. Recent developments in the formulation of honey dressings are also discussed in this chapter.

Keywords

Honey · Physico-chemical characterization · Formulation · Wound dressings

18.1 Introduction

In ancient cultures, natural products were the only available sources for treating most clinical conditions. Honey, for example, was used as a medicinal component for its antibacterial, antioxidant, and immunomodulatory effects which can be utilized in wound healing. However, the discovery of many synthetic drugs surpassed the use of the traditional "folk medicine." The use of antibiotics became the most common practice in the clinical field for treating all sorts of infections. This overuse of antibiotics led to the emergence of antibiotic-resistant bacteria, an issue that caused

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a comeback for the use of natural products in clinical medicine nowadays (Minden-Birkenmaier and Bowlin 2018).

Honey is the natural product of honeybees, *Apis mellifera*, which collect nectar from floral plants. It is a sweet syrup supersaturated with sugars in addition to the presence of some minerals, polyphenols, vitamins, carotenoids, amino acids, proteins, and enzymes, which differ depending on the floral source (Miguel et al. 2017). Honey is made up of nearly 200 constituents with sugar accounts for 95–99% of the total content. Glucose and fructose are the main carbohydrates present in honey making it readily absorbed in the GIT, along with other disaccharides and oligosaccharides like maltose, sucrose, isomaltose, . . . etc. Besides sugar, water is an important part of honey as well. The presence of organic acids like gluconic acid contributes to the acidity and the taste of honey. Vitamins like B and C are also present whose composition in honey differs based on the type of the honeybee. Minerals are present in low concentrations, 0.1–1%, where potassium is the main mineral. Calcium, magnesium, sodium, sulfur, and phosphorus are also present (Eteraf-Oskouei and Najafi 2013). Out of the different amino acids found in honey, proline is the most important one. Multiple phenolic acids and flavonoids are present that are dependent on the origin of the honey and, hence, used as chemical markers for origin identification (Miguel et al. 2017).

The effectiveness of honey in treating wounds is due to these various components. It is found to have a broad range of antibacterial effect. The enzyme glucose oxidase in honey breaks glucose into gluconic acid and hydrogen peroxidase; the former lowers the pH of honey reducing protease activity, increasing tissue oxygenation and stimulating macrophage and fibroblast activity, while the later kills the bacteria sterilizing the wound. Invertase is another enzyme found in honey that hydrolyzes sucrose to glucose and fructose increasing the osmotic potential. Flavonoids remove the free radicals preventing tissue damage. Furthermore, honey being a viscous fluid provides coverage over the wound forming a barrier against the surrounding bacteria while keeping the wound hydrated (Minden-Birkenmaier and Bowlin 2018).

As the use of honey in treating wounds and infections has been recognized by our ancestors, scientists have performed numerous studies and extensive research to elaborate on this effect and the mechanisms behind it. Based on this, researchers have found multiple applications for honey as a therapeutic wound dressing and formulated the dressing using multiple techniques. This chapter will discuss the use and efficacy of honey as a wound dressing in several clinical conditions including its characteristic properties which make it possible. In addition, the chapter will discuss the different dosage forms of honey available that enable its use as a wound dressing and their performance in the light of healing rate and pain alleviation.

18.2 Types of Wounds

Skin is made up of multiple layers which cover the entire body that consists of muscles, bones, ligaments, and internal organs. By covering the body, the skin protects it from the external environment including microbes, heat, light, and injury. However, if the structure or the function of the skin is compromised it leaves the body susceptible to infection. This disruption in the skin due to an injury known as wound that can sometimes be simple and heals rapidly but can also be as serious as being life threatening (Ibrahim et al. 2018; Tang et al. 2019).

Injuries are very common in the worldwide population; most of the wounds can heal within a limited period of time by a series of well-organized processes. Different components work together to repair the skin tissue including platelets, keratinocytes, immune cells, microvascular cells, and fibroblasts. Usually, the healing process occurs without complications or significant intervention; such injuries are known as acute wounds.

However, when patients who get injured suffer from other diseases, this can impair the healing process and prolong it dramatically. This known as chronic wounds. With the extension of the period of wound healing and closure, wounds become vulnerable to excessive inflammatory phase, persistent infections, formation of drug-resistant microbial biofilms, and the inability of epidermal cells to respond to reparative stimuli (Demidova-Rice et al. 2012; Sarheed et al. 2016).

Thus, treatment is required to stimulate wound healing. Ideally, the treatment is required to provide, first, removal of the dead and necrotic tissue from the wound site to allow for new tissue cells to form, a process known as debridement. Then, microorganisms at the wound site need to be eradicated as their proliferation at the wound causes infection and inflammation. Finally, the epithelial cell needs to be stimulated to migrate to the wound and repair it, a process known as epithelialization. The application of dressing over the wound which is medicated with agents that promote these cellular and molecular processes is a very common practice (Demidova-Rice et al. 2012). A detailed description of wounds types in which honey is used for is mentioned later.

18.3 Wound Dressing

As a response to the injury of the skin, the wound-healing process commences, which is a complex multistep process to regain the normal structure of the skin. For a wound to heal first, an inflammatory response is initiated which is characterized by blood coagulation and attraction of immune cells to the injury site. The cells secrete cytokines, protecting against developing an infection. Endothelial cells also travel to the injury site secreting growth factors. Then, in the proliferative stage, an epithelial layer covers the wound to fill the spaces in addition to collagen deposition which contributes to reduction in wound size. Finally, the remodeling starts to restore the original integrity and structure of the skin.

The normal healing process can take up to 10 days, but some alterations and disturbances can occur to the process prolonging the healing, and leading to chronic infections. Thus, some substances can be applied onto the wound to facilitate the process of healing (Ibrahim et al. 2018). Applying a wound dressing is a common way to promote healing. It can consist of simple substances like cotton and gauze which only provide the advantage of forming a protective layer over the wound. A wound dressing may also contain a material with bioactive properties such as antimicrobial and antioxidant effects (Tang et al. 2019).

Ideally, a dressing should provide sufficient hydration to the wound, absorb the discharge formed in the wound site, be placed and removed easily avoiding any discomfort, and be porous enough to allow gaseous exchange. Preferably, the dressing should contain an agent with antimicrobial properties while being nontoxic and biocompatible (Wang et al. 2012). Many synthetic and natural candidates are considered as viable options to be incorporated in wound dressings. Honey is a common example because of its antibacterial, antiinflammatory, and antioxidant properties along with its ability to maintain wound closure and increasing the rate of reepithelialization (Tang et al. 2019).

18.4 Physical Characterization of Wound Dressings

To ensure patient adherence to the dressing applied onto the wound, certain desirable properties should be provided. To be proven as a good candidate for use in wound care by clinical professionals, the dressing should act as an enhancer of wound healing. This can be accomplished by offering enhancement in cell migration like growth cells, epidermal cells, leukocytes, etc. The dressing should also provide a moist environment and gaseous exchange to support angiogenesis while not permitting the entry of bacteria or any foreign matter. From the consumer's perspective, the dressing should also be easy to apply and is not painful upon removal. It is also preferred to be cost-effective in which the frequency of the application is reduced or the dressing is less expensive while still being sufficiently useful in wound treatment.

