

REVIEWS

Current Aspects and Perspectives Regarding the Usage of Honey in Different Wounds Treatment (Review)

Octavia TAMAS-KRUMPE^{1*}, Otilia BOBIȘ², Cornelia DOȘTEȚAN ABĂLARU³, Adrian CIOTLĂUȘ⁴ and Laurenț OGNEAN¹

¹*Department of Physiology, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Romania*

²*Life Science Institute, Apiculture and Sericulture Department, University of Agricultural Sciences and Veterinary Medicine, Cluj-Napoca, Romania*

³*Manager of S.C. Apilife Ro SRL, Romania*

^{3,4}*Member of the Romanian Society of Apitherapy*

**corresponding author: negreaoctavia89@yahoo.com*

Bulletin UASVM Veterinary Medicine 75(2)/2018

Print ISSN 1843-5270; Electronic ISSN 1843-5378

doi:10.15835/buasvmcn-vm: 2018.0017

Abstract:

Throughout time, honey proved to meet all the criteria for its usage as a topical treatment in wounds, due to its antibacterial, anti-inflammatory and antioxidant properties. A major importance was attributed to the compounds found in honey, such as glucose oxidase, methylglyoxal, low pH and hydrogen peroxide.

The aim of this review is to provide an updated scientific support regarding the current state and the perspectives on honey application in the veterinary medical therapeutics. We sustain the utility of this documentation because of the contradiction between the abundance of research in the human medicine field and their sporadic character in the medical veterinary one.

We assess that honey should not be simply considered as a 'folk remedy', but as a modern therapy. Moreover, this review intends to inform the veterinary clinicians about the therapeutic potential of honey, exerted especially on wounds healing and regenerative therapy.

Keywords: honey, wounds, therapy, medical field.

Introduction

Honey is a valuable natural product, rich in carbohydrates and biological active substances. Since ancient times, honey, the main product of the hive, has been particularly appreciated from a nutritional and therapeutic point of view. Made from the nectar of the working bees, honey is rich in sugars (76%), with less than 20% water, which makes honey a supersaturated solution, with a viscous appearance (Sato and Miyata, 2000). The carbohydrates present in honey are represented mostly by monosaccharides (fructose, glucose)

and in very small quantities, by disaccharides (sucrose, maltose, isomaltose, nigerose, turanose and maltulose) (De Melo *et al.*, 2018).

In the complex structure of honey, there are also other components, such as proteins (frequently enzymes), organic acids, vitamins (pyridoxine, thiamine, niacin, riboflavin, pantothenic acid), minerals (calcium, copper, manganese, phosphorus, potassium, sodium and zinc), pigments, volatile compounds, flavonoids, polyphenols, solid particles (Da Silva *et al.*, 2016).

Due to this very complex biochemical composition, various biostimulating and therapeutic effects were attributed to honey, being considered a promising product in medicine. Although honey has specific therapeutic indications in humans (Molan, 1999), in the veterinary clinics, it is still not yet sufficiently tested. The major therapeutic actions of honey focus mainly on its antioxidant, antimicrobial, anti-inflammatory effects, in animals, being tested in the healing process of several types of wounds.

Honey and wound care in history

Honey has been used as a traditional remedy in wound healing and tissue regeneration by different cultures, throughout time. The earliest document which showed evidence of the honey usage in wound care was found in Egypt, in the Smith papyrus dating between 2600 and 2200 BC. According to it, the Egyptians used to apply on wounds, a mixture consisting of honey and grease (Majno, 1975).

The Greeks have also used honey in the wound treatment for ages (Grossman, 1986). Hippocrates, for instance, promoted honey as being a considerable part in several ointments (Adams, 1939) and he also sustained that honey could be used to lower fever and reduce pain (Guthrie, 1958).

In ancient Rome, it was believed that honey could treat abscesses in the mouth, while a mixture of honey and fish fat could treat wounds (Cavallo, 2008). Furthermore, a dressing made from honey and different plants was also recommended for treating burns in the London Medical Papyrus, written around 1325 BC (Trevisanato, 2006).

Other references come from religious texts such as the Bible and Quran, in which honey is described as being "a drink of varying colors, wherein is healing for mankind" (Yusuf, 1987). The use of honey was also embraced by other civilizations, including Buddhists, Jews, Hindus and Chinese (Crane, 1975).

Nowadays, the abundance of drugs and particularly, the misuse of the antibiotics on a large scale, responsible for the outbreak of the antibiotic resistance have allowed honey to regain its place in the medical field. Therefore, in the past few years, more and more clinicians have reconsidered the treatment schedule for the wounds care and they have begun focusing on the usage of honey

in different types of injuries, such as acute and chronic wounds, ulcers (Samarghandian, 2017).

