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Effectiveness of Topical Honey Application on Wound Healing: Literature Review Study

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Abstract

The purpose of this study was to determine the wound healing process which has several phases. Another alternative for wound healing is to use honey which is known to have many bioactive components that have been proven effective and fast in the wound healing process. The method of writing literature is a literature review using several databases such as Pubmed, Google Scholar, Medline, Ebsco, Hindawi, Science Direct and Cochrane which were published in the last 10 years. The wound healing process has several phases, namely the hemostasis, inflammation, proliferation and remodeling phases. Each phase has its own healing time duration. Honey is a natural product formed from flower nectar and has been used by humans since ancient times around almost 5500 years ago. Honey has various benefits in the health sector. One of the benefits of honey is that it can prevent wound infections and accelerate the wound healing process. One study conducted by Yupanqui et al. stated that honey has natural antimicrobial properties and is a physical barrier at the wound site. Honey can be a topical therapeutic drug that is studied clinically for wound healing that contains antioxidants, antibacterials, antifungals, antivirals and other clinical benefits.

Introduction

Wounds are a disruption in the normal structure and function of the epidermis which is the first line of defense and protection against trauma. When the structure of the skin is disrupted, a wound healing process is needed to restore the skin to its original condition (Tashkandi, 2021). The wound healing process is needed to restore the integrity of damaged tissue and regenerate lost epithelium. This process is a dynamic and complex process consisting of four steps, namely hemostasis, inflammation, tissue proliferation and regeneration which are mutually continuous to restore the integrity of the skin to its original state (Scepankova et al., 2021). The duration of wound healing itself depends on age. The duration of wound healing in the elderly takes longer because it is influenced by the inflammatory response, the amount of collagen and the remodeling process itself (Hadi Nugroho et al., 2022). There are many methods for healing wounds, one of which is using antibiotics. The use of antibiotics aims to reduce the risk of infection, but currently many antibiotics are ineffective because of the increasing resistance rate. Another alternative for wound healing is to use honey (Tashkandi, 2021). Honey has been used by dermatologists as a traditional step in wound healing (Scepankova et al., 2021). Honey is known to have many bioactive components that have been proven effective and fast in the wound healing process. Honey, which consists of enzymes, water, sucrose, glucose, fructose,

amino acids, beeswax, pollen, pigments, minerals and glucose oxidase which converts sucrose into simple glucose, fructose and produces gluconic acid, each plays a role in the wound healing process (Yilmaz & Aygin, 2020). In addition, the acidic pH of honey (3.2 - 4.5) makes it difficult for microorganisms to proliferate, thereby accelerating wound healing (Maruhashi, 2020).

Research conducted by Yilmaz et al. found that honey has been shown to provide rapid epithelialization and wound contraction in the wound healing effect. Honey also has anti-inflammatory effects, debridement, reduces pain, ensures infection control, shortens wound healing time in acute and chronic wounds (Yilmaz & Aygin, 2020). However, the role of honey as a way to heal wounds still needs to be studied further, therefore this study was conducted to study more deeply the effectiveness of honey in healing wounds.

Methods

The method of writing literature is literature review. Literature search on the effectiveness of topical honey administration on wound healing was conducted using the keywords topical honey, honey and wound healing using several databases such as Pubmed, Google Scholar, Medline, Ebsco, Hindawi, Science Direct and Cochrane published in the last 10 years. After the appropriate literature was found, the writing of the literature manuscript began.

Result and Discussion

Wounds and Wound Healing Process

A wound is a physical injury that occurs due to damage to the inner and outer skin which results in skin rupture (Ayavoo et al., 2021). Fast and proper wound healing is needed for the re-formation of functional tissue after injury. Wound healing is an important physiological process consisting of the collaboration of many cell strains and their products. This complex phenomenon involves interactions between cells and cell matrices that drive the wound healing process. This process is described in several phases, namely the hemostasis, inflammation, proliferation and remodeling phases (Ayavoo et al., 2021; Gonzalez et al., 2016).

Hemostasis Phase

Hemostasis is the first phase of wound healing that will begin the process of stopping bleeding after blood vessel damage where this process takes place around the first minutes to hours after injury (Ellis et al., 2018; Rodrigues et al., 2019). There are three processes in this phase, namely: vasoconstriction, primary hemostasis and secondary hemostasis. Platelets are cells that play a role in this phase, in addition an important matrix component is fibrinogen. Platelets in uninjured skin do not stick to blood vessel walls or clump together. Fibrinogen (factor 1) is produced by hepatocytes and circulates in the blood where it is also present in platelets but is not broken down into fibrin fibers, which are an important component of blood clots (Rodrigues et al., 2019).

When the skin is injured, the immediate response to stop bleeding is vasoconstriction of the blood vessel wall, followed by primary hemostasis and secondary hemostasis which occur through two concurrent and mechanically interrelated pathways. Primary hemostasis involves platelet aggregation and platelet plug formation caused by exposure of collagen in the subendothelial matrix. Secondary hemostasis refers to the activation of the coagulation cascade in which soluble fibrinogen is converted to insoluble strands that form a fibrin meshwork. The platelet plug and fibrin meshwork combine to form a thrombus, which stops bleeding, releases complement and growth factors, and infiltrates cells necessary for wound healing (Ellis et al., 2018; Rodrigues et al., 2019).