There are various standardized tests available that should be carried out before the formulated product is put on the market in order to assess the performance of the dressing and ensure safe and effective product for the intended use. Such tests include the following:

18.4.1 Swelling Tests

An important characteristic the dressing is the absorption of exudate from the wound while maintaining moist conditions and avoiding leakage. Upon absorption, the dressing normally swells. The swelling behavior and the degree of swelling are measured during the development of the dressing to evaluate the extent of fluid absorption. Swelling depends on the composition of the dressing, temperature, pH, time, types of fluid, ...etc. The presence of polymeric and cross-linked molecules increases the degree of swelling. The swelling is measured by placing the dressing in solutions of varying pH because the wound pH changes during healing and moves toward the acidic region. The amount of fluid retained is measured and expressed as swelling degree (Roy et al. 2010; Agrawal and Purwar 2018). The incorporation of honey in wound dressings increases the swelling ratio due to its high sugar content which increases the osmolarity of the formulation (Mohd Zohdi et al. 2012).

18.4.2 Fluid Handling Capacity

This is mainly performed for hydrocolloid, alginate, and polyurethane foam dressings and it measures the amount of fluid retained in the dressing as well as the amount lost as moisture vapor. This enables to quantify the absorbency of the dressing and the moisture vapor loss. The presence of a gel-like structure on the dressing improves the fluid handling properties of the dressing. Dressings with increased fluid handling capability is advantageous for chronic wounds healing, as they minimize the incidence of skin maceration due to the immobilization of large amounts of exudates (Boateng et al. 2008).

18.4.3 Water Vapor Transmission Rate (WVTR)

Fluid from the wound that is lost as vapor needs to be measured. The process of fluid evaporation needs to be optimized because an increase in the loss of fluid would reduce body temperature. In contrast, if less fluid is lost, the pressure on the wound increases as the fluid builds up, which makes the wound more painful. It is noted that the dressing's permeability increases over time due to the absorption of fluids. Thus, it is necessary to measure the amount of body fluid that the dressing can transmit. The incorporation of honey in the dressing disrupts the diffusion of fluids, reducing the WVTR significantly (Boateng et al. 2008; Muktar et al. 2018).

18.4.4 Thermal Studies

It is also necessary to determine the thermal stability of the dressing at increasing temperatures through thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). The temperature of the dressing in the analysis is first set at room temperature and then raised gradually at the rate of 10 °C/min. The degradation of the composition is noticed throughout the process including the temperature at which degradation starts, temperature onset T_o, and the temperature when degradation is complete; temperature completion T_c. The addition of honey does not affect T_o significantly; however, it increases the T_c with increasing honey concentration. Thus, the high sugar content adds to the stability of the formulation (Muktar et al. 2018).

18.4.5 Tensile Strength

For use in clinical settings, dressings must have desirable mechanical properties by balancing between flexibility and rigidity. It should be durable, stress resistant, soft, flexible, pliable, and elastic. They should also be easy to apply and remove without causing additional trauma. To determine the brittleness or hardness of the dressing, tensile strength is measured which is the maximum stress applied to a point at which the film breaks. The addition of honey improves the elasticity of the dressing. The tensile strength also changes depending on the degree of hydrogen bonding interaction between the honey and the other components that varies with formulations. It also depends on the type and amount of the polymer and its molecular weight (Boateng et al. 2008; Thenmozhi et al. 2016).

18.4.6 Compressive Tests

Another way to characterize the mechanical properties of dressings is through performing compressive test. It measures the resistance of the formulation to deformation upon the application of compressive forces. This mechanical characterization is carried out using a device called the Instron Universal Mechanical machine at a cross-speed set at 10 nm/min (Boateng et al. 2008; Muktar et al. 2018). Varying results have been reported upon the addition of honey.

18.4.7 Bioadhesive Strength

As dressings are applied on a biological membrane, their adhesive property is to be determined. It is the force required to detach the sample from the surface of excised porcine skin. The determination of the degree of bioadhesion is especially important if the dressing is to be applied on a moist environment. It has been observed that bioadhesion depends on hydrophobicity, level of hydration, and rate of polymer erosion (Boateng et al. 2008).

18.5 Efficiency of Honey in Wound Care

As honey has been used to pack wounds since hundreds of years by our ancestors, it is becoming more crucial to present scientific evidence to support claims of its effectiveness in wound healing. Thus, many studies have been carried out to assess the various biological activities of honey. Following are the observed biological effects of honey that can explain its wound-healing property. The intensity of these effects in honey varies depending on the floral source. One of the most commonly researched types of honey is Manuka honey, which is collected by honey bees from the *Leptospermum scoparium* shrub, which is indigenous to New Zealand. However, other beneficial types of honey have been proved to exhibit medicinal properties such as jelly bush honey, Acacia honey, Gelam honey, Tualang honey, ...etc.

18.5.1 Antibacterial Effects

After injury, if the wound is colonized with bacteria, it restrains the healing process. Microbes produce various enzymes into the wound including proteases, collagenases, and elastases which destroy the connective tissue and the growth factors that are necessary to rebuild the skin. The oxidative condition produced by the bacteria activates excessive proteases. The endotoxins from the bacteria produce inflammation in the skin constricting the capillaries and cutting off the blood supply which is highly required to commence the repairing process. Honey cleans the wound by killing the bacteria while protecting the connective tissue and, hence, speeds up the healing (Molan 2006).

So, honey is applied onto wounds due to its antibiotic effect. This is attributed to various components and the physical properties of honey.

A summary of these factors is given in Fig. 18.1. High sugar content in honey provides the epithelial cells with glycogen in order to form new skin that will cover the wound. Glucose is also beneficial to the phagocytes whose function is to destroy the bacterial cells and the dead skin cells. It also plays a part in the osmotic action as it drives the fluid away from the wound. This removes the fluids from the wound which is, otherwise, a favorable condition for bacterial growth, provides a moist interface of diluted honey, and avoids the adherence of the dressing to the wound, thus easing its removal. This hyperosmolar effect is due to the high sugar content which can also dehydrate the bacteria. Honey, even though it is moist, does not support any bacterial growth because of its antibacterial properties.

The disinfection properties are also assisted by the production of hydrogen peroxide by peroxidase enzymes which remain below the inflammatory level; this, in turn, stimulates various cells required for cell multiplication and wound healing such as fibroblasts and epithelial cells. Stimulation of protein-digesting enzymes,

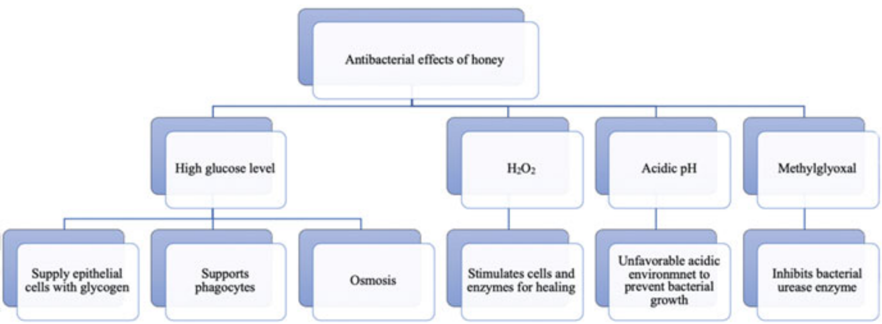

Fig. 18.1 Proposed mechanisms of antibacterial effects of honey

serine proteases and matrix metalloproteases, is also possible due to H_2O_2. The acidity of honey, which is pH 4.4, also contributes to the antibacterial effect and accelerates the healing. One phytochemical present in honey called methylglyoxal contributes to the antibacterial property through inhibition of urease enzyme which usually plays a role in bacterial growth. Bacteria not only invade the wound but also create a biofilm generating a highly resistant infection. Honey has the ability to penetrate the biofilm and inhibits its further growth, thus eradicating the infection. This is achieved by preventing the bacteria from binding with the skin at the wound, specifically the tissue fibronectin. Glucose and fructose play a major role in this activity (Ahmed et al. 2018).

