• Review Article •

Breast cancer-related endocrine therapy on ocular surface microbiota: mechanism and clinical significance

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Abstract

● Breast cancer is the leading malignancy among women worldwide, with endocrine therapy (*e.g.*, selective estrogen receptor modulators, aromatase inhibitors) serving as a cornerstone of treatment; although these therapies are effective against hormone-sensitive breast cancer, they alter patients' systemic hormone profiles, which may disrupt the balance of the ocular surface microbiota that maintains ocular homeostasis. This review systematically examines the mechanisms of mainstream breast cancer endocrine therapies, the dynamics of the ocular surface microbiota, the association between hormonal imbalance and ocular surface homeostasis, as well as the relationship between ocular surface flora alterations, and therapy-related ocular complications, integrating evidence from oncology, endocrinology, and ophthalmology to propose research frameworks and prevention strategies for therapy-related ocular complications.

● **KEYWORDS:** breast cancer; endocrine therapy; ocular surface microbiota

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INTRODUCTION

Breast cancer constitutes the most prevalent malignancy in the global female population, affecting over 2.3 million women annually according to 2022 GLOBOCAN estimates[1-2]. Within multimodal therapeutic strategies, endocrine therapies—including selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs)—serve as first-line interventions for hormone receptor-positive subtypes by systemically modulating estrogen signaling pathways[3]. Notably, the ocular surface, an immunologically active interface continuously exposed to environmental antigens, sustains a symbiotic microbiota critical for maintaining corneal epithelial integrity and tear film stability[4]. Emerging preclinical findings indicate that, once endocrine agents enter the systemic circulation, they can produce off-target effects through multiple mechanisms[5-7]. First, there is direct modulation of meibomian gland secretion patterns mediated by nuclear hormone receptors. Second, these agents can alter the lacrimal cytokine profiles, which in turn impacts the expression of antimicrobial peptides. Third, they can cause changes in blood-ocular barrier permeability, thereby facilitating microbial translocation. These pharmacological impacts potentially disrupt the ocular surface's homeostatic network, creating a dysbiotic state associated with clinical manifestations ranging from dry eye disease to microbial keratitis[6]. Elucidating these mechanisms holds dual clinical significance—enabling predictive biomarkers for treatment-related ocular morbidity while revealing novel targets for microbiome-based adjuvant therapies in cancer management (Figure 1).

MECHANISMS OF ACTION OF MAINSTREAM BREAST CANCER ENDOCRINE THERAPIES

Pharmacological Ovarian Suppression As the primary estrogen source in premenopausal women, ovarian-derived estradiol drives tumor progression in hormone receptor-positive (HR+) malignancies[8]. Pharmacological ovarian suppression, which is implemented through the utilization of gonadotropin-releasing hormone agonists (GnRHa), with goserelin being a prime example, elicits a prompt diminution of estrogen levels. This is achieved through the desensitization of the pituitary gland, resulting in a state of chemical castration that is functionally equivalent to that achieved by oophorectomy[9]. This initial therapeutic approach, which is the first-line intervention for high-risk premenopausal patients with HR+ breast cancer, has been shown in the EBCTCG Meta-analysis to reduce recurrence rates by 34%. However, it precipitously induces acute hypoestrogenic states that give

