Acta Scientific Veterinary Sciences (ISSN: 2582-3183)

Volume 7 Issue 8 August 2025

Research Article

Anti-Inflammatory Effects of Systemic Cannabidiol in Uveitis Following Phacoemulsification in Dogs: A Pilot Study

Michala de Linde Henriksen[1,2]*, Caitlin Bradley[2], Kim R Love[3], Krista Banks[2], Michael R Lappin[2] and Stephanie McGrath[2]

1Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, USA

[2]Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, USA

[3]KR Love Quantitative Consulting and Collaboration, Athens, GA, USA

***Corresponding Author:** Michala de Linde Henriksen; Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, USA.

DOI: 10.31080/ASVS.2025.07.0994

Received: June 03, 2025

Published: July 21, 2025

Abstract

Objective: Cannabidiol (CBD) is thought to have an anti-inflammatory effect. The aim of this pilot study was to investigate the anti-inflammatory effect of CBD on diabetic dogs undergoing phacoemulsification. The hypothesis was that dogs treated with CBD would have less short-term and long-term complications from uveitis due to CBDs anti-inflammatory effect.

Methods: This is a pilot study, including dogs with diabetic cataracts. CBD-group = treated with oral CBD 10mg/kg; MCT-group (control) = treated with oral medium-chain-triglyceride oil 0.1ml/kg. Both groups were treated PO BID for 28 days starting 7 days pre-surgery (Day-1) until 21-days post-surgery (Day-28). A physical examination and complete-blood-count and chemistry panel were performed on Day-1, Day-7 (day of surgery), Day-14, and Day-28. Parameters evaluated for uveitis post-surgery; short-term (flare, post-operative intraocular hypertension [POH]), long-term (glaucoma), as well as visual status (visual versus blind). The follow-up period was 12 months.

Results: CBD-group = 4 dogs (8 eyes), MCT-group = 3 dogs (6 eyes). No uveitis parameters were found to be different between the groups. One eye in each group developed glaucoma; the eye in the CBD-group was blind at the final follow up whereas the eye in the MCT-group was treated for glaucoma and was still visual. A statistically significant difference in alkaline phosphatase (ALP) was found over time for the CBD-group ($p < 0.001$) but not for the MCT-group ($p = 0.317$).

Conclusion: Oral CBD did not influence short-term or long-term parameters from uveitis following phacoemulsification in diabetic dogs. ALP was significantly elevated in the CBD-group. This liver enzyme should be monitored in any dogs treated with systemic CBD.

Keywords: Canine; Cataracts; CBD; Diabetes; Uveitis

Introduction

Cataracts in dogs is a common disease and it has been estimated that cataracts is the tenth most common dog disease in United States, with cancer and obesity being number one and two, respectively [1]. The two most common underlying causes for cataracts in dogs are diabetes mellitus and genetic predisposition [2,3]. Fifty percent of all diabetic dogs will develop cataracts within 170 days following their diagnosis, and 80% will have developed cataracts after 470 days [4]. Diabetes mellitus is a common metabolic dis-

ease in dogs and is reported worldwide to have a prevalence from 0.26% to 1.3% in the canine population [5-9]. For humans, 55% of blindness is caused by cataracts which makes it the leading cause of blindness worldwide [10].

Cataract surgery with phacoemulsification is the recommended surgical treatment that can restore vision when animals and humans have been diagnosed with cataracts [2,3,11]. Complications following phacoemulsification can be painful and blinding. The most common short-term complications of post-phacoemulsification in dogs are uveitis and post-operative ocular hypertension (POH: seen in 22.9-50% of cases). Long-term complications following phacoemulsification are glaucoma (5.1-18.8% of cases), and retinal detachment (1-2% of cases) [11]. These complications can have devastating irreversible blinding consequences for the dog if not treated immediately by decreasing the intraocular inflammatory response immediately following phacoemulsification. Dogs are therefore treated with an excessive number of anti-inflammatory drugs following surgery, drugs such as topical and systemic glucocorticoids and/or non-steroidal anti-inflammatory drugs (NSAIDs). Unfortunately, adverse effects of anti-inflammatory drugs are common and can cause substantial harm, such as corneal ulcerations following topical use, and significant systemic side effects such as vomiting, diarrhea, lethargy, melena, etc [12,13].

Cannabidiol (CBD) is a prominent phytocannabinoid produced by the Cannabis sativa plant and has been reported to have minimal side effects, except increased liver enzyme activities when used in high doses [14]. CBD has gained a lot of public and scientific attention the last several years due to its anti-inflammatory properties, potentially due to its effect on the Transient receptor potential vanilloid-1 (TRPV1) and inhibition of tumor-necrosis factor alpha (TNFα), both have major impact on inflammation [15]. TNFα has shown to be elevated in dogs with POH following phacoemulsification and it is speculated that systemic CBD could decrease TNFα present in aqueous humor and therefore have a positive effect on the inflammatory reaction post-phacoemulsification in dogs [16].

The aim of this pilot study was to investigate the anti-inflammatory effect of CBD on diabetic dogs undergoing phacoemulsification. The hypothesis was that dogs treated with CBD would have less short-term and long-term complications from uveitis due to CBDs anti-inflammatory effect.

Materials and Methods

This was a prospective cohort pilot study. Diabetic cataracts dogs presented to Colorado State University Veterinary Teaching Hospital (CSU-VTH) ophthalmology service for phacoemulsification and with owner's consent were enrolled in this study. The study was approved by the Colorado State University's Institutional Animal Case and Use Committee (IACUC #1619). All owners signed an 'Owner consent form'. The study was masked for all doctors and owners involved with the dogs until the last dog had finished its CBD treatment.