18.5.2 Deodorizing Effects

Wounds are usually accompanied by foul odor. This is usually attributed to the presence of both anaerobic and aerobic bacteria in addition to the necrotic tissue and to a range of different metabolites produced by the bacteria. Hence, odor is frequently considered as an indicator for the occurrence of infection and bacterial colonization. Various potential solutions are used in odor management; ideally the dressings used to pack the wound should show control of wound-associated odors (Akhmetova et al. 2016).

The wound's malodor can be caused by the ammonia, amines, and sulfur compounds produced by the bacteria at the wound due to the metabolism of tissue proteins. Honey has the ability to rapidly neutralize the smell (Molan 2006; Yaghoobi et al. 2013; Akhmetova et al. 2016; Ahmed et al. 2018). This deodorizing activity is possible due to the antimicrobial effect of honey. Additionally, it provides the bacteria with an alternative source of nutrition which on digestion and metabolism produces lactic acid rather than the malodorous compounds. And as honey does not support bacterial proliferation due to its low pH and water content, and high sugar content, the infecting bacteria is eradicated with minimum foul smell with the application of honey (Akhmetova et al. 2016). The mechanism of honey's deodorizing effect is described in Fig. 18.2.

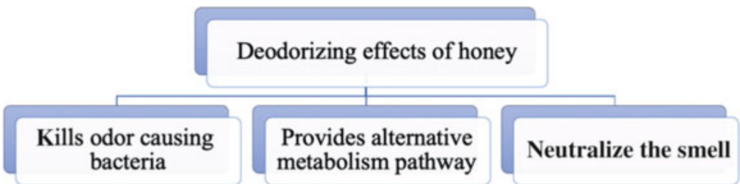

Fig. 18.2 Possible mechanisms of deodorizing effects of honey

18.5.3 Antioxidant Effects

Although oxygen is necessary for all body functions, its metabolism leads to the formation of free radicals. These free radicals can travel through cells and inflict molecular level. Such radicals are associated with various health problems and aging. In wounds, radicals also exacerbate cell damage and hinder tissue healing (Khalil et al. 2010). The process of oxidation caused by free radicals, superoxides, and other oxidants result in cellular damage and deterioration; thus some compounds are used, which can act as a defense against oxidative stress and are known as antioxidants.

Honey is found to have such a property as to be useful in promoting the closure and healing of wounds. The free radicals are formed at the site of injury during the inflammation process in the wound and produced by the respiratory mitochondrial chain. These radicals are known as reactive oxygen species (ROS). Any antioxidant compound implements its effect by producing ROS-reducing oxidative stress. Flavonoids, phenolic acids, and vitamin C in honey exert the antioxidant property which would mainly sequester the free radicals avoiding oxidative damage. It also stimulates the production of carbohydrates, proteins, lipids, and nucleic acids by the cells promoting the antioxidant response. Vitamin C can reduce peroxides. Honey also acts at the cellular level to reduce cellular damage by protecting antioxidant enzymes. Additional proposed mechanisms for the antioxidant behavior of honey include hydrogen donation, metallic ion chelation, flavonoids substrate action for hydroxyl, and superoxide radical actions (Yaghoobi et al. 2013; Ahmed et al. 2018). These are represented in Fig. 18.3.

18.5.4 Anti-inflammatory Effects

As a response to the injury, inflammation occurs in tissues in order to remove the foreign organisms. This is represented by redness, exudate, pain, and itching and if not treated, it can worsen chronic infection. This response is mediated by cytokines, cyclooxygenases, lipoxygenases, macrophages, TNF, ...etc. Thus, honey is

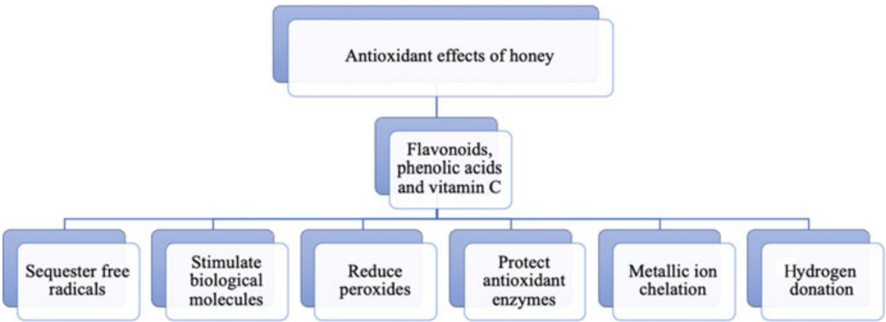

Fig. 18.3 Proposed mechanisms of antioxidant effects of honey

favorable in wound dressings as it can reduce the skin inflammation when applied to the wound. Honey has been shown to actively inhibit the expression of inflammatory mediators like cytokines. It also reduces the reactive oxygen species produced by the macrophages and leukocytes. The polyphenols are responsible for suppressing the lipoxygenases. Production of hydrogen peroxide can stimulate the growth of fibroblasts and epithelial cells. These are all proposed mechanisms for the anti-inflammatory property in honey although the exact mechanism is not completely understood (Ahmed et al. 2018).

Through the microscopic examination of skin, it was proven that inflammation started to subside after application of honey. The edema and exudates have been reduced, in addition to the soothing effect and pain relief produced after a while of applying honey onto the wound. The painfulness is decreased due to the reduction of pro-inflammatory prostaglandins and pressuring of the nerve endings.

Honey promotes the proliferation of new epithelial cells and the formation of connective tissue at the wound site, which may also lead to pain relief. Blistering and scarring of the skin upon injury have also been reduced due to honey. This has been attributed to a series of events including angiogenesis and growth factor formation that add to the fibroblasts and epithelial cells at the wound minimizing scarring. These cells can be destroyed by protease activity; however, the acidic property of honey inhibits this effect as it is not a favorable environment for the protease. Reducing inflammation removes a major obstacle in the healing process and speeds it up (Yaghoobi et al. 2013; Ahmed et al. 2018).

Honey contributes to improved wound healing by increasing collagen synthesis, fibroblast migration, and keratinocyte closure rate. This promotes the wound's ability to close, treating the injury (Minden-Birkenmaier and Bowlin 2018). The different antiinflammatory effects that honey offers are summarized in Fig. 18.4.

