A Crosstalk Between Antiinflammatory and Wound-Healing Properties of Honey

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Keywords

Inflammation · Honey · Wound healing · Tissue regenration

15.1 Introduction

The human race has been using honey for more than 4000 years. It has been described to have medicinal properties in Islamic, Hindu, and other literatures. The Islamic holy writing, Quran, mentions it as an agent to cure human illness (Khan et al. 2014). Wound healing is a multistep process orchestrated by the recruitment of many cells, cytokines, growth factors and other downstream signaling molecules. Wound management is a matter of high concern in today's modern medicine era. Proper wound healing has a predominant effect on the quality of life. Large resources are utilized around the world for wound management, and, thus, it is a challenge for health care professionals. Skin medicine is a growing field of research and researchers all over the globe do find a great interest in naturopathy. Among various natural medicinal ways to treat wounds, apitherapy, using honey, is of real use. Apitherapy is a type of alternative therapy to treat wounds, infections, and other

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M. U. Rehman, S. Majid (eds.), *Therapeutic Applications of Honey and its Phytochemicals*, https://doi.org/10.1007/978-981-15-7305-7_15

diseases using bee-derived products (Sun et al. 2019). Honey has been used for the treatment of wound and many other ailments since antiquity. Honey-driven wound repair has been studied in a number of experiments. Different types of honey have different pharmacological properties. As far as meta-analysis regarding this chapter that was done, we considered Manuka honey that has been extensively studied and has been found to be highly efficient in wound healing and skin regeneration. Various studies have explained the crosslink between the antiinflammatory, antioxidative, and wound healing actions of honey. Reepithelialization, fibrous tissue generation, neovascularization, release of certain growth factors, and antiinflammatory and anti-infective responses might be responsible in eliciting the wound-healing effects of honey. This might be attributed to a wide range of bioactive compounds present in honey making it suitable candidate for clinicians and researchers to use it as a healing agent. Honey has been used to make different hydrogels with agents like chitosan, pectin, etc., as dressing pads for treating a wide variety of wounds. So far many experimental trials conducted point to honey as a potential agent for wound healing, but further high-end research is required to exactly determine the mechanism of action at the genomic, transcriptomic, and proteomic levels. This chapter gives a vivid insight into the applicability of honey in dermal medicine for wound healing, skin renewal, and regeneration.

15.2 Wounds

A wound is any disruption or a discontinuity in skin which if left unattended can be a potential source of infection for the body. Wounds occurring due to any accident or skin burning can progress to ulcers which are complicated and difficult to manage. Diabetic ulcers occur in patients with chronic diabetes having decreased peripheral blood supply due to severe sensory neuropathy. Diabetic foot in diabetic patients is a major cause of food amputations leading to disability and morbidity. Wound healing poses a high economic burden to all nations and is an area of interest in regenerative medicine (Abou Zekry et al. 2020).

15.2.1 Process of Wound Healing

Wound healing is a complex cascade of cellular and biochemical reactions occurring in tissue soon after any disruption or injury that occurs. It begins with the inflammatory reaction followed by a proliferatory phase and tissue remodeling (Ghuman et al. 2019). Wound healing is a continual mechanism involving a number inflammatory markers and transcription factors. Injury induces inflammatory reactions involving many growth factors, formed blood elements, cytokines, and extracellular matrix.

At the site of the injury, tissue-regenerating signals are released which bring in the neutrophils and monocytes from the blood to the wound area; this marks the beginning of the first phase or the inflammatory phase of the wound-healing process. In the tissue, monocytes become macrophages which induce the release of various

