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Growing interest but limited evidence on the usefulness of cannabidiol in treating ophthalmic disease in dogs: a review

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ABSTRACT
The 2 most known cannabinoids are Δ9-tetrahydrocannabidiol (THC) and cannabidiol (CBD). Both chemicals are extracted from the cannabis plant but can also be synthetically produced. Δ9-Tetrahydrocannabidiol is extracted from the subspecies of the cannabis plant known as the marijuana plant, which contains a high concentration of THC (0.3% to 30%). Δ9-Tetrahydrocannabidiol is a major psychoactive and intoxicating component of the cannabis plant and is not recommended for use in dogs due to its toxic effect. Cannabidiol is extracted from the subspecies of the cannabis plant known as the hemp plant and must contain less than 0.3% THC. Cannabidiol is a major nonpsychoactive component of the cannabis plant, and its effect has been investigated for epilepsy, neoplasia, and osteoarthritis in dogs. Public interest in the medical use of cannabinoids for various diseases and disorders has grown in the last couple of years. The attention has extended to veterinary medicine, where veterinarians and pet owners are curious about what diseases the nontoxic CBD can be used for to treat companion animals. The use of CBD for ophthalmic diseases has also been investigated due to its anti-inflammatory and neuroprotective effects. Intraocular pressure regulation for glaucoma, corneal diseases (eg, keratitis and corneal pain), uveal diseases (eg, endotoxin-induced uveitis), and retinal/optic nerve head diseases (eg, diabetic retinopathy) are areas where CBD's effect has been investigated in humans and animals. The aim of this review is to give an update on what is known regarding the use of cannabinoids, especially CBD, for ophthalmic diseases in dogs.

Keywords: anti-inflammatory, antioxidant, cannabidiol (CBD), intraocular pressure, neuroprotective

Cannabis refers to all products extracted from the cannabis plant (*Cannabis sativa*) and the word "cannabis" will in this review be used for the cannabis plant and products from the cannabis plant that are associated with Δ9-tetrahydrocannabidiol (THC), also known as marijuana or weed.[1] Cannabis is one of the oldest drugs used for medical and therapeutic purposes. It has been mentioned in Chinese medical books from 2,000 years ago.[2] Cannabis has since been introduced to the rest of the world by different sources. Napoleon Bonaparte's troops brought cannabis from Egypt to Europe in the early 1800s, most likely for recreational purposes.[2] Later, cannabis was introduced to Western medicine by William O'Shaughnessy, where it was used for convulsive disorders and tetanus.[2,3] Cannabis found its way to the US with Spanish immigrants and was widely used by American pharmacies from the 1850s until it became illegal in 1937.[4,5] With time, cannabis became associated with narcotics and eventually the Marijuana Tax Act in 1937 and the Controlled Substances Act of 1970 made cannabis illegal to use in the US.[4]

Cannabinoids are chemical substances extracted from cannabis and have been shown to potentially have drug-like effects.[1,2] The 2 most known cannabinoids are THC and cannabidiol (CBD), and these cannabinoids are extracted from the cannabis plant but can also be synthetically produced.[1] Δ9-Tetrahydrocannabidiol can be extracted from the subspecies of the cannabis plant known as "marijuana," which contains a high concentration of THC (5% to 30%). It is this high concentration of THC that causes the psychoactive and intoxicating effect of cannabis, whereas CBD does not have any psychoactive or intoxicating effect. "Hemp" is another subspecies of the cannabis plant and contains less than 0.3% THC. Cannabidiol can be extracted from both hemp and marijuana, whereas THC can only be extracted from marijuana due to the low THC concentration in hemp **(Figure 1)**.[1,6–10]