18.5.5 Debridement Effects

The persistence of necrotic tissue at the wound increases the risk of infection, especially for bacteria like methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*. So, necrotic tissue removal is a common procedure in the treatment of wounds and promotes wound healing. It consists of the removal of foreign matter, infected tissue, and slough from the wound, leaving the healthy tissue

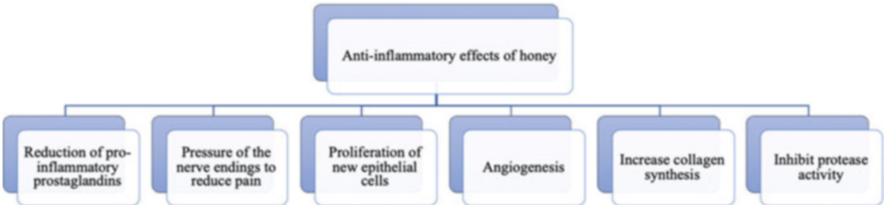

Fig. 18.4 Proposed mechanisms of antiinflammatory effects of honey

exposed. It is especially essential for patients that are frail, elderly, or have a weak immune system, so the first step is to identify any underlying diseases such as diabetes, heart, vascular or lung diseases, poor immune system, ...etc., that may be the reason for delay in wound healing. Then nonviable tissue needs to be removed along with a reduction in edema, exudate, and bacterial bioburden. This can be achieved by applying a dressing containing a molecule with debriding effect.

The debriding effect of honey has been reported in various studies where it has been shown that honey promotes autolytic debridement. It is a process in which the body naturally dissolves its own necrotic tissue by phagocytosis with the help of macrophages and lymphocytes. In order for this process to take place, moisture should be available at the wound interface. Here, honey is capable of pulling moisture out of the wound by its osmotic effect thus rehydrating the tissue. Then the fibrin that connects the necrotic tissue with the skin is digested and broken through the stimulation of plasmin. This process of autolysis makes honey a viable debriding agent (Mitchell 2018).

Many studies have shown the effect of honey on wounds in which patients achieved a faster rate of debridement when compared with other products like hydrogels. This has been achieved without the need for any surgical interventions for the removal of tissue. Detachment of the necrotic tissue from the skin occurred within 5–7 days, attributed to the activation of proteases; it is then removed by forceps (Molan 2009). Another study has shown that with medical grade honey patients achieved complete autolytic debridement in almost a month. It concluded that the use of honey is recommended when wounds contain more than 40% devitalized tissue that needs to be debrided rapidly. However, some pain can be associated with the increase in osmotic pressure causing some discomfort which may not be favorable to all patients (Evans and Mahoney 2013).

18.5.6 Antiviral Effects

Viral infections are ubiquitous around the world, and the search for new antiviral agents has become increasingly important due to the failure of some established agents typically due to the emergence of resistance. Furthermore, some agents are unsuitable for some patients due to immune deficiency, breastfeeding, the use of multiple medications, some serious side effects, high cost of medications, and many other reasons. Many studies have been performed to study the antiviral effect of naturally derived substances to achieve low cost with minimum toxic effects (Hashemipour et al. 2014).

Honey has been a natural compound that is found to demonstrate some antiviral properties, and different mechanisms have been proposed to explain this behavior. Some compounds found in honey are thought to be responsible for its antiviral effect. These include copper which is present in trace amounts, ascorbic acid, flavonoids, and hydrogen peroxide. These inactivate the virus and preventing its growth by inhibiting viral transcription and translation. It has also been found that honeybees have nitric oxide metabolites like nitrite and nitrate in the salivary glands.

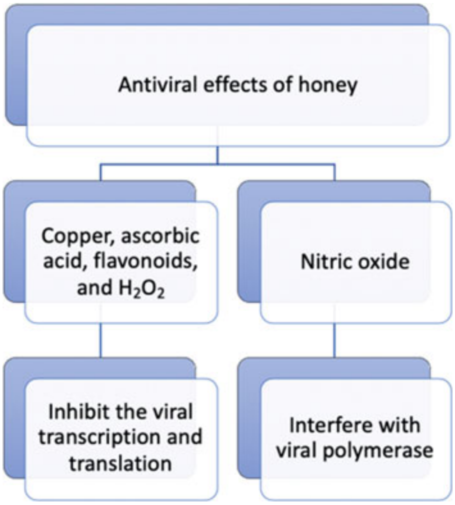

Fig. 18.5 Proposed mechanisms of antiviral effects of honey

The presence of nitric oxide also contributes to the antiviral activity in which it interferes with viral polymerase, nucleic acid, and/or viral capsid proteins, which would also further repress viral replication (Ahmed et al. 2018). A schematic presentation of these processes is given in Fig. 18.5.

The presence of antiviral properties in honey makes it helpful when packing wounds to prevent or eliminate any viral lesions formed or may form. Studies have shown honey to be an effective agent against herpes simplex virus, thus reducing the symptoms and signs of herpetic lesions (Miguel et al. 2017). Another study compared honey with acyclovir, a well-known antiviral, and found it to be effective in the topical treatment of recurrent lesions from genital and labial herpes (Yaghoobi et al. 2013). It was also concluded that honey can be as effective as 5% acyclovir in the management of herpes simplex labialis with regard to time to heal and pain resolution, making it an acceptable alternative to acyclovir cream (Semprini et al. 2019).

18.5.7 Antifungal Effects

The incidence of fungal infections is increasing in both community and hospital environments. Topical infections are a common form of fungal infections. However, due to the emergence of resistance in fungi against antifungal agents, researchers have been performing studies for new antifungals. Honey demonstrated antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, *Microsporum gypseum*, *Candida albicans*, *Saccharomyces*, and *Malassezia* species (Irish et al. 2006; Moussa et al. 2012; Ahmed et al. 2018).

Honey can serve as an effective antifungal by disrupting the cellular structure and morphology of the fungi. This occurs by inducing changes to the exopolysaccharide

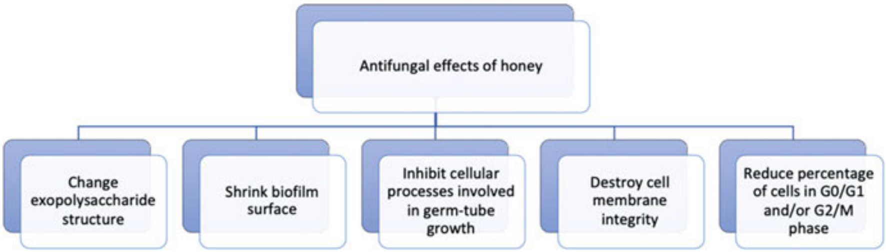

Fig. 18.6 Proposed mechanisms of antifungal effects of honey

structure which causes the disruption of cell membrane integrity and established biofilms, shrinking its surface and eventually leading to its death. It has also shown to have another direct effect on fungi membranes that would lead to the death of fungi and disruption of biofilms; the flavonoids in honey were found to inhibit some cellular processes that are involved in germ-tube growth that would cause poor growth of membranes. Flavonoids were also found to reduce the percentage of cells in G_0/G_1 and/or G_2/M phase (Ahmed et al. 2018). These effects are represented in Fig. 18.6.

A study performed to assess the topical application of honey in the management of seborrheic dermatitis and dandruff showed that patients receiving honey showed relief in scaling and itching within a week, and skin lesions healed within 2 weeks (Al-Waili 2001). When compared with steroid for the treatment of psoriasis and atopic dermatitis, honey proved to be effective and resulted in a 75% decrease in symptoms (Al-Waili 2003). Another study found that honey effectively treated 86% of patients with fungal infections characterized by rash, 78% with fungal infection of the groin, and 75% with fungal infection of arms and legs (Al-Waili 2004).