Study protocol

All enrolled dogs were treated with a standard treatment protocol for phacoemulsification (see 'Phacoemulsification' section below for this protocol). The Cannabidiol group (CBD group) of dogs were, beside the standard treatment protocol, also treated with systemic CBD at a dose of 10 mg/kg PO BID for the total of 28 days – starting 7 days pre-surgery and continuing for 21 days post-surgery. The CBD oil was donated to this study by Wolf Sciences and produced from broad-spectrum hemp extracts containing 100mg/ml CBD in MCT (Medium-Chain-Triglyceride) oil, and THC < 0.3% (Wolf Sciences, Conifer, CO, USA). Control dogs were, beside the standard treatment protocol, treated with the same MCT oil that was used in the CBD oil (MCT group) but with no CBD, at a dose of 0.1 ml/kg for 28 days - starting 7 days pre-surgery and continuing for 21 days post-surgery (Organic MCT oil – derived from Coconut oil; NOW®, Bloomingdale, IL, USA). The dose of CBD 10 mg/kg BID PO for four weeks was selected due to a pharmacokinetic study by Bartner and colleagues that found that a dose of 10 mg/kg CBD oil PO BID for six weeks was safe to use in dogs, whereas a higher CBD concentration (20mg/kg CBD oil PO BID for six weeks) significantly elevated blood Alkaline phosphatase (ALP) [17].

Inclusion and exclusion criteria: Only dogs with diabetic cataracts (immature, mature, hypermature) were included in the study. All sexes and breeds were included. All dogs were monitored for systemic side-effects during the study through physical examination, blood work (complete blood count [CBC] and serum biochemical panel [Chem] including triglyceride concentrations), and urinalysis (with aerobic culture and antibiotic susceptibility testing if indicated) at the initial appointment (Day-0). Blood work (CBC/Chem) was also performed on Day-7 (day of surgery), Day-14, and Day-28. The Day-0 systemic assessment would ensure that the dogs were healthy enough for anesthesia and that it would be safe to treat with systemic CBD for all 28 days. To be classified as a diabetic mellitus patient, the dogs should have been diagnosed with diabetes by their referral veterinarian and have had a blood glucose above normal limits (above 120 mg/dl) on a fasted blood sample as well as glucosuria before presentation to CSU-VTHs ophthalmology service. The dogs were presented for phacoemulsification and were already in treatment and controlled with systemic insulin by referral veterinarian's choice.

Ophthalmic examination

A complete ophthalmic examination was performed to determine if the dogs were appropriate candidates for phacoemulsification by assuring the dogs would regain vision post-surgery. The complete ophthalmic examination was performed by an American College of Veterinary Ophthalmologists (ACVO) board-certified ophthalmologist and a resident in the American Board of Veterinary Ophthalmologists (ABVO) program. The ophthalmic examination of both eyes (OU) includes neuro-ophthalmic examination and slit lamp biomicroscopy of the adnexa and anterior segment. If possible, the posterior segment was examined with slit lamp biomicroscopy and a fundic examination was performed on a pharmacological dilated pupil (Tropicamide 1% ophthalmic solution; Bausch+Lomb, Bridgewater, NJ, USA) with a headset and a 28D condensing lens. Intraocular pressure (IOP) was measured with tonometry (Tono-Vet; ICare® Finland Oy, Espoo, Finland) at dog setting. Tear production was measured with Schirmer tear test-1 (STT-1; Eye Care Product Manufacturing, LLC, Tuscon, AZ, USA), and fluorescein stain (Jorgensen Lab, Loveland, CO, USA) was performed to rule out corneal ulcerations. Gonioscopy of the iridocorneal angle was performed with a Koeppe gonio lens. A normal or narrow iridocorneal angle would still include the dog in the study whereas a closed angle would exclude the dog from the study. Dogs with immature, mature, or hypermature cataracts were included in the study.

All dogs had an ophthalmic examination as described above at Day-0, Day-7 (pre-surgery), Day-7 (post-surgery), Day-8, Day-14, and Day-28, as well as when they returned for recheck appointments during their first year following phacoemulsification. The scheduled recheck appointments were Month-3, Month-6, Month-9, and Month-12 but owners were informed that more rechecks could be needed in case of complications.

Standard treatment protocol for phacoemulsification Treatment

A standard phacoemulsification treatment protocol was started for all dogs from Day-0 (7 days pre-surgery) and continued for 21 days post-phacoemulsification. The treatment protocol included the following medications: topical Ofloxacin 0.3% ophthalmic solution QID (topical antibiotic), prednisolone acetate 1% ophthalmic suspension QID (topical steroid), diclofenac 0.1% ophthalmic solution BID (topical NSAID), and I-drop Vet (hyaluronic acid) lubrication QID (topical eye lubrication). Systemic amoxicillin-clavulanate at 14.5 mg/kg PO BID (systemic antibiotic) was started on Day-0 and continued for 14 days post-surgery and then discontinued.

Rescue protocols

In case a dog developed clinical signs of uncontrolled uveitis at any recheck appointment, the dog was started on systemic carprofen 2.2 mg/kg PO BID (systemic NSAID) for 7-14 days and then tapering or discontinued. In case a dog developed elevated IOPs within the first week following surgery - diagnosed as post-operative ocular hypertension (POH) - the dog was started on topical anti-glaucoma medications such as dorzolamide 2% ophthalmic solution BID, timolol 0.5% ophthalmic solution BID, and/or latanoprost 0.005% ophthalmic solution SID or BID, depending upon the severity of the IOP elevation. Leaking aqueous humor through the incision site to decrease IOP would also be performed within the first couple of hours following surgery, if necessary due to an elevated IOP nonresponsive to medical anti-glaucoma treatment.

Surgery

All dogs had a standard one-handed phacoemulsification performed with a Stellaris ELITE phacoemulsification machine (Bausch + Lomb, St. Louis, MO, USA) as described in Terhaar., *et al*. (2022) [16]. An intraocular lens (41D IOL; AS-IOL AJL Ophthalmic, Araba, Spain) was placed if it was possible (determined by the surgeon at the time of surgery). The phacoemulsification was performed either by one board-certified ophthalmologist (MdLH) and/or by a second or third year ABVO resident under supervision by MdLH.

Data analysis

Acute- and long-term clinical data

Three clinical signs of acute and active anterior uveitis were recorded in this study: IOP (measured in mmHg), aqueous flare (scale: 0-4+) [18], and POH (The highest IOP measured to be above 25mmHg within the first 7 days post-surgery).[11] Two long-term complications from chronic uveitis following phacoemulsification were also recorded: Glaucoma (measured in mmHg) and visual status (determined with neuro-ophthalmic examination). The long-term complications were evaluated for one year following phacoemulsification. Any ophthalmic or systemic complications throughout the first year following phacoemulsification was recorded.

