www.roavs.com EISSN: 2223-0343
RESEARCH OPINIONS IN ANIMAL & VETERINARY SCIENCES

Review Article

Recent advances in topical wound healing products with special reference to honey: A review

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Article history
Received: 28 Jan, 2015
Revised: 22 Feb, 2015
Accepted: 23 Feb, 2015

Abstract

Wound healing is a complex process involving several overlapping stages with many internal and external factors playing different important roles. Healing of wounds can be hindered in special cases and successful management becomes a serious challenge to the practitioner. Over the years, many natural and synthetic products have been tried in both human and animals in the hope that they facilitate the process of healing especially in unusual wounds. The main objective of this review was to collect documented scientific data regarding the use of a very special type of honey (Sidr honey) and its use for open wound management as well as its chemical and medicinal characteristics. In addition, a more comprehensive literature review of the most recent topical wound healing products is also provided.

Keywords: Wound healing; chronic wounds; dressings; bandages; Sidr honey

To cite this article: Ismail ZB, MA Alshehabat, W Hananeh, M Daradka, JH Ali and EKM El-Najjar, 2015. Recent advances in topical wound healing products with special reference to honey: A review. Res. Opin. Anim. Vet. Sci., 5(2): 76-83.

Introduction

Wounds are common and can be challenging to manage in both human and animals, especially non-healing wounds and wounds with secondary infection by multidrug resistant bacteria (Atiyeh et al., 2009). Ideally, topically applied wound treatment products should be non-toxic, biocompatible, and be able to achieve the intended clinical purpose without adversely affecting the progress of the natural wound healing process (Atiyeh et al., 2009). Traditionally, the basic principles related to wound care include copious wound lavage with sterile solutions to reduce microbial load, debridement of visible necrotic or contaminated tissues and applications of appropriate wound dressings (Atiyeh et al., 2009; Thomas et al., 2009).

Until today, there has been no single optimal treatment that enhances the resolution of problem wounds or alters the different cellular components or their functions that are responsible for proper healing (Sell et al., 2012). Various synthetic and biomaterials have been investigated for the purpose of enhancing wound healing in both humans and laboratory animals (Hammad et al., 2011; Li et al., 2012; Mardas et al., 2012). Results of such experiments were varied and inconsistent in most instances. As a result, periodical modifications or reassessment of treatment protocols used in different phases of wound healing have been common in order to find the single most effective treatment regimen (Hammad et al., 2011; Li et al., 2012; Mardas et al., 2012). Hence, the main objective of this review was to collect documented scientific data

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regarding the use of a very special type of honey (Sidr honey) for open wound management as well as its other chemical and medicinal characteristics. A more comprehensive literature review of wound topical management is also provided.

Recent advances in topical medications for wound treatment

Glycerol

Glycerol has been used for treatment of various health problems (Fluhr et al., 2008; Stout and McKessor, 2012). Many beneficial effects have been reported after the use of glycerol for treatment of skin disorders including promotion of wound healing, amelioration of the skin protective (barrier) function, hydration status and mechanical features (Fluhr et al., 2008). In addition to its antimicrobial and antifungal effects, glycerol provides moist wound environment crucial for wound healing (Saegeman et al., 2008; Fluhr et al., 2008). Currently, glycerin is one of the most commonly used topical treatments in wound dressings applied during the proliferative phase of wound healing (Stout and McKessor, 2012).

Tripeptide copper complex (TCC) hydrogel

Tripeptide copper complex (TCC) hydrogel has been found to stimulate the formation of granulation tissue in dogs during the first week of open wound healing, thus promoting the process of wound healing (Swaim et al., 1996). It has also been found to enhance the healing of ischemic open wounds in rat models (Gul et al., 2008). More interestingly, wounds of rabbits treated with TCC have been found to complete the formation of granulation tissue faster than control animals (Gul et al., 2008). Treated wounds were found significantly smaller and competed granulation tissue formation faster and contained significantly lower concentrations of TNF-alpha and MMP-2 and MMP-9 than control wounds (Canapp et al., 2003).

Zinc

Topical treatment with zinc compounds has been found to stimulate epithelialization in surgically created wounds in rats and rabbits (Lansdown et al., 2007; Boateng et al., 2008). Enhanced wound contraction has also been reported in rabbits treated with zinc oxide (Boateng et al., 2008). In addition, zinc was shown to decrease *Staphyloccocus* load in the wound and to induce no cellular abnormalities (Boateng et al., 2008). Moreover, topical application of zinc oxide was found to enhance the healing of chronic and acute wounds in addition to a considerable antibacterial and anti-inflammatory effects (Voicu et al., 2013).

