Ocular inflammation is a serious and frequently encountered problem in veterinary ophthalmology. The causes of ocular inflammation are varied and include primary ocular disorders such as keratitis sicca, chronic superficial keratitis (degenerative pannus), and lens-induced uveitis and disorders secondary to systemic disease processes such as mycoses, autoimmune disease, septicemia, and rickettsial infections, to name but a few. The treatment of ocular inflammatory disease is varied and based on the segment of the eye involved, etiology, and severity of inflammation. Primary therapy should be directed toward removing or controlling the inciting cause, although concurrent nonspecific anti-inflammatory therapy is often indicated to prevent further ocular injury. Nonspecific therapy is directed at suppressing the inflammation regardless of etiology. Nonspecific therapy includes corticosteroids, nonsteroidal anti-inflammatory agents (NSAIDs), atropine, azathioprine, megestrol acetate, and cyclosporine. Treatment of ocular inflammation must be immediate and aggressive if adverse sequelae are to be avoided. In all cases, all commercially available ophthalmic medications are specifically formulated for use in the eye. Their pH, concentration, osmolality, and melting temperature all are designed to facilitate penetration[1]. In all cases of eye irritation or inflammation, a mild, eye-cleaning solution is important to help remove debris and irritants, soothe and lubricate the eye.

For many years, the tear film has been characterized as having three layers: a mucus layer close to the corneal epithelial surface, an aqueous layer, and, finally, a most superficial layer of meibomian lipid that acts to reduce evaporation[2]. More recently, studies have shown that this cut-and-dried distinction between layers is not strictly correct—the corneal epithelium has a surface glycocalyx composed of membrane-spanning mucins (including MUC1, 3, 4, 12, 13, and 16), with these having signalling capabilities through their cytoplasmic tail and extracellular epithelial growth factor-like domains[3]. The aqueous layer, far from being solely aqueous in nature, is filled with cleaved membrane-bound mucins, small soluble mucins (MUC 7 and 9), and much larger gel-forming mucins (including MUC2, 5, 6, and 19)[4]. Mucins are formed in conjunctival goblet cells, whereas tear film lipid arises from the lid meibomian glands. The aqueous component of the tear film is produced in the dog from the lacrimal gland dorsolateral to the globe and is closely associated with it; it is also produced by the gland of the nictitating membrane. Recently, it has become clear that to understand the physiology of tear production and the pathophysiology of dry eye, the entire unit of the lacrimal glands, ocular surface, and innervation connecting them needs to be considered fully to describe the pathologic events occurring in KCS.

Because of the complex interactions among the lipid, aqueous, and mucin tear components, abnormalities in the quantity or quality of any of these three primary components may alter the fluid dynamics and thus compromise the functions of the tear fluid. Hypertonicity and dehydration of conjunctival and corneal epithelia are the most common events associated with deficiency of one or more of the tear components. Hypoxia of the corneal epithelium and subepithelial corneal stroma may then occur.

Because an overwhelmingly high percentage of the total tear volume is aqueous tear, quantitative tear deficiency is considered synonymous with insufficient production of aqueous fluid. Diseases causing decreased secretion of aqueous tears are diseases of the lacrimal glands or the nerve supply to these glands. Dry-eye states associated with lacrimal gland hyposecretion are collectively referred to as keratoconjunctivitis sicca.

Keratoconjunctivitis sicca is characterized by desiccation of the ocular surface with accompanying inflammation, pain, progressive corneal disease, and reduced vision. Tear-

deficient eyes have an increased susceptibility to ocular surface infections caused by colonization of either opportunistic or pathogenic microorganisms. Lack of efficient moisturization may result in frictional irritation to surface cells by the eyelids or third eyelid. Potentially toxic tissue metabolites-that is, lactic acid, desquamated cells, denatured mucus, and other organic debris-may accumulate on the ocular surface.

