ORIGINAL ARTICLE

The Potential Use of Honey in Ophthalmology

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SUMMARY

Honey is considered to be a natural product with antibacterial and anti-inflammatory properties. Its successful application in the treatment of chronic wounds and burns has promoted its further clinical use in other clinical departments, including ophthalmology. One of the major advantages of honey is its multi-factorial antibacterial action and the fact that there is no risk of developing bacterial resistance to it.
In this work we discuss the current knowledge and new perspectives for honey therapy in treatment of eye diseases such as dry eye disease, age-related macular degeneration, cataracts and bullous keratopathy.

Key words: honey, eye diseases, natural product, treatment

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INTRODUCTION

Honey has been used as a sweetener since time immemorial, but the ancient Greeks and Egyptians also used it for healing wounds. It is precisely this use of honey in the process of healing primarily difficult to heal wounds that is becoming increasingly established in renowned clinics in developed countries (UK, USA and Australia). Upon the use of natural products in healthcare, great emphasis is placed especially on safety, and for this reason using of "medicinal honey" has begun. Some types of honey can be a reservoir of bacterial spores which could cause problems in the healing of wounds, especially in the case of deep wounds in anaerobic conditions. Certified medicinal honey eliminates potential bacteria spores, as well as their vegetative forms, with the aid of gamma radiation without a negative impact on the actual healing effect of the honey.
Honey has become the object of several clinical trials, which have attempted to demonstrate the effectiveness of honey in the treatment of chronic wounds, in which parameters such as length of the process of healing and reduction of infection were observed. The main result of all the clinical trials is reduction of the time of healing, eradication of the infection, reduction of the use of antibiotics and last but not least, reduction of the time of hospitalisation. Positive results from the application of honey to chronic wounds have meant that honey has begun to be used and tested also in other branches of medicine, i.e. everywhere where it is essential to eliminate infections, which have often been caused by multi-resistant bacteria. Ophthalmology has become one of the promising areas with the potential for topical application of honey. There are a few cases of evidence of the success of treatment using honey on certain eye disorders – dry eye syndrome, bullous keratopathy, and in the treatment of corneal turbidities in patients after overcoming herpetic keratitis. It has also been demonstrated that honey reduces reddening, swelling and the time required for the eradication of the bacterial infection in the case of conjunctivitis.
In the submitted work we focus on the use of honey in ophthalmology and clarify the potential mechanisms of the effect of honey in the treatment of eye disorders.

Honey as a prophylactic agent in ophthalmology

With the increasing number of invasive surgical procedures in ophthalmology, a clinical environment is being created in which micro-organisms have the possibility to infect the eye. For the purpose of preventing complications which may occur following a surgical procedure, in the majority of cases fluoroquinolones are used. These postoperatively prevent development of infections in the anterior segment of the eye. Primarily following cataract surgery, the most frequently described risk is the occurrence of endophthalmitis. A substantial amount of cases of postoperative endophthalmitis (48-70%) are caused by coagulase-negative staphylococcus.
Although a wide spectrum of antibiotics have effective antimicrobial activity and penetrate into the eye structures, the rapid development of fluoroquinolone resistance may preclude their use in regular practice. With regard to the long-term use of antibiotics, the occurring antibiotic resistance in eye inflammations is becoming a serious worldwide problem. Treatment of specific eye disorders, including dry eye syndrome, also requires application of immunosuppressive agents such as cyclosporine A or steroids.
It has been determined that patients with dry eye syndrome are more resistant to bacterial conjunctivitis treated by fluoroquinolones. The dominant aerobic microorganism isolated in patients treated for dry eye syndrome from the conjunctival sac is coagulase-negative Staphylococcus aureus. Similarly, Albietz and Lenton pointed to the fact that honey significantly reduced formation of the whole colony-forming units in the eyelids and conjunctivae in patients with dry eye syndrome after one and three months of therapy.
In our recent study, forest honey was used as a potential prophylactic

antimicrobial agent in 49 patients for whom a surgical procedure was planned – cataract surgery or vitrectomy. The comparative antibacterial potential against ofloxacin, a second generation fluroquinolone, was recorded in the eradication of ocular pathogens in the perioperative period. Honey in 25% (w/v) concentration substantially reduced the occurrence of Gram-positive bacteria, including coagulase-negative Staphylococcus aureus, as well as Gram-negative bacteria identified in the eye. No difference was recorded in prophylactic effectiveness between local application of 0.3% ofloxacin and 25% honey solutions in patients planned for a surgical procedure. Thus honey may offer effective protection against ocular pathogens resistant to antibiotics which could endanger the eye and consequently the visual acuity and quality of life of the patient.