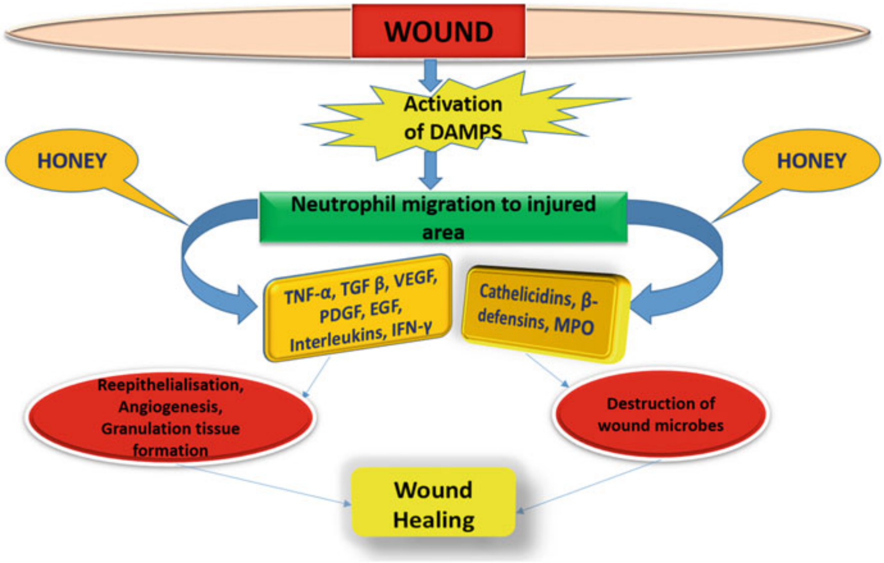

Fig. 15.1 Wound or injury induces neutrophil migration from blood to the injured area leading to the activation of inflammatory mediators which cause wound healing

growth factors like vascular endothelial and platelet-derived growth factors (VEGF and PDGF) (Komi et al. 2019). VEGF induces angiogenesis, a process of generation of new vessels, and also promotes deposition of collagen. On the other hand, PDGF has a role in generating a hemostatic plug by attracting platelets to the injury area. PDGF also has a role in increasing the DNA content and glycosaminoglycans at the wound area. The combined effect of VEGF and PDGF leads to the formation of granulation tissue, which is pivotal for the wound-healing mechanism (Qing 2017).

This inflammatory reaction is followed by the initiation of the proliferatory phase which is marked by epithelialization and angiogenesis in the region of the wound (Dwivedi et al. 2017). The growth of epithelial cells along with the recruitment of fibroblasts to the injured area causes the formation of an extracellular matrix and prominent granulation tissue (Fig. 15.1).

After reepithelialization, neoangiogenesis, and extracellular matrix formation the reconstruction of new tissue in place of wound begins. This is characterized as tissue remodeling stage. In the wound area, fibrolysis of the previously formed fibrin clot occurs, and a new matrix is laid by the fibroblast to support the cells aiding the wound-healing process (Rodrigues et al. 2019). This newly formed extracellular matrix has an abundance of type III collagen fibers which has more crosslinks and is well arranged to give more tensile strength to the affected area.

15.2.2 Treatment Adopted and Drawbacks

There are different classes of wounds depending upon the level of tissue damage inflicted in the injured area. Classically, wounds are treated by the administration of antiinflammatory corticosteroids, antibiotics, antiseptics, and some analgesic agents (Sjöqvist et al. 2019). Photobiomodulation, i.e., using various wavelengths of light including laser and LED, for the treatment of wounds is another noninvasive approach for wound care (Mosca et al. 2019).

15.2.3 Natural Ingredients in Wound Healing

In Ayurvedic medicine, many plant extracts have been known to possess potential wound-healing properties. Data show that almost 164 medicinal plants have been indicated to aid in wound healing (Gupta and Jain 2011). Recently, the leaf extract of *Boerhavia diffusa* was found to enhance wound healing in both in vivo and in vitro models (Juneja et al. 2020). The keratinocyte viability of the human skin cell line, HaCaT, was significantly increased using this extract. *Terminalia catappa* has been reported to cause increased wound healing in rats by increasing hydroxyl proline and DNA content in the wound area (Nugroho et al. 2019). Water extract of roots of *Rheum emodi* cause wound healing by decreasing inflammatory markers, viz., IL-2, IL-6, and TNF-α in the blood and increasing the accumulation of glucosamine, hydroxyproline, and DNA content in the wound tissue (Ahmad et al. 2017). Many other natural plants and their pharmacologically active biocompounds are being studied as potential wound-healing agents.

