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(REVIEW ARTICLE)

Natural honey and diabetic wound healing: A review of literature

Ofor Casimir Chijioke [1,*], Ramalan Mansur Aliyu [2], Ohanme Eugene Ohams [1], Anele Donatus Onyebuchi [3], Ajegi Innocent Fountain [4] and Nwakelu Benjamin Nwaforcha [5]

[1] *Department of Pharmacology and Therapeutics, Ebonyi State University, Abakaliki, Nigeria.*
[2] *Department of Pharmacology and Therapeutics, Bayero University, Kano, Nigeria.*
[3] *Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, Abia state University, Uturu, Abia state, Nigeria.*
[4] *Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, Nigeria.*
[5] *Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, College of Medicine, Alex Ekwueme Federal University, Ndufu Alike, Ebonyi State Nigeria.*

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Abstract

Honey has been used widely for the treatment of various types of chronic burns, necrotic diabetic foot and post-operative split skin wounds. Despite the fact that wounds in diabetic patients are similar to wounds in normal patients, the healing process is different from that of other wounds. The most worrisome aspect of diabetic wounds is that the healing process is unduly prolonged. Poor oxygenation of tissues occurs in diabetic wounds and is caused by early inflammatory responses and a heavy load of Reactive Oxygen Species (ROS) induced by high blood sugar levels in diabetic patients. The formation of advanced glycation end-products (AGEs) under severe hyperglycemic conditions and interaction with their receptors (RAGE) are also known to impair wound healing among diabetic patients. The antioxidant, anti-inflammatory and antibacterial effects of natural honey significantly promote the healing process in diabetic wounds. This is due to the presence of hydrogen peroxide (H_2O_2) produced by the action of glucose oxidase on glucose in the honey, nitric oxide and the hyperosmolar nature of natural honey. Honey also stimulates angiogenesis in the wound environment thereby enhancing wound healing in diabetics. The potent antioxidants in natural honey include, phenolics, flavonoids, ascorbic acid and certain enzymes such as catalase.

Glucose oxidase from the bee crop slowly breaks down glucose into gluconic acid, which lowers the pH of honey, and the presence of hydrogen peroxide helps to kill bacteria in diabetic wounds. In a wound site, the lower pH of honey (3.5–4) reduces protease activity, increases oxygen release from hemoglobin, and stimulates the activity of macrophages and fibroblasts, while the hydrogen peroxide content sterilizes the wound and stimulates vascular endothelial growth factor (VEGF) production.

Keywords: Honey; Antioxidant; Glucose; Wound; Diabetes

1. Introduction

Over the years, the management of diabetic wounds has continued to pose a huge therapeutic challenge due to some unfortunate peculiarities of the diabetic wounds occasioned by the cascade of metabolic changes in diabetes mellitus (1). The wound healing process remains a complex clinical problem and has been extensively investigated in order to develop an ideal method for enhanced wound stability while minimizing the formation of scar tissues and other major complications to ensure optimal functions of the affected individual (2). Honey is known to exert some therapeutic

* Corresponding author: Ofor Casimir Chijioke

impacts in the management of diabetic wounds. These include: antioxidant, antibacterial, anti-proliferative and anti-inflammatory effects (3, 4, 5, 6).

The use of honey traditionally for the treatment of wounds has been in practice for ages. Several findings from scholars of archeology from countries like Greece, Italy and Egypt have shown that natural honey has remained an effective treatment for wounds of various etiology (1, 7). The use of honey in the treatment of wounds suffered a temporary setback with the arrival of antibiotics into the global clinical stage (6). This shortfall was short-lived on account the emergence of resistance to many antibiotics in clinical use by many species of bacteria on account of antibiotic abuse and increasing population of mutant bacteria species.