CBD concentration in plasma

All dogs had blood collected in sterile Sodium Heparin blood collection tubes (Becton, Dickinson and Company, Franklin Lakes, NJ) on Day-0, Day-7, Day-14, and Day-28. This blood tube was centrifuged following collection, and plasma was transferred to an Eppendorf tube and stored in a -80C freezer until analysis. The plasma samples were analyzed for CBD concentration (ng/ml) following the last dogs Day-28 recheck appointment. The samples were analyzed with liquid chromatography and tandem mass spectrometry (LC-MS/MS) as described in Jost., *et al*. (2024) [19].

Blood levels of interest

Blood levels were measured on Day-0, Day-7, Day-14, and Day-28. Alkaline phosphatase (ALP), triglyceride, cholesterol, fructosamine, and glucose were the blood levels that were of interest due to a potentially positive or negative effect from systemic CBD on these levels [17,20]. ALP and triglyceride were also measured on Day-42 to evaluate the levels three weeks following discontinuing CBD treatment.

Statistical analysis

For eye-level outcomes, IOP and STT both use linear mixed effects models, with random intercepts for individual dogs and eyes within dog included (note, IOP was natural-log transformed to meet the distribution assumption of this model). These models both included an effect of treatment, day, and an interaction of treatment and day. Maximum IOP only had one measurement for each eye following treatment; a linear mixed effects model with a random intercept for dog and a fixed effect of treatment was used. Due to low variability in outcomes at certain time points (making a single parametric analysis difficult), aqueous flare was first analyzed with a series of three Mann-Whitney U tests to compare the two groups to one another on Day-8, Day-21, and Day-28 (the only days with non-zero flare recorded for any animal); this was followed by two Friedman tests to compare aqueous flare on these same three days to one another within each treatment group.

All blood levels except for fructosamine were analyzed with mixed effects models including a random intercept effect for individual dogs; this accounts for repeated measures within dogs over time. These models included an effect of treatment, day, and an interaction of treatment and day (which allows for the two treatments to have different outcomes on some days and not others). ALP used a mixed effects gamma regression model, while glucose, triglyceride, and cholesterol values were found to meet the normal distribution assumption of linear mixed effects model. Fructosamine was only measured on Day-0 and had therefore no repeated measures and only an effect of group was analyzed using an independent t-test (following a natural log transformation).

All analyses were prepared using IBM SPSS Statistics 29.0 (IBM, Armonk, NY, USA) and a p-value < 0.05 was considered statistically significant; where post-hoc tests were performed, p values were adjusted for familywise error rates using a sequential Bonferroni procedure.

Results

Animals

A total of seven dogs were enrolled in this pilot. Four dogs were treated with CBD oil (CBD group; n = 4 dogs [n = 8 eyes]) and three dogs were treated with MCT oil (MCT group; n = 3 [n = 6 eyes]). Table S1 gives an overview of the dogs enrolled in this study including breed, age, and sex. Table S2 gives an overview of each dog's phacoemulsification parameters such as cataract stage, absolute phacoemulsification time, placement of an IOL, etc.

It was necessary to rescue three dogs in this pilot study; Dog-3 was discontinued on its CBD treatment on Day-14 (7 days post-op) due to a significant elevation of ALP (ALP increased from 1425 to 7772 IU/L from Day-7 to Day-14). The owner had also discontin-

Dog #	Group	Breed	Age	Sex	Weight
1	CBD	Beagle	10	FS	15
2	CBD	Shih Tzu	8	FS	5.6
3	CBD	Mixed breed	8	MN	16.5
4	CBD	Great Pyrenees	7	MN	49
5	MCT	Border Collie	10	MN	22
6	MCT	Terrier Mix	9	MN	7.6
7	MCT	Mixed breed	10	MN	18

Table S1: The table gives an overview of the seven dogs that were enrolled in this pilot study including breed, age (measured in years), sex, and weight (measured in kg). CBD: Cannabidiol, MCT: Medium-chain triglyceride, FS: Female spayed, MN: Male neutered.

Dog #	Group	Cataract stage	APT Phaco time OD	APT Phaco time OS	EPT Phaco time OD	EPT Phaco time OS	IOL placed	Comments
1	CBD	M/M	02:38.00	01:46.21	00:41.40	00:35.58	y/y	No comment
2	CBD	M/M	02:34.00	03:56.79	00.50.23	01:31.34	y/n	OS posterior capsular tear and anterior vitrectomy performed
3	CBD	HM/HM	03:19.30	01:49.59	01.31.87	00:46.68	y/y	No comment
4	CBD	LIM/LIM	01:13.31	01:03.14	00:24.41	00:22.09	y/y	No comment
5	MCT	LIM/LIM	01:15.50	00.30.50	00.30.50	00:35.58	y/y	No comment
6	MCT	LIM/LIM	12:00:48	12:00:58	12:00:20	12:00:27	y/y	No comment
7	MCT	HM/HM	06:28.87	02:28.54	05:37.57	02:11.31	y/n	OS posterior lens capsule tear

Table S2: The table gives an overview of the seven dogs enrolled in this study and their phacoemulsification (phaco) parameters including stage of cataract, absolute phaco time (APT) and effective phaco time (EPT) – both measured in minutes, as well as if an intraocular lens (IOL) was placed or not (yes [y] or no [n]). M: Mature, LIM: Late immature, HM: Hypermature.

ued topical prednisolone acetate a couple of days before the Day-14 recheck. The dog stayed systemically healthy throughout the entire study period except for OD being blind on Day-28. IOP had stayed within normal limits for OD at each recheck, but the eye had signs of chronic glaucoma with clinical findings such as cupping of the optic nerve and optic nerve head atrophy. It was therefore suspected that an IOP spike had caused OD to develop blindness in this dog. Dog-6 was rescued with systemic NSAID on Day-14 (seven days post-op) due to increased aqueous flare OU (OD 2+ and OS 3+). Dog-6 was in the MCT group, and the study drug (MCT oil) was continued at the same time as the dog was started on Carprofen 2.2mg/kg BID PO. Dog-7 was the third dog that was rescued. This dog was in the MCT group, and the drug was discontinued due to the dog developing diarrhea and inappetence on Day-5 following start on the study drug. The drug was discontinued, and the dog returned to normal the day after (no diarrhea and normal appetite), and had surgery as planned on Day-7. It was elected to keep this dog in the study since the dog was in the control group (MCT group) and could therefore still count as a control dog. It is worth noticing that this dog had measurable CBD blood levels throughout the entire study despite being in the MCT group.