Inflammatory Phase

The inflammatory phase occurs during the first 48-72 hours after tissue injury. This phase is principally represented by a series of complex molecular signals that ultimately facilitate the infiltration of neutrophils and monocytes into the wound bed to prevent unnecessary tissue damage and eliminate pathogenic organisms and foreign debris (Ayavoo et al., 2021; Ellis et al., 2018). The main goal of this stage of wound healing is to prevent infection. Neutrophils are the first cells to infiltrate the wound within one hour of injury and migrate in sustained numbers for the first 48 hours. This process is mediated through various chemical signaling mechanisms, including the complement cascade, activation of interleukins and transforming growth factor beta (TGF-b), which cause neutrophils to move down a chemical gradient. This process is called chemotaxis. Neutrophils have several main mechanisms to destroy debris and bacteria. First, neutrophils can destroy foreign particles, a process called phagocytosis. Second, neutrophils can degranulate and release various toxic substances (lactoferrin, proteases, neutrophil elastase and cathepsin) that will destroy bacteria. Neutrophils can act as chromatin and protease 'traps' that capture and kill bacteria in the extracellular space. When neutrophils have completed their task, they undergo apoptosis (Harper et al., 2014). The inflammatory phase of wound healing will last as long as necessary, ensuring that all excess bacteria and debris from the wound are cleared, but prolonged inflammation can cause extensive tissue damage (Harper et al., 2014).

Proliferation Phase

After the inflammatory phase, proliferation becomes the next discussion with a focus on the closure of the wound surface called re-epithelialization, restoration of blood vessel tissue and formation of granulation tissue. Re-epithelialization occurs requiring proliferation of keratinocyte cells which lasts about 2-3 days after injury (Landén et al., 2016). The purpose of the proliferation phase is to reduce the area of affected tissue through contraction and fibroplasia and form an epithelial barrier activating keratinocytes. This phase is responsible for the closure of the lesion itself, which includes angiogenesis, fibroplasia and re-epithelialization. These processes begin in the lesion microenvironment within the first 48 hours and can develop up to day 14 after the onset of the lesion (Gonzalez et al., 2016).

The process of forming new blood vessels is known as angiogenesis which is an important process, because nutrients and oxygen are needed during wound repair. This process is initiated by growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF). Proteolytic enzymes are secreted which aim to dissolve the basal lamina then endothelial cells exit the blood vessels to proliferate and migrate towards the source of angiogenic stimuli that form the lumen of the blood vessels, differentiate into arteries and venules and mature through the recruitment of pericytes and smooth muscle cells (Landén et al., 2016).

Remodeling Phase

The last stage in the wound healing process is remodeling, when fibroblasts rearrange the collagen matrix for wound closure. the remodeling process continues for several months and in this phase scar tissue is created. Chemokines play an important role in regulating angiogenesis and the recruitment of inflammatory cells that release cytokines and growth factors to accelerate wound healing. An imbalance in the chemokine environment can interfere with the wound healing process causing wounds to heal slowly or excessive scar formation. Slow healing wounds can occur in diseases such as diabetes, where there is excessive inflammation that can prevent the wound from progressing to the proliferative stage and lead to the development of chronic wounds that do not heal. Excessive scarring, such as hypertrophic scars, occurs when there is excessive collagen production in the wound. In this case, the scar is often thick, raised, and may be red. Given the importance of chemokines in the

wound healing process, there is therapeutic potential to target chemokines as a treatment for faster healing by reducing scar formation (Ridiandries et al., 2018).

Topical Honey Therapy

Honey is a natural product formed from flower nectar by honey bees and has been used by humans since ancient times, almost 5500 years ago. Ancient peoples, such as the Greeks, Chinese, Egyptians, Romans, Mayans and Babylonians consumed honey both for nutritional purposes and for its medicinal properties (Samarghandian et al., 2017). Honey is a topical therapeutic drug that has been studied clinically for wound healing. honey contains antioxidants, antibacterials, antifungals, antivirals and other clinical benefits (Firmanda et al., 2024; Ranneh et al., 2021).

Honey contains hyperosmolar acid sugar produced from plant nectar by honey bees consisting of enzymes including water, sucrose, glucose, fructose, amino acids, pigments, minerals, glucose oxidase which will convert sucrose into simple glucose and fructose and produce gluconic acid. The components contained in honey can improve the wound environment and accelerate wound healing (Yilmaz & Aygin, 2020).