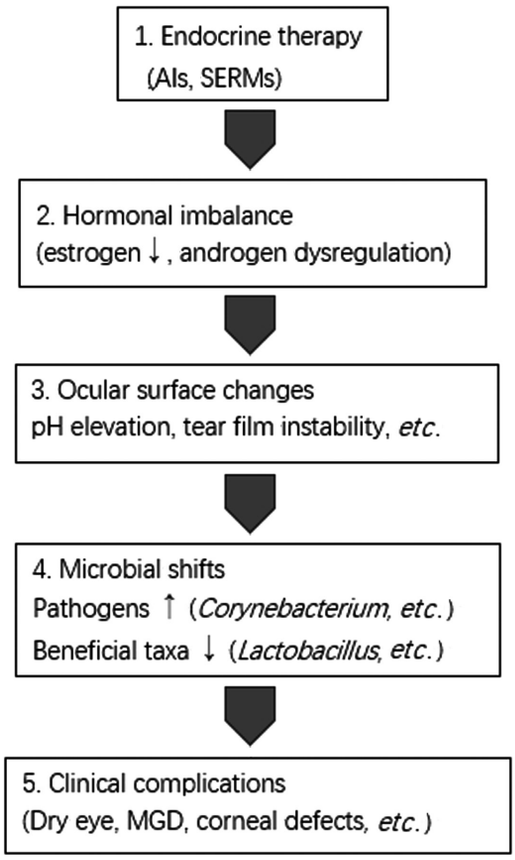

Figure 1 Effect of breast cancer-related endocrine therapy on ocular surface AIs: Aromatase inhibitors; SERMs: Selective estrogen receptor modulators; MGD: Meibomian gland dysfunction.

rise to physiological consequences across multiple systems[10]. The precipitous 90%-95% serum estradiol decline[5] disrupts estrogen-regulated ocular surface homeostasis, potentially altering meibomian gland function and mucin secretion patterns[11].

Selective Estrogen Receptor Modulation Tamoxifen, a prototypical SERM, exerts tissue-specific agonistic/antagonistic effects through estrogen receptor alpha/estrogen receptor beta (ERα/ERβ) dimerization dynamics[12]. While exerting an antagonistic effect on estrogenic signaling within breast tissue, the partial agonistic activity of (the agent) in other physiological systems accounts for the paradoxical effects observed. Specifically, it contributes to the preservation of bone density, yet simultaneously elevates the risk of endometrial hyperplasia, with a relative risk (RR) ranging from 2.4 to 6.0[13]. Longitudinal studies reveal cumulative ocular toxicity: 6.3% of long-term users (>5y) develop crystalline retinopathy, with 17% showing subclinical macular changes on optical coherence tomography (OCT)[14-15]. These alterations are associated with an ERβ-mediated impairment of the phagocytic function of the retinal pigment epithelium. Additionally, they are linked to changes in the cytokine profiles of the tear film, characterized by an increase in interleukin-6 (IL-6) and a decrease in transforming growth factor-beta (TGF-β)[16].

Aromatase Inhibition Strategies Postmenopausal estrogen synthesis relies on peripheral aromatization of adrenal androgens. Third-generation AIs achieve >97% enzyme inhibition through distinct mechanisms[17]: non-steroidal AIs (anastrozole/letrozole); reversible competitive binding to cytochrome P450 heme group, and steroidal AIs (exemestane); irreversible suicide inhibition *via* androstenedione analog formation.

AI therapy reduces circulating estrogens to undetectable levels (<3 pg/mL), exacerbating age-related ocular surface changes[18]. Bicer *et al*[16] found that AIs have a greater impact on tear function compared with tamoxifen. Microbiome analyses associated with these trials have demonstrated a significant enrichment of *Corynebacterium* species[19].

Emerging Targeted Combinations

mTOR pathway inhibition Everolimus, an mTORC1 inhibitor, reverses endocrine resistance by blocking PI3K/Akt/mTOR hyperactivation-a pathway upregulated in 70% of metastatic HR+ cases[20]. Due to its lipophilic characteristic, everolimus can readily penetrate the ocular tissues. Animal model studies have shown that it exerts a dose-dependent inhibitory effect on corneal neovascularization. Specifically, at a dose of 5 mg/kg, a 35% reduction in corneal neovascularization was observed[21].

CDK4/6 Inhibition Palbociclib/ribociclib/abemaciclib disrupt cell cycle progression through selective CDK4/6 blockade. When combined with endocrine therapy, these agents improve median progression-free survival from 14.5 to 24.8mo in advanced HR+/HER2- disease[22]. Preliminary ocular safety data indicate 9.2% incidence of blurred vision, potentially linked to RB1 phosphorylation-dependent alterations in lacrimal gland ion transport[23].

CURRENT COMPREHENSION OF THE DYNAMICS OF THE OCULAR SURFACE MICROBIOTA: THE OCULAR SURFACE MICROBIOME AS THE SENTINEL OF OCULAR HOMEOSTASIS

Microbial Ecosystem Architecture The ocular surface constitutes a unique mucosal interface harboring a low-biomass but functionally critical microbial community. Advanced 16S rRNA sequencing reveals core commensals including *Staphylococcus epidermidis* (15%-30% relative abundance), *Corynebacterium macginleyi* (8%-15%), and *Cutibacterium acnes* (5%-12%), forming a dynamic biofilm matrix with host-derived mucins and antimicrobial peptides[24]. This tripartite symbiosis—comprising bacteria, epithelial cells, and tear film components—maintains ocular surface integrity through quorum sensing-mediated population control[25].