Platelet rich plasma (PRP)

Many clinical studies documented the regenerative properties of the platelet-rich plasma (PRP) and their role in treatment of chronic skin wounds and ulcers (Alsousou et al., 2009; Lacci and Dardik, 2010). PRP serves as a growth factor and has both mitogenic and chemotactic properties (Everts et al., 2006; Petrova and Edmonds, 2006). It contains a high level of platelets and a full complement of clotting and growth factors (Mehta and Watson, 2008). Many clinical studies documented the regenerative properties of the platelet-rich plasma and their role in treatment of chronic skin wounds and ulcers (Alsousou et al., 2009; Lacci and Dardik, 2010).

Aloe vera

In a study evaluating the curative impact of Aloe vera fresh gel on healing of experimentally infected full-thickness open wounds in dogs, it has been shown that both quantity and quality of collagen fibbers have been improved after treatment with Aloe vera. fresh gel (Ghasemi et al., 2009). An aloe vera derivative called “acemannan” has been found to act as a growth factor in order to enhance wound healing. Acemannan is available in foam or hydrogel forms (Swaim and Bohling, 2008). Stimulation of collagen I synthesis, vascular endothelial growth factor and keratinocyte growth factor 1 as well as fibroplasia have been reported after treatment in rat model with acemannan (Jettanacheawchankit et al., 2009). Furthermore, promotion of wound contraction and epithelialization as well as acceleration of granulation tissue formation have been noticed after the use of acemannan hydrogel for treatment of wounds involving the paws pads of dogs.

Sildenafil

By promoting angiogenesis, Sildenafil citrate (Viagra) has been shown to be effective in enhancement of wound healing process in dogs (Brueckner et al., 2009; Derici et al., 2010; Farsaie et al., 2012). In fact, sildenafil citrate gel application was found to decrease significantly the size of the skin wound in a dose independent manner during wound healing and in a dose dependent manner thereafter (Gursoy et al., 2014). Moreover, topically applied sildenafil on skin wounds was proved to enhance significantly wound contraction, fibroblast deposition and granulation tissue formation, and macrophage migration, collagen regeneration, and epithelialization (Jamshidzadeh and Azarpir, 2011).

Ascorbic acid

Oral administration of ascorbic acid prior to laparotomy in diabetic rats has been reported to expedite incisional wound healing processes (Kamer et al., 2010). Furthermore, a D-glucose polysaccharide named “maltodextrin” produced as gel or powder that contains 1% ascorbic acid has been used successfully for stimulation of wound healing in severely

contaminated and infected wounds (Hedlund, 2007). Maltodextrin provides glucose essential for metabolic activities of cells involved in wound healing (Hedlund, 2007). Moreover, maltodextrin has been found to play an important role in creating a favourable moist environment for wound healing as well as reducing the wound odour, oedema, exudates and infection. Enhancement of epithelial cells growth as well as early development of granulation tissue may result from the use of maltodextrin for topical treatment of wounds (Hedlund, 2007). Antibacterial efficacy of maltodextrin as well as its ability to inhibit bacterial growth recommended its use for contaminated or infected wounds (Hedlund, 2007). It can be used as a wound contact dressing layer during the early two phases (inflammatory and proliferative) of wound healing.

Tocopherol

The clinical effects of using vitamins to enhance wound healing have been studied in several animal models (Lin et al., 2012). Among of which, only vitamin C has been shown to accelerate healing in human subjects (Lin et al., 2012). Other recent researches also evidenced an accelerated wound healing pattern in diabetic rats after topical application of tocopherol cream (Lin et al., 2012). Vitamin E after oral administration was found to enhance wound in aging and diabetic rat models (Noor Aini et al., 2003; Musalmah et al., 2005). Intraperitoneal injection of Raxofelast, a hydrophilic vitamin-E-like compound was also found to positively effect on healing of incised wounds in diabetic rats (Galeano et al., 2001). Other recent researches also evidenced an accelerated wound healing pattern in diabetic rats after topical application of tocopherol cream (Lin et al., 2012) as well as polysaccharides-rich extract of a polypore mushroom Ganoderma lucidum (Cheng et al., 2013).

Pomegranate (*Punica granatum*)

The extract of dried pomegranate peel has been formulated as a water-soluble gel with different concentrations and tested for its wound healing potency in Wistar rats (Adiga et al., 2010; Hayouni et al., 2011). Complete wound healing was observed on day 10 in animals treated with 5% formulated gel, whereas it required 16-18 days to be achieved in control animals treated with blank gel. More recently, it has been reported that oral administration of Pomegranate seed extract in rabbits significantly enhanced the rate of surgical wound closure (Kandemir et al., 2013).

