Role of Honey in Curing Complicated Surgical Wounds

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Abstract

Healing of a wound is very complex and dynamic process that leads to regain the continuity of the tissue. It takes place in different phases including hemostasis, inflammation, proliferation and regeneration. Honey has been used in curing wounds and eliminating infectious agent from ancient times. Due to the production of hydrogen peroxide, osmolarity and polyphenols, honey has natural property of killing microbes. Honey decreases the activity of cyclooxygenases that interfere the production of prostaglandins. Honey can also reduce the edema at wound site by decreasing the pressure on small vessels of wound and thus provides oxygen and other nutrients for fast recovery. Honey has anti-oxidant property because of phenolic acids, flavonoids, tocopherols, ascorbic acid and different enzymes. When honey is applied over the wound, it promotes the removal of dead tissue due to its moist nature. Medical- Grade honey can be used safely for wounds, as it is treated with gamma rays to remove any clostridial spore and is free from any contaminating organisms. Honey plays a major role in tissue-engineering template because it can eradicate infection, help to decrease inflammation and improve the integration of tissue.

Keywords: Wound, Honey dressings, Anti-bacterial, Anti-inflammatory, Promote healing

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Introduction

Skin acts as a physical barrier against infectious microorganisms and has three layers including epidermis, dermis and hypodermis. Wound is the discontinuity of normal structure of the outer layer of skin i.e. epidermis. This discontinuity compromise the defensive function of skin (Kus et al., 2020). Complicated wound is the one that does not heal at expected time due to many complications like infection, inflammation, seroma and tissue separation. Healing of a wound is very complex and dynamic process that leads to regain in the continuity of the tissue (Guo and Dipietro, 2010; Schreml et al., 2010; Khaleghverdi et al., 2021).

Healing of wound is a complex process. It takes place in different phases including hemostasis, inflammation, proliferation and regeneration. After initial vasoconstriction, vasodilation takes place. It permits the entry of many inflammatory cells that cause the release of many mediators and cytokines for angiogenesis, re-epithelialization and thrombosis (Bowden et al., 2016). Hemostatis, chemotaxis and increase in permeability of vessels prevent damage in inflammatory phase of wound healing. They seal the wound, eliminate infectious agent and increase the migration of cells (Bowden et al., 2016).

Granulation of tissue, replacement of damaged tissue and formation of new vasculature take place in proliferative phase and it is a time taking phase. In regeneration phase, there is a contraction of wound, remodeling of the new tissue and increase in the tensile strength of tissue (Figure 1) (Kus et al., 2020).

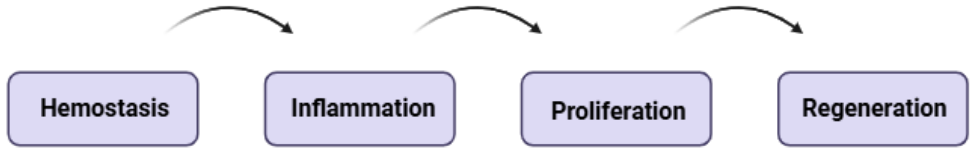

Fig. 1: Phases of Wound Healing (Drawn by using biorender)

Bio-activity of Honey on Complicated Wounds

Honey is sweet, viscous and acidic in nature. It is composed of carbohydrates (fructose 40%, glucose 30%, sucrose 5%), 20% water and other components (Alghamdi et al., 2020). The honey is best for burns, ulcers and traumatic wounds. More viscous honey act as a barrier between skin and external environment, thus promotes healing (Hixon et al., 2019).