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Δ9-Tetrahydrocannabidiol and CBD have recently made a medical and recreational resurgence.[1,6] In 1996, California was the first state to legalize cannabis for medical use.[7] Since then, more states have followed suit. In 2018, the Agricultural Improvement Act[8] removed hemp from the list of controlled substances and defined hemp as *Cannabis sativa* and any part of that plant, including the seeds and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a THC concentration of not more than 0.3% on a dry weight basis.[8–11] As of July 2024, cannabis has been legalized for recreational use in 24 states and for medical use in 38 states in the US.[6,12] Since cannabis has started to regain legal status across the US, public interest in the medical use of THC and CBD for various diseases and disorders has grown. It is especially the nonpsychoactive and nonintoxicating CBD that has been popular among the public due to its potentially healing effect.[13] According to Forbes Health, 60% of US adults have either used or tried a CBD product in 2024.[13] Also, the CBD market has increased significantly over the last couple of years. United States CBD products accounted for $1.8 billion in sales in 2022 compared to only $108 million in 2014.[14] Interest has also extended into the veterinary world, where veterinarians and pet owners are interested in knowing what diseases CBD can treat in our companion animals. This review will give an update on what we know so far regarding the use of cannabinoids, especially CBD, for ophthalmic parameters and diseases and how this can be applied to dogs.

Cannabinoids

Δ9-Tetrahydrocannabidiol and CBD are the 2 most common phytocannabinoids extracted from the cannabis plant and used to treat a variety of diseases.[15] Δ9-Tetrahydrocannabidiol has been investigated for its potential as a drug due to its efficacy for AIDS and cancer patients with weight loss, nausea, and vomiting.[16] Δ9-Tetrahydrocannabidiol and CBD efficacy is reportedly associated with the endocannabinoid system, a complex biological regulatory system whose function is still under investigation.[17]

