Review

Use of nutraceuticals in the management of Keratoconjunctivitis sicca

Dr+Vet by Böthmen Pharma

Introduction

Keratoconjunctivitis sicca (KCS), also known as dry eye syndrome, is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles. KCS has a prevalence in dogs of 0.4% according to a recent study carried out by the BSAVA (British Small Animal Veterinary Association) (1). KCS can occur because of reduced production of the aqueous portion of the tear film (quantitative deficiency) and/or excessive evaporation of the tear film (qualitative deficiency). Both phenomena render the protective function of the tear film deficient. KCS mainly affects structures of the cornea and conjunctiva. Among the causes of KCS in animals are racial predisposition, hypothyroidism, medications (atropine, sulfonamides), surgical excision of the third eyelid gland, distemper, and, mainly, autoimmune factors (2).

Several different types of KCS can be identified depending on the layer of the tear film that is affected, although in any of them, the key pathological mechanism of the disease will be tear hyperosmolarity, which will damage the ocular surface by causing an inflammatory process.

When there is a reduction in the production of the aqueous component of the tear film under normal evaporation conditions, it will be quantitative keratoconjunctivitis sicca. If there is excessive tear evaporation in the presence of a functional lacrimal gland, we will speak of qualitative keratoconjunctivitis sicca (3).

In any case, on many occasions in which there is a dysfunction of the lacrimal glands with reduced tear secretion, we will find in these patients a hybrid form in which both characteristics of aqueous deficiency and increased evaporation will be present (3). In pets, the qualitative form can be observed in any breed, although it will be more common in brachiocephalic animals with lagophthalmos (inability to completely close one or both eyelids) or in pets in which, due to a deficiency in the lipid layer of tear film, greater loss occurs due to evaporation (4). Dysfunctions in the meibomian glands as a result of marginal blepharitis, blepharoconjunctivitis, meibomianitis and dermatological diseases are the main causes that have been associated in both pets and humans for the qualitative form of the disease (5).

Even though it is relatively common, qualitative KCS often goes unnoticed in general clinics because the results of the Schirmer test (STT-1) are usually within normal values and the tests recommended for its diagnosis such as Tear Break-Up Time (TBUT) or the OSA-VET® (veterinary ocular surface analyzer) (6), are less widely used in non-specialized centers. Therefore, many patients who suffer from this variant of the disease do not receive adequate and effective treatment, worsening their symptoms and quality of life.

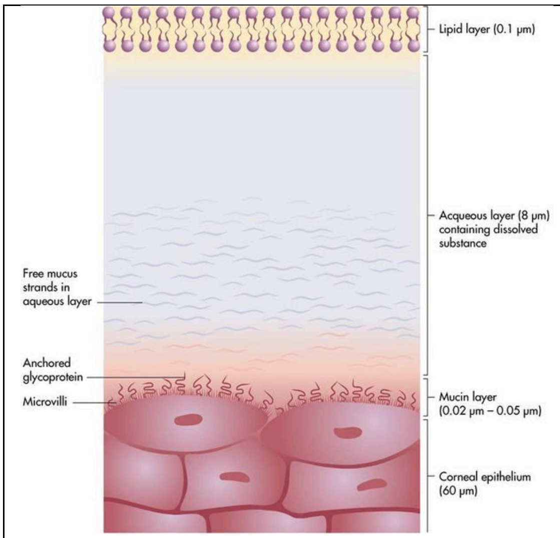
Current therapies for KCS rely on immune-suppressive treatments represented by Cyclosporine A, glucorticoids, Tacrolimus and artificial tears in order to recover an adequate eye's lubrication (7).

In this review, we focus on the different ingredients that could help to improve the symptomatology of KCS and that are included in our product **Lacrimalis+**.

The tear layer

The tear film provides lubrication and hydration to the ocular surface. It is a source of oxygen, immunoglobulins, lysozymes, lactoferrin and defensins.