In addition to the low pH value and the high proportion of the sugar content, antibacterial effect of honey consists especially in the presence of antibacterial honey-bee peptide (defensin-1) and the generation of hydrogen peroxide. This multifactorial effect of honey substantially reduces the possibility of the occurrence of bacteria resistant to honey, which enables its long-term use in clinical practice.

Honey and dry eye syndrome

Dry eye syndrome is a multifactorial disorder, resulting in symptoms such as discomfort, feeling of foreign body in the eye, instability of lachrymal film with potential damage to the surface of the eye, accompanied with increased osmolarity of the lachrymal film and inflammation. Dry eye syndrome is a very common disorder, which affects 5-30% of the population. With emphasis on the pathogenesis of this disorder, it is important to state that dry eye syndrome is treatable but cannot be completely eliminated.

Artificial tears are the main treatment in the case of dry eye syndrome, but despite the fact that they improve the symptoms and objective finding, there is no evidence that they are capable of rectifying the fundamental process of inflammation which is an accompanying manifestation of dry eye syndrome. A wide range of preservative agents, including benzalkonium chloride, are used in the production of artificial tears for the purpose of limiting secondary bacterial, mycotic and amoeba eye infections caused by admixtures in the solution. The long-term application of drops with a preservative agent may cause the disintegration of contact of the epithelial cells, allergic reactions, reduced density of the goblet cells or inflammation. Recently a study was published stating that benzalkonium chloride in a concentration of more than 0.005% significantly reduces the viability of the human epithelial cells of the cornea. Furthermore, benzalkonium chloride may accumulate in the ocular tissues and have a cytotoxic effect on the ocular cells if it is applied at high concentrations, or over an extended time interval. This evidence points to the fact that either therapy using artificial tears without preservative agents or another form of therapy should be chosen in the treatment of dry eye syndrome. In cases with an advanced or "severe" degree of dry eye syndrome, with regard to the inflammation pathomechanism of this disorder, local and/or systemic anti-inflammatory treatment may be commenced. Corticosteroids applied topically are an effective anti-inflammatory agent, but in the long-term perspective they are not suitable due to their side effects.

Honey provides both important therapeutic properties – antimicrobial and anti-inflammatory. For this reason it appears to be a suitable candidate for the therapy of dry eye syndrome. Inasmuch as the use of honey in clinical practice is increasing and the development of new medicinal products on the basis of honey is also advancing considerably, it is possible to expect that dry eye syndrome shall become one of the target conditions for alternative therapy with honey. Unfortunately, to date only 1 study has been published on the treatment of dry eye syndrome by means of the instillation of drops from honey solution, in which a positive influence of 20% honey eye drops on the condition of the cornea and conjunctiva in patients with dry eye syndrome was demonstrated. The best results were achieved in patients in whom the therapy was commenced in a timely manner, if central visual acuity was within the norm and the corneal epithelium was not damaged. With the exception of local irritation in some patients, no other adverse reactions were documented. This can be caused by the acidity of honey.

As mentioned in the previous chapter, honey is used as an anti-inflammatory agent, demonstrating beneficial immunomodulatory properties in the treatment of inflammation. Acute inflammation caused by oxidative stress is associated with the production of reactive oxidative species (ROS) from neutrophils. Honey demonstrates antioxidant properties and shares in reducing the production of ROS, and can thereby effectively alleviate inflammation. These properties are attributed to polyphenolic substances including flavonoids, which are a variable but regular component of all types of honey. Recently Bashkaran et al. (2011) compared the anti-inflammatory and antioxidant effect of honey with a corticosteroid preparation (prednisone) in the treatment of alkali burn in rabbit eyes. The authors did not record any significant difference in local manifestations between both therapeutic groups, or in the histopathological examination of the cornea. Similarly, another in vivo study confirmed the anti-inflammatory effects of honey on experimental animals. Topical application of honey on rats with endotoxin-induced keratitis led to a reduction of inflammatory cytokines (IL-12 and TNF-a), chemokines and angiogenic factors (VEGF and TGF-b). Honey was thus demonstrated to be an effective product with anti-inflammatory properties, comparable with conventional preparations.

Honey and age-related eye disorders

Cataracts and age-related macular degeneration are a significant reason for the reduction of visual acuity and blindness in developed countries.

At an age of over 65 years, a certain degree of turbidity of the lens is demonstrable in 50% of the population, and at the age of over 75 years approximately 70% of the population are afflicted with cataracts. A lesser degree of turbidity of the core of the lens and its yellowish colouring can be observed also in much younger age groups. It is evident that the pathogenesis of the formation of cataracts with increasing age is of a multifactorial character, and has not yet been fully clarified. With regard to the incidence of cataract of the lens, a number of mechanisms have been identified which could play a role in the pathogenesis of cataracts. Amongst the most widely studied pathomechanisms are: non-enzymatic glycation, oxidative stress and polyol metabolic pathway.

