UP-TO-DATE USE OF HONEY FOR BURNS TREATMENT

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SUMMARY. Made by bees from the nectar of flowers, used since ancient times to treat wounds and burns, honey has lately acquired a growing interest from the international scientific community and has been the subject of many specialized studies and communications. This article highlights the up-to-date knowledge on qualities, properties and mode of appliance of honey in the treatment of wounds of various etiologies, particularly burns, through an extensive retrospective analysis of data from the literature. This article aims to review and provide a synthesis of current issues regarding the complex action of honey on burn wounds, evidenced by in vitro studies, laboratory experiments and clinical trials published in the specialized literature. The present work analyzes extensively the anti-infectious and anti-inflammatory properties of honey, as well as its favorable effect on wound regeneration. Effectiveness of topical administration of honey is evidenced both by a series of experiments on laboratory animals and by clinical trials. This article also draws the attention of both medical staff and patients to the possibility of using this product, and to its acceptability in practice.

Keywords: honey, burns, clinical studies, effectiveness, acceptability

Introduction

Honey is a viscous concentrated solution of sugars produced by bees (Apis mellifera) that collect and process the blossom nectar (flowers or floral honey) or sweet juices on certain plant species (honeydew or forest honey). Honey is one of the most complex and valuable natural biological products used since ancient times, both in nutrition and medicine (through internal and external means). Among other medical uses, honey has served in wound care since ancient times:1-4

- Sumerian civilization (fragments of pottery, 2100-2000 BC)
- Ancient Egyptian civilization (The Edwin Smith Papyrus, 2600-2200 BC)
- Ayurveda and Chinese medicine
- Ancient Greek civilization (Dioscorides’ “De Materia Medica”, for treating fistulising wounds; Hippocrates)
- Ancient Rome civilization (Pliny, for treating infected wounds)
- Mentions in the Bible and the Quran.

After having served an important role in the medical tradition of many peoples for millennia, honey was “rediscovered” by modern medicine as a topical agent for treating wounds and burns.4 Therapeutic properties of honey have been scientifically highlighted by numerous in vitro studies, laboratory experiments and clinical trials performed during the last century. However, the impression that the use of honey in wound treatment would not have scientific support5 still persists sometimes in the medical community.

Moreover, the current promotion of different types of modern dressings for wounds (for instance, nanocrystalline silver dressings) hides the fact that there is little published evidence to support the use of these products.5, 6 A recent systematic review of publications on the use of advanced dressings in the treatment of pressure ulcers revealed that their widespread use is not supported by good quality studies.5, 7 Thus, the vast amount of evidence that proves the efficiency of honey and supports its use in wound treatment, compared with the existing evidence for other wound care products, allows us to consider the use of honey as a viable option for wounds treatment.5

The ideal topical preparation for wounds should meet the following criteria:5, 9

- Bactericidal and fungicidal action, rapid set up and wide spectrum, even under the unfavorable situations of heavy exudation or wound infection;
- Enhancement and acceleration of the physiologic process of wound healing (granulation, epithelialization, contraction);
- No local or systemic adverse effects (allergy, toxicity etc.), even if applied for prolonged periods;

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• Moderate cost, even if applied twice a day;
• Patient comfort, ease of application, pain reduction; and
• Patient and healthcare compliance.

According to performed studies, the topical use of honey for wounds and burn care meets most of the above mentioned features.

Material and methods

A plethora of data is available in the literature regarding the use of honey for burn treatment, providing comprehensive analyses. These are accessible from databases, such as Medline, from journals, such as Burns and the Annals of Burns and Fire Disasters, from search engines and from specialized books. No restrictions were applied regarding the source or date of publication, with the most representative and reliable studies being selected. The complex activity of honey in burns lesions was evidenced by its properties and effects (anti-infectious, anti-inflammatory, antiexudative, antioxidant, wound healing, wound debriding and nutritional), as revealed from the studies undertaken. Effectiveness of topical administration of honey was highlighted both by a series of experiments on laboratory animals, and by clinical trials. Risks, application procedures and acceptability of honey in practice were also investigated.