The mammalian tear film is made up of three layers (Figure 1):



The innermost layer is composed of mucin, which is secreted by conjunctival goblet cells and which function is to provide a smooth corneal surface to improve the spread of the tear film (8).

The intermediate layer is the aqueous one, secreted by the lacrimal glands and responsible for the main metabolic and defensive functions of the tear (9).

The outermost layer is the lipid layer, secreted by the meibomian glands and the main functions of which is to limit evaporation, improve the adhesion of the tear film to the cornea and provide the necessary surface tension to prevent tear overflow (6).

Figure 1. Layers of the tear film

Omega-3 Fatty Acids

Omega fatty acids, a family of monounsaturated and Polyunsaturated Fatty Acids (PUFAs), primarily encompasses three subtypes – Omega-3, Omega-6 and Omega-9 fatty acids. Among these, Omega-3 and Omega-6 are essential PUFAs which cannot be synthesized in mammals' bodies. There are three types of Omega-3 fatty acids: alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In the Omega-6 family, Linolenic acid is a chief member (10).

ALA metabolizes to EPA and DHA, whereas linoleic acid forms arachidonic acid, upon metabolism. As arachidonic is a precursor for the formation of pro-inflammatory mediators, prostaglandins, thromboxanes and leukotrienes, linoleic acid is involved in aggravating inflammatory responses in the body. In contrast, Omega-3 fatty acids have been proven to possess anti-inflammatory, antithrombotic, anti-arrhythmic and antiangiogenic properties (10).

Because mammals are limited in their capacity to biosynthesize omega-3 PUFAs de novo, their tissue status is modifiable via diet or supplement intake of DHA and EPA. Fish oil from cold-water fish (e.g., salmon, tuna, herring) is an important source of Omega-3 (11).

Various studies found that ALA significantly decreases the levels of several inflammatory mediators, namely vascular endothelial growth factor (VEGF) besides inhibiting the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1b and tumor necrosis factor (TNF-α). They also restitute the altered physiologies of various antioxidant enzymes (12).

EPA possesses anti-inflammatory properties due to its ability to affect the intracellular signaling pathways and, thereafter, the gene expression of various inflammatory mediators involved during an inflammatory response. This mainly occurs via EPA-induced inhibition of NF-jB, subsequently DHA is more related to its antioxidant properties and is involved in several cognitive processes while also linked to correct signaling between neurons. DHA has an important anti-inflammatory function in neuronal systems and the formation, development, and functioning of the brain and retina (2).

The anti-inflammatory action of omega-3 fatty acids on the meibomian glands is via 2 pathways: (14)

- By blocking the gene expression of proinflammatory cytokines, tumor necrosis factor-a, interleukins, proteoglycan degrading enzymes and cyclooxygenase-2.
- By producing anti-inflammatory factors (e.g., prostaglandin E3 and leukotriene B5).

There are a lot of studies that proved the efficacy of EPA and DHA fatty acids in the management of KCS in humans, and a few in veterinary medicine (14–19). We want to emphatize about three of them:

Haleh Kangari et al. (14) performed a randomized, double-blind clinical trial to assess the effect of oral omega-3 fatty acids on tear break-up time (TBUT), schirmer's score (STT), and ocular surface disease index (OSDI). This study demonstrated that oral consumption of omega-3 fatty acids (twice daily for a month) s associated with a decrease in the rate of tear evaporation, an improvement in dry eye symptoms, and an increase in tear secretion.

In the study performed by Danielle Alves et al. (2), they studied the effect of Omega-3 supplementation in dogs with KCS. They had three treatment groups: topical acrolimus only, tacrolimus + omega-3 oral supplementation and tacrolimus + omega-3 oral supplementation + antioxidants (vitamin C, E and selenium) for 6 months. In this study they analyzed the results of the inhibiting the expressions of pro inflammatory cytokines (13).