In the case of senile transformation, the main typical manifestations are biochemical changes of lens proteins with the formation of pigmentation, lower concentration of potassium and glutathione, higher concentration of sodium and calcium and increased hydration of the lens. The mass of the lens and its anterior-posterior dimension increases, together with a decline in accommodative capability.

At least 50 million people are afflicted with a reduction of visual acuity due to cataracts, and of these up to 17 million people are severely afflicted with disability. Aldose reductase inhibitors have been examined in an extensive study as a promising agent in the medicamentous therapy of cataracts. It has been demonstrated that a number of flavonoids have anti-cataractogenic properties in vitro, caused by the inhibition of aldose reductase. Quercetin has been demonstrated to be the most effective aldose reductase inhibitor, and is used as a positive control in the numbers of studies. Further flavonoids such as luteolin, kaempferol and hesperidin also demonstrate substantial inhibiting activity.

Flavonoids are a regular component of natural honey, especially dark types of honey; however, the content of these biologically active molecules is different in the individual types of honey. The use of honey drops for the treatment of cataracts is a folk custom in certain tropical regions of America. In a recent study, Vit and Jacob characterised the anti-cataract activity of 20 flavonoids by using a model of an osmotic cataract for the purpose of identifying the connection between apparent anti-cataract properties of honey eye drops and their flavonoids. The authors of the study determined that 4 derivatives of luteolin substantially inhibited the occurrence of cataracts in sheep lenses incubated in 45% hypotonic HEPES solution for a period of 24 hours. These preliminary results indicate that honey or its biologically active components demonstrate potential anti-cataractogenic properties.

Honey and bullous keratopathy

Bullous keratopathy is characterised by stromal oedema of the cornea with epithelial or subepithelial bullae caused by a loss of cells and endothelial decompensation. In advanced stages, subepithelial fibrosis, formation of a posterior collagen layer, retrocorneal fibrotic membrane or vascularisation of the cornea may occur. The cause may be inflammation (superficial or intraocular), trauma, surgery of the anterior segment of the eye, or also of the posterior segment (tamponade) causing a loss of endothelial cells, a loss of cells following transplantation of the cornea (endothelial rejection), Fuchs endothelial dystrophy (genetically conditioned loss of endothelial cells), or absolute glaucoma. With regard to the fact that the chamber fluid penetrates into the stroma of the cornea due to the influence of the impaired barrier function of the endothelium, a stromal oedema forms, which results in the reduction of transparency of the cornea with symptoms such as lachrymation and pain caused by epithelial bullae, which may crack, thus exposing nerve endings.

This complication following a cataract surgery occurs in less than 1% of cases, but with regard to advances in cataract surgery it is possible to expect a further reduction of the incidence of this complication. Damage to the endothelium may be a consequence of mechanical contact with instruments or the lens during the surgery, a toxic reaction to the solutions used during the surgery, inexperience of the surgeon or lengthy and intensive inflammation process in the postoperative period. In patients a development of bullous keratopathy occurs when the thickness of the stroma increases by approximately 30%. In the case of epithelial oedema, the corneal epithelium loses its homogeneity and its surface becomes irregular. This irregularity of the surface causes a reduction of visual acuity together with symptoms such as a halo around lights, glare, photophobia caused by light dispersion. In the past, perforating keratoplasty was the most effective method of treatment of the symptomatic stage of the disorder; at present, deep posterior lamellar keratoplasty is also indicated. Medicamentous treatment of bullous keratopathy using 5% NaCl solution has been useful with regard to the relatively low osmotic effects. However, upon application of hypertonic saline solution in early stages of the disorder, when only the stroma is afflicted by the oedema, visual acuity improves markedly, another possibility of therapy is temporary covering with a contact lens.

On the basis of these facts it is evident that honey can be used as an alternative medicamentous treatment of bullous keratopathy. The osmotic pressure of honey is extremely high, exceeding 2000 milliosmoles/kg. Mansour et al. presented a clinical study, in which 16 patients with oedema of the corneal epithelium who had not been indicated for a surgical procedure underwent local therapy with honey. A honey drop was applied to the cornea 4-5 times per day. They found out that all corneas manifested an immediate regression of the corneal oedema. The bullae of the epithelium disappeared in two eyes. All the patients felt irritation upon topical application, but this attenuated upon repeated application and the discomfort was reduced to a minimum. Topical application improved central visual acuity, reduced pain from bullous keratopathy and enabled visualisation of the structures of the anterior and posterior segment. Similarly honey was applied to the corneas of 24 patients with bullous keratoptahy. An improvement of visual acuity and a clarification of the cornea were recorded in all patients within 1 hour of topical application of honey.