1- Anti-Bacterial effects of Honey

Honey has been used in curing wounds and eliminating infectious agent from ancient times (Nair et al., 2020). Due to the production of

hydrogen peroxide, osmolarity and polyphenols, honey has natural property of killing microbes (Fang, 2004; Vandamme et al., 2013; Minden-Birkenmaier and Bowlin, 2018; Oryan et al., 2019). It has both bacteriostatic and bacteriocidal properties (Vandamme et al., 2013; Al-Nahari et al., 2015; Almasaudi et al., 2016). In past years, the use of honey was reduced with the arrival of antibiotics. But now due to the drug resistance, honey has regained its value as antimicrobial agent (Combarros-Fuertes et al., 2020). The non-healing wounds are at high risk of developing infection like burn wounds.

It is challenging to treat the wounds with biofilm because of the shield of polysaccharide material (Vestby et al., 2020). Honey is the best against such wounds that show resistance towards antibiotics (Natarajan et al., 2001; Gethin and Cowman, 2008; Nair et al., 2020). It is also very effective against biofilms because it stops the formation of polysaccharide shield over wounds (Cooper et al., 2011; Sindi et al., 2019; Proaño et al., 2021).

Anti-Inflammatory Role of Honey

When there is a local injury, the inflammation takes place to treat the affected site and to provide protection against infectious agent. Inflammation is very important in the healing process otherwise situation becomes worse (da Silva et al., 2021). Honey decreases the activity of cyclooxygenases that interfere the production of prostaglandins (Nooh and Nour-Eldien, 2016; Yadav et al., 2018).

The prostaglandins are very important for inflammatory phase because they can dilate the blood vessels, elevate the crossing across vessels, cause entry of white bloods cells and trigger the sensation of pain (Kassim et al., 2010). The affected tissues produce free radicals during inflammation, honey can decrease the disturbance caused by free radicals and avoid cell death (Oryan et al., 2016). Honey can also reduce the edema at wound site by decreasing the pressure on small vessels of wound and thus provides oxygen and other nutrients for fast recovery (Molan, 2011).

Anti-oxidant Property

Honey has anti-oxidant property because of phenolic acids, flavonoids, tocopherols, ascorbic acid and different enzymes (Al-Mamary et al., 2002; Gheldof and Engeseth, 2002; Oryan et al., 2016). The by-product of Maillard reaction, melanoidins, play a primary role in enabling the honey to scavenge the radicals (Brudzynski and Miotto, 2011a; Brudzynski and Miotto, 2011b).

These compounds decrease the side effects of reactive nitrogen species RNS and reactive oxygen species ROS, stop the activity of those enzymes that are involved in the formation of super-oxide anions and decrease the production of free radicals by interrupt their chain reactions (Pyrzynska and Biesaga, 2009). When the wound becomes chronic, neutrophills and macrophages release more reactive oxygen species against infectious agent (Majtan, 2014). The high level of ROS involves in tissue damage and delays the process of healing. These species also lead to oxidative stress (Schäfer and Werner, 2008). Furthermore, the flavanoids in honey provide protection against reactive nitrogen species (M Alvarez-suarez et al., 2013).

Honey Promotes Angiogenesis

Angiogenesis is the formation of new vessels that takes place during proliferation of cells. These new vessels provide adequate oxygen to the wound tissues for proper healing. Extracellular matrix and serum provide signals for this process (Kumar et al., 2015). The honey has high levels of sugar and other minor components that help in providing proper nutrients and to proliferate endothelial cells. Some studies have shown that anti-angiogenesis is regulated by modulated prostaglandin E_2 and by the production of vascular endothelial growth factor (Eteraf-Oskouei et al., 2014).

Honey Promotes Healing Rate

By regenerating new tissues, honey promotes healing (Al-Waili, 2003). The acidic nature of honey minimizes the microbial growth, enhances the action of macrophages and neutrailizes the byproduct of bacterial metabolism that is ammonia, because ammonia can cause damage to healing tissue. This low pH of honey helps to provide more oxygen in blood from hemoglobin (Gethin and Cowman, 2008). A 1% concentration is enough to release cytokines, tumor necrosis factor and interleukins from monocytes (Majtan et al., 2010). These factors stimulate migration and spreading of keratinocytes that helps in wound healing and they also stimulate the synthesis of collagen from fibroblasts (Rossiter et al., 2010).

