# Dry Eye and Probiotics

Subjects: Pathology
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Probiotics are defined as live microorganisms that present health benefits when administered in adequate amounts. Prebiotics refer to substrates that microorganisms use to bestow health benefits upon host. Evidence regarding their effects on the ocular surface, especially dry eye, are now just emerging. Both rodent and human studies regarding gut microbiota in Sjögren's syndrome and environmental dry eye are explored, and we discussed the effects of prebiotics and probiotics on dry eye in this section.

Keywords: dry eye ; dysbiosis ; gut microbiota

## 1. Prebiotics and Probiotics

Probiotics are defined as live microorganisms that present health benefits when administered in adequate amounts [1]. Prebiotics refer to substrates that microorganisms use to bestow health benefits upon the host [2]. Both probiotics and prebiotics have received much spotlight over the past decade for their advantages in coordinating gut microbiota to help ameliorate several diseases [3]. While several studies have obtained beneficial effects in several autoimmune diseases [3] [4], evidence regarding their effects on the ocular surface, especially dry eye, is now just emerging (**Table 1**).

**Table 1.** Effects of probiotics or prebiotics on dry eye in rodent and human studies.

| Author, Year | Tx | Tx Period | Subjects | Representative Gut Microbiota | Change in OS/LG/dLN |
|---|---|---|---|---|---|
| | | | **Rodent Study** | | |
| Kawashima, 2016 [5] | Fish oil, lactoferrin, zinc, vitamin C, lutein, vitamin E, γ-aminobutanoic acid & *E. faecium WB2000* | 2 days | DS rats | N/A | Tear secretion↑<br>ROS↓(LG) |
| Kim, 2017 [6] | *L. casei, L. acidophilus, L. reuteri, B. bifidum & S. thermophiles* | 3 weeks | NOD.B10.*H2*$^{b}$ | N/A | Tear secretion↑<br>Corneal staining↓<br>Inflammation foci$^{a}$↓(LG)<br>CD8$^{+}$IFN-γ$^{hi}$ T cell↓(dLN)<br>$T_{reg}$ cell↑(dLN) |
| Choi, 2020 [7] | *L. casei, L. acidophilus, L. reuteri, B. bifidum & S. thermophiles* | 3 weeks | NOD.B10.*H2*$^{b}$ | ↑*Lactobacillus helveticus, L. hamsteri, L. reuteri, L. casei, L. brantae, L. amylovorous, Akkermansia municipila, Aerococcus viridans, B. bifidum, Streptococcus salivarius*<br>↓*Lactobacillus intestinalis* | Tear secretion↑<br>Corneal staining↓<br>Immune response genes$^{b}$↓(LG)<br>IL-10↑(OS)<br>IL-1b↓(OS) |
| | | | **Human Study** | | |
| Kawashima, 2016 [5] | Fish oil, lactoferrin, zinc, vitamin C, lutein, vitamin E, γ-aminobutanoic acid & *E. faecium WB2000* | 8 weeks | DES$^{c}$ | N/A | Scored subjective symptoms$^{d}$↓<br>Tear secretion↑ |
| Chisari, 2017 [8] | *S. boulardii MUCL 53837 & E. faecium LMG S-28935* | 30 days | DES$^{e}$ | N/A | Subjective dry eye symptoms$^{f}$↓<br>TBUT↑<br>Tear secretion↑ |

| Author, Year | Tx | Tx Period | Subjects | Representative Gut Microbiota | Change in OS/LG/dLN |
|---|---|---|---|---|---|
| Chisari, 2017 [9] | *B. lactis DSM 25566 & B. bifido DSM 25565* | 30 days | DES[e] | N/A | Tear secretion↑ TBUT↑ |
| Kawashima, 2019 [10] | Hydrogen-producing milk | 3 weeks | DES[c] | N/A | TBUT↑ (♀) |

[a] Inflammatory foci score; >50 inflammatory cells/focus = 1, 25–50 inflammatory cells/focus = 0.5; [b] Ptprc, Hmgb2, Psmb8, H2-Aa, H2-K1, Psme1, Tap1, Tap2 & Psmb9; [c] Subjects with dry eye symptoms, qualitative or quantitative disturbance of the tear film (Schirmer test ≤ 5 mm or TBUT ≤ 5 s) and total fluorescein staining score of at least 3 points.; [d] Total score, foreign body sensation, dry eye sensation and ocular fatigue (evaluated by Dry Eye-Related Quality-of-Life Score); [e] Subjects defined to have dry eye syndrome clinically or pathologically; [f] Dry eye symptom severity, frequency of pain or soreness in ocular fatigue, eyelid heaviness, eye redness and foreign body sensation (evaluated by Ocular Surface Disease Index); Tx, treatment; OS, ocular surface; LG, lacrimal gland; dLN, draining lymph node; DS, desiccating stressed; B6, C57BL/6J mice; ROS, reactive oxygen species; DES, dry eye syndrome; TBUT, tear break up time; ♀, female; 8-OHdG, 8-hydroxydeoxyguanosine.