15.2.4 Honey as a Traditional Medicine

Almost 320 different varieties of honey have been isolated which originate from the floral parts of different plants, each variety possessing different properties (Meo et al. 2017). Honey is a sweet, nontoxic, viscous, and nonallergic natural product synthesized by bees. Honey is a complex of many carbohydrates mainly fructose (about 38%), glucose (about 32%), and also some amount of maltose and sucrose (Bagde et al. 2013). It is a depot of many proteins, B-complex vitamins, vitamin C, and minerals like calcium, potassium, sodium, etc. Honey is a rich source of a varied number of pharmacologically essential bioactive compounds like flavonoids such as pinobanksin, pinocembrin, and chrysin, and certain other compounds in minor concentration such as luteolin, quercetin, 8-methoxykaempferol, isorhamnetin, kaempferol, and galangin (Gill et al. 2019).. The constituents of phenolic acids and volatile norisoprenoids are 4-hydroxybenzoic acid, dehydrovomifoliol, benzoic acid yields, kojic acid, 2-methoxyphenyllactic acid, and methyl syringate (MSYR) (Alvarez-Suarez et al. 2014).

15.2.5 Honey and Wound Healing

Honey has been known as a wound healing agent since ancient periods. It is used in our homes as a healing and soothing base for various skin inflammatory conditions and burns. Wound areas are inflammatory regions of the body and can be seats for oxidative reactions. There exists a predominant crosstalk between oxidative stress and inflammation, which both in turn affect the healing of wounds (Ruiz et al. 2013).

Peroxidation leads to generation of superoxides and peroxynitriles, which trigger the inflammatory cycle inside the cell (Lugrin et al. 2014). Imbalances in the prooxidation and antioxidation mechanisms perpetuate the generation of reactive oxygen and reactive nitrogen species (ROS/RNS) which act as trigger for inflammatory cascade in the body. Inflammation induces the emigration of inflammatory cells like neutrophils and macrophages to the affected area. Signaling molecules like cytokines, inflammatory markers, and other transcription factors regulate the inflammation. Patients suffering from chronic rhinitis and sinusitis when given a nasal spray based on Manuka (*Leptospermum*) or thyme honey showed significant relief from epistaxis, and it was effective in downregulating the expression of IL-6, IL-13, IL-8, MCP-1, and macrophage inflammatory proteins (MIP)—1β in the nasal tissue (Manji et al. 2018; Hashemian et al. 2015). Also, decreased expression of inflammatory markers like IL-8,TNF-α, IL-1β, p-JNK, and IκB kinase β occurs when different types of honey (Manuka and Gelam) were used against *H. pylori*–induced gastric cancer cells (Keenan et al. 2012). In colon cancer, HT-29 cells treated with Gelam honey in combination with ginger exerted antiinflammation by modulating RAS/ERK and PI3K/AKT downstream signaling pathways (Tahir et al. 2015). Antiinflammatory activity of Gelam honey was observed in LPS-treated endottoxemic shock in rats wherein a significant reduction was seen in inflammatory molecules like p65 and high mobility protein group B1 (HMGB1), MPO activity, and neutrophil migration (Kassim et al. 2012). Another honey type called as stingless bee honey was able to decrease NF-κB and MAPK activity and, at the same time, upregulated the expression of transcription factor Nrf2, which is marker for oxidative stress (Ranneh et al. 2019).

The wound-healing property of honey might be due to its multiple inherent properties like maintaining a barrier so as to stop infection entry to wound, antiinflammatory, antibacterial action, and increasing circulation and tissue growth (Hananeh et al. 2015; Wilkinson et al. 2011). Many studies done so far deduce a strong interrelation between the antiinflammatory property of honey and its wound-healing and tissue regeneration effects. Honey decreased the size of the wound and the infiltration of leukocytes and neutrophils in intraoral and second-degree burn ulceration induced experimentally in rats (Bucekova et al. 2017). Downregulated expression of inflammatory mediators (IL-12, TNF-α, IFN-γ) and tumor growth factor (TGF)-β with reduction in neutrophils and leukocyte levels was seen in Lewis rats having corneal abrasion and keratitis (Uwaydat et al. 2011). Cecal abrasions in rats were greatly healed after honey administration as there was a significant reduction in inflammatory parameters and formation of postoperative adhesions in the abdomen (Giusto et al. 2017a, b). Honey dressing used for thermal burns proved

Table 15.1 Various honey types and the signaling proteins involved in wound healing