Disruption of this equilibrium, whether by immunosuppression (*e.g.*, CD4+ <200 cells/μL) or microenvironmental shifts (pH >8.0), permits pathogen expansion (*Pseudomonas aeruginosa* virulence factor upregulation 4.7-fold), predisposing to microbial keratitis (incidence 27/10 000 contact lens users)[26-27].

Functional Paradigms of Ocular Microbiota Bioprotective mechanisms: The ocular surface microbiota attaches to the surface of the epithelial cells of the ocular surface, forming a biofilm-like structure, for example, commensal *Staphylococcus epidermidis* expresses fibrinogen-binding adhesins that competitively inhibit *Staphylococcus aureus* corneal adhesion (IC50=2.5 μmol/L)[28-29]. Furthermore, the metabolite-mediated defense can inhibits microbial growth, and plays a crucial role in maintaining homeostasis, such as *Corynebacterium spp*. produce copiotrophic siderophores (corynebactin Kd=10^{-23} M) that sequester iron, limiting *Acanthamoeba* proliferation by 78% *in vitro*[30]. Unfortunately, a similar effect has not been observed in humans from these results, warranting additional research.

Immunological Crosstalk Innate immune priming: The ocular surface microbiota can stimulate the local immune system of the ocular surface, promoting the maturation and differentiation of immune cells such as lymphocytes and macrophages, and enhancing the immune defense ability of the eyes. TLR2 activation by commensal lipoteichoic acids enhances neutrophil extracellular trap (NET) formation efficiency by 40% against *Candida albicans*[31-32].

Adaptive regulation: The ocular surface microbiota helps to maintain the immune tolerance state of the ocular surface, preventing the immune system from generating an excessive immune response against the normal tissues of the ocular surface. Through interacting with immune cells, they can induce the generation of immune regulatory cells such as regulatory T cells, inhibit the excessive activation of the inflammatory response, and avoid the occurrence of autoimmune eye diseases[33]. In addition, IL-17RC+Treg differentiation induced by ocular surface microbes can maintain corneal allograft survival in murine models[34].

Metabolic Symbiosis Vitamin synthesis: Some of the ocular surface microbiota are capable of synthesizing certain vitamins, such as B vitamins. These vitamins can be absorbed and utilized by the tissues of the ocular surface and participate in the metabolic processes of the cells on the ocular surface, which is of great significance for maintaining the normal structure and function of the epithelial cells of the ocular surface[35].

Tear film modulation: Microbial neuraminidases transform tear glycoconjugates into sialic acid, resulting in a 15% increase in sialic acid levels in dry eye conditions. This transformation enhances ocular surface wettability, as evidenced by a 12° reduction in the contact angle[27]. The ocular surface microbiota plays a crucial role in regulating the pH and osmotic pressure of the ocular surface microenvironment. Specifically, it can modulate the ion concentration and composition within tears. This modulation is essential as it facilitates the uptake and utilization of nutrients by the cells on the ocular surface[28].

Microenvironment Stabilization pH buffering: The ocular surface microbiota can regulate the pH value of the ocular surface by metabolic activities, keeping it within a relatively stable range. Lactate secretion by *Streptococcus mitis* maintains conjunctival pH at 7.4±0.2 through H^+/HCO_3-co-transport[36].

Regulating the composition of tears: Some microbial communities are able to produce specific enzymes or metabolites, participating in the synthesis or decomposition of certain components in the tears, and maintaining the normal composition and function of tears[26].

Pathogen Antagonism Bacteriocin warfare: Some beneficial bacteria on the ocular surface are capable of producing substances with antibacterial activity, such as bacteriocins and hydrogen peroxide, and these substances can directly inhibit or kill other harmful microorganisms[4]. For example, certain *Staphylococci* can produce bacteriocins, which have an inhibitory effect on pathogenic bacteria such as *Staphylococcus aureus*, and some other lactic acid bacteria can produce hydrogen peroxide, which has a broad-spectrum antibacterial effect and helps maintain the balance of the microbial community on the ocular surface[35].