Short-term uveitis parameters

No significant differences could be observed between the CBD group and the MCT group regarding the recorded values for aqueous flare, IOP, or STT (all $p > 0.05$; Figure 1, Table S3, Table S4, Table S5). Both groups had a statistically significant increase in IOP on Day-7 (post-surgery) relative to Day-0 ($p < 0.001$) and Day-7 (pre-surgery) ($p < 0.001$), but by Day-28 IOP had significantly decreased from this post-surgery measurement ($p < 0.001$). There were no statistically significant differences in flare between the two groups on any day following surgery. Five out of eight eyes (63%) from the CBD group developed POH within the first seven days post-op whereas three out of six eyes (50%) developed POH from the MCT group. The highest IOP that was measured for the CBD group was 57mmHg, and for the MCT group was 70mmHg (Figure 1, Table S3). There was no statistically significant difference between the two groups with respect to maximum IOP ($p = 0.863$).

Dog #	Group	Flare Day-0	Flare Day-7 Pre-op	Flare Day-8	Flare Day 14	Flare Day 28	Comments
1	CBD	0/0	0/0	3+/3+	0.5+/0.5+	0/0	No comment
2	CBD	0/0	0/0	3+/3+	0.5+/3+	0.5+/0.5+	No comment
3	CBD	0/0	0/0	2+/3+	0.5+/1+	0.5+/1+	Discontinued on study drug on Day 14 due to significantly elevated ALP The owner had DC topical pred acetate a couple of days before day 14 recheck because he had run out of the drug
4	CBD	0/0	0/0	2+/2+	0.5+/1+	0.5+/1+	No comment
5	MCT	0/0	0/0	3+/3+	0.5+/0.5+	0.5+/0.5+	No comment
6	MCT	0/0	0/0	3+/3+	2+/3+	2+/3+	Started on oral carprofen on day 14 due to significantly more aqueous flare OU than expected
7	MCT	0/0	0/0	3+/3+	0.5+/0.5+	0.5+/0.5+	The test drug was discontinued on day 5 due to diarrhea and inappetence

Table S3: Aqueous flare (Flare) score for the seven dogs (OD/OS) in this pilot study. Flare was subjectively measured in 0: no flare, 0.5+: trace of flare, 1+ (mild), 2+ (moderate), 3+ (severe), 4+ (extremely severe). CBD: Cannabidiol, MCT: Medium-chain triglyceride, ALP: Alkaline phosphate, Pred acetate: Prednisolone acetate 1% ophthalmic suspension, DC: Discontinued.

Dog #	Group	IOP Day-0	IOP Day-7 Pre-op	IOP Day-7 post op	IOP Day-8	IOP Day 14	IOP Day 21	Comments
1	CBD	13/10	11/11	41/42	21/20	10/11	12/12	Latanoprost OU BID
2	CBD	13/10	16/10	22/28	25/8	10/7	24/7	Latanoprost OU
3	CBD	7/6	7/27	48/3*	20/16	7/13	10/14	Latanoprost OD, Seidel test negative OS but suspicious of leaking – monitored
4	CBD	9/11	5/10	19/53	10/19	14/57	13/13	Latanoprost OU
5	MCT	11/10	7/8	42/23	12/7	19/17	12/12	Latanoprost OU, Leaking AH from OD one time
6	MCT	12/13	15/13	70/25	18/20	12/19	9/11	Latanoprost OU, Leaking OD one time
7	MCT	15/12	13/12	17/23	18/14	38/35	7/9	Latanoprost OU

Table S4: Intraocular pressure (IOP) for the seven dogs (OD/OS) in this pilot study. IOP was measured in mmHg. Post-operative ocular hypertension (POH) is marked with BOLD. Severely decreased IOP is marked with one asterisk (*). CBD: Cannabidiol, MCT: Medium-chain triglyceride.

Dog #	Group	STT Day-0	STT Day-7 Pre-op	STT Day 14	STT Day 21
1	CBD	NM	NM	18/18	15/7
2	CBD	23/18	12/22	NM	17/16
3	CBD	23/20	NM	21/22	16/13*
4	CBD	25/26	22/22	20/21	17/17
5	MCT	NM	21/15	19/21	17/18
6	MCT	16/21	17/19	16/18	17/17
7	MCT	21/21	NM	24/21	16/18

Table S5: Schirmer tear test-1 (STT) measured for the seven dogs (OD/OS) in this pilot study. STT was measured in mm/min. CBD: Cannabidiol, MCT: Medium-chain triglyceride, NM: Not measured. Black asterisk (*) indicates that this dog was started on cyclosporine 0.2% ophthalmic ointment (Optimmune®) OU BID following day 21 due to suspicion for keratoconjunctivitis sicca (KCS) developing.

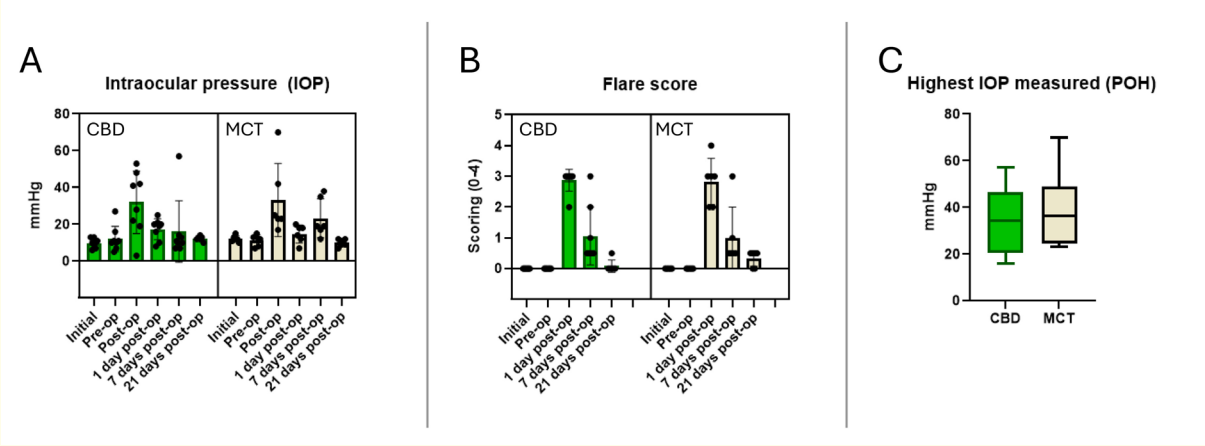

Figure 1: Short-term complications were measured, and no differences were seen between the two groups (CBD group versus CBD group) and flare score (0-4+), intraocular pressure (IOP), and post-operative intraocular hypertension (POH).