Anti-inflammatory effect of honey

A wound is being defined as the destruction (accidental, violent or surgical) of a tissue's integrity, with damage inflicted also on the adjacent areas (Martinotti and Ranzato, 2014). On the other hand, a plethora of studies pointed out that honey has an anti-inflammatory effect, which is crucial for the wound healing process (Al-Waili *et al.*, 2011). In addition to this, clinicians have observed that honey reduces both edema and exudate, minimizes the risk of scars appearance and has a soothing effect, when applied to inflamed wounds. It also reduces the pain caused by pressure on nerve endings and the existing amount of prostaglandin in the inflammatory process (Wijesinghe *et al.*, 2009). Prostaglandins and nitric oxide are major players in the process of inflammation. Honey is known to increase nitric oxide end products and decrease the prostaglandin levels. Furthermore, investigations have confirmed that nitric oxide is expected to promote wound angiogenesis by inducing the expression of vascular endothelial growth factor (Simon *et al.*, 2009).

Other investigations revealed that Manuka honey contains a novel glycoside, called leptosin, which inhibits myeloperoxidase, an enzyme that is believed to be responsible for the inflammatory processes (Kato *et al.*, 2012).

In areas of excessive inflammation, high levels of protease activity take place, which can either slow or stop the wound healing progress, by destroying growth factors, the protein fibers and fibronectin in wounds, which are necessary for the activation of fibroblasts and migration of epithelial cells. In this regard, honey's low pH has proven to inhibit protease activity (Tonks *et al.*, 2007).

It is worth mentioning that honey, thanks to its osmotic properties, resulting from the high level of simple sugars (80%) possesses the amazing ability to debride necrotic tissue, which serves as a basic source for bacterial infection and related inflammation. Moreover, it prevents the dressing sticking to the wound and protects the granulating edges, and hence, it stimulates cell division (mitosis) (Molan, 2009).

The anti-inflammatory effect of honey may be explained by several mechanisms of action, such as: inhibition of the classical complement pathway;

inhibition of Reactive oxygen species (ROS) formation; inhibition of leukocyte infiltration; inhibition of Cyclooxygenase (COX-2) and inducible Nitric oxide (NO) synthases expression. Recent studies revealed that honey inhibits the matrix metalloproteinase 9 (MMP-9), a protease which is responsible for the degradation of matrix and cell growth-promoting agents in chronic wound fluids (Majtan *et al.*, 2013).

Antioxidant activity of honey

Due to its oxidative potential oxygen is a harmful factor through its active forms: superoxide anion radical, the peroxide anion, hydrogen peroxide, as well as free radicals such as the hydroxyl radical, the alkoxy radical and the peroxide radical. All these active forms of oxygen are generically called reactive oxygen species (ROS) (Andrei *et al.*, 2014). Antioxidants counteract deterioration caused by ROS. The components present in honey, which provide an antioxidant effect consist of flavonoids (chrysin, pinocembrin, pinobanksin, quercetin, kaempferol, luteolin, galangin, agigenin, hesperetin, myricetin), phenolic acids (caffeic, coumaric, ferrulic, ellagic, chlorogenic), ascorbic acid, catalase, peroxidase, carotenoids, and products of the Maillard reaction (Bertoncelj *et al.*, 2007). Of all those listed above, it appears that the phenolic acids and flavonoids are responsible for the well-established antioxidant activity of honey (Nagai *et al.*, 2001).

Moreover, it was also reported that the botanical origin of honey has a major influence on its antioxidant activity, while processing, handling and storage affect honey's antioxidant effect only to a minor degree (Beretta *et al.*, 2005). Besides this, a strong correlation was found between the antioxidant activity and the color of honey. Many researchers confirmed that honeys with dark color have a higher total phenolic content and consequently, a higher antioxidant capacity. For instance, Tualang honey, honeydew honey and buckwheat honey possess strong antioxidant activity due to their color intensity and phenolic compounds (Rodriguez *et al.*, 2015).

Antimicrobial properties of honey

Nowadays, the resistance to antibiotics has become an inevitable consequence of their intensive use in clinics, and for this reason, an alternative strategy was urgently needed. This

imperious demand has led to a re-evaluation of the therapeutic use of honey. Another important aspect refers to wounds, especially chronic wounds, which represent a worldwide concern, because of the microbial complications, including local infection, delayed healing and rapid spread of multi-resistant pathogens (Israili, 2014).

The antimicrobial activity in most honeys is typically due to two main mechanisms. The first one refers to the inhibition of the microbial growth by hydrogen peroxide (H_2O_2), which is produced by enzymatic activity, while the second one is associated with the inhibition of the microbial growth through non-peroxide activities. These non-peroxide activities rely especially on the activity of phenols and organic acids (Irish *et al.*, 2011).

The pronounced antibacterial activity of honeys is considered to happen mainly due to hydrogen peroxide production. The H_2O_2 found in honeys exerts bacteriostatic and DNA-degrading activities on the bacterial cells (Brudzynski *et al.*, 2011).

The non-peroxide antimicrobial activity of honey is frequently associated with a floral source (Allen *et al.*, 1991); in addition to this, a special attention deserves Manuka honey, which is produced by the flowers of *Leptospermum scoparium*, a New Zealand plant. The intense antibacterial activity of Manuka honey comes from methylglyoxal (MGO), a compound which is present in large amounts in Manuka nectar and derives from dihydroxyacetone (Adams *et al.*, 2009).