Quorum quenching: The ocular surface microbiota can also inhibit the growth of pathogenic bacteria by changing the microenvironment of the ocular surface. They can reduce the redox potential of the ocular surface, making the ocular surface environment unfavorable for the growth of aerobic bacteria. Alternatively, they can produce some acidic metabolites, reducing the pH value of the ocular surface, thereby inhibiting the growth of pathogenic bacteria that are sensitive to an acidic environment[26,37].

HORMONAL IMBALANCE AND OCULAR SURFACE HOMEOSTASIS

The ocular surface ecosystem is profoundly influenced by endocrine dynamics, particularly in patients undergoing estrogen-depleting therapies such as AIs or ovarian function suppression[38].

Estrogen Deficiency Impacts Estrogen exerts multifaceted regulatory effects on ocular surface physiology. Beyond maintaining corneal epithelial integrity and lacrimal gland function, this hormone governs cellular metabolic processes essential for epithelial renewal and repair[39]. Therapeutic estrogen suppression induces the thinning of ocular surface

mucosa with diminished regenerative capacity and the altered tear film composition through modified meibomian lipid profiles and the metabolic reprogramming of surface epithelium, potentially disrupting nutrient availability for commensal microbiota[12].

These microenvironmental shifts may facilitate ecological succession within ocular surface microbiota, enabling opportunistic species to outcompete traditional symbiotic communities[40].

Androgen Signaling Disruption The androgen axis plays complementary roles in ocular surface protection through modulating the secretory rhythms of the meibomian gland, maintaining the architecture of the tear film and regulating the expression of the antimicrobial peptide.

Endocrine interventions may impair androgen receptor signaling, leading to destabilized tear film kinetics, accelerated tear evaporation rates and pH alterations in the ocular surface niche[41].

Such cascading effects create selective pressures that reshape microbial colonization patterns, potentially predisposing to dysbiosis-related ocular surface disorders.

Ocular Surface Microenvironment Remodeling Endocrine therapies induce bidirectional modifications in tear film dynamics and acid-base equilibrium, creating pathophysiological cascades that disrupt microbial homeostasis.

Tear film pathophysiology: Selective estrogen receptor modulators, with tamoxifen being a prime example, bring about a quantitative reduction in the levels of lactoferrin and lysozyme. Additionally, they induce a hyperosmotic shift, with values exceeding 316 mOsm/L, through the mechanism of electrolyte disproportion. This hyperosmotic microenvironment triggers epithelial apoptosis *via* TRPV1-mediated pathways and exerts selective pressure on microbiota by inhibiting osmosensitive commensals like *Corynebacterium spp*. and giving a competitive advantage to extremophiles, for example, in the formation of *Staphylococcus aureus* biofilm[42-43].

Ocular surface acid-base dynamics: Therapeutic agents disrupt the carbonic anhydrase-mediated pH regulation process. This disruption leads to a shift from a neutral towards an alkaline environment, with the baseline pH changing from 7.4 to a range of 7.8-8.2. Such pH alteration not only disturbs the ecological niches of acidophilic symbionts but also activates the alkaline-dependent virulence factors present in pathogens[26]. These coordinated changes predispose to proteolytic degradation of mucin layers, dysregulation of quorum sensing networks and emergence of polymicrobial consortia with enhanced antibiotic resistance[12,37].

Immunomodulatory Consequences Endocrine therapeutics induce systemic and localized immune reprogramming through dual mechanisms of cellular immunity suppression and cytokine network dysregulation. These collective deficits including Leukocyte Functional Attenuation lead to compromised immune surveillance at the ocular interface, failure in pathogen-associated molecular pattern (PAMP) recognition, and disrupted homeostasis maintenance between commensals and opportunistic pathogens[44]. Estrogen deprivation triggers a proinflammatory shift, which is characterized by Th1/Th17 polarization, anti-inflammatory cytokine collapse, and danger signal amplification[45]. This low-grade inflammatory milieu modulates microbial gene expression profiles *via* NF-κB-mediated pathways. It also facilitates biofilm formation by way of IL-8-induced bacterial adhesion molecules. Moreover, it instigates dysbiosis through the disruption of nutritional immunity, specifically, an imbalance in siderophore competition[46].