S. no.	Type of honey	Antiinflammatory pathway	References
1.	Manuka	Downregulation of IL-6, IL-13, IL-8, MCP-1, and MIP-1β expression	Manji et al. (2018), Hashemian et al. (2015)
2.	Manuka and Gelam	Downregulation of IL-8,TNF-α, IL-1β, p-JNK, and IκB kinase β expression	Keenan et al. (2012)
3.	Gelam	RAS/ERK and PI3K/AKT, decrease p65, high mobility protein group B1 (HMGB1), MPO levels	Tahir et al. (2015) Kassim et al. (2012)
4.	Stingless bee honey	Decrease NF-κB and MAPK activity, upregulation of Nrf2	Ranneh et al. (2019)
5.	Manuka	Upregulation of TNF-α, IL-10, VEGF, and TGF-β	Sell et al. (2012)
6.	Acacia, buckwheat, and Manuka	Upregulated expression of MMP-9, CDK2, integrin-β3, cdc25C, and p42/44 MAPK	Ranzato et al. (2012)
7.	Buckwheat honey	Upregulated expression of syndecan, focal adhesion kinase (FAK), and rasGAP SH3 binding protein 1	Ranzato et al. (2012)
8.	Acacia and buckwheat Honey	Upregulated expression of EMT markers like HPRT-1, cadherin-2, WNT family, VIM, and STEAP-1	Ranzato et al. (2012)

to have better wound-repairing activity, lesser infection, faster reepithelialization and decreased inflammatory reaction as compared to mafenide acetate dressings (Maghsoudi et al. 2011). A meta-analysis study of honey inferred that antiinflammatory, antibacterial, and antioxidative properties aid in wound healing. Honey is known to decrease prostaglandins' level which has a major role in inflammation, microbial killing, and the healing process.

Laceration wounds are a serious category of wounds, and medical grade honey has been successfully used in alleviating the infections and decreasing dehiscence in horse (Mandel et al. 2020). Dehiscence of wounds is a common complication after wound repair, occurring due to extra tension due to limb movements (Wilmink et al. 2002). Hence, the intralesional application of honey could help in enhancing wound healing by decreasing the infection rate and degree of dehiscence. Honey from *Teucrium polium*, a medicinal plant, promoted reepithelialization, angiogenesis, and fibrous tissue growth, yielding increased wound healing and tensile strength as observed by histopathology and tensiometry in incision wounds in rats (Alizadeh et al. 2011). A topical application of honey and peppermint (*Mentha pulegium*) combination accelerated the healing of rat cutaneous ulcers (Takzaree et al. 2020). This signifies the synergistic effect of honey (Tables 15.1 and 15.2).

Among the various constituents of honey, hydrogen peroxide (H_2O_2) synthesized in honey by the enzyme glucose oxidase acts as a potent antibacterial agent and can fight against many antibiotic-resistant strains of bacteria (Bucekova et al. 2017; Johnson et al. 2005). On the other hand, it is a known fact that Ca^{2+} has a promising

Table 15.2 List of various honey-based hydrogels

S. no.	Honey-hydrogels	References
1.	PVA/honey hybrid nanofibrous	Kanimozhi et al. (2020)
2.	Honey plus egg white/poly(vinyl alcohol)/clay	Rafati et al. (2020)
3.	Honey, pomegranate peel extract, and bee venom	Abou Zekry et al. (2020))
4.	Honey-chitosan nanofibers	Sarhan and Azzazy (2015) Movaffagh et al. (2019)
5.	Honey-coated nanocellulose	
6.	Pectin-honey hydrogel (PHH)	Giusto et al. (2017a, b)
7.	Hyaluronic acid (HA), acemannan gel (AG), and Manuka honey (MH)	Iacopetti et al. (2020)
8.	Acacia honey with sodium alginate	Iftikhar et al. (2010)

role in wound healing and tissue management (Ranzato et al. 2009). Inhibition of wound healing and closure occurs when the Ca-chelating compound, BAPTA, is added to a culture of immortalized skin keratinocytes (HaCaT), exhibiting a prominent role of Ca ions in tissue regeneration (Ranzato et al. 2008). Investigations have revealed that efflux of H_2O_2 through AQPs causes subsequent release of Ca^{2+}, and Ca^{2+} further helps in the initiation of wound healing and tissue (Martinotti et al. 2019). The intracellular entry of Ca^{2+} is facilitated by melastatin transient receptor potential 2 (TRPM2) and Orai1 channels.