Results and discussions

The anti-infectious property of honey, a traditional remedy for the treatment of infected wounds, was confirmed through laboratory research. Honey has proven to have a broad-spectrum anti-infectious action against at least 80 species of micro-organisms including Gram positive and Gram negative bacteria, aerobes and anaerobes, some fungal species of Aspergillus and Penicillium and all the common dermatophytes, including types of bacteria multi-resistant to antibiotics, such as Pseudomonas, Acinetobacter, methicillin-resistant (MRSA) and coagulase-negative Staphylococcus aureus, with a minimum inhibitory concentration (MIC) generally below 10%, usually inferior to that present in wounds where the honey was applied. The increasing interest in the use of honey in infected wounds is strengthened by the widespread development of bacterial resistance to antibiotics, as well as evidence that honey is fully effective against such antibiotic-resistant bacteria. There was no loss of bacterial sensibility to honey over time and no appearance of bacteria resistant mutants. In many cases, honey acted where other antibacterial therapies failed, possibly because honey is effectively including aggregated bacteria in biofilms; a situation where antibiotics and silver dressings proved ineffective.

The antibacterial property of honey was first recognized in 1892 by the Dutch scientist van Ketel. Many considered this property to be entirely due to the osmotic effect of high glucidic concentrations. Honey possesses a level of osmolarity which is able to inhibit microbial growth. But the antibacterial quality of honey is also due to other factors. Honey contains an agent that was called “inhibine” before its identification as hydrogen peroxide. This is a well-known antimicrobial agent that is produced by the enzyme glucose oxidase in honey, secreted by the hypopharyngeal glands of bees. Under the action of glucose oxidase, glucose oxidation makes gluconolactone and hydrogen peroxide.

Hydrogen peroxide produced by honey may also accelerate the healing process observed when honey is applied to wounds. Hydrogen peroxide has been involved in many cell types in the human body as a stimulus for cell proliferation, for the growth of fibroblasts and epithelial cells to repair damage, for the development of new capillaries in damaged tissue, as part of the normal inflammatory response to injury or infection. Low concentrations of hydrogen peroxide have been proposed to stimulate wound healing, instead of recombinant growth factors, but only if the concentration of hydrogen peroxide could be carefully controlled in order to avoid tissue damage by production of oxygen radicals at high concentrations.

The production rate of hydrogen peroxide by glucose oxidase largely depends on the degree of honey dilution, and it is minimal in concentrated honey. The fact that the antibacterial properties of honey are amplified when it is diluted has been clearly observed and reported since 1919. The maximum accumulated hydrogen peroxide concentration of hydrogen peroxide (1-2 mmol/L) is found in diluted honey solutions at concentrations between 30% and 50% (v/v), at least 50% of the maximum level at concentrations between 15-67% (v/v). Variation of glucose oxidase activity by diluting honey can be explained by enzyme inactivation due to the low pH of concentrated honey and the availability of free water required to activate the enzyme in honey (water in concentrated honey is almost entirely bound by carbohydrates). This variation suggests that honey enhances its antimicrobial activity when applied to the wound, as it dilutes and neutralizes the exudate at this level. The amount of hydrogen peroxide found inside the wound depends on the balance between its production rate (honey glucose oxidase) and the rate of destruction (plasma enzymes such as catalase and glutathione peroxidase).

Additional non-peroxide antibacterial factors were identified in some honeys treated with catalase to remove the hydrogen peroxide activity, for example methylglyoxal in Manuka honey from New Zealand, bee-defensin-1 and melanoidins. Honey is produced from various floral sources and its antibacterial potency varies wide-
ly (up to 100 times) depending on its origin and processing. Therefore, it was proposed that honey should be selected for clinical use according to the antibacterial activity levels determined by bacteriological tests. However, in clinical trials of honey of floral origin and antibacterial potency there was found to be no correlation in the difference in effectiveness of treating burns. It was noted that applying honey causes a reduction in inflammation and scar contractures, and that the antioxidant effect of honey in neutralizing free radicals, together with antibacterial action, low pH, high viscosity and hygroscopic effect, all contribute to the efficiency of honey in burns treatment. The anti-inflammatory activity of honey on the wound reflects more than just intrinsic antibacterial properties. Laboratory studies have shown that, at concentrations of only 0.1%, honey activates phagocytes and stimulates proliferation of peripheral blood B lymphocytes and T lymphocytes in cell cultures. Honey (at a concentration of 1%) also stimulates monocytes in cell culture to release cytokines: tumor necrosis factor alpha (TNFα) and interleukin (IL: IL1 and IL6), which activates immune response to infection and initiates tissue repair processes. It has also been shown that honey stimulates the production of antibodies in mice in response to antigens of Escherichia coli. These findings suggest that part of the effectiveness of honey in eliminating and preventing infection in the wound may be due to the strengthening of the body’s own immune system, as well as the antibacterial activity of honey. In addition, the glucose content in honey and acidic pH (usually pH between 3 and 4) can support the macrophages to destroy the bacteria.