Mechanistic Effects of Endocrine Therapies on Ocular Surface Microbiota

Antimicrobial properties of therapeutic agents Certain endocrine modulators exhibit inherent antimicrobial properties that may secondarily influence ocular surface microbiota. While these agents primarily target endocrine pathways, systemic distribution enables drug metabolites to reach periocular tissues, exerting direct or indirect effects on microbial communities. For example, some drugs may have certain antibacterial activities and nonspecifically inhibit the growth of some bacteria on the ocular surface, *e.g*., tamoxifen's antibacterial effects[47], while other drugs may promote the growth of certain specific microorganisms, thus changing the composition of the ocular surface microbiota[48].

Tamoxifen's biphasic ocular actions Notably, tamoxifen demonstrates dual temporal effects on ocular physiology[47]. First, there is short-term modulation: the drug's local estrogenic agonist activity transiently upregulates ERβ expression in conjunctival goblet cells, enhancing mucin secretion. Second, there is chronic adaptation: prolonged exposure induces receptor desensitization accompanied by microbial dysbiosis. Preclinical models show that tamoxifen causes ocular surface changes. These include more Staphylococcus colonization, which is linked to higher IL-6 levels. There's also an imbalanced Th17/Treg ratio that hampers pathogen clearance, along with local immunosuppressive signs[49].

Aromatase inhibitor-induced microenvironment alterations The hypoestrogenic state induced by aromatase inhibition significantly modifies ocular surface homeostasis through multiple mechanisms. It leads to reduced lysozyme activity in the tear film, elevated pH levels that foster opportunistic pathogens such as Pseudomonas aeruginosa, and structural deterioration of both meibomian glands and the corneal architecture[11].

RELATIONSHIP BETWEEN OCULAR SURFACE DYSBIOSIS AND OCULAR COMPLICATIONS

Changes in ocular surface microbiota composition are strongly associated with diverse ocular complications, potentially contributing to infectious, immune-mediated, and other ocular disorders. The following sections provide a detailed analysis.

Infectious Ocular Complications Bacterial Keratitis: Under physiological conditions, commensal ocular flora inhibits pathogenic bacterial growth through nutrient competition and competitive adhesion. Dysbiosis within the ocular surface microbiome, such as that induced by antibiotics leading to the depletion of beneficial bacterial species, can potentially enable the pathogenic overproliferation of *Staphylococcus aureus* or *Pseudomonas aeruginosa*. These pathogens can invade corneal tissue, leading to bacterial keratitis, corneal ulceration, and vision loss[33].

Conjunctivitis: Microbial dysregulation within the conjunctiva may potentiate the overproliferation of indigenous conjunctival bacteria, such as *Corynebacterium* and *Staphylococcus* species, or enhance the colonization of exogenous pathogens. This dysbiosis can trigger conjunctivitis, characterized by conjunctival hyperemia, increased discharge, and foreign body sensation[5]. Notably, poor hygiene environments increase ocular surface contamination risk, which—combined with reduced local immunity—predisposes individuals to acute bacterial conjunctivitis[50].

Dacryocystitis: The lacrimal drainage system plays a critical role in maintaining ocular surface microbial equilibrium through tear flow. Dysbiosis may enable bacterial retrograde migration into the lacrimal sac, with pathogens such as Streptococcus pneumoniae and Staphylococcus aureus causing dacryocystitis. Clinical manifestations include epiphora, lacrimal sac erythema, and localized tenderness[51].

Immune-Mediated Ocular Complications Dry eye disease: Normal ocular microbiota stimulates local cytokine production and immunoregulatory factors to maintain ocular surface immune homeostasis. Dysbiosis can exacerbate inflammatory responses, impinge upon lacrimal gland function, thereby reducing tear production, and undermine the integrity of the epithelial barrier, which in turn increases tear evaporation. Patients, especially those undergoing endocrine therapy, commonly report experiencing symptoms such as dryness, a foreign-body sensation, and a burning sensation[18,25,52].