Honey for Debridement

The debridement promotes healing by removing dead tissues until the blood oozes out. If we remove it manually, it will cause pain and produce harmful chemicals that cause damage to the normal tissues surrounding the wound (Molan and Rhodes, 2015; Oryan et al., 2016; Yilmaz and Aygin, 2020). When honey is applied over the wound, it promotes the removal of dead tissue due to its moist nature. Increase in the osmotic pressure takes out the lymphatic fluid from deeper tissues which causes the removal of dead and infected tissue (Krishnakumar et al., 2020; Yilmaz and Aygin, 2020).

Honey for Immune System

Honey plays its role in the lymphocytes activation and also involve in neutrophill phagocytosis (Molan, 2011; Barui et al., 2013). It promotes the secretion of cytokines, tumor necrosis factor and interleukins which activate the immune system (Abuharfeil et al., 1999; Tonks et al., 2001; Tonks et al., 2003). Honey also produces antibodies against antigens that depend upon thymus and against those antigens that are thymus independent (Tonks et al., 2007).

Effect of Acidity on Wound Healing

The chronic wounds have a basic pH. The wound healing can be promoted by lowering the pH of affected site. The glucose contents of

honey and acidic pH reduce the pH of wound and promote the activity of macrophages. But some infectious agents show resistance toward acidic pH. Hence, low pH of honey is not only the reaon for its healing role (Castanie-Cornet and Foster, 2001; Zaika, 2001; Gock et al., 2003). Other components of honey like amino acids, sugars and vitamins also involve in cell growth and repair of damaged tissues (Eteraf-oskouei and Najafi, 2013; Stewart et al., 2014; Angioi et al., 2021; Azmi et al., 2021).

Topical Application of Honey

Use of Medical Grade Honey

The medical-grade honey can be used safely for wounds, as it is treated with gamma rays to remove any clostridial spores and is free from any contaminating organisms (Combarros-Fuertes et al., 2020). The medical-grade honeys are formed under hygienic measures. The unique Manuka Factor UMF in Leptospermum derived Manuka honeys is best for killing bacterias (Scepankova et al, 2017). The medical-grade honey can be used directly over the affected area and then covered with bandage. In wounds, where the amount of exudate is more, consistency of honey becomes less viscous, thus its application over the wound becomes difficult. In such cases, honey takes more time for wound healing (Krishnakumar et al., 2020; Rossi and Marrazzo, 2021).

The US Food and Drug Administration FDA has approved many honey based products like gels and ointments (Hossain et al., 2021). These gels and ointments have been used in ulcerative wounds of diabetic patients (Nair et al., 2020). For application, we apply a thin layer of honey based gel or ointment over the affected area and cover with dressing, but it causes pain upon removal (Rezvani et al., 2019). Therefore, we focus on the development of other useful products which act as secondary absorbent (Datta et al., 2018; Rajput et al., 2020; Schuhladen et al., 2020).

Advanced Wound Care Products

In the past years, bandages and other dressings were used to cover the wound and provide protection against infectious agents. But, with the passage of time, new methods have been introduced for wound dressing (Negut et al., 2020). Advanced honey products keep the wound moist and help in fast healing (Öhnstedt et al., 2019). The control of infectious agent, ability to degrade with new tissue formation, no toxic effect on cells and compatibility are the properties of modern dressings. Honey plays a major role in the tissue-engineering template because it can eradicate infection, help decrease inflammation and improves the integration of tissue (Martinotti and Ranzato, 2018).