Among the different types of honey, dark brown honey has a maximal concentration of flavonoids and phenolic compounds, which have potent ROS-scavenging potential (Afonso et al. 2020). Afterward, using a scratch wound-healing assay of normal human dermal fibroblasts (NHDF), it was shown that cell migration and, hence, wound healing was potentiated after 36 h of dark brown honey treatment (Afonso et al. 2020). Propolis and honey showed a synergistic wound healing effect as observed in both macroscopic and microscopic changes (Takzaree et al. 2016). Human skin fibroblast showed an increased wound healing after different honey exposures as revealed in scratch wound and chemotaxis assays (Ranzato et al. 2013). Significant interleukin-4 (IL-4), IL-6, and IL-8 upregulation was observed. Honey has many immunomodulatory compounds which help in the activation of different cells responsible for accelerating immune responses during injury and their healings. Immunomodulators like arabinogalactans help in monocytes activation, MRJP1 for macrophages, and a 261 MW component for neutrophil activation (Majtan 2014). Full thickness burns need excision as they do not heal spontaneously, and closure of the resulting wound is a problematic issue. Experimentally infected full thickness burn wounds showed decrease in the wound size and reduction in bacterial growth in *Pseudomonas aeruginosa*–inoculated wounds when treated with Tualang honey (Khoo et al. 2010).

Cutaneous wounds created in rats were healed significantly on topical application of Thyme honey, increasing fibroblasts, which marks its role in tissue proliferation (Takzaree et al. 2017). Recently, abdominal wounds in pediatric patients showed early granulation tissue formation, epithelialization, debridement of necrosed tissue, and no infection when medical grade honey was locally applied at the wound site (Smaropoulos and Cremers 2020). This signifies the broad applicability of honey as a first line of treatment for wounds and also with a merit of causing minimal scars after healing (Smaropoulos and Cremers 2020).

An in vitro study using sterile Manuka honey in culture media revealed the healing properties of honey. In vitro wound healing assay using a lyophilized preparation rich in growth factors (PRGF) supplemented with honey revealed enhanced rates of migration of human fibroblasts (hDF), macrophages, and endothelial cells (hPMEC) (Sell et al. 2012). This might be due to the increased downstream synthesis of cytokines like TNF-α, IL-10, and VEGF, and many physiologically activated growth factors such as TGF-β. This study is of wider importance as it demonstrates how honey can play a role in enhancing the wound-healing action of plasma-derived compounds.

Various other types of honey have been successfully used in treating different wounds. Ulmo honey (*Eucryphia cordifolia*) finds its clinical application in wound healing only when supplemented with vitamin C or ascorbic acid (Schencke et al. 2015). Increased circulation, fibroblastosis, reepithelialization, and renewal of tissue were seen 14 days postburn induction in guinea pigs (Schencke et al. 2015). Ulmo honey has been found to show its significant antibacterial action against methicillin-resistant *Staphylococcus aureus* (MRSA), the main causative agent for wound and skin infections (Acevedo et al. 2017). Therefore, this property makes it a potential candidate for wound-healing actions. Also, venous ulcer healing was accelerated in adult patients using Ulmo honey and oral vitamin C combination (Schencke et al. 2015). Ulmo honey's rapid healing action is attributed to its antiinfection and antiinflammatory properties, proper debridement of the old tissue, and also easy application. The mechanism behind the wound-healing property of honey might be the creation of a high acid milieu and hydrogen peroxide synthesis.

Three different varieties of honey, viz., chestnut (*Castanea sativa*) honey, blossom (multifloral) honey, and rhododendron (*Rhododendron luteum*) honey produced significant healing and wound contraction in full-thickness wounds induced in rabbits (Nisbet et al. 2010). All these types of honey caused maximum epithelialization, collagen and hydroxyproline production, angiogenesis, and fibroplasia as compared to wounds left untreated almost equally.