As well as the antibiotic activity of honey, a number of studies have shown its anti-inflammatory, anti-edematous and anti-exudative activities. This is evidenced by assessment of local wound evolution, biochemical tests of indicators of inflammation (decreased malondialdehyde and lipid peroxide values) and histopathology exams (decrease of inflammatory cells). Possible mechanisms of inflammatory activity are: inhibition of complement, inhibition of nitric oxide production by macrophages, inactivation and suppression of reactive oxygen species (ROS) by phagocytes, decrease of thermal injury-induced oxidative stress by controlling free radicals that are formed in the burn wound and an anti-inflammatory factor identified as apalbumina-1, a protein secreted by bees. The anti-inflammatory effect and suppression of ROS, which overstimulate fibroblasts, lead to a reduction of fibrosis and hypertrophic scarring. In contrast, synthetic anti-inflammatory drugs do not promote wound healing (non-steroidal anti-inflammatory substances are cytotoxic drugs, and corticosteroids inhibit the growth of epithelium).

In some experimentally induced burns, there was no obvious infection, but honey continued to cause a decrease in inflammation. This shows that the anti-inflammatory activity of honey is a direct action and not a side effect of eliminating infection by antibacterial activity. The direct anti-inflammatory activity of honey is also highlighted by the finding that honey is as effective as prednisolone in a trial on induced colitis in rats, and a statistically significant (p <0.001) reduction of postoperative peritoneal adhesions on the cecum and ileum in another trial on rats. Also, a laboratory experiment demonstrated the direct anti-inflammatory activity of honey, by a significant (p<0.001) reduction of ROS released from monocytes in culture that had been stimulated with Escherichia coli lipopolysaccharide.

Studies have also revealed an intrinsic antioxidant activity of honey, by controlling free radicals and ROS. The ROS act as messengers that amplify the inflammatory response and this process can be blocked by antioxidant substances present in honey at a high level. Also, ROS produced by phagocytes in inflamed tissues activate proteases that are normally inactive and their activated forms digest extracellular matrix and cell growth factors that are essential for tissue repair.

Besides its own anti-infectious, anti-inflammatory and antioxidant actions, honey creates a physical barrier and moist local environment, due to its high viscosity and to the drawing of fluids by osmosis. This promotes healing of burn wounds because wounds heal faster when kept moist as opposed to when they are left to dry out and form a scab. A moist environment allows the growth of epithelial cells, the contraction of fibroblasts to approach the wound edges, as well as non-adherence of dressings to the wound, leading to easy and painless dressing changes, without the risk of breaking newly formed epithelium. Also, a local environment allows the protein-digesting enzymes in the wound tissues to work and loosen any scab and dead tissue.

Honey is further known to have a wound debriding action, as found in clinical trials. Honey activates plasminogen and increases plasmin enzyme activity, which lyses fibrin attaching slough, by suppression of the macrophage plasminogen activation inhibitor. Plasmin digests fibrin, which attaches debris on wound surface, but does not digest collagen extracellular matrix, which is necessary for tissue repair.

Honey also has a nutritional action in the wound, directly through osmotic flow of lymph, which brings nutrients needed for healing, but also directly through an intake of easily metabolized carbohydrates, amino acids, vitamins and minerals. Studies have shown that wounds heal faster if they are supplied with a mixture of nutrients. Honey provides glucose support for epithelial cells, leukocytes and for the process of glycolysis. The epithelial cells require a reserve of carbohydrates for energy migration over the wound surface to restore epithelium.
Leukocytes create the respiratory (oxidative) burst that produces hydrogen peroxide, which is the dominant component of macrophages antibacterial activity. Finally, glycolysis is the major mechanism of energy production by macrophages, allowing them to function in damaged tissues and exudates where oxygen is often limited. In addition, the high osmolality of honey causes interstitial fluid drainage, thus providing nutritional support for tissue regeneration which can otherwise only occur around points of angiogenesis (seen as granulation). Inducing the osmotic flow will also contribute to lifting and removing waste and debris from the wound, which may even eliminate the need for surgical debridement. It also contributes to the lack of adherence of the dressing to the wound. A fluid layer of honey is in contact with the surface of the wound and it may be slightly raised to allow removal of any residue by rinsing. Thus, dressing changes are painless with no risk of damage or tearing of newly formed tissue.

