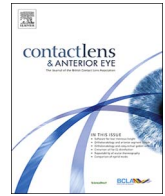




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Review article

Drugs – Do we need them? Applications of non-pharmaceutical therapy in anterior eye disease: A review

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ABSTRACT

Natural products have been in use long before the introduction of modern drug therapies and are still used in various communities worldwide for the treatment of anterior eye disease. The aim of this review is to look at the current non-pharmaceutical modalities that have been tried and assess the body of existing evidence behind them. This includes alternative medicine, existing non-pharmaceutical therapy and more recent low and high tech solutions.

A detailed search of all available databases including MEDLINE, Pubmed and Google was made to look for English-language studies for complementary and alternative treatment modalities (CAM), natural therapies and new modalities for anterior eye disease such as blepharitis, dry eye and microbial keratitis. We have included a broad discussion ranging from traditional treatments like honey and aloe vera which have been used for centuries, to the more recent technological advances like Intense Pulsed Light (IPL), LipiFlow and photoactivated chromophore for corneal cross linking in infectious keratitis (PACK-CXL).

Alternative management strategies may have a role in anterior eye diseases and have a potential in changing the way we currently approach them. Some of the available CAM could play a role if incorporated in to current management practices of not only chronic diseases like blepharitis and dry eye, but also acute conditions with significant morbidity like microbial keratitis. Further large-scale randomized control trials stratified by disease severity are required to improve our understanding and to evaluate the use of non-pharmaceutical therapy against current practice.

1. Introduction

Anterior eye disease constitutes a major part of the workload for eye care professionals with a number of chronic conditions such as dry eye, blepharitis and meibomianitis associated with high levels of morbidity as well as varying levels of benefit from conventional treatment regimens, in particular pharmaceutical regimens.

The National Center for Complementary and Alternative Medicine, part of the National Institute of Health, defines complementary and alternative medicine (CAM) as a “group of diverse medical and health care systems, practices and products that are not presently considered to be part of conventional medicine.” Complementary medicine is used with conventional therapy, whereas alternative medicine is used in lieu of conventional medicine. Many aspects of CAM are rooted in ancient systems of healing, such as those of China and India, the most well known example of which is acupuncture.

CAM existed long before the introduction of modern pharmaceutical management and is still widely used in various communities

worldwide. It includes a variety of approaches and therapies taken from around the world, which historically have been poorly adopted in conventional Western medicine. In Western medicine, our evidence-based learning is centered on modern, conventional medical practice. However, the employment of CAM is becoming increasingly recognized as an important arena of health care.

At the opposite side of the spectrum are new and relatively high tech commercial developments to target specific conditions where the disease mechanisms are thought to be more fully understood. In between the two extremes are a myriad of non-pharmaceutical options.

In this article we review the known and proposed mechanisms of action and evidence of efficacy for a range of non-pharmaceutical therapies that may be of use in the management of some common anterior eye conditions. The review is diverse in its coverage and includes long-standing treatments, CAM and some of the latest developments in anterior eye disease.

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2. Methods of literature review

Databases searched included MEDLINE, AMED, Pubmed, Google, Google Scholar and Embase. These databases were last accessed in July 2017. Search terms included: review; alternative medicine; alternative therapy; complementary medicine; complementary therapy; complementary and alternative medicine; corneal infection; corneal ulcer; blepharitis; meibomian gland dysfunction; dry eye; honey; manuka; acacia; collagen cross linking; PACK-CXL; riboflavin; UVA; UVC; aloe vera; tea tree oil; coconut oil; Melaleuca alternifolia; acupuncture; serum drops; Eye Peace; Oculeve; Lipiflow; neurostimulation; IPL; scleral lens; omega-3; omega-3 drops.

3. Treatment modalities

The different modalities/option for potential treatment for anterior eye disorders are discussed below. There is overlap between the conditions that they may benefit and this is discussed under each one with the evidence base behind them and how they work.

3.1. Local application

The ocular surface has an important protective role similar to other mucous membranes of the body. The anatomy of the surface and the composition of tears provide a physical and immunological barrier serving the visual apparatus. In the following sections, we attempt to cover local application of CAM therapies being used in the management of anterior segment eye diseases.

3.1.1. Honey

Honey has been used for millennia as a health remedy, possessing both antimicrobial and wound-healing properties. As early as 350 BCE, Aristotle had noted honey to be ‘good as a salve for sore eyes and wounds.’ Honey is a viscous product with a high osmolarity. Its antimicrobial properties are thought to be due to its mildly acidic pH, hydrogen peroxide content and an array of other phytochemical components [1]. These properties have enabled honey to be used medicinally in wound therapy [2]. There are many different types of honey available, and they vary vastly in their antimicrobial efficacy. The most widely known medicinal honey is Manuka honey, produced in New Zealand and southeastern Australia from the nectar of the *Leptospermum scoparium* flower. Manuka honey is reported to have an inhibitory effect on 60 different bacterial species [3]. Interestingly, Manuka honey’s antibacterial efficacy is maintained even if the hydrogen peroxidase component is destroyed [3].

