

HONEY, MORE THAN JUST FOOD: THE POSSIBILITY OF APPLICATION IN REGENERATIVE MEDICINE

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Honey has long been recognized as a special natural product, not only because of its nutritional value, but also because of its healing properties. Although it is mostly composed of carbohydrates, it also contains numerous enzymes, amino acids, organic acids, polyphenols, minerals, vitamins and other substances, whose presence varies depending on the type of honey and its botanical and geographical origin. Thanks to its antimicrobial properties, as well as its beneficial effect on wound healing, tissue repair and regeneration, honey could have a potential role in the fields of tissue engineering and regenerative medicine.

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Introduction

Honey is produced by honey bees (genus *Apis*) through processing nectar and honeydew (1) using enzymes of their hypopharyngeal glands (2). Nectar honey can be monofloral (from the nectar of one plant type) or polyfloral (obtained from various nectar types). Honeydew honey is obtained by processing plants secretions or excretions of plant-sucking insects. Strictly speaking, pure monofloral honey cannot be obtained, because many other honey plants bloom at the same time as the main plant. Monofloral honey is considered to be one that is obtained mainly from a certain plant and has a characteristic composition and properties (3, 4).

Since ancient times, honey has been in human use, primarily as a food. With the development of human civilization, the possibilities of using this natural product expanded, so it began to be used, for example, as a medicine and preservative (5). Such use is based on its antioxidant, antibacterial,

antifungal, antiviral, immunomodulatory, wound healing and many other properties (6, 7), for which there is growing evidence in the scientific literature.

Injury of any tissue is followed by repair. Tissue repair means that tissue architecture and function are restored after injury through regeneration and replacement processes. Regeneration completely restores damaged tissue to its normal form. Repair of severe tissue injuries or those which are not prone to regeneration ends by filling the injury site with connective tissue and is accompanied by scarring. It is replacement process. Most tissue repair involves both of these processes. Along with tissue repair, it is important to prevent wound infection, which can prolong the healing process and also lead to additional damage not only to injured parts of tissue, but also to healthy surrounding tissue (8). Honey antimicrobial and pro-healing activity, as well as the possibility of preventing scars, makes it a good candidate for use in regenerative medicine (9).

Chemical composition of honey - the main features

Honey has complex chemical composition and contains a large number of biologically active substances. Richness of honey content is due to its plant origin, but also to the components that bees add to nectar. In honey are found different carbohydrates, enzymes, amino acids, organic acids, polyphenols, minerals, vitamins and many other substances.

The most common compounds in honey are carbohydrates, over 90% of its dry weight, and they

are mostly in the form of monosaccharides fructose and glucose. Less common are disaccharides and trisaccharides such as: sucrose, isomaltose, panose, maltotriose, melezitose, erlose, isomaltotriose, isopanose, maltopentaose and others (10, 11). The high content of carbohydrates in honey is considered to be the main reason for its high osmolarity (12).

Right after carbohydrates, water is the next most represented honey component ranging from 17 to 20% (11).

Proteins are also constituents of honey, but are present in much smaller quantities, such about 0.5%. They are mainly in the form of enzymes (such as α -amylase, β -amylase, glucose oxidase, invertase, catalase) and amino acids, whose most common representative is proline, which makes up to 85% of the total amino acid content. Proteins originate from pollen (primary source) and secretions of bee glands (13-15). Bee antimicrobial peptide, defensin-1, is also honey constituent (16, 17). Likewise, another antimicrobial bee-derived peptide named hymenoptaecin can be also found in some honey types (17).

Polyphenols are products of secondary plant metabolism. They can be classified into two groups: flavonoids and non-flavonoids (phenolic acids) (15). The content of these compounds varies among different honeys, so their qualitative content can be used to determine the floral origin of honey (18). Their presence is associated with the honey anti-oxidant and antimicrobial properties (19).