18.6 Clinical Applications

In addition to the nutritional value of honey, its therapeutic value has been illustrated since ancient cultures. As the biological activity of honey has been explored more rigorously over the years and its antibacterial and antioxidant effects have been proven, honey is being incorporated in various treatment regimens for managing different types of injuries. It is sometimes surpassing other widely used therapeutic agents such as silver sulfadiazine, povidone iodine, hydrogen peroxide, etc., to become the first-line therapy for wound management. Examples of such clinical applications are as follows:

18.6.1 Diabetic Foot Ulcer

An aggravated complication of diabetes is diabetic foot. About 15% of all diabetic patients are at risk of developing diabetic foot. It occurs due to the neuropathy that is prevalent in most patients who experience a loss of sensory nerve in the periphery along with changes in peripheral blood vessels. With repetitive minor injuries that are left unattended due to loss in sensation, it turns into major ulceration which leaves the foot highly vulnerable to infection. It can be as serious as leading to amputation if neglected (Alexiadou and Doupis 2012).

Applying wound dressing is a part of managing diabetic foot ulcers; various dressings can be applied to accelerate the healing of injuries. This is essential as the healing process in diabetic patients is extremely slow. These wounds are characterized by severe hypoxia and high levels of reactive oxygen species which would only worsen the inflammation of the injury site. Honey, with its broad-spectrum bactericidal properties, is a type of effective dressing that can eradicate infection and promote healing in addition to stimulating the autolytic debridement by hydrogen peroxide production, where old dead tissue is removed allowing new tissue to be formed (Alam et al. 2014; Kateel et al. 2016; Wang et al. 2019).

Multiple studies have been performed to assess the effectiveness of honey dressings in wound healing rates, bacterial clearance, and debridement times in diabetic foot ulcers. Evidence showed removal of exudates and deodorization of the wound within the first week, reduction in inflammation within 10 days, and bacterial eradication within a month. Results also suggest a correlation between the use of honey dressing and the increase in wound healing, bacterial clearance rate, and a shorter debridement time. However, honey is ineffective with more serious injuries such as with exposed bone but can be used after revascularization (Moghazy et al. 2010; Wang et al. 2019).

18.6.2 Postray Amputation

Further complications can occur that is associated with diabetes foot ulceration. If the ulceration is left without attention and treatment, the condition aggravates to diabetic gangrene which in most cases involves the lower limbs. Such a severe injury increases the risk of mortality due to the lack of proper treatment. Usually, the toes are the first to get infected; then the infection spreads further to the joint followed by the metatarsal bones. This extensive spread of infection is untreatable where surgical intervention is the only solution involving the amputation of the affected bones. The amputation of the toes is known as ray amputation, which may include only the distal metatarsal head or the entire metatarsals. The former is known as partial ray amputation while the latter is called complete ray amputations. However, the recovery is a slow process which would increase the social, psychological, and economic burden on the patient. Thus, researchers have been studying different possible agents to be applied onto the wound to improve the healing process following the surgical procedure (Alam et al. 2014; Mohamed et al. 2014).

A study was performed by a group of scientists where honey was applied on the wound after amputation to accelerate the healing process. Initially the wound was macerated and cleaned by application of povidone-iodine in order to reduce the bacterial burden as much as possible. Then the wound was dressed using honey. As per the results, honey achieved 60% healing rate within the first 2 weeks. The following week the healing rate reached up to 90% and after a month complete wound healing was observed. It was concluded that honey provided an effective alternative for the management of such wounds and is becoming more acceptable by patients as it is efficacious, aesthetically acceptable, and cost effective (Mohamed et al. 2014).

18.6.3 Burns

Burn is a very common skin injury which varies in degree and can result in a substantial loss of skin protection function. This makes the skin at risk of serious infection. If untreated, it can lead to serious deformities and disabilities. Slow healing can leave major scars that would affect the patient psychologically as well. Thus, burns need to be dressed with agents that will clear the infection and speed up the healing leaving minimum irregularities (Al-Waili et al. 2011; Gupta et al. 2011). As honey has been used by the ancient cultures like the Greeks, Romans, Chinese, Egyptians, ...etc., to pack burns, and it is still one of the most commonly used agents used in burn dressings (Smaropoulos et al. 2011).

Several studies performed proved the effectiveness of honey in superficial and partial thickness burns when compared with silver sulfadiazine; a common agent used in burns. This has been attributed to the antioxidant property of honey. Burns have been categorized as oxidative injuries where the free radicals increase at the injury site causing peroxidation, which is the reason for considerable scarring in the burned tissue. The application of honey reduces scarring and pigmentation along with reduction in pain and inflammation and promotes tissue granulation. This would reduce the healing time and the hospital stay, making the use of honey more cost-effective and thus favorable to many patients. However, the effectiveness of honey in full-thickness burns is limited and surpassed by tangential excision and skin grafting (Subrahmanyam 2007). The debriding effect of honey has also been found beneficial in burn treatment by promoting the dead tissue removal and fastening the formation of new ones (Molan and Rhodes 2015).

On assessing its effectiveness in burn patients, it was found that honey outperformed various formulations containing agents like polyurethane film, amniotic membrane, potato peel, and silver sulfadiazine according to studies performed in the UK (Moore et al. 2001), France (Al-Waili et al. 2011), and Netherlands (Postmes et al. 1997).

Another study performed in Pakistan to evaluate microbial eradication found that only 4% of the patients treated with honey returned with positive bacterial culture as opposed to 18% in patients treated with silver sulfadiazine.

In India, studies showed complete control of infection within a week when treated with honey in almost 90% of the study group and the appearance of new healthy tissue within 15 days in the majority of the patients (Al-Waili et al. 2011). However, some patients seemed to dislike the use of honey because of some pain caused on its application and, therefore, preferred other formulations (Edwards 2013). Honey seemed to be beneficial in burn dressing in pediatrics as well, reducing granulation time and enhancing bacterial eradication (Bangroo et al. 2005).

18.6.4 Nonhealing Wounds

Patients suffering from diseases like diabetes mellitus, chronic venous insufficiency, peripheral artery disease, immobility, and cancer suffer from slow wound healing. The extended period of time for healing is a burden both financially and physically. Thus, a wet therapy is proposed in which the wound is dressed not only with gauze but with an agent that would reduce the long duration of healing. Honey is an inexpensive and favorable choice with its acceptable biological activities and physical properties.

Studies performed by applying honey onto the wounds of patients with concomitant diseases showed higher number of completely healed wounds, faster wound size reduction, less intense wound odor, and reduced wound pain intensity (Vyhlídalová et al. 2018; Zeleníková and Vyhlídalová 2019). It has also proven beneficial in treatment of wounds infected by antibiotic-resistant bacteria like methicillin-resistant *Staphylococcus aureus* (MRSA), where it is now considered one of the first-line treatments of such infections (Visavadia et al. 2008).

18.6.5 Pilonidal Sinus

Pilonidal sinus is a disease that occurs at the sacrococcygeal region, specifically at the hair follicles and more commonly in men than women. The patient suffers from a painful sinus tract along with chronic abscess. It causes severe discomfort and inability to perform normal activity (McCallum et al. 2008). It occurs due to excessive stretching and recurrent trauma to the follicles that enlarge and rupture, ending up with damaged tissues and hair follicles. As the inflamed area gets infected, treatment is required and the use of honey dressing is a plausible option (Woo et al. 2015). Research proves that the use of honey in recurrent or chronic pilonidal sinus is effective, showing early and rapid granulation tissue formations and wound closure as early as 2–5 weeks with complete wound healing within a period of 65 days (Thomas et al. 2011; Woo et al. 2015; Elhorbity et al. 2018).