Honey, over the years, has assumed a prominent position in the management of wounds of different types, including diabetic foot ulcers. Glucose oxidase from the bee crop slowly breaks down glucose into gluconic acid, which lowers the pH of honey, and the presence of hydrogen peroxide, help to kill bacteria (7). In a wound site, the lower pH of honey (3.5–4) reduces protease activity, increases oxygen release from hemoglobin, and stimulates the activity of macrophages and fibroblasts, while the hydrogen peroxide content sterilizes the wound and stimulates vascular endothelial growth factor (VEGF) production (7). Invertase, another enzyme contained in natural honey, slowly dissociate sucrose into glucose and fructose components, increasing the osmotic strength of the honey solution. In addition, the flavenoids derived from the floral nectar sources helps to neutralize free radicals created by the hydrogen peroxide (7, 8, 9). This review x-rayed the concepts in current researches on the overall effect of natural honey in the management of diabetic wounds.

2. The Physiological Process of Wound healing in Diabetic Patients

Normal wound healing involves a series of processes and events. These events include, coagulation, inflammation, cell proliferation, tissue remodeling, and replacement of damaged tissue (6). Hamdam et al (Hamdam et al., 2017(2) however in their study, reported four stages in the process of wound healing:

- Coagulation and haemostasis;
- Inflammation;
- Proliferation; and
- Wound remodeling.

The different stages occur at particular periods of time. The initial coagulation can occur over several minutes, the last stage which is the stage of tissue remodeling may proceed for a period of several months to one year depending on the prevailing circumstances in the wound environment (10, 11).

Honey has been used widely for the treatment of various types of chronic burns, necrotic diabetic foot and post-operative split skin wounds (12, 13, 14). Despite the fact that wounds in diabetic patients are similar to wounds in normal patients, the healing process is grossly different from that of other wounds. The most worrisome aspect of diabetic wounds is that the healing process is unduly prolonged probably due to compromised immunity. Poor oxygenation of tissues also occurs in diabetic wounds. This is caused by early inflammatory response by the system and a heavy load of Reactive Oxygen Species (ROS) induced by prolonged high blood sugar levels in diabetic patients (15, 16).

The formation of advanced glycation end-products (AGEs) under hyperglycemic conditions and interaction with their receptors (RAGE) are also known to impair wound healing among diabetic patients (17). The roles of several poorly regulated cellular functions such as defective T-cell immunity, defects in leukocyte chemotaxis, phagocytosis, bactericidal capacity, fibroblasts and epidermal cells dysfunctions are all implicated in diabetic wounds. The occurrence of these dysfunctional cellular functions can be blamed on inadequate bacterial clearance and delayed or impaired repair of wound in people with diabetes (18).

Angiogenesis primarily occurs in the proliferative phase of wound healing. The development of new blood vessels from pre-existing helps to furnish the required oxygen to the wound. This is an important stage in the wound healing process. This dynamic process is strongly regulated by signals from serum and the surrounding extracellular matrix environment (19). Natural honey has been shown to stimulate angiogenesis in diabetic wounds. This was demonstrated in an in vitro study with analogues of angiogenesis and an endothelial proliferation assay (20).

A more recent in vivo model study by Chaudhary et al., 2019 (21) reported the same findings in their experiment. This evidence-based position as reported in current researches underscores the importance of natural honey in the process of diabetic wound healing. Integration of natural honey into the therapy for diabetic wounds should be explored more extensively as this will help to improve the quality of life of patients with diabetes mellitus.

3. Mechanisms of honey-induced wound healing

The findings from some animal studies and of several randomized clinical trials have provided compelling evidence that honey can accelerate the wound healing process (7, 22). These studies showed that application of honey including medical grade honey has been associated with reduced scar formation and enhanced epithelialization. Application of natural honey in diabetic wounds has also been found to improve wound contraction, angiogenesis and minimized inflammation and oxidative stress (23, 24, 25). A number of factors such as being a natural product, affordability, safety and result-oriented in treatment of all categories of wounds make the use of honey an attractive and viable option in wound treatment of diabetic patients.