Several studies demonstrated that no resistant bacteria (*Escherichia coli*, MRSA, *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*) have been isolated after the exposure of wounds to Manuka honey (Alvarez-Suarez *et al.*, 2014). Moreover, MGO and hydrogen peroxide have been reported to be even more potent in combination with other substances found in honey, such as ascorbic acid (Molan, 1999).

Other powerful antibacterial compounds present in honey are bee defensin-1 and lysozyme. The bee defensin-1 is a peptide, which was first found in honey by Kwakman *et al.* (2010) and since then, it has been regarded as one of the most powerful agents in natural honey. Lysozyme was detected in honey products, usually occurring at a level of 5–10 mg/mL and occasionally, found at a

level of 35–100 mg/mL, if the honey was freshly extracted from the comb. In older samples, the amount of lysozyme was decreased (Molan, 1992).

Honey's mild acidic environment (pH 3.5) also retards bacterial growth. For instance, standard bacteria *Escherichia coli* and *Staphylococcus aureus* had their growth delayed by 70% when exposed to acidic environment of pH 3.5. Their preferred growth was at pH 6.0-7.0 (Tan *et al.*, 2010).

Thanks to its antimicrobial activity, honey can promote the healing process even in wounds which do not respond to conventional therapy, including wounds infected with MRSA (methicillin-resistant *Staphylococcus aureus*) or multi-drug resistant *Pseudomonas aeruginosa* (Yao *et al.*, 2011).

Clinical impact of honey as a topical treatment

In the last few years, the use of honey in the prophylactic and therapeutic management of wounds and other skin injuries has captured the attention of many researchers and practitioners in the human and veterinary medical clinics. Thus, many opinions have emerged, suggesting that honey, through its antibacterial, antioxidant and anti-inflammatory effects, is highly effective in the treatment of wounds, burns, skin ulcers (Medhi *et al.*, 2008).

According to the recorded evidence, honey can heal superficial wounds and burns even faster than conventional treatment (which included polyurethane film, paraffin gauze, soframycin-impregnated gauze) (Martinotti *et al.*, 2015). Honey, as topical treatment for infected postoperative wounds has proved to be more effective than antiseptics (Jull *et al.*, 2015). The results of comparative clinical research regarding the possible differences between the therapeutic effects of honey and the various medicinal products are not yet sufficiently convincing, which means that it is necessary to maintain and continue investigations in this field.

In acute and chronic mixed wounds, the healing effect of honey is difficult to assess because of their complex, often polyfactorial etiology (Munstedt and Lang, 1997). However, there are studies which show that honey has provided better results in the treatment of acute and chronic heterogeneous wounds than sugar or silver sulphadiazine (SSD) dressings (Mphande *et al.*, 2007).

Most of the investigations regarding the effects of honey on chronic wounds come from the humans' medical field. Even so, they are of moderate or low quality, because of the size of the trials, which were small and because of the comparative products, which are not relevant to the current practice anymore (Mandal and Mandal, 2011). An important study was performed by Mayer *et al.* (2014), which revealed that honeydew honey had improved chronic venous leg ulcers within six weeks in 25 patients.

In the medical veterinary field, the majority of the investigations were experimental studies, using honey under raw form. In this context, an experimental research proved that using Japanese honey (Acacia, Buckwheat and Chinese milk vetch honey) on full-thickness wounds in mice had reduced the size of the wound area in the inflammatory phase (Nakajima *et al.*, 2013). The healing effects of honey on experimental wounds were also registered on albino Wistar rats. The wounds were represented by circular skin incisions on the back regions (Oguz *et al.*, 2018). Another recent study showed that the healing of traumatic wounds in ten cats by second intention with the use of honey was more cost/benefit effective than closing wounds by advanced surgery. The wound healing process resulted in a very good cosmetic appearance, without any complications (Lukanc *et al.*, 2018).

Nowadays, honey is used for the treatment of various wounds more frequently in humans than in veterinary medical field, even though there are recorded data proving the efficacy of honey in both fields. An interesting aspect is that Manuka honey is the one type of honeys that is considered the current 'standard' in wound care, due to its antibacterial action, existing a variety of standardized and marketed products also in the medical veterinary field (Creasy, 2016).

According to the data presented, it appears that the main therapeutic effects of honey are manifested by its antibacterial, anti-inflammatory and antioxidant effects, which have underpinned many studies in the world over the last years.

Conclusions

Despite the plethora of studies and clinical observations regarding the use of honey in wounds' healing, nowadays there are only few products

containing honey, which are standardized and marketed in the medical veterinary field.

Considering both the history and the therapeutic outlook of honey, we strongly support the idea that honey deserves more attention from veterinary clinicians than just their passing curiosity, as well as the evaluation of its bacteriostatic or bactericidal action. We also believe that the present review summarizes the bibliographic data which are extremely useful to veterinary clinicians in order to support the use of honey in therapeutic regenerative formulas for different types of wounds in animals.

To conclude, honey, regardless of its type, should not be simply considered as a 'folk remedy' passed down from the centuries, but as a modern therapy, being an inexpensive and easily available product, with a large proven efficacy in wounds therapy.

Declaration of interests: The authors report no conflict of interest.

Acknowledgments. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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