18.6.6 Venous Leg Ulcers

Ulceration is a loss of the skin integrity, specifically the dermis layer and if it does not heal within the expected time or shows little tendency to heal, it is said to be chronic. A venous leg ulcer is a chronic ulceration in the lower limbs in which the inability of the veins to prevent backflow of the blood results in increasing the blood pressure in the leg veins. This causes the appearance of severe open wounds in the leg that can become highly infected. Treatment of such ulceration includes compression therapy and the use of agents that can promote wound healing. Compressing on the ulceration accelerates venous flow and reduces venous reflux and edema. The emergence of bacteria in the wounded area causes tissue damage and delays healing. So, the addition of an effective antimicrobial agent in the dressing is also common in order to promote healing and fight infection. Honey wound dressing is found to be effective in these cases (Velasco 2011; Alavi et al. 2016).

Many studies have shown honey dressings are helpful to some degree in the treatment of venous leg ulcers. It has been found that honey dressing did not improve the rate of healing of the wound significantly or cause any reduction in the size of the ulceration after 12 weeks when compared with standard therapy. However, it did help in controlling the infection, thus reducing healing duration to some extent and most importantly reducing the cost of treatment as honey is a relatively inexpensive therapeutic agent. A conclusion is drawn that since honey is a promising wound-healing agent it has the potential to be used in the treatment of such chronic wounds. Nonetheless, research in this field is still limited, and additional trials need to be conducted to reach to more accurate conclusions (Jull et al. 2008; Mayer et al. 2014; Holland and Norris 2015).

18.7 Honey Formulations

18.7.1 Hydrogel

A hydrogel is a matrix of multiple crosslinked insoluble hydrophilic polymers as illustrated in Fig. 18.7. They form a highly absorbent network with a water content of up to 96%. When hydrogels are used to formulate wound dressings, these water molecules are used to maintain a moist environment. However, it is not fully

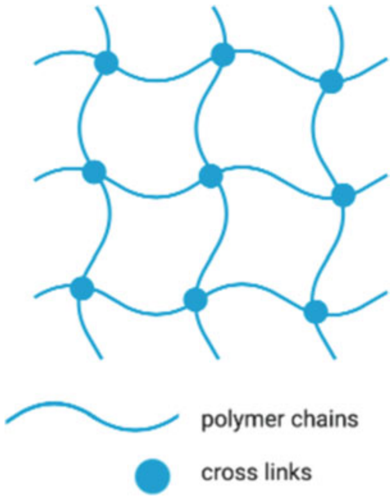

Fig. 18.7 Hydrogel structure

hydrated to make it capable of absorbing the exudate from the wound. Due to the intrinsic porosity of the hydrogel, it allows fluid and gas exchange but the degree of permeability varies with different formulations. It can also promote autolytic debridement as it supports the rehydration of nonviable tissues. Hydrogels may stimulate cell growth, migration, and maturation as it is found to mimic the structural functionality of the extracellular matrix (Jones et al. 2006; Saghazadeh et al. 2018).

Different compositions of hydrogel are available that can be either synthetic or naturally derived. Glycosaminoglycans, for example, enhance cell proliferation as they are the main component of skin tissue. Hyaluronic acid, when included in the hydrogel, improves its resilience along with cell differentiation. Collagen can also be helpful by improving the adherence property of the dressing. Chitosan is highly hydrophilic and improves cell adhesion, migration, growth, and differentiation. Additionally, it is more favorable nowadays due to its discovered bactericidal properties at higher concentrations (Saghazadeh et al. 2018).

Honey-based hydrogels have also been prepared and evaluated for wound dressing by incorporating honey into a mixture of polyvinyl pyrrolidone (PVP) 15% and polyethylene glycol (PEG) 1%, along with a 1% protein free agar solution, poured into a mold and covered by a polyethylene sheet. In order to promote the bactericidal effect of the wound dressing, it needs to be sterilized by gamma irradiation. Honey was found to improve the swelling of the dressing more significantly than hydrogels, supporting exudate absorption due to the honey's high osmolarity. Additionally, honey provided an earlier antiinflammatory and reparative response with a significant acceleration in dermal healing (Yusof et al. 2007; Mohd Zohdi et al. 2012).

It has also been reported that mixing honey with different hydrogel composites promotes the wound healing properties of the dressing. When chitosan and honey are mixed together at significantly lower concentration, a synergistic antibacterial effect is achieved. The presence of protonated positive ions allows the capture of bacteria by the hydrogel, leading to a loss in their physiological function (Wang et al. 2012). Honey added to poly(vinyl alcohol) and carboxymethylate chitosan also showed a significant inhibition in microbial growth (Afshari et al. 2015). Honey also adds to the tensile strength of the dressing; when added to an equal composition of chitosan and alginate, honey shows a good elongation strength property required for wound coverage. A combination with gelatin, although shows improved hydration and swelling property, does not possess desirable mechanical strength (Kurhade et al. 2013). Honey-based alginate hydrogel dressings also showed an acceleration in reepithelization and fibroblast growth making it another productive approach to support dermal wound healing (Nazeri et al. 2015). Many honey dressing products have been formulated using hydrogel techniques and have reached the market. Examples of such products are listed in Table 18.1.

18.7.2 Electrospun Nanofibers

The process of electrospinning produces fibers by passing the polymer solution that is charged using an electrical current through a syringe onto a metallic ground plate

Table 18.1 Marketed products of honey-containing hydrogel dressing

Product name	Type of honey	Description	Manufacturer	References
Manuka Health Wound Dressing with Manuka Honey	Manuka honey	Sheet of cross-linked polyacrylamide hydrogel–containing honey	Manuka Health NZ	Molan (2011)
Manuka Health Breast Pad with Manuka Honey	Manuka honey	Sheet of cross-linked polyacrylamide hydrogel–containing honey	Manuka Health NZ	Molan (2011)
L-Mesitran Hydro	30% medical grade honey	Sheet of acrylic polymer hydrogel–containing honey	Triticum	Halstead et al. (2015)
Gentell Honey Hydrogel	Manuka honey	Hydrogel-containing honey	Gentell	Schoukens (2009)

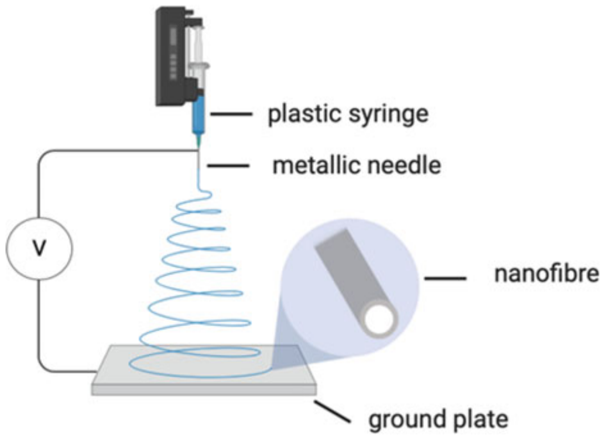

Fig. 18.8 Process of electrospinning

forming thin fibers with micro- to nanoscale diameters. The process is illustrated in Fig. 18.8. Such matrices are known to have a high surface-to-volume ratio with good porosity. These nanofibers are good candidates for wound dressing as they improve wound healing by the reduction of necrosis and enhancement of vascularization. Various polymers are used for the formulation of fibers including polycaprolactone (PCL), poly(L-lactic acid) (PLA), and poly(L-lactic acid-co-glycolic acid) (PLGA). The interconnected web allows better fluid absorption, and its porosity allows for drainage of the wound exudates while permitting atmospheric oxygen to enter (Maleki et al. 2013; Saghazadeh et al. 2018; Fahimirad and Ajalloueian 2019).