Honey may significantly facilitate wound healing in diabetes mellitus patients through several mechanisms. These include:

3.1. Antioxidant effect of honey on wound healing

Hydroxyl radicals and hypochlorite anions are formed from superoxide anions produced from bio-activated polymorph nuclear neutrophils (PMNs) at the wound site and they are considered to be important in impaired wound healing. The superoxide anion may also react with the nitric oxide that is produced by macrophages to form peroxynitrite, a third strong oxidant that damages the surrounding tissues (10, 26). Among the potent anti-oxidants found in natural honey are, phenolics, flavonoids, ascorbic acids and certain enzymes such as catalase (27, 28, 29).

These antioxidants found in honey enhance wound healing through two processes: first, the antioxidants fight against microorganisms and decrease infections at the site of the wound (30, 31). Second, the anti-oxidants reduce inflammation caused by the wound and aid the healing process (31, 32).

3.2. Antibacterial and anti -inflammatory activities of natural honey

The broad spectrum antimicrobial activity of honey has been reported in various studies. Honey has been demonstrated to exert both bacteriostatic and bactericidal activities in many studies (8, 32).

The properties of natural honey that contribute to its antimicrobial activity against diabetic wound are as follows:

3.2.1. Anti-inflammatory activity of natural honey

Inflammation is the response of a living tissue to a local injury and plays a fundamental role as a defense and protection mechanism to avoid infections and to repair the affected tissue. The inflammatory phase is a necessary part of wound healing; however, when this response is not adequate, an overproduction of inflammatory mediators by immune cells, which do not respond to initial triggers, might be produced, becoming a problem for wound resolution (33). The anti-inflammatory activity of honey is a consequence of different mechanisms. During the inflammatory phase, the affected tissues release a high concentration of free radicals. The antioxidant compounds in honey act synergistically and can reduce the damage caused by these radicals, and therefore prevent tissue necrosis (34).

In addition, in vitro and in vivo studies have demonstrated that honey reduces the activity of cyclooxygenases 1 and 2 (COX1 and COX2) that intervene in the synthesis of prostaglandins (35, 36). Prostaglandins participate in the inflammatory response by producing vasodilation, increasing the permeability of blood vessels and allowing the passage of leukocytes, acting as an antiplatelet agent, and stimulating the nerve endings of pain. The reduction in prostaglandin concentration in plasma may induce a diminution of inflammation, edema, and pain (37). Inflammation is the response of a living tissue to a local injury and plays a fundamental role as a defense and protection mechanism to avoid infections and to repair the affected tissue. The inflammatory phase is a necessary part of wound healing; however, when this response is not adequate, an overproduction of inflammatory mediators by immune cells, which do not respond to initial triggers, might be produced, becoming a problem for wound resolution (33, 38).. The anti-inflammatory activity of honey is a consequence of different mechanisms. During the inflammatory phase, the affected tissues release a high concentration of free radicals. The antioxidant compounds in honey act synergistically and can reduce the damage caused by these radicals, and therefore prevent tissue necrosis (34).

Moreover, honey can inhibit the expression of tumor necrosis factor (TNF-α) and reduce the concentration of pro-inflammatory cytokines through the attenuation of nuclear factor kappa B (NF-κB). Moreover, honey can inhibit the expression of tumor necrosis factor (TNF-α) and reduce the concentration of pro-inflammatory cytokines through the attenuation of nuclear factor kappa B (NF-κB) (35). Furthermore, NF-κB is involved in the activation of the inducible Nitric oxide synthase enzyme (iNO). During inflammation, iNO is induced by cytokines, TNF-α, interleukins, and bacterial endotoxins, producing nitric oxide. Nitric oxide is a free radical that acts as a mediator in acute and chronic inflammation and favors the healing process of tissues. However, an excess of NO or an overproduction at the wrong time can be detrimental and contribute to the development of pathologies related to inflammation (37, 38).

Another advantage of the anti-inflammatory action of honey is the decrease in edema, thus reducing the pressure on the microvasculature of wound tissue that allows the availability of oxygen and nutrients required for growth of tissue and wound repair (38). This effect also allows the control of the wounds' exudate with an appropriate moisture balance, which is still a concern in wound healing process (38,39). Naturally honey, therefore helps in the modulation of inflammation in diabetic wounds, thereby promoting healing of the wounds.