STT, conjunctival cytology, TBUT and green lissamine test. The conclusions of this study were that the use of omega-3 (EPA and DHA) improved the clinical signs of KCS, increasing the STT and TBUT values and promoting resolution of corneal ulcers. They found that the best results of the study were for the group with treatment of tacrolimus + omega-3.

There is another study, performed by Simona Destefanis et al. (7), with two groups of patients with KCS both treated with standard immunosuppressive therapy. The control group was fed with standard diet and the treatment group was fed with a nutraceutical diet.
The nutraceutical diet used in this clinical evaluation consisted in a commercial mixed formula based on fish proteins, rice carbohydrates, *Cucumis melo, Ascophyllum nodosum, Astaxanthin , Aloe vera, Carica papaya, Punica granatum, Camellia sinensis, Polygonum cuspidatum, Curcuma longa, Piper nigrum*, zinc and Omega 3/6. They concluded that the nutraceutical approach appears to significantly increase the eye's tear production and to clinically ameliorate the conjunctival inflammation status as well as the corneal keratinization, corneal pigment density and mucus discharge in chronic KCS dogs poorly responsive or unresponsive to immune-suppressive therapy.

Lactoferrin

Lactoferrin (LF) is an iron-binding protein from the transferrin family that has been reported to have numerous functions. It is found in most exocrine secretions (tears, milk and others) and in the secondary granules of neutrophils. Antimicrobial and anti-inflammatory activity reports on lactoferrin identified its significance in host defense against infection and extreme inflammation (20).

Lactoferrin regulates inflammatory cytokines production in a mode resembling to other anti-inflammatory cytokines by suppressing inflammation interacting with macrophages and restraining the production of inflammatory cytokines by cells (21). Lactoferrin is known to suppress the production of TNF-α, IL-1β, IL-6 and IL-8 in human mononuclear cells (in vitro) (22) and improve production of IL-10 and IL-4 (in vivo) (23).

Tear LF levels have been reported to be an indicator of lacrimal secretory function. LF concentration in tears has been reported to decrease in dry eye patients. Tear secretion decrease gradually over the age and LF concentration is also decreasing with the age. Therefore, it is reasonable that a LF decrease would have some relation to lacrimal gland function (24).

Dogru et al. had demonstrated that oral administration of LF for 1 month improved tear stability and the ocular surface epithelium condition in human dry eye patients with Sjogren syndrome (a several alteration of the lacrimal glands) (25).

One study performed by Kawashima M et al. (26) revealed a correlation between lacrimal gland secretory function and age-induced dry eye disease in rats, which may stem from oxidative stress. In another study (24), they investigated whether orally administered LF is effective in preventing lacrimal dysfunction and whether this effect is related to the antioxidative properties of LF, concluding that dietary LF seemed to provide an efficient treatment alternative to improve tear secretion in aged mice, increasing the production and stability of the tears in mice.

LF receptors are present in human nerve tissues and are upregulated with neural damage. Bovine LF administration has been reported to stimulate nerve growth factor secretion and aid neural healing in mice (27).

In summary, LF may attenuate oxidative stress damage and suppress inflammatory mediators in the lacrimal glands, as well as preserve the lacrimal gland function Although the detailed mechanisms remain to be clarified, we believe that the effect of LF on tear secretion is a combination of its direct impact on the lacrimal glands and the overall improvement in body metabolism. Thus, the use of LF as a nutritional supplement may be a novel and safe treatment alternative for patients with dry eye syndrome. (24).

Zinc is an essential micronutrient for all organisms, critically required for normal cellular processes as well as for normal metabolism. The eye has an unusually high zinc content, with the highest amount of zinc concentrated in the retinal pigment epithelium (RPE) followed by the retina. Zinc exists in the other ocular tissues, in the following (descending) order of content: the ciliary body, iris, optic nerve, sclera, cornea, and the lens (28).

Zinc plays a key role in fundamental cellular processes such as DNA synthesis, RNA transcription, cell division, and activation, as well as in prevention of cell apoptosis. So a zinc deficiency may affect negatively to the normal functions of the retina (29,30).