Honey can be electrospun with other polymers to produce nanofibers which are applicable for wound healing. Honey with poly(vinyl alcohol) gave a uniform and smooth nanofiber where honey can reach up to 40%. The dressing can be loaded with additional medicinal molecules, and the presence of honey gives an initial burst release within a short duration of time (Maleki et al. 2013). Honey-loaded alginate/PVA nanofibrous membrane is another formulation that showed enhanced bactericidal effect against both gram-positive and gram-negative bacteria along with antioxidant activity. However, honey led to a decrease in swelling ratio in this formulation (Tang et al. 2019).

Silk fibroin are electrospun to form biocompatible scaffolds known for biocompatibility, mechanical integrity, and permeability to oxygen in addition to facilitating cellular attachment, migration, and proliferation. However, these scaffolds contain hydrophobic regions hindering the process of water retention. The addition of honey into the formulation improves cell adherence and swelling, proving that honey has the capability to augment moisture retention. It has also been shown that honey enhanced the release of growth factors for better wound healing (Kadakia et al. 2018). On studying the antibacterial effect of these silk fibrous matrices, it was proved to be highly efficient against both gram-positive and gram-negative bacteria, being stronger against *E. coli and P. aeruginosa* as compared with *S. aureus* and MRSA. The wound-healing rate also showed improvement with honey incorporation (Yang et al. 2017). Honey electrospun with poly(ε-caprolactone) (PCL) nanofibrous sheets showed similar results where researchers established their usefulness in promoting healing and clearing bacteria from the wound environment (Minden-birkenmaier et al. 2015).

18.7.3 Cryogels

The concept of tissue engineering has emerged as an alternative for skin and bone repair. It is concerned with the regeneration and replacement of these tissues, especially with large critical wounds where there has been a substantial loss in skin. The application of bioengineered scaffolds is now superseding the use of skin grafts for the purpose of skin repair. Cryogels are an example of such tissue-engineered scaffolds that are now widely applied in the field of skin healing and repair. Cryogel is a gel matrix formed by the polymerization and cross-linkage of different polymeric agents. After the polymerization process occurs, temperatures are brought down to below zero. The ice crystals will form pores within the structure due to subsequent thawing, leading to the production of a supermacroporous polymeric material, i.e., the cryogel structure. The process of cryogel formation is demonstrated in Fig. 18.9. The interconnected macropores in the cryogels are beneficial when working with viscous biological fluids, like honey, in which it can be incorporated into the cryogel (Hixon et al. 2017; Bakhshpour et al. 2019).

For the purpose of tissue engineering, cryogels could act as an artificial extracellular matrix. Cryogels can promote healing by providing support to the cells and stimulating cell migration and penetration to the surface including immune cells to initiate wound-healing processes. Cryogels are also known to be both biocompatible and biodegradable, and their characteristic macropores allow the absorption of high volume of tissue fluids (Bakhshpour et al. 2019). In one study, honey has been incorporated into the cryogel structure as it is an antimicrobial agent to form both silk

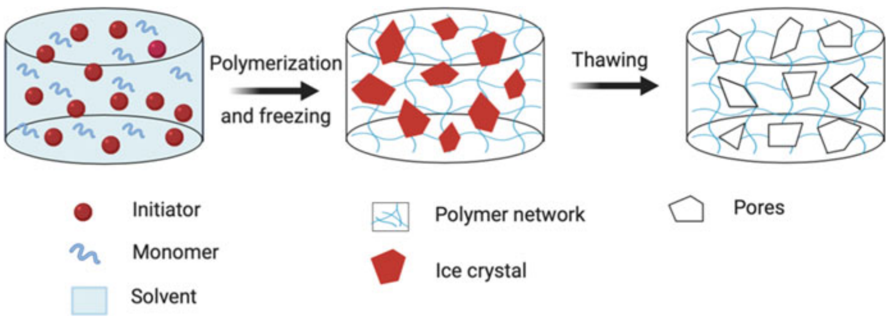

Fig. 18.9 Process of cryogelation

and gelatin cryogels. The silk ones were found to be of highest porosity, enabling better swelling property. Honey also reduced the peak stress in the cryogels making them more durable and resistant to fracture upon compression. The presence of honey, a thick substance, did not affect the cell proliferation and infiltration property of the cryogel while introducing an antimicrobial property against *Staphylococcus aureus*. The antimicrobial property was found to be achieved through the sustained release of glucose over time (Hixon et al. 2018).

Although honey improves cell infiltration and bacterial eradication, it causes a compromise to the mechanical stability of cryogels. This is a major limitation of the addition of honey to cryogels, which needs to be addressed in future studies. Additionally, there is a risk of losing part of the honey content during washing or sterilization, an issue that also needs consideration. One suggested solution is the use of a combination of polymers to achieve the desired mechanical strength (Minden-Birkenmaier and Bowlin 2018).

18.7.4 Honey-Impregnated Dressings

One of the most common traditional ways of wound care is the application of gauze on the wound. Such a conventional dressing can be made of woven or nonwoven gauze which is sterilized; when kept over the wound, it allows absorption of the exudate from the wound. However, this gauze does not provide a good barrier against infection by microbes present in the environment and is, thus, considered permeable to both fluids and bacteria. Furthermore, upon its removal it causes pain and leaves particulate matter in the wound (Khalique et al. 2014; Saghazadeh et al. 2018). The use of medicated gauze is an improved practice in the treatment of wounds, specifically medicated with molecules of antibacterial properties in order to reduce risk of infection. Honey is such a molecule as it exhibits antibacterial activity against a broad spectrum of bacteria including *Staphylococcus aureus* including MRSA, *Pseudomonas aeruginosa*, etc. (Kamaratos et al. 2014).

The honey-impregnated dressing can be prepared by mixing starch, glycerol, and water to form a starch-based gel and then honey is added to the mixture. A standard

Table 18.2 Marketed products of honey-impregnated dressing

Product name	Type of honey	Description	Manufacturer	References
Activon Tulle	Manuka honey	Nonadherent impregnated gauze dressing	Advancis Medical	Honeysett (n.d.); Molan (2011)
Actilite	Manuka honey and Manuka oil	Nonadherent impregnated gauze dressing	Advancis Medical	Morgan (2015)
MelMax	Buckwheat honey	Nonadherent impregnated gauze dressing; honey mixed with polyhydrated ionogens	Dermagenics	Hampton et al. (n.d.); Molan (2011)
MelDra	Buckwheat honey	Impregnated open-weave acetate fabric	Dermagenics	Sarheed et al. (2016); Molan (2011)
Algivon	Manuka honey	Impregnated alginate fiber dressing pad	Advancis Medical	Parker (n.d.); Molan (2011)
HoneySoft	Chilean multifloral honey	Impregnated polyvinylacetate dressing	Taureon	Molan (2011)

sterile gauze is dipped in the solution till saturation and then pressured to remove any excess solution. Finally, it is refrigerated to harden the formulation and then sealed in sterile packages (Zam et al. 2018). The presence of honey proved to be more beneficial than conventional dressings. In infants, it achieved healing of infected wounds within 7–21 days where the conventional dressing failed. In another study, honey achieved debridement within 1 week in almost all the patients, rendering the wounds dehydrated and odorless with new granulation tissue being formed, eliminating the need for surgical debridement (Mathews 2002). A honey-impregnated dressing also achieved healing in burns within almost 15 days (Subrahmanyam 1996). Diabetic patients also benefited from honey-impregnated dressings where almost three-thirds of the population showed complete healing and infection eradication (Kamaratos et al. 2014; Imran et al. 2015). Examples of dressings formulated as honey-impregnated dressings that have reached the market are mentioned in Table 18.2.