The acidity of honey (usually pH less than 4) may contribute to the antibacterial action of macrophages, since an acidic pH inside the vacuole is involved in destroying the ingested bacteria. Also, local acidification promotes healing of the wound by preventing the appearance of the non-ionized histotoxic form of ammonia, resulting from the action of urease (from urease-producing microorganisms) on urea in the extracellular fluid. In an acidic medium, ammonia (NH₃) is converted to ionized, nontoxic, ammonium ion (NH₄⁺). In addition, the acidification of the wound increases oxygen intake and pH₂O₂ on wound surface by increasing oxyhemoglobin-hemoglobin dissociation, due to an appropriate shift in the oxyhemoglobin-hemoglobin dissociation curve (Bohr effect) and thus improves the rate of healing. High carbohydrate levels conferred by honey can be used by bacteria in preference to amino acids in the serum and dead cells, thus creating lactic acid instead of ammonia, various amines and sulfur compounds, that are the cause of malodor in burns.

Honey also increases the rate of healing by stimulating leukocytes to release cytokines and growth factors that activate tissue repair and by stimulating the keratinocytes transcription of genes for TNF-α, IL-1β and TGF-β.

Evidence from experiments on laboratory animals

Experimentation on animals has enabled analysis of the action of honey in standard wounds produced by dermal burns (intermediate or full thickness) or by skin excision (excision models). These experiments with standard wounds allowed better comparison of results and histopathological examinations of wounds, as well as the usual measurements of decreasing wound size (their contraction) and the healing time. Also, animal experiments with honey allow objectivity of results by eliminating the placebo effect, which would occur in clinical trials.

Experimental research on animals has shown the effectiveness of topical administration of honey in wound healing compared to the control, to sugar or to silver sulphadiazine. In addition, they suggested the importance of using only floral honeys, properly processed and the synergistic effect of concomitant oral administration of honey in promoting wound epithelialization.

Evidence from clinical studies

Many controlled clinical trials have been performed, some being randomized, which compared honey with different products (silver sulphadiazine, Betadine, saline compresses, paraffin dressings, hydrogel etc.) for treatment of wounds of various etiologies, including burns of various depths. An article published in December 2011 recorded 33 randomized controlled trials (RCTs), with a total number of 3,556 participants. A meta-analysis of Cochrane systematic reviews of local and systemic interventions for wounds, published in 2012, found robust evidence for the use of topical honey to reduce healing times in burns.

Various trials reported that honey is effective in cleaning infected wounds. Honey acted as a barrier, preventing wounds from becoming infected and cross infection. Gangrenous and necrotic tissues were debrided easily and were replaced quickly with granulation tissue and advancing, progressive epithelialization.

Studies highlighted fast cleansing and enzymatic or chemical debridement of wounds after application of honey, with the absence of eschar forming on burns. Honey was also found to deodorize very smelly wounds. Several studies have shown that honey caused the formation of clean and healthy granulation tissue, which allowed early grafting on a clean, adequate bed, with prompt graft taking. It has also been reported that honey promotes wounds epithelialization and accelerates healing, with minimal scar formation. Honey was further observed to improve wound nutrition, blood circulation, and lymph flow, and to reduce inflammation, edema and exudate.

Honey has been reported to be calming and soothing when applied to wounds and to reduce pain from burns. Other studies showed that honey either did not cause any local pain on dressing or caused only a momentary stinging sensation. It was also shown not to cause irritation, or allergic reactions, and to have no harmful effects on tissues. Honey dressings were observed to be easily applied and removed, without adhesions or bleeding, with any residual honey being easily removed by simply rinsing. However, a prospective clinical trial showed that deep dermal burns heal more slowly with honey than with early surgery (tangential excision and grafting). Other uses for honey included skin...
Honey is then spread on the wound before being covered with a dry sterile gauze dressing. The amount of honey used varied from a thin layer (applied 2-3 times per day) to a thick layer or, more often, pouring the honey over the wound. Additionally, honey can be used on large areas by applying it 2-3 times per day, without affecting its antibacterial activity.