Light-induced retinal degeneration and visual cell loss in rats results in gene expressional changes related to inflammation, apoptosis, cytokine production, and innate immune responses; and these pathways can be suppressed by zinc supplementation, in combination with Age-Related Eye Disease Study (AREDS) antioxidant supplement formula and other antioxidants (31).

Copper is an essential trace element with the specific ability to easily accept and donate electrons; thus, it plays an important role in oxido-reduction and the scavenging of free radicals. Copper is added in various multi vitaminic formulations due to its strong link with zinc levels; high levels of zinc intake may cause copper deficiency anemia (32).

Vitamins (C, E)

Vitamin C, also known as ascorbic acid, is an important water-soluble vitamin. Vitamin C is available in many forms, but there is little scientific evidence that any one form is absorbed better or has more activity than another. Most experimental and clinical research uses ascorbic acid or sodium ascorbate. Natural and synthetic l-ascorbic acid are chemically identical, and there are no known differences in their biological activities or bioavailabilities (33).

Vitamin C is also a highly effective antioxidant, protecting essential molecules in the body, such as proteins, lipids, carbohydrates, DNA, and RNA, from damage by free radicals and reactive oxygen species that can be generated during normal metabolism (34).

The eye has a particularly high metabolic rate, and thus has an added need for antioxidant protection. Plasma concentrations of vitamin C, an indicator of intake, are related to levels in the eye tissue (35). In the eye, vitamin C may also be able to regenerate other antioxidants, such as vitamin E (36).

Vitamin E is a lipid-soluble antioxidant that exists in four common forms in nature: α-tocopherol, β-tocopherol, δ-tocopherol, and γ-tocopherol (37). α-Tocopherol is the form of vitamin E that is actively maintained in the human body and also the major form in blood and tissues (38).

The main function of α-tocopherol in humans appears to be that of an antioxidant. α-Tocopherol attacks free radicals to neutralize them. When a molecule of α-tocopherol neutralizes a free radical, it is altered in such a way that its antioxidant capacity is lost. However, other antioxidants, such as vitamin C, are capable of regenerating the antioxidant ability of α-tocopherol. Other functions of α-tocopherol that would be of benefit to ocular health include effects on the expression and activities of molecules and enzymes in immune and inflammatory cells (34).

Increased dietary levels of Vitamin E have been correlated with increased concentrations in the retina (37).

Minerals (Zn, Cu)

Zinc is an essential micronutrient for all organisms, essential for normal cellular processes and metabolism. The eye has an unusually high zinc content, with the highest amount concentrated in the retinal pigment epithelium (RPE), followed by the retina. Zinc is present in the other ocular tissues, in the following (descending) order of content: ciliary body, iris, optic nerve, sclera, cornea and lens (22).

Zinc plays a key role in fundamental cellular processes such as DNA synthesis, RNA transcription, cell division and activation, as well as in the prevention of cell apoptosis. Thus, zinc deficiency can adversely affect the normal functions of the retina and eye (23,24).