The main organic acid in honey is gluconic acid. Citric acid, acetic acid, formic acid and many others are represented as well. Organic acids originate from nectar, or are formed from sugars by the action of bee enzymes during honey production (20). Presence of organic acids, primarily gluconic acid, in honey is the main cause of its low pH.

Vitamins and minerals are present in small amounts. Among vitamins, those from B complex and C vitamin are the most common, while among minerals it is primarily potassium, but a whole range of other minerals is represented too. Minerals are also a very stable component of this natural product (14).

The wide range of substances contained in honey gives it special properties that increase its nutritional value, and at the same time are important for human health. The share of these substances in honey is generally not constant, and largely depends on the type of honey and its botanical and geographical origin. Likewise, some compounds contained in honey are subject to changes due to chemical reactions during long-term storage (14).

Antimicrobial effects of honey

Having in mind the richness and diversity of compounds found in honey, its antimicrobial properties cannot be attributed only to one of them, but to the whole constellation of molecules that give it special antimicrobial characteristics.

Foremost, the pH value of honey is in between 3.2 and 4.5, so it represents an acidic

environment unfavorable for growth of microorganisms. In addition, high osmolarity of honey, due to its high sugar content, is also one of the factors responsible for its antimicrobial properties (5, 21), given that osmotic stress leads to changes that are reflected in depolarization and increased permeability of bacterial cell membrane, as well as reduction in cell size (22). However, a study which compared different natural honeys with culinary processed commercial honey has shown that in the case of the latter there was no antibacterial effect, indicating that this effect is not only conditioned by the honey sugar content (23). In fact, the result of this comparison suggests that not only high osmolarity and low pH are participating in its antimicrobial effect, but that some other honey compounds have such function.

Hydrogen peroxide is considered to be one of the main honey's constituent that has antimicrobial properties. It arises from glucose as a product of reaction catalyzed with bee-derived enzyme, glucose oxidase (24). In the previously mentioned study, specifically, several different types of honey from various Danish floral sources were examined and their antibacterial activity was compared with culinary processed commercial honey and raw and medical grade Manuka honey (MH). Not only was it found that all honey types had an antibacterial effect, except the commercial one, but also that some of the examined honeys had an even stronger antibacterial effect than MH. Antibacterial action of tested honeys, especially those that had a stronger antibacterial effect, was attributed primarily to the content and activity of hydrogen peroxide (23). Natural role of hydrogen peroxide is in preventing the development of microbes in unripe honey, and after its maturation this role is taken over by a high concentration of sugars, while glucose oxidase is inactivated. This enzyme is reactivated upon honey dilution (25, 26). Thus, it is found that binding of enzyme to glucose is much easier in diluted honey, and production of hydrogen peroxide is more continuous, so honey antimicrobial effect is increased (27). The amount of hydrogen peroxide in different honeys varies, and this depends on the type of honey and its dilution (26, 28). Although there is, to some extent, a positive correlation between the degree of honey dilution and hydrogen peroxide concentration, hydrogen peroxide activity is highest at 30-50% honey dilution (26). In fact, the presence of free water molecules in honey is important for maintaining the native conformation and enzymatic activity of the glucose oxidase, as well as the activity of the enzyme catalase. Catalase is an enzyme of pollen origin that participates in destruction of hydrogen peroxide. So, the total amount of hydrogen peroxide in honey also depends on the relationship between actions of these two enzymes (29). There is also synergy between hydrogen peroxide and gluconic acid, which some authors underline as crucial for honey antibacterial activity. It has been shown that these two components lead to bacterial membrane depolarization and destruction of bacterial cell wall in dose-dependent manner (22).