Long-term uveitis parameters

One eye (OD from Dog-3) from the CBD group was diagnosed with glaucoma (1/8 eyes, 13%). IOP was never measured to be elevated in OD, but the dog had clinical signs of chronic glaucoma with cupping and atrophy of the optic nerve head. This eye (OD from Dog-3) was the only eye that was blind (due to glaucoma) at the end of this study after a one-year follow-up period. One eye (OD from Dog-7; 1/6 eyes, 17%) from the MCT group was diagnosed with glaucoma three months post-phacoemulsification and treated with transscleral cyclophotocoagulation. This eye was still visual at its one-year post-phacoemulsification follow-up examination. Table 1 gives an overview of ophthalmic diseases that were found in the seven dogs that were enrolled in this pilot study.

Blood level analysis

Four dogs were enrolled in the CBD group and all four dogs had no detectable CBD blood level on Day-0, but they all had detectable CBD level on Day-7, Day-14, and Day-28. Dog-7 was enrolled in the MCT group but had low measurable CBD blood level throughout the entire study including Day-0 (Figure 2. Table S6). This was the same dog that was discontinued on the study drug (MCT oil) on day five due to diarrhea and inappetence. None of the other two dogs that were in the MCT group had detectable CBD levels at any point.

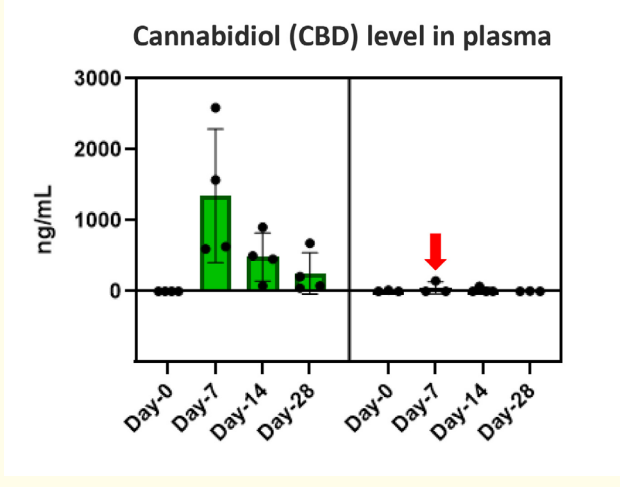

Figure 2: Cannabidiol (CBD) level was measured in plasma from both groups. An interesting observation was that one dog in the MCT group had low measurable CBD in plasma throughout the entire study (red arrow is pointing at this dog's measurable CBD blood level = 149 ng/ml).

Dog #	group	Breed	Age	Sex	Other diseases pre-surgery	Diseases developed post-surgery	Vision status 12-months post-surgery
1	CBD	Beagle	10	FS	Distichiae OS KCS OU	Retinal hemorrhage OU[1] Horner's syndrome OS[2] Lipid keratopathy OS	Visual OU
2	CBD	Shih Tzu	8	FS	Corneal ulceration OS (healed pre-sx)	KCS, OU	Visual OU
3	CBD	Mixed breed	8	MN	Distichiae OD	Chronic glaucoma OD[3]	Blind OD Visual OS
4	CBD	Great Pyrenees	7	MN	No	Inferior eyelid mass (meibomian adenoma) OD	Visual OU
5	MCT	Border Collie	10	MN	No	No	Lost to follow-up 6-weeks post-surgery
6	MCT	Terrier Mix	9	MN	No	KCS OU Lipid keratopathy OU Nyctalopia OU	Visual OU
7	MCT	Mixed breed	10	MN	No	Glaucoma OD[4] Retinal hemorrhage OU[5]	Visual OU

Table 1: Overview of cases enrolled in this pilot study. CBD: Cannabidiol, MCT: Medium-chain triglyceride. [1]Retinal hemorrhage diagnosed at the three months recheck (OS) and six months (OD), [2]Horner's syndrome diagnosed at the three months recheck, [3]The intraocular pressure was never measured to be elevated OD but the eye lost its menace, dazzle and pupillary light reflexes between the three week and five week recheck, and the eye had signs of chronic glaucoma with optic nerve head cupping and atrophy on the three months recheck; [4]Glaucoma diagnosed three months post-phacoemulsification and controlled with transscleral cyclophotocoagulation procedure, [5]Retinal hemorrhage diagnosed on the three months recheck.

Dog #	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Dog 7
Treatment	CBD	CBD	CBD	CBD	MCT	MCT	MCT
CBD - day 0	0	0	0	0	0	0	18.4
CBD - day 7	633	597	1570	2590	0	0	149
CBD - day 14	503	456	904	273	0	0	71.8
CBD - day 28	677	207	42.2	79.4	0	0	4.44
Normal range: 0 ng/mL							
ALP - day 0	1196	3950	231	64	222	446	93
ALP - day 7	1438	4433	1425	161	209	485	114
ALP - day 14	3086	8794	7772	260	342	683	217
ALP - day 28	6317	11751	1986	212	360	644	151
ALP - day 42	1597	2594	473	128	308	657	134
Normal range: 15-140 IU/L							

Glu - day 0	460	647	46	230	76	125	227
Glu - day 7	153	125	208	234	76	295	214
Glu - day 14	71	285	61	397	241	178	445
Glu - day 28	152	610	54	376	416	251	325
Normal range: 70-115 mg/dL							
Trigly - day 0	174	67	122	272	355	518	439
Trigly - day 7	195	1579	1159	382	408	570	603
Trigly - day 14	224	423	252	1137	1014	535	588
Trigly - day 28	164	788	109	767	1130	1292	325
Trigly - day 42	532	1293	665	263	1224	502	326
Normal range: 30-120 mg/dL							
Chole - day 0	671	392	328	440	394	557	320
Chole - day 7	579	371	324	452	295	554	317
Chole - day 14	546	419	262	408	319	636	319
Chole - day 28	560	382	305	443	313	642	270
Normal range: 130-300 mg/dL							
Fructo - day 0	470	540	381	657	471	565	519
Normal range: 210-350 µmol/L							

Table S6: Blood levels for the seven dogs in this pilot study. CBD: Cannabidiol, ALP: Alkaline phosphatase, Glu: Glucose, Trigly: Triglyceride, Chole: Cholesterol, Fructo: Fructosamine. Red numbers are indicated for Dog 3 – this dog was discontinued on treatment drug after Day 14 due to significantly elevated ALP. The red numbers are therefore not included in any statistical calculations. The normal range for the different blood tests is given for dogs.