Lantana (*Lantana camara*)

Many researches and experimental trials conducted on rats revealed several medicinal properties of West Indian lantana (*Lantana camara*) including antibacterial, anti-inflammatory, antifungal, antioxidant, anti-carcenogenic, anti-hyperglycemic and many others (Reddy, 2013). Furthermore, ethanolic extract of *L. camara* leaves has been found to enhance wound healing in adult male rats (Reddy, 2013). More interestingly, enhanced wound contraction, collagen synthesis and accelerated wound healing have been demonstrated after the topical application of *L. camara* aqueous leaf extract in rats (Nayak et al., 2009). A recently published research has also concluded that topical application of ethanol extract of *L. camara* has resulted in dose dependent promotion of wound healing in diabetic rats (Mekala et al., 2014).

Chitosan

Chitosan, a derivative of the naturally occurring polymer Chitan is widely available in nature with many proven medical properties (Dai et al., 2011). It has been found to exert wide spectrum antimicrobial effects, promotes the healing of various types of wounds, as a haemostatic agent, and has been used as a carrier for many drugs and growth factors (Dai et al., 2011). The positive effect of sterilized, medical grade chitosan powder on wound healing of rats has been also reported more recently (Ong et al., 2008; Sandeep et al., 2014).

Stem cell therapy

Stem cells are undifferentiated cells that have the ability to renew and differentiate into progenitor or precursor cells of one or several specific cell types (Yolanda et al., 2014). There are two main types of stem cells; foetal and adult stem cells. Adult stem cells are more commonly used and easier to obtain with little technical and ethical obstacles (Yolanda et al., 2014). These can be collected from bone marrow and fat tissue, but can be obtained from any other tissue. It has been used with variable degrees of success for regeneration of the myocardium, bone, tendons, cartilage, and skin (Wang et al., 2007). A recent experimental research revealed a novel treatment of full thickness cutaneous wounds created in rabbits with a single topical application of autologous bone marrow-derived cells with placental extract (Akela et al., 2012). Treatment group showed an accelerated wound healing pattern compared to other groups. The study also suggested the topical application of autologous bone marrow-derived cells with placental extract for effective treatment of chronic non-healing wounds occurring in both humans and animals (Akela et al., 2012).

Honey

Honey is a sweet viscid material made by honey bees (*Apis mellifera*) using the nectar portion flowers. Honey varies in its physical and chemical properties. It is classified based on several criteria including water content, clarity, colour, aroma, and methodology of

processing and packaging. Honey has been used by many ancient cultures as a full nutritious food as well as a remedy for many illnesses. Pure honey is mainly composed of approximately 80% carbohydrates (40% glucose, 40% fructose), approximately 20% water, and traces of protein, traces of minerals, vitamins and contains no fat (Simon et al., 2009; Al-Waili et al., 2012). Honey is a natural product that can possibly be contaminated during collection or packaging (Simon et al., 2009; Al-Waili et al., 2012). Raw honey is the honey that does not undergo further processing such as boiling or pasteurization (Simon et al., 2009; Al-Waili et al., 2012). Medical-grade honey is a purified-type honey that undergoes gamma radiation to help destroy the spores of *Clostridium botulinum* (Simon et al., 2009; Al-Waili et al., 2012).

Using honey as a wound care product has been recognized because it is believed to positively influence the wound healing process. Today, there are several medical grade honey-based dressings that are approved by the United States Food and Drug Administration (FDA). Various mechanisms have made honey superior to many other available medically-approved wound care products. Honey has a hygroscopic effect by attracting and holding excessive fluid from the surrounding environment and thus reduces inflammatory oedema and exudation associated with the healing process (Simon et al., 2009; Al-Waili et al., 2012). Reduction in inflammatory oedema and exudation also may decreases pain (Simon et al., 2009; Al-Waili et al., 2012).

The high sugar content in honey provides a source of energy to both the viable cells as well as wound invading bacteria (Al-Waili et al., 2011). Wound invading bacteria preferably utilizes high glucose content over traces of amino acids in honey, which in turn produces lactic acids rather than malodorous products thus reducing unpleasant odours associated with many types of wounds (Al-Waili et al., 2011).

Honey's low water content creates high osmolarity conditions in contaminated wounds. As a result, nutrients will be dissolved within the lymph drawn from the wound area for tissue regeneration (Al-Waili et al., 2011).

In recent years, honey has gained more popularity as an efficient natural antibacterial wound care product especially in wounds infected with multidrug resistant bacteria such as *Staphylococcus, Streptococcus, Pseudomonas* and *E. coli* (Al-Waili, 2011; Godlee, 2013; Cooke et al., 2015). Recent studies have suggested an *in vitro* superior efficacy of honey against resistant bacteria such as methicillin resistant *Staphylocuccus aureus* (MRSA), vancomycine resistant *Enterococcus* (VRE) and others (Kwakman et al., 2008; Kwakman et al., 2011a; Ewnetu et al., 2013; Jenkins et al., 2014; Cooke et al., 2015). However, there have been some reports suggesting variations in the honey's antibacterial properties when derived from different plant sources (Kwakman et al., 2008; Blair et al., 2009).

