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Maqui berry extract and Omega-3 – the natural ingredient combination to keep your eyes moist

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A common but unfavorable side effect of modern lifestyle is designated as “dry eye syndrome” (*keratoconjunctivitis sicca*). Some might argue that the phrase “syndrome” is overstated since one has to differentiate between a real disease and a discomfort attributed to exposure. The latter condition originates from decreased blinking rates due to visually extensive use of computers and smartphones, wearing contact lenses, cigarette smoke, air conditioning or pollution. In addition, women are more affected by dry eyes, which may be triggered by hormonal changes. At the same time, symptoms correlate with increasing age – dry eyes is a common condition in people aged 50 years and older and the prevalence for dry eye symptoms appears to rise steadily [1, 2]. Besides certain medications for instance antidepressants or beta-blockers, laser surgery or specific autoimmune disorders can enhance the risk to develop dry eye symptoms, too [3, 4].

Apart from the cause of dry eye conditions, the symptoms are the same: redness, itching, foreign body sensation, sensitivity to light, a blurred vision or also eye fatigue are typical features of eye dryness [4]. As dry eye symptoms underlie complex mechanisms, it is crucial to understand the basic anatomy and physiology of the visual organ. To keep the eye moist and provide it with essential nutrients and molecules different types of glands and cells are involved. Tears and tear film comprise three sophisticated layers namely i) an outer lipid layer, ii) a middle aqueous layer and iii) an inner mucin layer (see Fig. 1) [5].

The oily lipid layer is produced by the Meibomian glands and functions as a protective film against evaporation of the aqueous part below. The lacrimal gland is the source of the second aqueous phase that contains the watery portion of tear fluid, in which electrolytes and major proteins like antibodies and enzymes are present for antimicrobial activity. Furthermore, it nourishes the cornea and the conjunctiva.

The inner mucin layer originating from goblet cells, allows the aqueous phase to spread evenly, and maintains the ocular surface wet and hydrophilic [5, 6, 7]. Dry eyes can be divided in two forms with blurring boundaries since one type might affect the other one: one form is defined as an “aqueous insufficiency” in which a reduction of aqueous tear film secretion from the lacrimal glands is prevalent. The second form describes an “evaporative dry eye” arising from a Meibomian gland dysfunction and results in a deficient lipid layer and thus an unstable tear film [8].

A key aspect of dry eye symptoms, especially those that originate by the aforementioned environmental factors like smoking, pollution or air conditioning but also triggered by aging, is the formation of reactive oxygen species (ROS) thus oxidative cell stress. ROS such as hydrogen peroxide (H_2O_2), superoxide

anion radicals ($\cdot O^-$) and hydroxyl free radicals ($\cdot OH$) lead to an imbalance between antioxidants and oxidants in favour of oxidants, which results in an increased tear film osmolarity and inflammatory reactions of the ocular surface. In this context, several studies also implicate oxidative cell stress in the pathogenesis of serious ophthalmic disorders such as age-related macular degeneration, cataract and glaucoma [9, 10]. The typical treatment of dry eyes, especially the mild forms, are over-the-counter drugs such as artificial teardrops, ointments and gels. But also lacrimal plugs, prescription anti-inflammatory treatments with corticosteroids or a change of medication and lifestyle habits may ameliorate symptoms.

It was shown that nutrition might have beneficial effects on the proper function of the ocular organ, too, which is a quiet comfortable way – to not just relief symptoms but to address the elicitors and to keep the eye moist. In regard to oxidative stress antioxidants like cocoa, sea buckthorn oil, and various vitamins have been shown to ameliorate inflammatory processes in corneal epithelial cells and to enhance ocular surface and tear film stability [11]. In general, functional foods gain more and more importance in modern times with demanding daily life and an increasing number of cancer, cardiovascular diseases and other chronic sufferings. Especially the secondary plant metabolites class of polyphenols are interesting and promising because of their well-known nutritional and health benefits. Polyphenols are divided into several classes and subclasses. One such a subclass, namely anthocyanidins, are responsible for the red to dark purple coloring of many vegetables and may play a preventive role against cancer or cardiovascular diseases due to their antioxidant, anti-inflammatory and detoxification activity [12]. Berries in general are the fruits with the highest concentrations of anthocyanidins. In this context, an outstanding and yet quite unknown Chilean fruit called maqui berry (*Aristotelia chilensis*) exhibits a unique phytochemical profile that hallmarks maqui berries to the richest identified natural source of delphinidins – the anthocyanidin group that possess the most effective free radical scavenging activity in comparison to other anthocyanidins like malvidins or cyanidins (see Fig. 2) [13].