The ALP blood level was significantly different over time for the CBD group ($p < 0.001$) and not for the MCT group ($p = 0.317$), although it did not rise to the level of a significant difference between the two treatment groups on any day (CBD versus MCT on Day-0 $p = 0.329$, Day-7 $p = 0.169$, Day-14 $p = 0.088$, Day-28 $p = 0.77$, Day-42 $p = 0.314$; figure 3, Table S6). The lack of significant differences between the two groups could be due to the small sample size in this pilot study. Specifically, the ALP blood level was significantly higher in the CBD group on Day-14 and Day-28 than on Day-0 ($p < 0.001$ for both) and Day-7 (Day-14, $p = 0.010$; Day-28, $p = 0.020$). Treatment with CBD was discontinued on Day-28 ~~for all dogs~~ and an ALP blood sample was collected three weeks following the dogs being off their study drugs (Day-42). This blood sample showed that all four dogs (100%) in the CBD group had significantly lowered their ALP from when CBD was discontinued to Day-42 ($p = 0.010$).

Dogs that were rescued/lost to follow-up

Dog-3 was discontinued on study drug (CBD) on Day-14 due to significantly increased ALP. Table S6 shows how CBD and ALP decreased over time from the dog was discontinued on the study drug until Day-28 for CBD, and Day-42 for ALP. Dog-7 who had a low

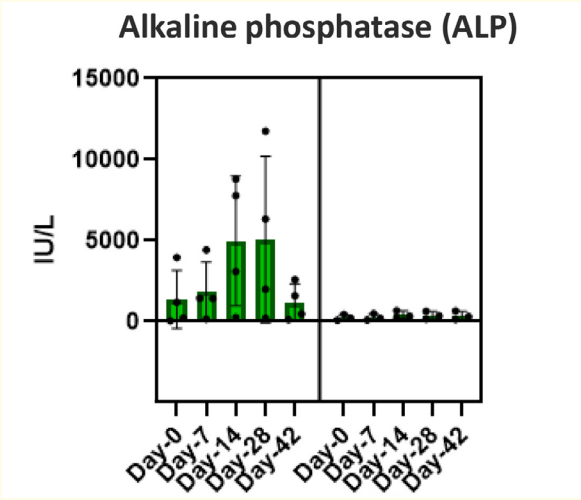

Figure 3: Alkaline phosphatase (ALP) was not significant between the two groups (CBD group versus MCT group) but was significantly different over time for the CBD group ($p < 0.001$) but not for the MCT group ($p = 0.317$).

blood level of CBD throughout the entire study period did not show signs of increased ALP throughout the entire study period. Dog-5 was a part of the MCT-group and completed the entire treatment protocol as planned. The dog was lost to follow-up six weeks post-phacoemulsification and it can therefore not be ruled out that this dog could have developed long-term complications.

No other significant differences were observed in the blood level of glucose, triglyceride, cholesterol, or fructosamine between the two treatment groups throughout the study period (glucose $p = 0.671$, triglyceride $p = 0.584$, cholesterol $p = 0.870$, $p = 0.934$; Table S6).

Discussion

The purpose of this pilot study was to investigate oral CBD's ability to decrease short-term and long-term uveitis parameters in dogs undergoing phacoemulsification for diabetic cataracts. The hypothesis was that dogs treated with CBD would have decreased uveitis and therefore less short-term and long-term complications from post-surgery uveitis due to CBD's anti-inflammatory effect. Unfortunately, no differences in short-term and long-term uveitis parameters were found between the CBD group versus MCT group. It is worth noticing that dogs in the CBD group had significantly higher ALP blood levels than the MCT group, which is a known side-effect from systemic CBD. ALP is a liver enzyme and the significant elevation when treated with oral CBD could cause systemic complications in diabetic dogs such as liver damage [20].

The ophthalmic short-term uveitis parameters that were evaluated in this study were flare-score and IOPs, as well as the maximum IOP, measured from day 0 to 7 post-surgery, as an indication for POH. A study by Liu., *et al*. from 2005 has shown that systemic CBD were able to decrease experimentally induced posterior uveitis in mice [21]. This study concluded that CBD could potentially be used as an anti-inflammatory for uveitis. Liu and colleagues used the objective biochemical measurement of the TNF-α level as the indicator for inflammation, and they measured a significant decrease of TNF-α in vitreous from CBD treated mice. The inflammatory indicator in our case series was a flare-score and it could be discussed if flare-score is a reliable indicator for inflammation. The flare-score is a subjective evaluation of proteins in the aqueous humor and is used as an indication for a break-down of the blood-aqueous barrier (BAB). Flare-score above zero indicates breakdown of the BAB which is pathognomonic for anterior uveitis [18]. A study by Terhaar and colleagues confirmed that flare-score

is an acceptable non-invasive method to confirm anterior uveitis in our veterinary patients [22]. The Terhaar et al study found a positive correlation between flare-score graded by board-certified veterinary ophthalmologists and total protein (TP) and proteins measured with Nanodrop in aqueous humor from horses with uveitis [22]. By not finding a significant difference in flare-score between groups in our pilot study, we conclude that there is no evidence that oral CBD in a dose of 10mg/kg BID has a significant effect on decreasing anterior uveitis in diabetic dogs following phacoemulsification.