There are two different types of honey, depending on the species of flower pollinated by bees. They can be distinguished by their primary antimicrobial action: 'peroxide' and 'non-peroxide'. The activity of the first type, the 'peroxide' honey group, is related to glucose oxidase, which is an enzyme secreted by bees in the presence of water, converting the glucose in honey into gluconic acid and hydrogen peroxide (H2O2). The bactericidal effect, even at the low concentrations produced in honey, is thought to be one of its main antimicrobial mechanisms. Peroxide production is higher when honey has a lower sugar concentration due to the higher activity of the enzyme glucose oxidase in the presence of water. When honey is applied to a wound, water is drawn from the wound due to the high osmolarity of honey, which helps the release of hydrogen peroxide. The second type, the 'non-peroxide' honey group, is related to the antimicrobial molecule methylglyoxal (MGO). Manuka honey is the best known non-peroxide-based honey. Manuka tree (Leptospermum scoparium) flower nectar contains high amounts of dihydroxyacetone and so does its honey derivative. Dihydroxyacetone is converted non-enzymatically through the Maillard reaction to MGO. The presence of MGO in honey is believed to inhibit the enzyme glucose peroxidase. Both types of honey contain additional molecules that provide direct antimicrobial effects, including polyphenolic compounds (phenolic acids, flavonoids and tannins) and antimicrobial peptides such as bee defensin-1. Honey has a broad spectrum of antimicrobial activity, making it an ideal candidate for preventing and treating bacterial infections. Honey can also fight other pathogens such as fungi and viruses such as Candida albicans, Candida auris, herpes simplex virus, and varicella-zoster virus (de Groot et al., 2021; Pleeging et al., 2022).

Effectiveness of Topical Honey on Wound Healing

Honey has various health benefits. One of the benefits of honey is that it can prevent wound infections and accelerate the wound healing process. Research conducted by Yupanqui et al. states that honey has natural antimicrobial properties and is a physical barrier at the wound site (Yupanqui Mieles et al., 2022). This study is also supported by research by Martinotti et al. which states that the antimicrobial properties of honey come from the production of H2O2 where the H2O2 produced can provide bacteriostatic activity and DNA degradation in bacterial cells (Martinotti & Ranzato, 2018). In addition, the high sugar content in honey can increase local nutrition in damaged areas. Honey also has a low pH which can optimize the migration and organization of collagen carried out by fibroblasts (Martinotti & Ranzato, 2018; Yupanqui Mieles et al., 2022). Research conducted by Scepankova et al. stated the same thing, where various contents of honey have the potential to be used in the wound healing process, either by direct application or in hydrogel (Scepankova et al., 2021). Another advantage of using honey

according to Saikaly et al. is that there is no evidence of allergy to honey so it tends to be safe to use as a wound healing agent (Saikaly & Khachemoune, 2017). Honey has been widely studied for its benefits for various wound healing. Research conducted by Clark et al. stated that in cases of burns, honey was significantly preferred for complete healing time of superficial thickness wounds with an average reduction in healing time of 5 days compared to sulfadiazine (Clark & Adcock, 2018).

This study is in line with research conducted by Minden et al. where the healing rate of partial thickness burns increased in patients given topical honey compared to standard care and shortened the healing time by 4-5 days (Minden-Birkenmaier & Bowlin, 2018). Research conducted by Jull et al. (2015) also stated something similar where dressing with honey accelerates the healing of partial burns compared to conventional dressings (Jull et al., 2015). Research by Angioi et al. (2021) stated something similar where applying honey to burns was shown to increase the healing rate of skin regeneration and reduce scar tissue (Angioi et al., 2021). In addition to burns, the function of honey in treating post-operative infected wounds was also carried out by Clark et al. where the study stated that more patients recovered with topical honey treatment compared to antiseptic washing followed by gauze dressings. The study also stated that complications such as wound defects and re-stitching were less common in those treated with honey (Clark & Adcock, 2018). Research conducted by Jull et al. (2015) also stated something similar where topical honey heals post-operative infected wounds faster than antiseptics or saline solutions (Jull et al., 2015). These results are also supported by Hadi et al. where the study stated that wound healing with honey dressings was faster than normal saline and better at eradicating infection (Hadi Nugroho et al., 2022).

Honey can also be used as a better alternative for wound debridement compared to hydrogel (Peter & Tanya, 2015). Research conducted by Ayse et al. where the bioactive components contained in honey can reduce inflammation, edema, pain, have a debridement effect and accelerate granulation and epithelialization. The study also stated that honey provides better aesthetic results than other treatments in the wound healing process, shortens the duration of hospitalization in chronic wounds and provides cost efficiency (Yilmaz & Aygin, 2020). Another study conducted by Wang et al. stated that honey can also be given to patients with diabetic ulcers where honey effectively shortens wound cleaning time, wound healing time, bacterial clearance time, increases wound healing rate and bacterial clearance rate during the first one to two weeks of use (Wang et al., 2019). Research by Firmanda et al. and Clark et al. also stated something similar where both studies stated that honey has a clinical effect in healing acute and chronic wounds, including treating diabetic ulcers (Clark & Adcock, 2018; Firmanda et al., 2024).

Conclusion

The wound healing process is a dynamic and complex process consisting of hemostasis, inflammation, tissue proliferation and regeneration to restore skin integrity. Several things can be done to maximize the wound healing process, one of which is by using honey. Honey with its various contents has been proven to accelerate the wound process and prevent infection, so that in everyday clinical practice honey can be used.

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