Both preclinical and clinical studies revealed the berries impressive potential in protection and balancing of the visual organ as well as oxidative cell stress induced by light. In a 2013 study, Tanaka and colleagues demonstrated that maqui berry extract (MaquiBright®; MBE, Anklam Extrakt GmbH) protected murine photoreceptor cells when exposed to light-induced cell death (apoptosis and necrosis) *in vitro*. Further, the extract and its active anthocyanin components prevented the increase in ROS production in the retinal cells measured 24 h after irradiation. These data indicate that MBE has a strong antioxidant activity and the ability to scavenge light-induced free radicals [14]. Just one year later in 2014, another research group used a blink-suppressed dry-eye-model in which four groups of rats were exposed to fan for three consecutive days. Each group of rats received either no extract, black currant extract, bilberry extract or a standardized MBE. Interestingly, just the MBE could significantly prevent a decrease in tear fluid generation, which was analyzed

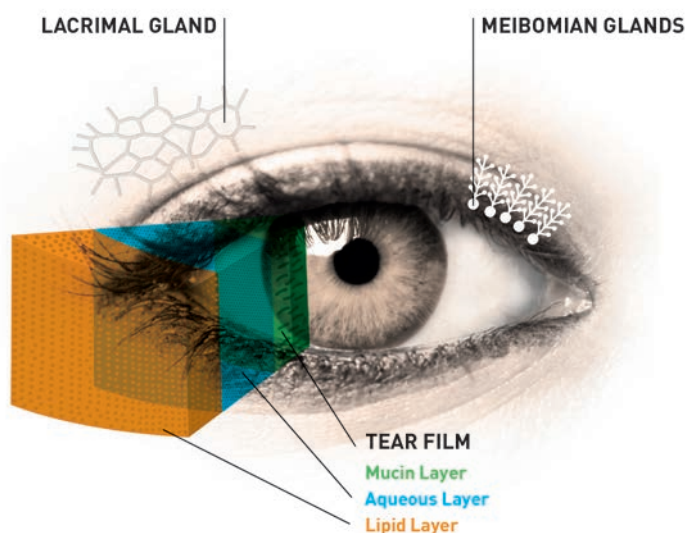


Fig. 1: Ocular Surface and Major Glands



Photo: Anklam Extrakt GmbH

Fig. 2: Maqui berry (*Aristotelia chilensis*)

by the Schirmer's test. In this specific examination, a paper strip is inserted into the eye for five minutes to determine the production of tears by the length of wetting the paper strip [15]. In the same year a first pilot trial with an open design was conducted in which in total 13 volunteers with mild symptoms of dry eyes were randomly assigned to either a 30 mg or 60 mg MBE treatment group. Already after 30 days of daily oral intake both treatment groups exhibited a significant increase in tear fluid generation measured with the aforementioned Schirmer's test. Additionally, the participants had to answer and rate a Dry Eye-Related Quality-of-Life Score questionnaire (DEQS) where a maximum severity score of 60 can be reached. With an intake of 30 mg per day, the basal DEQS was reduced by 47% from 41.0 down to 21.8 – clearly demonstrating a subjective amelioration of dry eye symptoms [16]. In a randomized double-blind placebo-controlled parallel design follow-up trial with 74 participants, the previous findings of the pilot study could be confirmed: within four weeks of 60 mg MBE intake the tear fluid generation increased significantly. Furthermore, the subjective feeling of how the quality of life is affected (evaluated on the basis of a DEQS) as well as certain physical conditions in the context of dry eyes that were measured with a "Visual Analogue Scale" were improved [17]. The data demonstrate that the daily oral intake of a botanical supplement can restore tear fluid generation and thus ameliorate bothersome symptoms by directly addressing the causes that originate from the lacrimal glands – unlike artificial teardrops that do not cure but solely mask the symptoms.

Another dietary intervention, namely oils, have shown beneficial effects in numerous clinical studies targeting tear fluid management, too. In particular, omega-3 fatty acids that are essential to human health can be ingested directly from dietary sources such as fish or several vegetables like avocado, nuts or flax seeds or alternatively may be supplemented with e.g. fish oil capsules. There are several different types of omega-3 fatty acids but the most scientific research concentrates on just three: alpha-linolenic acid (ALA), eicosapen-