The exact mechanism of action of honey as an effective antibacterial agent has been investigated but largely remain obscure (George and Cutting, 2007; Majtan et al., 2011; Al-Waili, 2011; Cooke et al., 2015). Suggested mechanisms are many and include low water content, high acidity, high osmolality, presence of natural hydrogen peroxide that is produced by the action of glucose oxidase in honey, and scavenging properties attributed to phenolic compounds (Mavric et al., 2008; Adams et al., 2009; Kwakman et al., 2010; Al-Waili, 2011; Jervis-Bardy et al., 2011; Leong et al., 2012; Cooke et al., 2015). Hydrogen peroxide produced in honey also plays a protective role that prevents tissues from damage (Mohd Zohdi et al., 2012; Nakajima et al., 2013; Cooke et al., 2015).

In addition to being a natural antibacterial, honey also has other wound healing attributes. Various studies have reported that honey may stimulate macrophage migration, angiogenesis and fibroplasia. Honey also contains high levels of antioxidants which provide further tissue protection against oxygen radicals (Mohd Zohdi et al., 2012; Nakajima et al., 2013). In addition, Baghel et al. (2009) mentioned that honey has no adverse effects on tissues.

Several studies have documented the efficacy of using honey in wound treatment as well as its superior activity when compared to many other modern wound healing products (Molan, 2006; Kwakman et al., 2008; Lay-flurrie, 2008; Al et al., 2009; Ferreira et al., 2009; Al-Waili et al., 2011; Kwakman et al., 2011b; Tan et al., 2012; Yaghoobi et al., 2013). Recent studies in different animal models found that honey-treated wound sites and burns healed more rapidly when compared with control wounds (Lay-flurrie 2008; Tan et al., 2012). Moreover, honey resulted in enhanced healing process, minimized healing time and reduced scarring. In addition, Anyanechi and Saheeb (2015) found that application of honey dressings benefit the healing process of dehiscenced mandibular wounds after resection surgery.

Recently, daily application of Manuka honey on experimentally created wounds on the distal thoracic limb of horses for 12 days showed less retraction when compared with the control group(Bischofberger et al., 2011). The use of honey mixed with beef fat or butter for treatment of human intractable wounds, skin ulcers and burns has been described for over three thousand years (Bischofberger et al., 2013).

Sidr honey

Among various monofloral honeys produced in the Arabian Peninsula, Sidr honey is considered one of the finest. Traditionally, Sidr honey has been utilized as an

effective treatment for infected wounds. In addition, Sidr honey obtained from Sidr tree has been known to cure liver diseases, chronic rhinosinusitis and gastro-intestinal ulcers in humans (Alandejani et al., 2009). A recent research utilized Sidr honey in rat model showed that honey inhibited histamine, carrageenan- induced paw oedema, acetic acid-induced writhing, formalin-induced writhing, and significantly reduced yeast-induced pyrexia with no observed toxic side effects (Alzubier and Okechukwu, 2011). Furthermore, Sidr honey has expressed numerous medicinal effects including antibacterial, anti-inflammatory, antipyretic and analgesic (Alandejani et al., 2009; Alzubier and Okechukwu, 2011).

Physical and chemical analysis of Sidr honey showed that this honey contains several phytochemicals: steroid, flavonoids, tannins, saponins and alkaloids (Alandejani et al., 2009; Alzubier and Okechukwu, 2011). The phytochemical content of this honey is thought to contribute the majority of its potent medical properties (Alzubier and Okechukwu, 2011). The *in vitro* antibacterial activity of Sidr honey was investigated (Alzubier and Okechukwu, 2011). The potent bactericidal activity of this honey against *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms was evidenced by another recent study (Alandejani et al., 2009). Also, the study concluded that both Manuka and Sidr honeys have superior antimicrobial properties that surpass the activity of commonly used antibiotics (Alandejani et al., 2009). More interestingly, in addition to its antibacterial and anti-inflammatory activities, this honey has a variety of other medicinal effects such as anti-parasitic (Nilforoushzadeh et al., 2007), antifungal (Kacaniova et al., 2011), antiviral (Yaghoobi et al., 2013) and anti-carcenogenic (Bardy et al., 2008; Jaganathan et al., 2010) activities.

Conclusion and future perspective

For a variety of exclusive advantages, honey is considered an effective, safe and inexpensive topical treatment for management of large, intractable and open wounds. Benefits of using Sidr honey for the treatment of open acute and chronic, clean and contaminated wounds in both human and animals appear promising and further studies are recommended in both human and animal models.

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