As described in most clinical trials, the following points provide the generalities of the procedure for applying honey:

- First the wound is cleansed with saline (possibly also hydrogen peroxide, Dakin solution, Betadine or chlorhexidine). Sometimes it is necessary to make an initial surgical toilet, by opening abscesses, purulent drainage collection and necrotic tissue removal.
- Honey is then spread on the wound before being covered with a dry sterile gauze. The amount of honey used varied from a thin layer (applied 2-3 times per day) to a thick layer or, more often, pouring the honey over the wound. Others used bandages soaked in honey or honey spread on gauze or “honey pads”. Alginate dressings impregnated with honey are a good alternative to cotton/cellulose dressings, as the alginate converts into a honey-containing soft gel.

Wound cavities were either filled with honey-impregnated dressings or filled directly with honey and then covered with gauze.

- Dressing changes, mostly daily, varied from 2-3 times per day to once every 2-3 days, depending also on the appearance and evolution of the wounds (clean wounds with reduced exudate require less frequent dressing changes).
- Liquid honey can be used on large areas (be it naturally fluid or made so through vigorous stirring or by heating below 40°C). Crystallized honey can easily be made fluid through careful heating. Overheating of honey should be avoided, since the enzyme glucose oxidase in honey that produces hydrogen peroxide, a major component of honey’s antibacterial activity, is easily inactivated by heat.

All of the aforementioned experiments, research and innovations, as well as clinical utilization, highlight the increasing interest and confidence in honey as an effective remedy for wound care. Honey, “the oldest wound dressing material known to medicine,” was used systematically for wound treatment, as well as for its benefits as a food and form of medication. In the early 1940s, however, when antibiotics came onto the scene, honey was no longer used to the same degree in wound therapy. Just as with colloidal silver, honey is now being reconsidered for wound healing due to the rising problem of bacteria with multiple resistance to antibiotics. Unlike with antibiotics, studies have shown no development of bacterial resistance and no emergence of mutants resistant to honey, whose remarkable therapeutic properties are recommended in wound care, as well as modern pharmaceuticals.

Studies have also shown high patient acceptability to honey therapy due to the favorable effects observed in practice: decreased pain, reduced wound size, and deodorizing effects. Any reservations or even opposition to the use of honey in wound treatment, due to lack of standardization and to its sticky and fluid nature, are now overcome by the manufacture and marketing of honey-based products. Such products have been licensed and approved for topical treatment of wounds (available in Australia since 1999, in Europe since 2004 and in North America since 2007). There are currently several trademarks (Activen, HoneySoft, Manuka Health, MediHoney, MelMax, MelDra, L-Mesitran etc.) and a wide range of sterilized products containing honey, registered as medical devices and commercially available for the treatment of wounds.

Conclusions

In vitro and in vivo studies have highlighted a broad range of activities provided by honey in burn treatment. These include anti-infectious, anti-inflammatory, anti-ex-
udative, antioxidant, wound healing, wound debriding and nutritional properties. In evidence-based medicine, research and clinical studies have shown the efficiency of honey in superficial and partial thickness burns therapy, when compared to other dressing products, making it a viable option as a valuable topical agent in clinical practice. However, as honey also appears to delay healing of partial and full thickness burns when compared to surgical treatment (early excision and grafting), its use requires further exploration. More detailed controlled trials are required to establish the best indications, methods and modalities of honey administration for each type and stage of burn. It is also necessary to have criteria for honey selection over other forms of treatment in burn management, which, of course, will also depend on the preferences and experience of those involved.

RÉSUMÉ. Fabriqué par les abeilles à partir du nectar des fleurs, utilisées depuis l’Antiquité pour traiter les plaies et les brûlures, le miel a récemment acquis un intérêt croissant de la communauté scientifique internationale et a fait l’objet de nombreuses études spécialisées. Cet article met en évidence les connaissances les plus récentes sur les qualités, les propriétés et le mode d’action du miel dans le traitement des plaies d’âge diverses, en particulier de brûlures, à travers une analyse rétrospective approfondie des données de la littérature. Cet article vise à examen les enjeux actuels de l’action complexe du miel sur les plaies de brûlures, comme en témoigne les études in vitro, des expériences en laboratoire et des essais cliniques publiés dans la littérature spécialisée. Cet article présente une analyse approfondie des propriétés anti-infectieuses et anti-inflammatoires du miel, ainsi que son effet favorable sur la régénération de la peau. L’efficacité de l’administration topique de miel est mise en évidence à la fois par une série d’expériences sur des animaux de laboratoire et par des essais cliniques. Cet article attire également l’attention du personnel médical et des patients sur la possibilité d’utiliser ce produit et de son acceptabilité dans la pratique.

Mots-clés: miel, brûlures, études cliniques, efficacité, acceptabilité

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