Abnormalities or deficiencies of tear components other than aqueous fluid are considered to be qualitative disorders[5]. Abnormalities of the lipid and mucin components of the preocular tear film may result from diseases of the eyelid margins and conjunctiva. Chronic keratoconjunctivitis with epithelial edema and superficial corneal neovascularization, with or without ulceration, characterizes qualitative tear diseases. Tear components other than lipid and mucin that carry probable clinical significance include tear proteins, *all-trans* retinal, cholesterol, glucose, and electrolytes. Although less common than quantitative or aqueous deficiencies, qualitative abnormalities are recognized as primary or secondary causes of ocular surface disease in companion animals.
Distributional abnormalities resulting from lagophthalmos, buphthalmos, eyelid paresis, corneal anesthesia, third eyelid deformities, or frictional irritants may result in an abnormal tear covering or rupture of the tear film with surface drying. These disorders therefore must be distinguished from primary quantitative or qualitative tear deficiencies.

In an effort to determine baseline tear pH in dogs, horses, and cattle by use of a microelectrode[6], mean ± SD pH of tears in cattle, dogs, and horses was found to be 8.32 ± 0.14, 8.05 ± 0.26, and 7.84 ± 0.30, respectively. The tear pH of the 3 species was more alkaline than most values reported in humans, so it is likely that the ocular pH comfort zone for these species is more alkaline than in humans. Because veterinarians often prescribe topically administered ophthalmic preparations formulated for humans, one could assume that production of more alkaline ophthalmic drug preparations could increase the ocular comfort of treated animals. However, alkalization of these preparations would decrease their shelf life[7] and would come at a substantial cost or require other modifications, which are not always possible, for improved drug stability.
Rheology is also an important parameter when designing an eye product as tear replacement medication[8].

1. Witch Hazel (Amamelis virginiana) water

Making use of the medicinal properties of *Hamamelis virginiana*, Native Americans have for centuries been using decoctions of witch hazel leaf and bark. HM leaf (*Hamamelidis* folium) contains 3–8% or, according to some sources, up to 10% tannins, mainly gallotannins, proanthocyanidins, flavone glucosides, phenolic acids including caffeic and gallic acids, small amounts of essential oils, and a mixture of paraffins. HM bark (*Hamamelidis* cortex) contains 9–12% tannins, mainly hamamelitannins, catechins, gallocatechin, epicatechin gallate, proanthocyanidins, flavonoids, some essential oils, fats, waxes, and resin-like constituents. Dermatological formulations that contain HM are used mainly for their antiinflammatory activity. Hamamelitannins and proanthocyanidins isolated from the ethyl acetate-soluble portion of the bark have been shown to produce in vitro inhibition of 5-lipoxygenase[9]. Inhibition of vascular permeability and a vasoconstrictor effect of the crude extract have been observed in animal studies[10]. Reductions in cutaneous blood flow and skin temperature have also been demonstrated in humans (aqueous propylene glycol extract) [11] as has a reduction in UV erythema (distillate)[12]. Studies by the authors using an experimental irritation model (sodium lauryl sulfate irritation test) showed that HM distillate produced significant reductions in skin

redness (chromametry a*-value) and cutaneous blood flow (laser doppler). The effect of HM distillate was clearly weaker than that of hydrocortisone[13].
The antimicrobial activity of a distillate of *Hamamelis* (Aqua *Hamamelidis*), and urea was investigated[14]. The studies presented here show that HM distillate and U have antiseptic activity, also against *Staphylococcus aureus* and *Candida albicans*. Quantitative comparison of the in vivo antimicrobial activity of distillate of HM and U with that of other antiseptic agents such as chlorhexidine digluconate 1% and fuchsine 0.5% reveals that the latter achieved a quantitatively significantly more impressive reduction in bacterial counts than HM distillate and U. While HM distillate and U should not be used in skin conditions primarily for their antiseptic activity, this effect may confer added benefit when HM distillate and U are indicated for their antiinflammatory, barrier-stabilizing and hydrating effects. This additional antimicrobial activity is particularly welcome in the management of atopic dermatitis and intertrigo because the organisms involved in the pathogenesis of these conditions are susceptible to the HM distillate U combination.