A variety of studies have evaluated systemic CBDs effect on IOP in different animal species as well as in humans [15,22]. These studies have given inconsistent results with some studies concluding CBD's ability to increase IOP, and other studies have concluded that CBD can decrease, or even has no effect on IOP. One possible theory explaining these inconclusive results is that CBD reacts to different IOP regulating receptors in different species.[15] A study by Jost and colleagues evaluated IOPs in healthy research Beagle dogs over a period of 36-months.[19] This study did not find any indications that CBD at two different doses (5mg/kg or 10mg/kg SID PO) had any effect on IOP when compared to a control group. In our pilot study, we wanted to evaluate if CBD could decrease the possibility of POH development post-phacoemulsification. Unfortunately, our pilot study did not find any significant differences between IOPs at any of the different rechecks between the CBD group versus MCT group. Also, no significant difference was found between POH for the two groups with 63% POH in the CBD group, and 50% POH in the MCT group. Therefore, this study is consistent with the theory that CBD does not have any effect on IOP in dogs.

Long-term complications from uveitis following phacoemulsification, such as chronic glaucoma and retinal detachment, causing blindness are devastating outcomes for not only owners but also the surgeons performing the surgery [11,12]. Our pilot study followed the enrolled dogs for one year post-surgery, to monitor for any long-term complications such as glaucoma, retinal detachment or other complications causing blindness that could be related to the surgery. One dog in each group developed glaucoma in one eye (CBD group = 13% versus MCT group = 17%) with no significant differences between these two groups. It could therefore not be concluded that CBD treatment during the time of surgery will have a positive anti-inflammatory and supportive effect on long-term complications such as glaucoma in dogs. Only one of the two glaucoma eyes was blind at the one year recheck. This dog (Dog-3) never showed elevated IOP in the glaucoma eye at its recheck appointments but the fundic exam revealed classic glaucoma findings such as optic nerve head cupping and atrophy on its six months recheck and the eye was confirmed blind. The owner of this dog discontinued the topical treatment with prednisolone acetate 1% ophthalmic suspension during the initial three weeks rechecks post-surgery because he had run out of medication and did not attempt to refill. Compliant owners are an important aspect of a successful outcome following phacoemulsification, but it is also important for clinical trials. Incompliant owners can turn into a bias for a study, and it can be speculated if Dog-3 would not have developed blindness if the owner had followed the treatment plan as agreed upon. The other glaucoma eye (Dog-7) had elevated IOP on its three months recheck and had a transscleral cyclophotocoagulation procedure performed to the eye. The procedure was successful, and the eye was still visual at the one year recheck.

Other non-blinding long-term complications that were seen in the enrolled dogs during their first-year post-phacoemulsification were Horner's syndrome and retinal hemorrhage. One of the dogs in the CBD-group had developed post-ganglionic Horner's syndrome at the three months recheck post-surgery (Dog-1). No underlying reason for this Horner's syndrome was found and it was less severe but still present at the one year recheck. Retinal hemorrhage was also found in the dog with Horner's syndrome (Dog-1) three months following surgery, and another dog (Dog-7) in the MCT group was also found to have retinal hemorrhage at the three months recheck with no underlying reason except being diabetic. Horner's syndrome and retinal hemorrhage have been reported as common findings in diabetic dogs following phacoemulsification [24,25].

A significant difference was found in the ALP blood level in the CBD group only on Day-14 and Day-28 of CBD treatment when compared to Day-0 and Day-7. Systemic CBD is known to elevate the ALP level in dogs [17,20]. Diabetic dogs were specifically se-

lected for our pilot study series since studies have shown a positive effect of systemic CBD on controlling glucose level in diabetic patients [26]. This study did not find any differences in glucose level between the CBD group and the MCT group. Instead, the significantly elevated ALP level was the reason for why the study drug was discontinued in one dog in the CBD group following Day-14. This significant elevation of ALP in the CBD group is concerning for our canine patients, and especially for the diabetic dogs that already are systemically compromised. It is not known why the ALP elevates with CBD treatment but diseases such as liver damage are seen with elevated ALP blood levels [20]. None of the dogs in the CBD-group showed any signs of systemic diseases but it is still a complication that seems to be significant and it important to monitor systemic health in case a dog is treated with CBD.

Another interesting blood sample finding was a detectable CBD level in one of the dogs that belonged to the MCT group (Dog-7). This dog was discontinued on the MCT treatment on Day-5 due to diarrhea and inappetence when the dog was started on the MCT oil. Owners in this pilot study were instructed not to give their dogs any treats or products that contained CBD. It is known that dogs can have low blood levels of CBD due to coprophagia from other dogs that have ingested CBD [19,27].

A limitation of this pilot study was the number of dogs enrolled. Despite the low number of dogs, we still believe that this pilot study gives clinical important information to the veterinary ophthalmology community due to the significant findings of elevated ALP in the CBD-group and the lack of significance between the CBD group and the MCT group regarding ophthalmic findings. Another limitation for the study was the CBD and MCT products that were used. The concentration of 100mg/ml CBD in MCT oil was confirmed by the company but no third party was used to verify this concentration. The MCT oil that was used in this study was also not tested by a third-party lab for its purity. It would have been most correct to have had the concentration and purity for the CBD and MCT products verified by a third-party laboratory, but instead the plasma concentration of CBD in each dog was verified with LC-MC/MC.

The conclusion of this pilot study is that oral CBD at a dose 10 mg/kg BID PO does not seem to have a favorable effect on short-term or long-term complications from uveitis following phacoemulsification in diabetic dogs. The dogs in the CBD group had a significantly elevated ALP blood level on Day-14 and Day-28 and the systemic health should be monitored carefully in any dogs that are treated with systemic CBD. Despite this being a pilot study with only a low sample size, the significant elevation of ALP in the CBD group could indicate that oral CBD should not be given to diabetic dogs due to risk of liver damage. Future studies should investigate the safety of oral CBD in dogs with metabolic diseases such as diabetes mellitus.

Acknowledgements

The authors would like to acknowledge Colorado State University Veterinary Teaching Hospital's ophthalmology service for their huge impact on this study - especially the ophthalmology residents their consistent care of the enrolled dogs. The authors would also like to acknowledge Wolf Sciences for supplying the CBD solution for this study. The study was funded by Colorado State University's College Research Council (CRC) research grant, Fort Collins, CO, USA.

