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Mini Review

Bacterial Keratitis: What's Beyond Antibiotics

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Abstract

Background: Bacterial keratitis out coming by corneal opacities is a major cause of corneal blindness, among the top five causes of blindness worldwide. Management of corneal infections remains a major challenge, though progress in ophthalmic pharmacotherapy is accompanying with new antibiotic drugs, taken into account from one hand the growing evidence on bacterial resistance, and from the other hand an economical burden and affordability of treatment.

Aforementioned indicates a need for search an alternative approach for management of bacterial keratitis.

Objective: The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that honey may be useful in therapy of corneal infections.

Keywords: *Cornea; Bacterial keratitis; Medical care; Apitherapy*

Introduction

Bacterial keratitis out coming by corneal opacities is a major cause of corneal blindness, among the top five causes of blindness worldwide [1]. Management of corneal infections remains a major challenge [2], though progress in pharmacotherapy is accompanying with new antibiotic drugs.

The growing evidences suggest on bacterial resistance to antibiotics, particularly Staphylococcus aureus [3], Acinetobacter baumannii [4], and Enterococci species [5]. The prolonged over- and misuse of antibiotics [6,7] brings into scene resistance hot topic, requiring newest drugs development [8,9], which represents an economical burden. Taken into account these circumstances, currently it was noted increased use of alternative medicine [10-12], with promising results in different areas of medicine [13,14].

Aforementioned indicates a need for search for an alternative approach for management of bacterial keratitis.

Honey has been used in the treatment of eye diseases as medicine for thousands of years [15,16]. At present it is evidenced a renaissance in medicinal use of honey due to its antibacterial, anti-inflammatory and antioxidant properties [17-20]. It has high sugar content flavonoids, phenolic acids, organic acids and mineral in different compositions depending on its floral and geographical source [21]. Honey has been documented to have wound healing properties on skin [22], and since cornea and skin are both derived from surface ectoderm embryologically, it was hypothesized that honey could have the same potential effects in accelerating the migration and proliferation of corneal epithelial cells during corneal epithelial wound healing. Therapeutic potential of honey was confirmed by its use in eye diseases [23-25], specifically in different types of keratitis, bullous keratopathy [25], chemical and thermal burns [27, 28].

The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that honey may be useful in therapy of corneal infections.

Honey as a Medicine

Honey is produced by honey bees (*Apis mellifera)* and is formed by ripening nectar, honeydew, and bee secretions [29]. It contains more than 200 compounds [30], including 2 sugars, amino acids, vitamins, minerals, enzymes, flavonoids, phenolic acids, and antioxidants [31].

Currently different types of honey with standardized levels of antibacterial activity are available. The best known one is the Leptospermum scoparium (*L. scoparium*) honey derived from the manuka tree and also named as manuka honey with confirmed an inhibitory effect on around 60 species of bacteria, including aerobes and anaerobes, gram-positives and gram-negatives [32,33], including Escherichia coli (*E. coli*), Enterobacter aerogenes, Salmonella typhimurium, *S. aureus* [34,35]. Laboratory studies have revealed that the honey is effective against methicillin-resistant S. aureus (MRSA), β-haemolytic streptococci and vancomycin-resistant Enterococci (VRE) [36,37]. Tualang honey has variable but broad-spectrum activities against many different kinds of wound and enteric bacteria [38]. Natural honey of other sources can vary as much as 100-fold in the potency of their antibacterial activities, which is due to hydrogen peroxide production and subsequent generation of reactive oxygen species [34,39]. In addition, honey is hygroscopic, which means that it can draw moisture out of the environment and dehydrate bacteria, and its high sugar content and osmolarity and low level pH can also prevent the microbes from growth [40]. Currently available findings suggest about multifactorial genesis of anti-infective effect of honey [33,41].

Honey in Bacterial Keratitis

A large number of *in vitro* studies [43-47] have confirmed the broad-spectrum antimicrobial properties of honey in ocular topical use.

The results from the study of honey topical use four times daily in animal rat model of bacterial conjunctivitis induced by *E. coli,* Proteus sp., S. aureus, Klebsiella sp., and P. aeruginosa [43] suggest that honey reduces redness, swelling, purulent discharge, shortening recovery period independent of causative agent.

Another *in vitro* study revealed therapeutic effect of acacia honey on corneal abrasion wound healing [45].

Two animal studies have focused on the effect of honey in keratitis induced by Pseudomonas aeruginosa [46,47].

Nejabat., *et al.* [46] evaluated therapeutic potential of 90% concentrated natural honey in New Zealand Rabbits comparing it to ciprofloxacin and concluded that topical application of honey may be as effective as ciprofloxacin in P. aeroginosa induced keratitis. Research conducted by Uwaydat., *et al*. [47] also confirmed anti-angiogenic and anti-inflammatory properties of honey in Pseudomonas endotoxin-induced keratitis due to reduction of angiogenic factors (VEGF and TGF-β), inflammatory cytokines (IL-12) and chemokines (CC chemokine receptor 5(CCR-5)).

The latest case report of contact lens-induced corneal ulcer presented by Majtanova., *et al*. [48] and assessing the supplemental 25% honey solution use in addition to topical levofloxacin indicated that the patient reached positive clinical outcome. In addition, honey was shown to be highly effective in vitro against ocular isolates from corneal scrapings and contact lenses - Klebsiella oxytoca, Pseudomonas aeruginosa, Stenotrophomonas maltophilia and Pseudomonas spp. This encouraging clinical result suggest a need for wider honey incorporation into corneal infections treatment protocols. American Apitherapy Society showed a significant improvement in a corneal ulcer with topical honey when antibiotics, antiviral agents and corticosteroids had no effect [49]. According to Evidence-Based Complementary and Alternative Medicine a double blind clinical trial with 60 patients in Iran revealed the effectiveness of honey drop in treating Vernal keratoconjunctivitis [50].

In the latest research [51] the new indication for manuka honey is found. Optimal Antibacterial Manuka Eye Drops was used twice to three times daily as an adjunctive therapy to corticosteroid, aqueous suppressants, hypertonic sodium chloride five per cent, eyelid hygiene and artificial tears in the management of persistent post-operative corneal edema. The authors proved the efficacy of honey eye drops and advocated further investigation in clinical trials.

Antibacterial effect of honey was evaluated in prevention of endophthalmitis [52] in randomized clinical trial. The authors compared 0.3% ofloxacin and 25% honey administered five times a day for 7 days before and 5 days after surgery. They proved that both agents are comparable, since no significant difference in antibacterial effect was found between groups. It is recognized that honey may act as a prophylactic agent of endophthalmitis, but further studies are required to evaluate the bioavailability issue.

Currently available findings suggest that ocular topical application of honey is an effective alternative approach to treat bacterial keratitis.

Conclusion

There are potentially multiple biological bases for therapeutic effect of honey in microbial infections. The rationale for using honey in such eye disease as bacterial keratitis is that it has anti-bacterial, anti-inflammatory and antioxydative effects and at the same time no microbial resistance was discovered. Currently, there is growing evidence of the effectiveness of pharmacotherapy by honey and hopefully soon we shall meet it as a universal anti-infective agent. This therapeutic modality offers promising option for the ophthalmic therapeutic landscape.

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