taenoic acid (EPA), and docosahexaenoic acid (DHA). EPA and DHA are both designated as "long chain" fatty acids as they are composed of 20 and 22 carbons respectively and both have several double bonds that start at the third carbon atom from the tail end of the molecule, which also explains the name "omega-3". When ingested, nutritional lipids are metabolized in the intestinal lumen and result in breakdown products such as monoglycerides and free fatty acids. After absorption by enterocytes, the fats are distributed throughout the organism [18]. Omega-3s have a crucial function in the body since they are components of phospholipids and thus part of the cell membranes [19]. Fish oil supplements as well as an omega-3 rich diet are frequently recommended by healthcare professionals since they are thought to have few side effects. Although the exact mechanism and understanding of action of omega-3s is not yet fully elucidated, the essential fatty acids were recommended as initial therapy for eye dryness by the Dry Eye Workshop study group in 2007 and as well as by the International Workshop on Meibomian Gland Dysfunction four years later in 2011 [20, 21]. In this context, one of the often read clinical studies on the efficacy of omega-3 oils was published by Epitropoulos and colleagues in 2016. The trial involved 105 subjects in total and was designed as a multicenter, prospective, randomized, placebo-controlled, double-blind study in which the participants in the verum group had to take a daily dosage of 1680 mg EPA and 560 mg DHA compared to 3136 mg of linoleic acid in the placebo group over 12 weeks. The results of the study were quite impressive, as five measured dry eye parameters showed a significant improvement under omega-3 supplementation. The participants of the verum group showed a significant decrease in tear osmolarity, while the omega-3 index levels beneficially increased in parallel. Furthermore, the researchers also revealed a significant prolongation of the tear film breakup time (TBUT), a reduction of the inflammatory marker MMP9, as well as an enhancement in the patient's personal symptomology measured as "Ocular Surface Disease Index, OSDI" [22]. A Spanish study comprising 1,419 dry eye volunteers

(female majority with mean age of 59 years) with regular usage of artificial teardrops showed that the daily intake of a supplement containing a combination of omega-3 fatty acids, minerals, vitamins and antioxidants over 12 weeks results in a significant improvement of dry eye symptoms and was accompanied by better Schirmer's test and TBUT scores. Most striking, the frequency of use of artificial tears decreased significantly [23]. Next to their beneficial effect on the Meibomian glands and thus on the quality of the tear film lipid layer, omega-3 fatty acids also present good anti-inflammatory action since after consumption they are enzymatically elongated resulting in the production of PGE3 and leukotriene B5, both feature anti-inflammatory properties.

Additionally, EPA exhibits the ability to block gene expressions of pro-inflammatory cytokines like TNF α , IL-1 β or COX-2, whereas DHA has a protective activity on lacrimal gland and ocular surface cells from TNF α -induced programmed cell death [24, 25]. In 2018 the publication of a study in which 329 participants took an omega-3 supplementation in comparison to 170 persons in the control group who were treated with olive oil, arouse a controversial discussion about the efficacy of omega-3 fatty acids since at the end of trial there was no significant difference between the two test groups [26]. Nonetheless, there was a significant reduction of approximately 13 points in OSDI score in the omega-3 group that again demonstrated the potential of omega-3 fatty acids. Furthermore, the study also had some critical points concerning the framework conditions: for example, the patients were already under various interventions like artificial tears or gels, cyclosporine drops, or regularly used warm lid soaks and were allowed to continue their current therapies during the trial, which was defended as "real world conditions" by the researchers. Also the Global Organization of EPA and DHA Omega-3s (GOED) explained that corresponding negative press releases on the study results were overstated and misinterpreted [27]. Despite this aforementioned critical publication, a large body of research contributes to highlight the versatile beneficial effects of an omega-3

rich diet and interventional approaches on healthy eyes especially in regards to tear fluid management and other fields of indications. In addition, the European Food Safety Authority (EFSA) approved DHA with a health claim: *DHA contributes to the maintenance of normal vision* [28].

A new and innovative product, launched at CPhI Madrid in October 2018 combines the power of both presented nutritional and clinically proven approaches for the maintenance of moistened eyes: optibright™ is a supplementary double-action solution that unifies maqui berry standardised extract (MaquiBright®, Anklam Extrakt GmbH) with an omega-3 oil protected in a softgel capsule

– manufactured in partnership with Catalent. MaquiBright® is standardized to 35 % of total anthocyanins and a minimum of 25 % delphinidin – the most effective antioxidant anthocyanin. Due to its high content in antioxidant phytochemicals, MaquiBright® was shown to restore tear fluid generation by acting on stressed lacrimal gland cells. The second component is an omega-3 oil with 50 % DHA and 20 % EPA fatty acids manufactured in triglyceride form. As mentioned above the EFSA acknowledged DHA to contribute to the maintenance of normal vision [28]. The utilized omega-3 oil positively affects the lipid layer synthesis of Meibomian glands, stabilizes the tear film and thus prevents evaporation of the aqueous tear fraction.

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