Figure Legends

Figure 1: Short-term complications were measured, and no differences were seen between the two groups (CBD group versus CBD group) and flare score (0-4+), intraocular pressure (IOP), and post-operative intraocular hypertension (POH).

Figure 2: Cannabidiol (CBD) level was measured in plasma from both groups. An interesting observation was that one dog in the MCT group had low measurable CBD in plasma throughout the entire study (red arrow is pointing at this dog's measurable CBD blood level = 149 ng/ml).

Figure 3: Alkaline phosphatase (ALP) was not significant between the two groups (CBD group versus MCT group) but was significantly different over time for the CBD group ($p < 0.001$) but not for the MCT group ($p = 0.317$).

Bibliography

1. Bow Wow Meow pet insurance.

2. Bagley LH and Lavach JD. "Comparison of postoperative phacoemulsification results in dogs with and without diabetes mellitus: 153 cases (1991-1992)". *Journal of the American Veterinary Medical Association* 205.8 (1996): 1165-1169.

3. Davidson MG and Nelms SR. "Chapter 21: Diseases of the lens and cataract formation. In. Veterinary Ophthalmology (eds. Gelatt, Gilger, Kern) fifth edition (2013). Wiley-Blackwell, Ames, Iowa, USA (2013): 1199-1233.

4. Beam S., *et al.* "A retrospective-cohort study on the development of cataracts in dogs with diabetes mellitus: 200 cases". *Veterinary Ophthalmology* 2 (1999): 169-172.

5. Heeley AM., *et al.* "Diabetes mellitus in dogs attending UK primary-care practice: frequency, risk factors and survival". *Canine Medicine and Genetics* 7 (2020): 6.

6. Guptill L., *et al.* "Time trends and risk factors for diabetes mellitus in dogs: analysis of veterinary medical data base records (1970-1999)". *Veterinary Journal* 165.3 (2003): 240-247.

7. Fracassi F., *et al.* "Breed distribution of canine diabetes mellitus in Italy". *Veterinary Research Communications* 28.1 (2004): 339-342.

8. Davison LJ., *et al.* "Study of 253 dogs in the United Kingdom with diabetes mellitus". *Veterinary Record* 156.15 (2005): 467-471.

9. Fall T., *et al.* "Diabetes mellitus in a population of 180,000 insured dogs: incidence, survival, and breed distribution". *Journal of Veterinary Internal Medicine* 21.6 (2007): 1209-1216.

10. Pascolini D and Mariotti SP. "Global estimates of visual impairment: 2010". *British Journal Ophthalmology* 96.5 (2012): 614-618.

11. Wilkie DA and Colitz CMH. "Chapter 22: Surgery of the lens. In. Veterinary Ophthalmology (eds. Gelatt, Gilger, Kern) fifth edition (2013). Wiley-Blackwell, Ames, Iowa, USA (2013): 1234-1286.

12. Uhl LK., *et al.* "Cataracts and phacoemulsification in the Siberian Husky: A retrospective and multicentric study (2008-2018)". *Veterinary Ophthalmology* (2021): 1-13.

13. Monteiro-Steagall BP., *et al.* "Review: Systemic review of non-steroidal anti-inflammatory drug induced adverse effects in dogs". *Journal of Veterinary Internal Medicine* 27 (2013): 1011-1019.

14. Iffland K and Grotenhermen F. "An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies". *Cannabis Cannabinoid Research* 2.1 (2017): 139-154.

15. Henriksen MdL and McGrath S. "Growing interest but limited evidence on the usefulness of cannabidiol in treating ophthalmic disease in dogs: a review". *Journal of the American Veterinary Medical Association* 262.S2 (2024): S25-S31.

16. Terhaar H., *et al.* "Pro-inflammatory cytokines in aqueous humor from dogs with anterior uveitis and post-operative ocular hypertension following phacoemulsification, primary glaucoma, and normal healthy eyes". *PLOS ONE* (2022): 1-21.

17. Bartner LR., *et al.* "Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs". *Canadian Journal of Veterinary Research* 82.3 (2018): 178-183.

18. Hendrix D. "Diseases and Surgery of the Canine Anterior Uvea". In: Gelatt K, Gilger B, Kern T, eds. *Veterinary Ophthalmology.* 5 ed. Ames, IA: John Wiley and Sons (2013): 1146-1198.

19. Jost HE., *et al.* "Long-term effect of oral cannabidiol administration to healthy adult dogs on tear production, intraocular pressure, and tear concentration". *Veterinary Ophthalmology* 27 (2023): 357-366.

20. Corsato Alvarenga I., *et al.* "Tolerability of long-term cannabidiol supplementation to healthy adult dogs". Journal of Veterinary Internal Medicine 38.1 (2023): 326-335.

21. Liu EK., *et al.* "Anti-inflammatory effects of cannabinoids in endotoxin-induced uveitis". *ARVO Annual Meeting Abstract* 46 (2005): 972.

22. Terhaar HM., *et al.* "The use of shotgun label-free quantitative proteomic mass spectrometry to evaluate the inflammatory response in aqueous humor from horses with uveitis compared to ophthalmologically healthy horses". *Veterinary Ophthalmology* 27 (2024): 40-52.

23. Miller S., *et al.* "Delta9Tetrahydrocannabinol and cannabidiol differentially regulate intraocular pressure". *Investigative Ophthalmology and Visual Science* 59.15 (2018): 5904-5911.

24. Foote BC., *et al.* "Retrospective analysis of ocular neuropathies in diabetic dogs following cataract surgery". *Veterinary Ophthalmology* 22.3 (2019): 284-293.

25. Landry MP., *et al.* "Funduscopic findings following cataract extraction by means of phacoemulsification in diabetic dogs: 52 cases (1993-2003)". *Journal of the American Veterinary Medical Association* 225 (2004): 709-716.

26. Weiss L., *et al.* "Cannabidiol lowers incidence of diabetes in non-obese diabetic mice". *Autoimmunity* 39.2 (2006): 143-151.

27. Lauinger CA and Peacock R. "Marijuana toxicosis in dogs in Melbourne, Australia, following suspected ingestion of human faeces: 15 cases (2011-2020)". *Australian Veterinary Journal* 100.3 (2022): 90-97.