18.7.5 Hydrocolloids

A hydrocolloid is a combination of gel-forming agents like carboxymethylcellulose (CMC), pectin, gelatin, or an elastomer. These molecules are hydrophilic colloid particles in which their combination forms a film or a layer that is usually used to dress wounds. A representation of this structure is given in Fig. 18.10. They produce a dressing that is used as a barrier to be placed on the wound for several properties it provides like being absorbent, self-adhesive, and waterproof. When placed on the

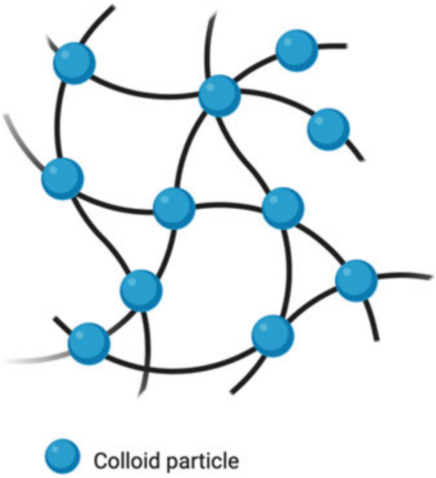

Fig. 18.10 Hydrocolloid structure

wound, the dressing shows a great ability to absorb exudates and swell into a gel-like mass. It offers a protective outer layer that can be either semiocclusive or occlusive against external environment like bacteria, foreign debris, and shearing while providing a moist healing environment. The presence of a hydrocolloid over the wound not only protects the wound but also accelerates the healing process as it stimulates autolytic debridement. It is noted that the wear time for a hydrocolloid dressing is usually up to 7 days, but it depends on the amount of exudates (Weller 2009; Sood et al. 2014).

Japanese researchers combined honey with a hydrocolloid dressing for the purpose of promoting reepithelialization, collagen deposition, and wound contraction as compared to hydrocolloid alone. It was illustrated that the use of honey decreased the wound area ratio but then it gradually increased followed by another decrease. The initial decrease was apparent in the inflammatory phase of the wound-healing process, while the increase was in the proliferative phase and the second decrease was in the remodeling phase. Thus, combining the Japanese honey with the hydrocolloid would avoid these repetitive phases of changes in the wound area; however, the wound healing would not be superior to that of the hydrocolloid dressing alone. A proposed solution was to alternate between the use of honey and hydrocolloid. The application of honey would be to reduce the inflammatory response induced at the wound site. Then this is switched to a hydrocolloid dressing to avoid reexpansion of the wound. Nevertheless, this hypothesis was nullified when it was clear that the reexpansion was unavoidable and the healing process was delayed (Nakajima et al. 2013; Mukai et al. 2015, 2017). More successful products using the hydrocolloid dressing in combination with honey have been formulated and have reached the market. Examples of such products are in Table 18.3.

Table 18.3 Marketed products of honey-containing hydrocolloid dressing

Product name	Type of honey	Description	Manufacturer	References
MANUKAhd	Manuka honey	Super-absorbent polyacrylic fiber coated with dry-touch absorbent hydrocolloid	ManukaMed	Saikaly and Khachemoune (2017)
MANUKAtex	Manuka honey	Nonadherent gauze coated with dry-touch absorbent hydrocolloid	ManukaMed	Saikaly and Khachemoune (2017)
Medihoney Honeycolloid	Manuka honey	Sheet of gelled honey	Dermasciences	Sarheed et al. (2016)

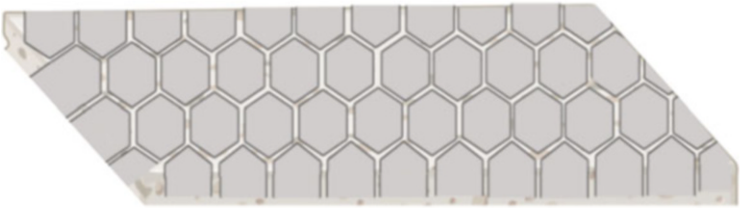

Fig. 18.11 Foam dressing structure

18.7.6 Foam Dressing

A foam dressing is made up of a hydrophilic or hydrophobic material. It forms an outer protective layer on the wound which provides thermal insulation while allowing vapor and oxygen exchange. Usually a foam dressing is composed of polyurethane or silicone foam. The former is generally designed as a multilayer where a hydrophilic layer is kept in contact with the wound surface to facilitate absorption with a hydrophobic backing above it. This facilitates the absorption of large quantities of wound discharge without any leakage to the exterior. The interior of the dressing is composed of small pieces of polyurethane surrounded by a polymeric film. The silicone-based dressing, on the other hand, is a mixture of two different elastomers which when combined produces a film that can expand to mold the wound shape. Foam dressings are characterized by their large interconnected pores as demonstrated in Fig. 18.11, which is supportive of cell infiltration, migration, and signaling. Their high absorptive property makes them good candidates for application on different leg ulcers (Jones et al. 2006; Weller 2009; Dhivya et al. 2015; Saghazadeh et al. 2018).

Honey has been investigated for the removal of necrotic tissues when applied on several cases of challenging wounds with the help of a foam dressing. After application the debridement effect was recorded in multiple patients where it was found that there was almost 75% increase in granulation tissue within 2 weeks of use with no side effects to be noticed. This would contribute to the success in wound healing for better patient care (Gray and Ishii 2015). In another study with less severe conditions, healing and exudate removal was observed after 2 weeks and

Table 18.4 Marketed products of honey foam dressing

Product name	Type of honey	Description	Manufacturer	References
Therahoney foam flex	Manuka honey	Dual-layer dressing; honey as primary layer and foam as secondary layer	Medline Industries	Saikaly and Khachemoune (2017)
Manuka Foam Air	Manuka honey	Non-adherent dressing of absorbent foam-fiber hybrid material	Links Medical Products	Saikaly and Khachemoune (2017)

reepithelization happened after 4 weeks (Robson 2004). Several pharmaceutical companies recognized the benefit of honey foam dressings and designed such products; some examples are listed in Table 18.4.

18.8 Conclusion

Despite the presence of numerous active molecules with desired properties for wound healing, research is now more directed toward benefiting from naturally driven agents. This is due to the increased resistance in all types of microorganisms against the recurrently used agents. It is also believed that utilizing natural products would make the product more cost-effective with fewer side effects. Honey is one of the common natural products that has been historically used by previous generations to treat wounds and injuries. It has reemerged in the clinical field for this application, and countless studies have been performed to explain its benefit and prove its effectiveness in the aspect of wound healing. It has been proven to have antibacterial, antioxidant, antiinflammatory, antiviral, antifungal, and debridement effects, which all contribute to accelerating wound closure and avoiding complications. In the market, many formulations have reached the shelves where honey was incorporated in wound dressings using different techniques. Studies are still on going in this field to optimize new formulations which can improve the healing rate further with lesser application times that can be more convenient and cheaper for the consumer.

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