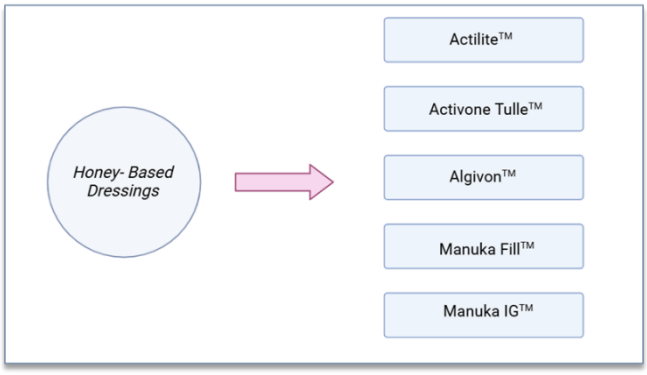

Fig. 2: Honey Based Dressings (drawn by using biorender)

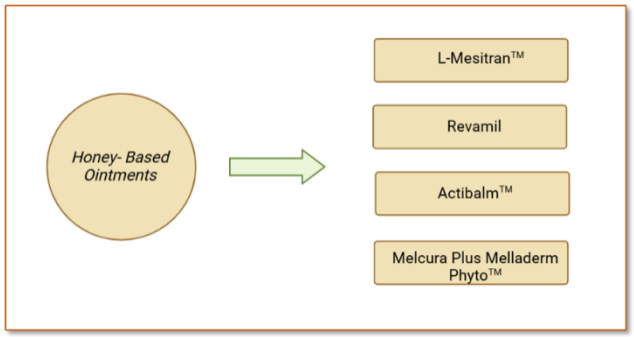

Fig. 3: Honey based ointments (drawn by using biorender)

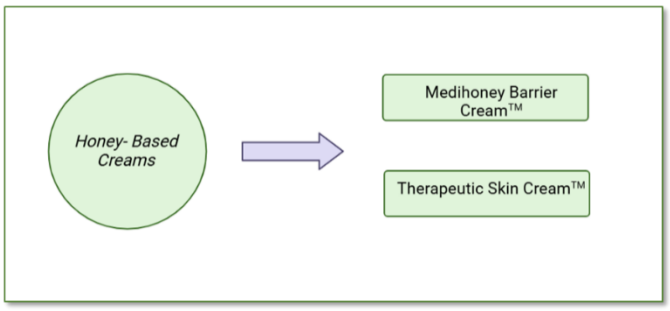

Fig. 4: Honey Based Creams (drawn by using biorender)

Honey based Hydrogels

The hydrogels contain high content of water and is made up of chitosan polymer and it can distribute wide range of medicinal agents at affected site (Croitoru et al., 2020). Honey in the hydrogels increase its capacity of water absorption and also facilitate scaffold against infectious agents (El-Kased et al., 2017). As hydrogels are transparent, we can observe wounds and burns without removing the dressing (Afshari et al., 2015). Different studies showed that hydrogels treated burn wounds heal in 12 days with intact outer layer but local oinments delay the wound healing and have 15% unclosed epidermal layer (Wang et al., 2012). The hydrogels also provide covering to biomolecules and involves in the migration and proliferation of cells (Li and Mooney, 2016; da Silva et al., 2019; Palmese et al., 2019).

Dressings

Honey based dressings include actilite, activone tulle, algivon, manuka fill, manka IG (Figure 2).

Ointments

Honey based ointments include L-mesitran, revamil, actibalm, melcura plus melladerm phyto (Figure 3).

Creams

Honey based creams include medihoney barrier cream and therapeutic skin cream (Figure 4).

Conclusion

Honey is very beneficial product for wound healing because of the presence of sugars, water, proteins, amino acids, vitamins, polyphenols and other useful components that keeps the wound moist. There are many other drugs for healing but all those products take more time to heal complicated wounds and also show resistance by their continuous use. Due to acidic nature of honey, it neutralize toxins produced by bacterias. Honey can heal burn wounds and ulcers efficiently than other local products, as ulcer is non-healing wound but if we continuously use honey-based products over it, ulcer wound starts to heal. We should study more about it and discover new products to promote its use in treating surgical complexities. If we use honey rather than repeating same drugs again and again, we will also overcome the issue of antibiotic resistance.

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