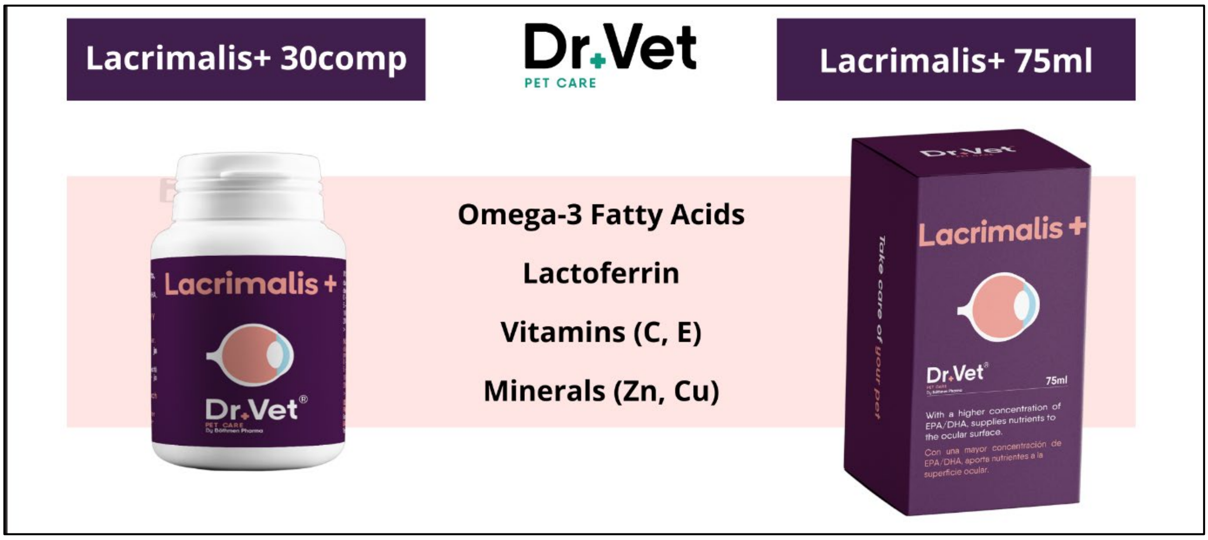
Copper is an essential trace element with the specific ability to readily accept and donate electrons, thus playing an important role in oxido-reduction and free radical scavenging. Copper is added to several multivitamin formulas because of its close relationship with zinc levels; high zinc intake can cause copper deficiency anemia (27).

Dietary multivitamin supplementation

There are a few studies with multivitamin supplements.

Motoko K. et al. (39) performed a preliminary study in a rat model and a prospective, randomized, double-blind, placebo-controlled study in humans examining the effect of a combined dietary supplement containing fish oil, lactoferrin, zinc, vitamin C, lutein, vitamin E, g-aminobutanoic acid, and Enterococcus faecium on dry eye. In the rat study, they found that the mixed supplement components suppressed the decrease in tear production in a dose-dependent manner. The combined dietary supplement in this study was designed to reduce oxidative stress. Vitamins C and E, zinc, lutein, and EPA/DHA were the major components of the supplement in this study and likely act as anti-oxidant and anti-inflammatory agents (39,40).

Paco Simó and Maria Simó from the Instituto Veterinario Oftalmológico (IVO) located in Barcelona have performed a comparative of 10 case reports of dogs with evaporative dry eye (41), utilizing **Lacrimalis+** with ocular lubricants and moisturizers. They reported an improvement in the results of the CIC, in the degree of Interferometry, an increase of 1 second in both NIBUT and TBUT and a slight reduction in tear production as indicated by STT-1 and Meniscometry. Concluding that the addition of a multivitamin + omega-3 + lactoferrin supplement in addition to the conventional treatment could help to improve the clinical symptoms of KCS in dogs. To read the full document: **click here**.



Bibliography

1. O'Neill DG, Brodbelt DC, Keddy A, Church DB, Sanchez RF. Keratoconjunctivitis sicca in dogs under primary veterinary care in the UK: an epidemiological study. Journal of Small Animal Practice. 2021 Aug 1;62(8):636–45.

2. Silva DA, Nai GA, Giuffrida R, Sgrignoli MR, Santos DR ds, Donadão IV, et al. Oral omega 3 in different proportions of EPA, DHA, and antioxidants as adjuvant in treatment of keratoconjunctivitis sicca in dogs. Arq Bras Oftalmol. 2018 Sep 1;81(5):421–8.

3. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017 Jul;15(3):438–510.

4. Williams DL. Immunopathogenesis of Keratoconjunctivitis Sicca in the Dog. Veterinary Clinics of North America: Small Animal Practice. 2008 Mar;38(2):251–68.

5. Ofri R, Orgad K, Kass PH, Dikstein S. Canine meibometry: Establishing baseline values for meibomian gland secretions in dogs. Veterinary Journal. 2007 Nov;174(3):536–40.