## 2. Effects Seen in Animal Studies

NOD.B10.H2$^{b}$ (NOD) mice treated with prebiotic xylooligosaccharides resulted in reduced sialadenitis and insulitis by increasing regulatory macrophages and activating $T_{reg}$ cells while lowering cytotoxic T cells [11]. Interestingly, this study also observed that a combination with antibiotics increased the clinical benefits of prebiotics regarding insulitis but not sialadenitis [11], which implies that each species of gut microbiota affects each target organ in a different manner. On the other hand, recent animal studies regarding dry eye and probiotics have commonly observed that while antibiotics treatment increases dry eye, prebiotics and probiotics induce clinical benefits with mitigation of inflammatory cells (**Table 1**). Kawashima et al. observed that *E. faecium WB2000* mixed with fish oil increased tear secretion and decreased reactive oxygen species production in lacrimal glands (LGs) of desiccating-stressed rats [5]. Two studies have observed that a probiotic composed of *L. casei, L. acidophilus, L. reuteri, B. bifidum, and S. thermophiles* for 3 weeks in NOD mice restored corneal barrier disruption and increased tear secretion [7][6]. We noticed a decrease in inflammatory cell infiltration in LG and $CD8^{+}$ IFN-$\gamma^{Hi}$ cells in the lymph nodes, while $T_{reg}$ cells increased [6]. While using the same probiotic in the same SS model, Choi et al. observed that proteins related with antigen presentation decreased in the LGs [7].

These animal studies indicate that probiotics and prebiotics can affect the gut microbiota and carry out variable clinical and immunological changes. Given that T and B cells are the main source of the mechanism in Sjögren's syndrome (SS) subjects while T cells are more dominant in environmental dry eye syndrome (DES), probiotics' and prebiotics' effects on the gut microbiota and subsequently to clinical and immunological manifestations may differ according to the type of studied animal model. These possible differences among studied animals should be considered in future animal studies.

## 3. Effects Seen in Clinical Studies

Clinical benefits from probiotics on dry eyes have been investigated in a few human studies (**Table 1**). Though *E. faecium* is known for being an opportunistic pathogen, some of its strains are validated to be safely used as probiotics [12]. Some strains possess pathways to enable the production of essential amino acids and vitamins, which are important in human health [12]. Likewise, Kawashima et al. observed that intake of *E. faecium WB2000* mixed with fish oil for 8 weeks alleviated subjective symptoms with increased tear secretion in DES subjects [5]. Similarly, a mixture of *E. faecium LMG S-28935* and *Saccharomyces boulardii MUCL 53837* decreased subjective symptoms with an increase in both tear secretion and tear break-up time [8]. *Saccharomyces* is also a well-known short-chain fatty acids (SCFAs)-producing bacteria [13]. *Lactobacillus* and *Bifidobacterium,* renowned for their many species associated with lactic acid and acetic acid production, are regarded as the main ingredient for various probiotics [14]. A pilot study by Chisari et al. reported that a 30-day supplementation of *B. lactis* and *B. bifido* significantly increased tear secretion and tear break-up time in 20 DES subjects compared to placebo [9]. Additionally, a processed $H_2$-producing milk, as a prebiotic supplement, exhibited similar clinical effects in DES subjects [10]. Despite these positive clinical results, the safety of probiotics use in immunocompromised SS subjects is warranted, where administration of *Lactobacillus spp*. was reported to possibly act as an opportunistic pathogen [15]. However, overall, clinical studies have observed probiotics to be safe and to not only alleviate subjective symptoms but also increase both tear secretion and tear break-up time. These clinical results suggest

the advantages of diverse probiotics as a supplementary treatment to DES. Therefore, future clinical studies concerning SS subjects are now necessary to further elucidate and expand probiotics' benefits.

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