Additionally, polyphenols as the constituents of honey are involved in its antimicrobial action as

well. These compounds can also contribute in hydrogen peroxide production, as was reported with honeydew honey (30). Polyphenols content varies between honey types. Forest honey (honeydew) is rich in polyphenols. It has more than ten times higher total phenolics and flavonoids contents than acacia honey, as it has been shown in an experiment in which forest honey, polyfloral and monofloral acacia honey from the Šumadija District (Central Serbia) were compared. This investigation has shown that all honey types have antibacterial activity against different bacterial strains, and this activity is most pronounced in forest honey. But forest honey has also shown antifungal activity against some fungal species such as *Trichoderma longibrachiatum*, *Trichoderma harzianum*, *Penicillium canescens* and *Penicillium cyclopium* (31). Phenolic fractions isolated from 33 Iranian honey samples have shown antimicrobial activity against four bacterial strains: *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecalis* and this property was attributed not only to honey's individual phenolic compounds but to their joint action (32).

Defensin-1 is a bee-derived antibacterial peptide, which has been found in royal jelly and honey (17, 28). The presence and amount of defensin-1 varies strongly and in some types of honey it is completely lacking (33). Mechanism of defensin-1 action is based on bacterial cell membrane permeabilization and then RNA, DNA and protein synthesis inhibition (34). Another antimicrobial peptide, hymenoptaecin, is variable honey component and it is assumed that its presence depends on the microbial pressures in honeybee colonies (17). This antimicrobial peptide forms pores in bacterial envelopes (35).

The antimicrobial activity of MH is based primarily on the methylglyoxal presence. Methylglyoxal is formed by conversion of dihydroxyacetone, highly present substance in nectar of manuka tree (*Leptospermum scoparium*) flowers, during honey storage (33). Investigation of the effects of different methylglyoxal dilutions on four bacterial strains (*Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*) has shown that methylglyoxal negatively affects bacterial fimbriae and flagella, damages bacterial cell membrane and causes changes in bacterial cell shape (36).

The application of honey in tissue repair and regeneration

The use of honey for medicinal purposes has been known since ancient times. Inter alia, many studies suggest that honey has a positive effect on wound healing, tissue repair and regeneration. Acacia honey was used in treatment of excision, incision, burn and dead-space wound models in Swiss Wistar rats of either sex (37). Honey was applied topically and, for that purpose, 5 or 10% concentration of honey was added to 2% w/w gel sodium alginate gel. The results of this study confirmed that honey treatment aids wound healing by increasing wound epithelization and wound contraction in the excision and burn wound model,

breaking strength of the wound in the incision wound model, as well as breaking strength, dry tissue weight, and hydroxyproline content in the dead-space wound model.

Application of honey to the wound site, can serve as a protective coating against infections, mimicking the action of antibiotics. Also, the high sugar content in honey is a good nutritional source for cells at the site of injury (9). Likewise, the high sugar content creates an osmotic pressure that triggers and draws lymph fluid from tissues at the site of application in wound treatment. This supports the process of removing debris and necrotic tissue, which is important at the beginning of tissue repair (16). Mphande and coworkers have investigated whether there was a difference between honey and sugar applied as dressing in wound management of 40 patients. Results of this investigation have shown that honey has greater antibacterial activity than sugar, and is more successful in promoting wound healing (38). Honey can reduce the pH at the wound site, while stimulating the activity of fibroblasts. The addition of acacia honey to culture media has encouraged migration and differentiation of cultured rabbit corneal fibroblasts. This effect was attributed to the high glucose content in honey, which served as an important source of energy for cells, subsequently to the hydrogen peroxide releasing and lowering the pH of the medium, which are also factors that can positively affect fibroblast proliferation (39).