Polyphenolic substances in honey and ocular health

Honey contains a wide spectrum of phytochemical substances, including polyphenolic substances, a class of natural products which manifest various pharmacological properties. Polyphenolic substances, including flavonoids and phenolic acids, are found in honey as secondary metabolites.

A recent study indicated that flavonoids may be involved in two main aspects of different processes of physiological vision and overall ocular health. Flavonoids may also play a role in antioxidant processes, which are exceptionally important for overall ocular health, in which oxidative stress represents a significant factor sharing in the reduction of visual acuity, including age-related macular degeneration. These phytochemical substances apply their antioxidant effect via different mechanisms: (i) direct reduction of high-reactive free radicals (superoxide and hydroxyl radical) to radicals with lower reactivity, (ii) inhibition of the iNOS (inducible form of NO-synthase) enzyme responsible for the production of dinitrous oxide, (iii) inhibition of enzymes involved in the production of ROS (cyclooxigenase, lipoxygenase, NADH oxidase, glutathione-S-transferase) and (iv) chelation of iron and copper cations which serve as accelerators of oxidation reactions.

One of the important processes sharing in eye disorders is neovascularisation – a pathological change which is characterised by uncontrolled growth of vascular tissue. Topical application of selected flavonoids (genistein, fisetin and luteolin) within a concentration range from 0.5 to 1 ng/ml has led to the inhibition of neovascularisation of the cornea in animals (Joussen et al, 2000). According to a recent scientific study, the flavonoid apigenin has also been demonstrated to be an effective angiogenesis inhibitor in vitro and in vivo. Apigenin inhibited the in vitro proliferation of human umbilical vein endothelial cells (HUVEC) and also of choroidal endothelial cells (CEC). Upon intraperitoneal application of apigenin in concentrations of 15 and 30 mg/kg, apigenin demonstrated anti-angiogenic properties in rats with laser-induced choroidal neovascularisation. Similarly, quercetin inhibited retinal and choroidal angiogenesis, proliferation and migration of cells of the endothelial cellular line RF/6A. A no less significant biological property of certain polyphenolic substances in honey is their antimicrobial activity. The antimicrobial activity of these substances is directly connected with their structure, in which the mechanism of their antimicrobial effect may be different, which has been documented by several studies. Polyphenolic substances may apply their antibacterial activity via (i) inhibition of synthesis of nucleic acids, (ii) impairment of the function of the cytoplasmatic membrane and (iii) inhibition of the energy metabolism of the bacterial cell.

In addition, certain polyphenolic substances prevent the formation of a bacterial biofilm. According to the study by Blanco et al., polyphenolic substances in green tea interfere with the polysaccharides which form glycocalyx through the disruption of their interactions, thereby inhibiting the formation of a biofilm in ocular staphylococcus isolates. Naringenin was recently presented as an antagonist with regard to the formation of the Escherichia coli and Vibrio harveyi biofilm, and may serve as a substance for the development of new pharmaceuticals.

Bioavailability of active polyphenolic substances from honey depends on their physicochemical and bio-pharmaceutical characteristics, as well as on the method of application. Only a small number of studies have been conducted focusing on the bioavailability and transfer of flavonoids into the structures of the eye. Local application has been demonstrated to be a more suitable form of application of flavonoids than an oral form, in particular due to the detection of higher and more effective concentrations of locally administered flavonoids in the ocular tissue. An ex vivo experiment demonstrated that quercetin is capable of penetrating into the lens, where its partial metabolic conversion to 3´-O-methyl-quercetin takes place, whereas both forms of quercetin suppress the opacification of the lens. On the other hand, the stability of flavonoids in water solutions is limited, and as a result it is essential to conduct additional experimental studies and to obtain relevant data on the pharmacokinetic and pharmacodynamic parameters.

CONCLUSION

The treatment of eye disorders is based on medicamentous or surgical therapy. In complicated cases, following the failure of conventional treatment, an alternative method of treatment is often used. Treatment using honey represents a promising method of alternative treatment. Honey can be used successfully in the reduction of symptoms of dry eye syndrome, as well as in the treatment of bullous keratopathy. In addition, honey demonstrates substantial antibacterial, anti-inflammatory and anti-cataract effects. On the other hand, the clinical results so far obtained in the application of honey in ophthalmology are limited, and it is essential to conduct more robust randomised clinical trials for the purpose of verifying the safety and efficacy of honey in the treatment of various eye disorders. Verification of the safety of use of honey in ophthalmology relates to timely diagnosis of potential allergic reactions to honey in patients.

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