15.2.6 Effect on Proteins Involved in Tissue Rearrangement and Regeneration

Flavonoids from honey have been successfully able to induce expression of matrix metalloproteinases (MMP-9) in human keratinocytes (Majtan et al. 2013). MMP-9 is a group of matrix endopeptidases which have a prominent role in tissue regeneration by increasing cell-cell adhesion and remodeling of the basement membrane (Li et al. 2020). Furthermore, honey has strong adhesive characteristics, providing adherence to skin grafts. Honey used in graft fixation allows minimum contracture of grafts, good fixation, and maximum healing growth (Maghsoudi and Moradi 2015). Upregulated expression of MMP-9 occurred with all honey types, viz., acacia, buckwheat, and Manuka in the human keratinocyte cell line (HaCaT) (Ranzato et al. 2012). These cells when scratch wounded recovered and showed reepithelialization with honey treatment.

Syndecan-4, a transmembrane proteoglycan, enhances formation of focal adhesions in the injury site. The role of syndecan-4 has been studied in wound healing through caveolin- and RhoG-regulated integrin endocytosis (Bass et al. 2011). Buckwheat honey showed a significant upregulated expression of syndecan in keratinocyte cell lines (HaCaT) (Ranzato et al. 2012). In the same study, gene expression of focal adhesion kinase (FAK) and rasGAP SH3 binding protein 1 was shown to increase (Ranzato et al. 2012; Meng et al. 2004).

Ranzato et al. (2012) also proposed the activation of cyclin-dependent kinase (CDK2) in a skin keratinocyte model. CDK2 has a predominant role in cell proliferation and tissue regeneration as it is involved in the transition from the G1 to the S phase of the cell cycle. In addition to CDK2, some other peptides that have roles in cytoskeletal rearrangements like vasodilator-stimulated phosphoprotein, integrin-β3, cdc25C, and p42/44 mitogen-activated proteins kinase were shown to increase when treated with honey having different floral origins.

15.3 Epithelial Mesenchymal Transition (EMT)

EMT is a phenomenon in which epithelial cells gain the properties of mesenchymal stem cells which can further dedifferentiate into any other cell type (Lamouille). Its role was first determined in embryogenesis during neural tube formation. EMT is required by cancer cells to metastasize and also in wound healing (Kong). During the wound-healing process the epithelial cells around the wound borders undergo EMT, and, therefore, the mesenchymal cells can undergo migration which is pivotal for regeneration. Snail2 is responsible for the EMT, and its overexpression accelerates wound healing (Hu et al. 2019).

Very few studies are available to validate the effect of honey on EMT. Honey samples from acacia and buckwheat led to upregulated expression of some EMT marker genes, viz., hypoxanthine phosphoribosyltransferase-1 (HPRT-1), cadherin-2, Wingless/Integrated (WNT) family, vimentin (VIM), and six-transmembrane epithelial antigen of the prostate-1 (STEAP-1) at the same time downregulating some other EMT markers, viz., keratin 14 and 19 in HaCaT cells (Ranzato et al. 2012). This suggests how honey helps in epithelial transition and, thus, causes reepithelialization and dedifferentiation in the keratinocytes. Also, a crosstalk between MMP-3 and EMT is also predominant with regard to healing and tissue regeneration. MMP-3 causes induction of EMT via activation of cadherin, Snail, Rac1b activation, VIM, and a-smooth muscle actin in mammary epithelial cells of the mouse model (Radisky et al. 2005). A meta-analysis postulated honey's vital role in promoting EMT and, hence, aiding a great extent in tissue remodeling and rearrangement (Nordin et al. 2017).