In-vitro studies have shown that honey has antibacterial effects against *E. coli*, *Salmonella spp.* and *P. aeruginosa* [4,5]. A rabbit study of induced *P. aeruginosa* keratitis compared the outcomes of 10 eyes treated with natural honey, 10 with topical ciprofloxacin and 6 eyes with no treatment [6]. A 90% concentration of honey was prepared by adding distilled water to natural honey. Ten eyes were each treated with topical application of honey and ten eyes were treated with 0.3% ciprofloxacin every four hours. After one week, cellular infiltration and organism density were similar between the honey and ciprofloxacin group. The control group displayed more severe disease as well as a higher rate of corneal perforation. This study therefore suggests that honey may be as effective as topical antibiotics in *P. aeruginosa* keratitis.

Other studies have shown that honey possesses corneal wound healing abilities. A recent in vitro study using corneal epithelial cells isolated from rabbits found that acacia honey accelerates corneal epithelial cell wound closure by increasing the expression of genes and proteins associated with corneal epithelial cell wound healing [7]. An animal study, from 2011, showed that topical application of honey to non-infected wounded corneas improved epithelial healing time, whilst decreasing inflammatory mediators in the corneal tissue [8]. This may

be relevant to recovery following microbial keratitis.

Another interesting case report involved a contact lens-induced corneal ulcer [9]. The patient had positive corneal scrapings for a range of bacteria – *Klebsiella oxytoca*, fluoroquinolone-sensitive *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* and *Pseudomonas spp.* Initial treatment was with intensive topical levofloxacin. When this failed to achieve a significant improvement, additional complementary therapy with honeydew honey solution was commenced five-hourly. This honey was gamma-irradiated and applied as a sterile 25% solution. Subsequent follow-up revealed improvement over the following week, with clearance of ocular pathogens and a significant improvement in visual acuity.

The evidence supporting the use of honey in bacterial keratitis is mainly based upon case reports. As a result, the methodology and standardization of the preparation of the honey is not uniform. A large-scale randomized control trial is warranted to assess the statistical significance of keratitis improvement.

Current treatment options for dry eye disease are aimed at controlling environmental factors, utilizing anti-inflammatory or immunomodulating eye drops such as cyclosporine and lifitegrast and managing symptoms with the application of artificial tears to increase ocular surface moisture and provide lubrication [10–12]. Cyclosporine ophthalmic emulsions have been approved by the FDA for the management of dry eye, however their use is currently limited by the most commonly cited side effect, pain, being a barrier to treatment and further research in to different formulations is awaited [13]. The use of artificial tears has many limitations; they often contain chemical preservatives – a caution for toxicity and for those with sensitive eyes, as well as lacking the complex biochemical formulation of natural tears that are critical to the maintenance of the tear film. Honey eye drops have been developed on the premise that bacteria are unable to grow in concentrated honey solutions due to its acidity and high glucose concentration, with demonstrated reduction in inflammatory markers on the ocular surface [14]. Manuka Dry Eye Drops are available in two formulations in Australia for treatment of dry eye disease. The drops contain a mix of honeys from Australian *Leptospermum*, commonly called Manuka or Jelly Bush, selected for their high and consistent level of antibacterial benefits. The first trials evaluating the effectiveness of honey eye-drops compared with conventional eyelid hygiene, lubricant drops and other treatments for the management of dry eye symptoms are currently underway. One such study randomized 118 participants with meibomian gland dysfunction (MGD) leading to evaporative dry eye to one of two treatment arms – use of Optigel Manuka Eye Gel (Melcare Biomedical Pty Ltd, Brisbane, Australia) or use of Optigel Manuka + Lubricant Eye Drops (Melcare Biomedical Pty Ltd, Brisbane, Australia). A third control group consisted of patients receiving conventional therapy. The study found the honey products significantly improved meibomian gland expressibility and reduced the need for lubricants. The eye drop formulation significantly improved staining and reduced the bacterial colony count in those treated [15].

3.1.2. Aloe vera

Aloe vera is a plant of the Liliaceae family that has been used as a herbal remedy since ancient times. Its efficacy in a range of medical settings is well documented, from wound management to diabetes [16].

Aloe vera is thought to facilitate wound healing through the regulation of proteases, specifically matrix metalloproteinases (MMP) [17]. MMPs work in part to degrade the extracellular matrix. Aloe vera has been shown to inhibit the production of MMP-9 in peripheral blood mononuclear cells [18], and MMP-2 and MMP-9 in periodontal disease [19]. Aloe vera modulates collagen production, cell migration and cell proliferation: all properties vital to wound healing [20]. It has also been shown to possess antibacterial, antifungal and antiviral effects against a range of pathogens in-vitro including *E. coli*, *E. faecalis*, *S. aureus* [21] and *Aspergillus* [22].

Aloe vera is not toxic to corneal cells in vitro [23]. Dilute aloe

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