Gradual release of hydrogen peroxide from honey applied to the site of injury can be initiated by its dilution with wound exudates. Thus honey, with its antimicrobial action, can prevent wound infection, and at the same time the concentration of hydrogen peroxide is such that it is not toxic to the tissue cells. Also, hydrogen peroxide within physiological range stimulates angiogenesis, a process which is considered as critical for tissue repair (26, 40). Namely, blood vessels' network development is an important part of any tissue repair process, since it allows nutrients, cytokines, growth factors, oxygen and many other molecules to reach damaged tissue (41-44). Martinotti and colleagues have identified hydrogen peroxide as main honey compound involved in regenerative process. Namely, using *in vitro* model of immortalized human keratinocyte cell line, they have demonstrated that extracellularly released hydrogen peroxide from honey enters cells through specific aquaporin channels. When found in cytoplasm, hydrogen peroxide facilitates extracellular Ca^{2+} influx by activating Ca^{2+} -permeable ion channels. An increase in intracellular Ca^{2+} levels facilitates wound healing, as Ca^{2+} is essential for activating various cellular-level processes involved in tissue regeneration (45). In order to activate hydrogen peroxide activity, researchers recommend diluting honey before using it as an antiseptic dressing on wounds to an extent appropriate to the presumed amount of fluid that will be released from the wound during treatment (26).

The activity of macrophages, cells whose role in tissue repair is already known, can also be modulated by honey constituents (46). Actually, tissue repair begins with an inflammatory reaction.

Inflammatory phase lasts up to two weeks, after which it needs to be silenced. Then, through anti-inflammatory mediators, synthesis of extracellular matrix and angiogenic process are promoted, which ultimately leads to tissue repair. Main actors of the inflammatory phase are macrophages which, depending on wound conditions, secrete a number of different molecules (47-49). Inflammatory process can be modulated under the influence of honey or its components, through inhibition or stimulation of the synthesis of various cytokines by macrophages and their monocyte precursors (46). Human monocytes exposed to MH *in vitro* were stimulated to produce pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), IL-6 and tumor necrosis factor- α (TNF- α) (50). Some authors attribute the stimulatory effect of honey on the inflammatory process to the presence of endotoxins as well (46). On the other hand, the anti-inflammatory effect of honey has also been described and it is attributed primarily to its flavonoid content. Thus, Candiracci and coworkers investigated the effect of a honey flavonoid extract on pro-inflammatory cytokine production by N13 microglia cells pretreated with lipopolysaccharide. Honey flavonoid extract has significantly reduced TNF- α and IL-1 β production (51). Given the both pro-inflammatory and anti-inflammatory effect, it can be altogether said that honey has immunomodulatory properties. Their mechanisms are very complex and conditioned by different honey components, which vary considerably by their presence and quantity, depending on the honey type. Further extensive research is needed in this field, but the assumption is that whether applied honey will have pro-inflammatory or anti-inflammatory effect depends on the wound environment (52).

Defensin-1, in addition to having antimicrobial properties, has also been shown to participate in wound healing process. This peptide in a culture of human keratinocytes promoted secretion of matrix metalloproteinase 9 (MMP-9), cell migration, as well as improved wound closure *in vivo* (53).

Since the use of honey in superficial wounds treatment has been shown as highly effective, the possibilities of its application in the repair of hard tissues are expanding. Here, the principle of honey action is essentially the same as that on soft tissues, and is largely a result of the action of its numerous components. Honey has been shown to be effective in treating small mandibular bone defects in rats (54). In this study, healing of mandibular defects, filled with sterile honey or untreated, was monitored. According to the presented results, defects' healing process in the experimental group was more significant than in the control group, indicating that honey may support bone healing. Often, in large bone defects' treatment, it is necessary to aid tissue repair with biomaterials, which are frequently on hydroxyapatite base (41-44, 47-49, 55-57). Combining hydroxyapatite with honey, in order to repair the rats' radius bone defects, turned out to be a better solution compared to the independent use of honey or hydroxyapatite (58). Another application in oral surgery was conducted within one small clinical trial, when honey was placed in the socket, immediately after surgical removal of impacted third