Allergic conjunctivitis: Alterations in the ocular surface microbiota have the potential to disrupt immune tolerance mechanisms. Emerging evidence points towards a cross-talk phenomenon between the gut microbiota and the ocular microbiota, commonly referred to as the “gut-eye axis”. Intestinal dysbiosis can enhance the ocular surface’s sensitivity to allergens *via* immune cell trafficking/metabolites, rendering individuals more susceptible to allergic conjunctivitis, which is characterized by symptoms such as itching, hyperemia, and tearing[26,35,46].

Immune-related corneal pathology: Microbial imbalance can activate ocular immune cells, triggering inflammatory mediator release and corneal tissue damage. In autoimmune disorders, dysbiosis may contribute to limbal stem cell deficiency and corneal ulceration, potentially impacting corneal transparency and visual acuity[33]. Regulating the gut microbiome through the consumption of *Limosilactobacillus fermentum* can inhibit corneal damage and inflammation in a mouse model of dry eye disease[7]. Notably, exemestane therapy is associated with corneal epithelial alterations[53].

Other Ocular Complications Meibomian gland dysfunction (MGD): Meibomian gland-derived lipids are essential for tear film stability. Dysbiosis may disrupt glandular secretory function, causing abnormal lipid composition, gland orifice obstruction, and altered secretion viscosity. These changes compromise tear film integrity, leading to ocular discomfort and visual fluctuation[54].

Corneal neovascularization: Chronic ocular surface inflammation from persistent dysbiosis may stimulate limbal vascular endothelial cell proliferation, resulting in pathological corneal neovascularization. This condition reduces corneal transparency, impairs vision, and may precipitate complications including corneal edema and scarring[55].

Ocular surface dysbiosis is intricately linked to multiple ocular pathologies. Microbial imbalance disrupts immune regulation, amplifies inflammatory cascades, and facilitates opportunistic infections—collectively contributing to conditions such as dry eye syndrome, conjunctivitis, and vision-threatening corneal complications. These alterations significantly impact patient quality of life and therapeutic outcomes (Table 1).

CONCLUSIONS AND FUTURE PERSPECTIVES

While endocrine therapy remains a cornerstone in breast cancer management for tumor control, its disruptive effects on ocular surface microbiota warrant critical attention. Emerging evidence indicates that hormonal fluctuations, along with the direct pharmacological actions of therapeutic agents such as exemestane, disrupt the microecological equilibrium of the ocular surface. This disruption consequently heightens the risks of ocular comorbidities. Future investigations should focus on the following directions. First, in terms of mechanistic elucidation, it is crucial to decipher the ocular pathways through which endocrine therapies affect the composition and function of ocular surface microbiota. Particularly, understanding their interaction with immune modulation and epithelial barrier integrity is of great significance. Second, for therapeutic innovation, efforts should be made to develop targeted interventions such as probiotic-based ophthalmic

Table 1 Ocular complications and associated microbial shifts in endocrine therapy recipients

Ocular complication	Associated microbial shifts
AIs-related dry eye disease	Enrichment of *Corynebacterium* spp. (especially *C. kroppenstedtii*, *C. macginleyi*)- Reduction of commensal *Staphylococcus epidermidis*- Decreased alpha-diversity of ocular surface microbiota
MGD	Overgrowth of *Cutibacterium acnes* (formerly *Propionibacterium acnes*) in meibomian glands- Dysbiosis of lipid-associated microbiota (reduced *Streptococcus* spp.)
Corneal epithelial abnormalities	Enrichment of pathogenic *Staphylococcus aureus* (methicillin-sensitive strains)- Loss of commensal barrier protection (*Lactobacillus* spp. reduction)
Ocular surface inflammation	Elevated pro-inflammatory microbial metabolites (lipopolysaccharides from Gram-negative bacilli; lipoteichoic acid from *Staphylococcus*)- Dysregulated microbiota-immune crosstalk (reduced *Bifidobacterium* spp.)

AIs: Aromatase inhibitors; MGD: Meibomian gland dysfunction.

formulations, *e.g.*, *S.epidermidis* strains that inhibit *S.aureus*[28], and microbiota-modulating agents to restore microbial homeostasis. Third, in terms of clinical translation, validating prophylactic and therapeutic strategies through longitudinal clinical trials is essential to mitigate ocular complications such as dry eye disease and corneal lesions and improve the quality of life of breast cancer survivors. Addressing these priorities will promote personalized ocular care in oncology, striking a balance between antitumor efficacy and the preservation of ocular surface health.

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