6. LJ Best DHDW. Diagnosis & Treatment of Keratoconjunctivitis Sicca in Dogs. Today's Veterinary Practice. 2014;(July/August 2014).

7. Destefanis S, Giretto D, Muscolo MC, Di Cerbo A, Guidetti G, Canello S, et al. Clinical evaluation of a nutraceutical diet as an adjuvant to pharmacological treatment in dogs affected by Keratoconjunctivitis sicca. BMC Vet Res. 2016;12(1).

8. SJ Hicks et al. Biochemical analysis of ocular surface mucin abnormalities in dry eye: the canine model. 1998. 709–718 p.

9. LC Helper. The effect of lacrimal gland removal on the conjunctiva and cornea of the dog. Journal of the American Veterinary Medicine Association . 1970;157:72–5.

10. Behl T, Kotwani A. Omega-3 fatty acids in prevention of diabetic retinopathy. Vol. 69, Journal of Pharmacy and Pharmacology. Blackwell Publishing Ltd; 2017. p. 946–54.

11. Fetterman JW, Zdanowicz MM. Therapeutic potential of n-3 polyunsaturated fatty acids in disease. American Journal of Health-System Pharmacy. 2009 Jul 1;66(13):1169–79.

12. Shen J hui, Ma Q, Shen S rong, Xu GT, Das UN. Effect of α-linolenic acid on streptozotocin-induced diabetic retinopathy indices in vivo. Arch Med Res. 2013 Oct;44(7):514–20.

13. Calder PC. Long-chain fatty acids and inflammation. Proc Nutr Soc. 2012 May;71(2):284–9.

14. Kangari H, Eftekhari MH, Sardari S, Hashemi H, Salamzadeh J, Ghassemi-Broumand M, et al. Short-term consumption of oral omega-3 and dry eye syndrome. Ophthalmology. 2013 Nov;120(11):2191–6.

15. Bhargava R, Kumar P, Kumar M, Mehra N, Mishra A. A randomized controlled trial of omega-3 fatty acids in dry eye syndrome. Int J Ophthalmol. 2013;6(6):811–6.

16. Huang JY, Yeh PT, Hou YC. A randomized, double-blind, placebo-controlled study of oral antioxidant supplement therapy in patients with dry eye syndrome. Clinical Ophthalmology. 2016 May 9;10:813–20.

17. Deinema LA, Vingrys AJ, Wong CY, Jackson DC, Chinnery HR, Downie LE. A Randomized, Double-Masked, Placebo-Controlled Clinical Trial of Two Forms of Omega-3 Supplements for Treating Dry Eye Disease. Ophthalmology. 2017 Jan 1;124(1):43–52.

18. Wojtowicz JC, Butovich I, Uchiyama E, Aronowicz J, Agee S, Mcculley JP. Placebo-controlled Clinical Trial of an Omega-3 Supplement for Dry Eye [Internet]. Available from: www.corneajrnl.com

19. Neves ML, Yamasaki L, De Carvalho Sanches O, Paiva Do Amaral MS, Stevanin H, Giuffrida R, et al. Use of linseed oil to treat experimentally induced keratoconjunctivitis sicca in rabbits [Internet]. 2013. Available from: http://www.joii-journal.com/content/3/1/4

20. Kanwar JR, Roy K, Patel Y, Zhou SF, Singh MR, Singh D, et al. Multifunctional iron bound lactoferrin and nanomedicinal approaches to enhance its bioactive functions. Vol. 20, Molecules. MDPI AG; 2015. p. 9703–31.

21. Crouch SP, Slater KJ, Fletcher J. Regulation of cytokine release from mononuclear cells by the iron-binding protein lactoferrin. Blood. 1992 Jul 1;80(1):235–40.