molars (59). In the honey-treated group, less pain, lower frequency of postoperative complications and less swelling was observed in comparison with the untreated group (control). The effects of honey on cartilage defects repair were also examined. In that purpose, MH, gellan gum (GG) and mesoporous silica-MS composite hydrogels were prepared (60). First, *in vitro* analysis has shown that these composites had significant changes in peak elastic and dynamic moduli during 45 days of *in vitro* incubation period with human mesenchymal stem cells. In addition, MS-composite hydrogels ensured good *in vitro* cytocompatibility and antibacterial activity in a co-culture model, so they were chosen for application in a subcutaneous implantation mice model. *In vivo*, there was no severe immune response, which means that GG-MH-MS composites represent a very promising tool for cartilage tissue engineering. Honey has the ability to modulate inflammatory cells activity which can actually increase its application as a scaffold additive in the cases of bone infection (61). For example, MH decreases inflammation and promotes collagen deposition and migration of fibroblast. Therefore, this type of honey can probably promote tissue-material integration/regeneration and accelerate healing of site that surrounds the wound (62-64). Cryogels are biomaterials that have favorable porosity, elasticity and ability to retain three-dimensional architecture, which makes them interesting for application in bone tissue engineering. To overcome the problem of bacterial infection, the application of honey for incorporation into cryogels has attracted a lot of attention recently (65). In the research conducted by Hixon and his team (61), different amounts of MH were incorporated into cryogel scaffolds made of either gelatin or silk fibroin. Likewise, MH properties were utilized in a sustained release fashion to help in the bone healing process, while cryogel structure was used as a tissue template. All types of cryogels were examined regarding the effects of MH on porosity, swelling potential, mechanical durability and cell compatibility. In order to mimic native bone, these scaffolds were mineralized. It was found that a 5% MH silk fibroin cryogel had the potential to inhibit bacterial growth while still maintaining adequate porosity, mechanical properties, and cell infiltration. These features are favorable for the application in bone tissue regeneration.

Conclusion

There are many characteristics of honey, which classify it as a natural product suitable for various medical purposes. In addition to the fact that its price is affordable and that it has an unlimited shelf life, honey has no side effects and is easy to apply to the site of interest. The antimicrobial and wound healing abilities of honey are based on the presence of numerous compounds that give it special characteristics. Application of honey to the site of injury creates a physical barrier between wound and its environment, prevents contamination, and accelerates healing process. Thanks to the antimicrobial properties of honey, its use provides the

possibility of reducing the utilization of antibiotics during wound healing treatment. In addition to the already proven positive effect on the healing of superficial wounds, its use in the healing of hard tissue defects is being investigated, after independent application or in combination with biomaterials. However, although for now the results of various researches are promising, there are not many scientific papers on the influence of honey in hard tissue repair, and more clinical studies are missing. Despite all mentioned positive effects of honey, some dilemmas remain. One of the issues is

the stability of its chemical components during prolonged storage. Likewise, not all mechanisms by which honey influences tissue repair and regeneration through its components have been fully investigated. Also, it is known that there are large differences in the representation of different compounds among honeys, which depend on their type, botanical and geographical origin. Therefore, in order to implement honey in the frameworks of regenerative medicine, it is necessary to standardize its individual components and their effective doses, especially in relation to different tissue types.

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MED, VIŠE OD HRANE: MOGUĆNOST PRIMENE U REGENERATIVNOJ MEDICINI

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Med je od davnina prepoznat kao dragoceni prirodni produkt, ne samo zbog svoje nutritivne vrednosti, već i zbog svojih lekovitih svojstava. Iako je u najvećoj meri sačinjen od ugljenih hidrata, on sadrži i brojne enzime, aminokiseline, organske kiseline, polifenole, minerale, vitamine i druge supstance, čija zastupljenost varira u zavisnosti od vrste meda i njegovog botaničkog i geografskog porekla. Zahvaljujući svojim antimikrobnim svojstvima, kao i blagotvornom efektu na zarastanje rana, reparaciju i regeneraciju tkiva, med može imati potencijalnu ulogu u oblastima tkivnog inženjerstva i regenerativne medicine.

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Ključne reči: med, zarastanje rana, reparacija tkiva, regeneracija tkiva, tkivno inženjerstvo

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