1. **Boric acid**

Boric acid, a mild germicidal agent, is commonly used in solutions for eye applications in cases of injury of infection, and lacrimal secretions may even slightly increase the bacteriostatic action[15].
In a study[16] assessing the effect of boric acid on the ocular surface, cells were treated with relevant concentrations of boric acid using two cytotoxicity assays. Additionally, the impact of boric acid on corneal epithelial barrier function was assessed by measuring TEER and immunostaining for tight junction protein ZO-1 in human corneal epithelial cells. Boric acid was also assessed in an in vivo ocular model when administered for 28 days. Boric acid passed both cytotoxicity assays and did not alter ZO-1 distribution or corneal TEER. Furthermore, boric acid was well-tolerated on-eye following repeated administration in a rabbit model.
Immediate irrigation with borate-buffer solution has been established as part of the protocol for emergency eye rinse for chemical injuries as it has been proven to retard or prevent the destructive effects of alkaline chemical exposure to the eyes[17].

1. **Carboxymethylcellulose**

Carboxymethylcellulose (CMC), a high-molecular-weight polysaccharide, is one of the most common viscous polymers used in artificial tears to achieve their prolonged residence time on the ocular surface. It has been shown to be efficacious in the treatment of aqueous tear-deficient dry eye
symptoms and ocular surface staining, and this effect has been found to be dose-dependent, with greater improvement observed with 1.0% CMC than with 0.5% CMC[18]. It is generally understood that it is the physical properties of CMC, such as its viscous and mucoadhesive properties, that contributes to its prolonged retention time in the ocular surface. CMC-based artificial tears have also been widely used after laser in situ keratomileusis (LASIK) to accelerate postoperative Although the precise role of CMC in the protective effect observed is not known, these findings suggest that CMC may be involved in the repair of the ocular surface.
The ability of carboxymethylcellulose (CMC), used in artificial tear formulations, to interact with corneal-epithelial-cells (HCECs) and facilitate corneal epithelial wound healing was investigated[19]. CMC was found to bind to corneal epithelial cells and remain bound for at least several hours. Further, CMC stimulate epithelial cell migration through its binding to matrix proteins and the enhancement of cell attachment to the matrix by CMC could be a major contributor to the observed closure of the scratched cell monolayer and re-epithelialization of rabbit cornea epithelial scrape wounds. The properties of this polymer may form the basis for the observed long-lasting benefits of clinical use of CMC.

In a systematic review and meta-analysis[20] of the comparative efficacy of two artificial tears, carboxymethylcellulose (CMC) and hyaluronate (HA) in the treatment of patients with dry eye disease, the efficacy of CMC appeared to be better than that of HA in treating dry eye disease, although meta-analysis results were not statistically significant.
A blinded, prospective, randomized clinical study[21] aimed to compare three different lubricant eye drops (LED) in healthy adult dogs undergoing general anaesthesia (GA) for non-ophthalmic surgery. Tear production rate was monitored by means of Schirmer tear test-1 (STT-1), and incidence of post-operative corneal abrasions/ulcerations was detected by corneal staining. A complete ophthalmic examination was performed before premedication, at extubation time and 24 h after GA in twenty-five non-brachycephalic dogs (fifty eyes) undergoing elective orthopaedic or spinal surgery procedures. Dogs were randomly allocated to one of three groups receiving as prophylactic LED either carboxymethylcellulose sodium (CMC), or 1% hyaluronic acid (GH), or 0.25% hyaluronic acid (GL). In each eye STT-1 was repeated every hour during GA, before instilling one drop of the assigned LED. In all groups STT-1 values drastically decreased during GA, while 24 h later nine eyes (18%) had STT-1 values lower than 15 mm/minute. All of the three formulations tested were fully effective in preventing corneal ulceration (0% in all groups), while 10% of eyes reported superficial de-epithelialization. Fluorescein staining demonstrated that hourly prophylactic LED application prevented exposure keratopathy during general anesthesia in 90% of the eyes in non-brachycephalic dogs.

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