22. Håversen L, Ohlsson BG, Hahn-Zoric M, Hanson LA, Mattsby-Baltzer I. Lactoferrin down-regulates the LPS-induced cytokine production in monocytic cells via NF-kappa B. Cell Immunol. 2002 Dec;220(2):83–95.

23. Sugiyama A, Sato A, Shimizu H, Ando K, Takeuchi T. PEGylated lactoferrin enhances its hepatoprotective effects on acute liver injury induced by D-galactosamine and lipopolysaccharide in rats. J Vet Med Sci. 2010 Feb;72(2):173–80.

24. Kawashima M, Kawakita T, Inaba T, Okada N, Ito M, Shimmura S, et al. Dietary lactoferrin alleviates age-related lacrimal gland dysfunction in mice. PLoS One. 2012 Mar 27;7(3).

25. Dogru M, Matsumoto Y, Yamamoto Y, Goto E, Saiki M, Shimazaki J, et al. Lactoferrin in Sjögren's syndrome. Ophthalmology. 2007 Dec;114(12):2366–7.

26. Kawashima M, Kawakita T, Okada N, Ogawa Y, Murat D, Nakamura S, et al. Calorie restriction: A new therapeutic intervention for age-related dry eye disease in rats. Biochem Biophys Res Commun. 2010 Jul;397(4):724–8.

27. Brock JH. The physiology of lactoferrin. Biochem Cell Biol. 2002;80(1):1–6.

28. Gilbert R, Peto T, Lengyel I, Emri E. Zinc Nutrition and Inflammation in the Aging Retina. Vol. 63, Molecular Nutrition and Food Research. Wiley-VCH Verlag; 2019.

29. Fraker PJ. Roles for cell death in zinc deficiency. J Nutr. 2005 Mar;135(3):359–62.

30. Prasad AS. Zinc: mechanisms of host defense. J Nutr. 2007 May;137(5):1345–9.

31. Wong P, Markey M, Rapp CM, Darrow RM, Ziesel A, Organisciak DT. Enhancing the efficacy of AREDS antioxidants in light-induced retinal degeneration. Mol Vis. 2017;23:718–39.

32. Zampatti S, Ricci F, Cusumano A, Marsella LT, Novelli G, Giardina E. Review of nutrient actions on age-related macular degeneration. Vol. 34, Nutrition Research. 2014. p. 95–105.

33. Gregory JF. Ascorbic acid bioavailability in foods and supplements. Nutr Rev. 1993 Oct;51(10):301–3.

34. Rasmussen HM, Johnson EJ. Nutrients for the aging eye. Clin Interv Aging. 2013;8:741–8.

35. Taylor A, Jacques PF, Nowell T, Perrone G, Blumberg J, Handelman G, et al. Vitamin C in human and guinea pig aqueous, lens and plasma in relation to intake. Curr Eye Res. 1997 Sep;16(9):857–64.

36. Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutr. 1999 Jun;69(6):1086–107.

37. Olson JH, Erie JC, Bakri SJ. Nutritional supplementation and age-related macular degeneration. Vol. 26, Seminars in Ophthalmology. 2011. p. 131–6.

38. Traber MG. Utilization of vitamin E. Biofactors. 1999;10(2–3):115–20.

39. Kawashima M, Nakamura S, Izuta Y, Inoue S, Tsubota K. Dietary Supplementation with a Combination of Lactoferrin, Fish Oil, and Enterococcus faecium WB2000 for Treating Dry Eye: A Rat Model and Human Clinical Study. Ocular Surface. 2016 Apr 1;14(2):255–63.

40. Sasaki M, Ozawa Y, Kurihara T, Noda K, Imamura Y, Kobayashi S, et al. Neuroprotective Effect of an Antioxidant, Lutein, during Retinal Inflammation. Investigative Opthalmology & Visual Science. 2009 Mar 1;50(3):1433.

41. Vesperinas MS, Domenech FS. COMPARATIVA DE 10 CASOS CLÍNICOS DE PERROS CON KCS CUALITATIVA [Internet]. Available from: https://ivoft.com/