15.4 Honey: A Healer in Diabetic Foot

Diabetes is a growing challenge throughout the world, and India is considered as the diabetic capital of world with 8.7% diabetic people between age 20 and 70 years (Maahs et al. 2010). Recently, a randomized study proposed the healing action of honey when used in dressings for diabetic foot ulcers. The honey dressings showed more prominent reduction in wound size as compared to dressings using povidone iodine (Koujalagi et al. 2020). This proves that honey could be a remarkable agent for ulcer healing and tissue remodeling in diabetic patients having foot ulcers. Manuka honey is a pharmacologically valuable type of honey obtained from *Leptospermum scoparium* (Manuka tree) and, thus, has gained great attention within the scientific community. Recently, the study revealed that topical application of Manuka honey on the excision wound of diabetic rats helped in significant wound closure due to early epithelialization with well-formed keratinized squamous epithelium with normal collagen tissue around hair follicles on histological examination (Gill et al. 2019). Manuka honey is a rich source of methyl syringate (MSYR) to which its myeloperoxidase activity inhibition is owed, leading to the antibacterial action of honey in wounds. Myeloperoxidase has bactericidal action but also causes tissue damage in the area of inflammation due to MPO-derived oxidants (Aratani 2018). Hence, specific MPO inhibition is required for proper tissue regeneration. Myeloperoxidases are known to be active in infected wounds in comparison to noninfected wounds; hence, its inhibition is vital for wound healing (Hasmann et al. 2013). Another compound widely held responsible for the pronounced antibacterial activity of Manuka honey is methylglyoxal (MG) (Mavric et al. 2008). MH, widely marketed as Medihoney, has been found to act as a potent antibacterial agent against *Campylobacter* species (Lin et al. 2009) and many other resistant bacterial strains (George and Cutting 2007). Diabetic ulcers treated with honey showed significant healing by enhancing granulation tissue formation, preventing leg amputations in diabetic patients, a grave complication in chronic diabetes (Eddy and Gideonsen 2005). Mountain honey dressing used for wounds created in mice models was able to induce healing and decrease incision sizes significantly (Reddy and Al Habsi 2020). Beri honey–impregnated dressing applied for healing diabetic foot ulcers led to significant reduction of wound healing duration (Imran et al. 2015). So far, many investigations revealed that honey dressings can be successfully used, but clinicians are reluctant to use them in clinical trials.

15.4.1 Drawback of MG

MG, glyoxal, and 3-deoxyglucosone are dicarbonyl compounds formed by the oxidation or peroxidation of lipids and glucose are reactive species. These dicarbonyl compounds have been found in many foods (Nagao et al. 1986) and also in honey (Adams et al. 2009). The presence of MG in honey at one hand provides the antibacterial properties and is useful in healing as well. MG attacks lysine, arginine (Arg), and cysteine residues of collagens to form complex and irreversible molecules: advanced glycation endproducts (AGEs) (Sassi-Gaha et al. 2010). There are crosslinks in collagen due to increased molecular size which disrupt the normal matrix of the tissue (Sassi-Gaha et al. 2010). Also, AGEs decrease keratinocyte migration (Song et al. 2008). Collagen is important in wound healing and tissue remodeling, and any disruption in collagen structure or physiology can directly diminish the wound-healing process.

In addition to the collagen abnormality, MG has significant effects on derailing peripheral blood circulation which decreases the migration of active cells to the ulcer site (Price and Knight 2009). Blocking AGE receptors could restore impaired wound healing as already reported in diabetic mice (Goova et al. 2001). MG in MH can also significantly decrease wound healing in diabetic patients as MH has the highest concentration of MG as compared to other types of honey (Majtan 2011). Hence, MG can regulate pathogenesis in diabetic ulceration and needs to be considered in future studies for honey's wound healing action.