3.2.2. The acidity of honey

Several findings suggest that the acidity of honey is one of the factors that contribute to its antimicrobial activity. Application of honey on wounds creates an acidic pH in the medium and aids the killing of bacteria by macrophages (8). The acidity of honey creates an environment that facilitates the release of oxygen from the hemoglobin that is required for newly growing cells and the stimulation of white blood cells (17). Also, acidifying a wound through honey application can potentially reduce the protease activity and provide a suitable environment for increasing fibroblast activity thereby promoting wound healing (39, 40).

3.2.3. Osmotic effect of honey

Honey is a hyperosmolar substance and therefore, creates an unfavourable and harsh environment for the growth and survival of microorganisms especially in wounds (8, 9). The high osmolar levels of substrates such as honey, glucose and sugar pastes can inhibit microbial growth because water molecules are bonded chemically to the sugar molecules. This invariably creates a non-conducive environment for the survival and thriving of the organisms. Ultimately, this will lead to the death of the microorganism concerned (22). Therefore, the hyperosmolar condition created by honey is important for treating infections because it prevents the growth of bacteria and encourages rapid wound healing (8). Hyperosmolar substances naturally draw fluid into the wound area to make a viscous solution, thus providing a protective layer against infection from adjourning environment (9).

3.3. Effect of hydrogen peroxide (H_2O_2) in honey on wound healing

Hydrogen peroxide that is found in honey is continuously produced by oxidation of glucose by the enzyme, glucose oxidase. This enzyme is secreted into nectar from the hypopharyngeal glands of bees. Hydrogen peroxide is a documented potent antibacterial agent (41). Glucose oxidase is inactive in concentrated honey solutions (because of the low pH) but upon honey dilution, it is activated and produces H_2O_2 (42, 42). The H_2O_2 produced by honey is not cytotoxic because its H_2O_2 concentration is approximately 1000 times lower than that of the 3% solution commonly used as an antiseptic (42).

The low concentration of H_2O_2 may act as a "messenger" in healing promotion and may stimulate both fibroblast proliferation and angiogenesis (41, 42, 43). It is worthy of note that the high antioxidant levels in honey could confer protection of wound tissues from oxygen radicals that may be produced by H_2O_2 (24, 42).

3.4. Effect of nitric oxide (NO) in honey on wound healing

Nitric oxide plays an important role in the immunological and inflammatory responses, cell movement and killing mechanism of bacteria and viruses. It also supports different types of organ-related functions. Nitric oxide is very active in the proliferative stage during wound healing in patients, (Rahid et al., 2022). The end products of nitric oxide are present in honey, and the concentrations of these metabolites vary significantly according to the type of honey being used (44,45). The presence of nitric acid metabolites in honey as well as the increased production of NO products by honey in different body fluids improves wound healing and provides the antimicrobial and immune-regulatory actions of nitric oxide. In addition, increased NO production from honey could explain the various effects of honey on immunity, bacterial infections and wound healing (43, 44, 45).

4. Conclusion

Natural honey has been found to promote wound healing especially in diabetic patients owing to its broad spectrum antimicrobial activity that is enhanced by its osmotic effect, nitric oxide and hydrogen peroxide content and its acidity. The antioxidant activity of natural honey has also demonstrated a strong promise in the outcomes of wounds especially in diabetics. It is therefore, recommended that natural honey should be incorporated into the protocol for the treatment of wounds in hospitals and homes. The use of natural honey also have the advantage of being easily accessible and relatively cheap especially in poor resource countries of the world. Further studies should however be carried out to extensively compare the outcome of the use of natural honey as a mono-therapy with the outcome obtained from the use of conventional antibiotics in the treatment of diabetic wounds in hospitals.

Compliance with ethical standards

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Disclosure of conflict of interest

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Authorship

OCC conceptualized the study and participated in the literature search, RMA, OEO, ADO, AIF and NBN participated in the literature search and drafting different sections of the manuscript. All the authors reviewed and approved the final manuscript.

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