15.5 Honey Hydrogels for Wound Dressing

Nanotechnology has gained tremendous attention in the scientific world of today. It is a growing field of research, and wound healing using biocompatible nanofibrous materials is in vogue. Nanofibrous dressings are known to have better efficiency of exudate absorption, more surface area, and high porosity as compared to conventional dressings (Miguel et al. 2018). Biocompatible hydrogels possess some unique hydrophilicity and biocompatibility and, therefore, are ideal for wound dressing. High-end techniques like electrospinning, UV and FTIR spectroscopy, and XRD have been used to synthesize PVA/honey hybrid nanofibrous scaffolds that are used as bandaids or dressing pads (Kanimozhi et al. 2020). A hydrogel dressing made from honey plus egg white/poly(vinyl alcohol)/clay accelerated wound healing and also reduced the rate of infection in the wounds (Rafati et al. 2020). Nanofibers generated using honey, pomegranate peel extract, and bee venom have proved to be highly efficacious in wound healing (Abou Zekry et al. 2020). These honey-fabricated nanofibers increased wound closure percentage, enhanced epithelial bridging, and decreased cellular infiltration in the wound area. Manuka honey dressing pads, called as Medihoney®, have been found to be quite helpful in absorbing wound exudates and accelerated wound healing (Fan and Roos 2019). Furthermore, honey-chitosan nanofibers demonstrated antibacterial activity against *S. aureus* and *E. coli*, proposing the potential use of honey nanofibers in protecting wound infections (Sarhan and Azzazy 2015). Honey-coated nanocellulose was found to be an efficient and rapid delivery medium for noninfectious wound healing (Abu et al. 2020). Pectin is efficiently being used for drug delivery and as a scaffold for cells. Also, it finds application as a skin medicine for wound healing and skin regenerations along with honey. Pectin-honey hydrogel (PHH) served as an effective dressing agent as compared to honey alone (Giusto et al. 2017a, b). Wound contraction was more pronounced, and a histopathological study revealed development of hair follicles and epithelialization, indicating efficient wound healing. Better wound healing due to pectin may be due to direct and continuous contact of the hydrogel with the wound compared to honey only. Another Gelam honey-based hydrogel dressing formulation stimulated wound healing by attenuating wound inflammation, increasing rate of wound contracture, and reepithelialization at a greater efficiency as compared to silver sulphadiazine (SSD) burn healing ointment (Yusof et al. 2007). Application of hyaluronic acid (HA), acemannan gel (AG), and Manuka honey (MH)–based dressing base promoted wound healing of skin wounds by promoting cell proliferation and neovascularization (Iacopetti et al. 2020). Immunohistochemistry showed a positive reaction for CD3, CD20, KI67, vWF, and VEGF, indicating the healing efficacy of MH-based hydrogels. Chitosan, a high-molecular-weight compound, is also used in combination with honey to make hydrogel to potentiate wound healing in rat models with full-thickness wounds. Chitosan/honey hydrogel (1:3) serves as an optimal formulation for effective wound dressing (Movaffagh et al. 2019).

Another topical hydrogel prepared using acacia honey with sodium alginate was able to produce significant wound healing in different wound models (Iftikhar et al. 2010). An early epithelialization and increased wound contracture percentage, breaking strength, and hydroxylproline content were seen in these models. Many honey dressings and gels have been used but still results need proper validation (Jull et al. 2008) so as to bring the products into use at the bed side. Increased wound closure time, synthesis of granulation tissue, and enhanced Ki-67 and HO-1 expression were seen in diabetic wounds on application of hydrogel incorporated with chestnut honey as compared to water hydrogels.

15.6 Conclusion

This chapter discusses vividly the wound-healing property of honey. Honey has been in use for healing since ages. Almost every household utilizes honey keeping in mind its beneficial effects. Traditional medicinal practice utilizes honey for inflammatory diseases, wound healing, as a laxative, etc. It maintains irritable and constipated bowels by acting as a lubricant and increasing peristaltic motions. Inflammation is associated with injuries, and, hence, antiinflammatory drugs are vigorously used for wound healing. Natural medicine derived from various sources has been put into use as antiinflammatory and wound-healing agents. Many experiments have shown that honey can be used as an excellent wound healer due to its antiinflammatory and antiinfective properties. Downregulating the expression of inflammatory compounds like IL-12, TNF-α, IFN-γ, and TGF-β in injured tissues proves the potency of honey as a wound healer. Being a storehouse of many antioxidative compounds like flavonoids and other phenols, honey has potency in decreasing ROS generated in an injured area. Honey accelerates wound contractions and closure, increases hydroxyproline content, and potentiates epithelialization in a wound site. Studies have shown that the production of H_2O_2 in honey leads to entry of Ca^{2+} ions through AQPs in the wound area, which help in wound healing and subsequent generation of new tissue. Though many published records have mentioned honey's mechanism of action for wound healing robust trials need to be done in this regard. Furthermore, many studies have shown the presence of MG in honey which although an antibacterial agent can decelerate wound healing. Therefore, such compounds need further specification and a detailed study. Gene expression profiles must be formulated which can validate the wound-healing action of honey. Different honey types obtained from varied floral tress need to be studied thoroughly as there exist many differences in the pharmacological properties. Sophisticated techniques like gelatine zymography, reverse transcription PCR, and Western blot should be performed in order to know how honey aids in tissue management and wound healing. This can further help to intricate and formulate honey hydrogels and dressing pads for different wounds. Though wide literature regarding wound healing and tissue management properties of honey can be found the subjacent molecular approaches for its mechanism of action are largely lacking. Various omics approach like genomics, transcriptomics, proteomics, phenomics, etc., should be adopted at the earliest to study the wound healing and tissue regeneration properties of honey so that it can be used a potential wound healer.

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