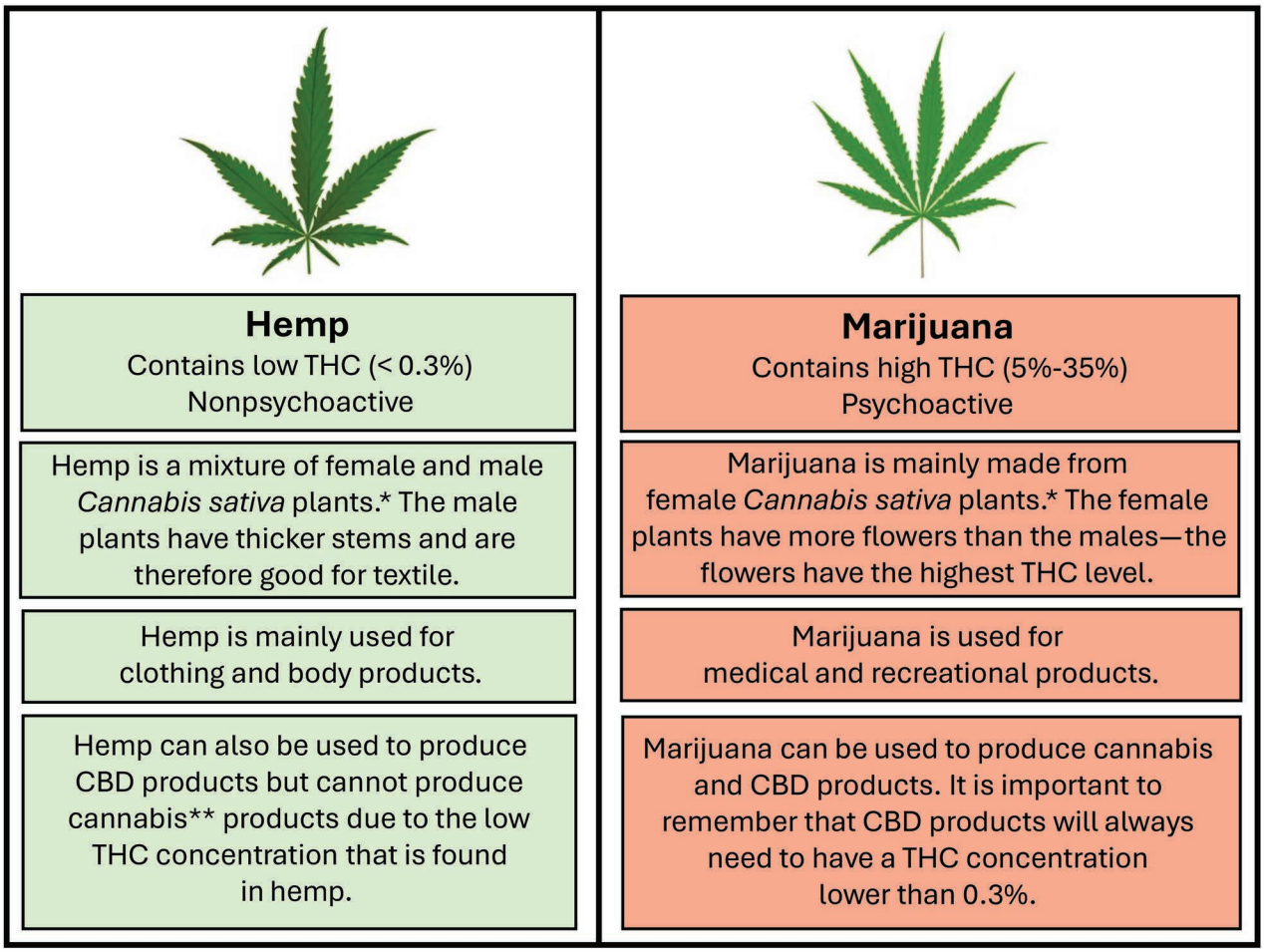

Figure 1—An overview of important differences between hemp and marijuana. *_Cannabis sativa_ is mostly used to produce hemp and marijuana, but 2 other cannabis plants, _Cannabis indica_ and _Cannabis ruderalis_, can also be used. **Cannabis in this review refers to products that contain higher Δ9-tetrahydrocannabidiol (THC) than 0.3% by dry weight. It is important to remember that THC products (> 0.3% THC) should never be used in dogs due to their psychoactive activity; cannabidiol (CBD) products with less than 0.3% THC (dry weight) can be used in dogs.

It is believed that THC's effect comes from an affinity for the 2 cannabinoid receptors (CB_1R and CB_2R), as well as from other nonspecific cannabinoid receptors, such as the G protein–coupled receptor (GRP), which is a receptor for peptide hormones.[18–20] The higher intoxicating and psychoactive effect of THC in dogs than in humans is reported to be associated with dog's larger amount of brain cannabinoid receptors.[21] Death secondary to THC ingestion by dogs has been reported, particularly following ingestion of a combination of THC products with chocolate or an artificial sweetener (eg, xylitol) in brownies or cookies, respectively.[21,22] Systemic THC products are not recommended to be used in dogs for any reason due to their intoxicating effect.

The interest in using CBD as an alternative treatment option has increased significantly over the last couple of years due to its potential anti-inflammatory, antioxidant, neuroprotective, and anticancer properties.[16] Specifically, CBD's effect has been investigated for epilepsy, neoplasia, and osteoarthritis in dogs.[23–26] The use of CBD for ophthalmic diseases has also been studied due to its anti-inflammatory and neuroprotective effects.[16,20] Keratitis and corneal pain, endotoxin-induced uveitis, diabetic retinopathy, and intraocular pressure regulation are areas where CBD's effect has been investigated in humans and animals **(Figure 2)**.[16,20]

The mechanism of action for CBD seems to be more complex than for THC. Studies[20,27] have shown that CBD has a poor affinity for the 2 cannabinoid receptors (CB_1R and CB_2R), and it has even been shown that CBD has an antagonistic effect on these receptors when used together with THC. The anti-inflammatory effect of CBD is thought to have an association with its affinity for transient receptor potential vanilloid-1 (TRPV1), which plays an important role in pain and inflammation.[17,28] Transient

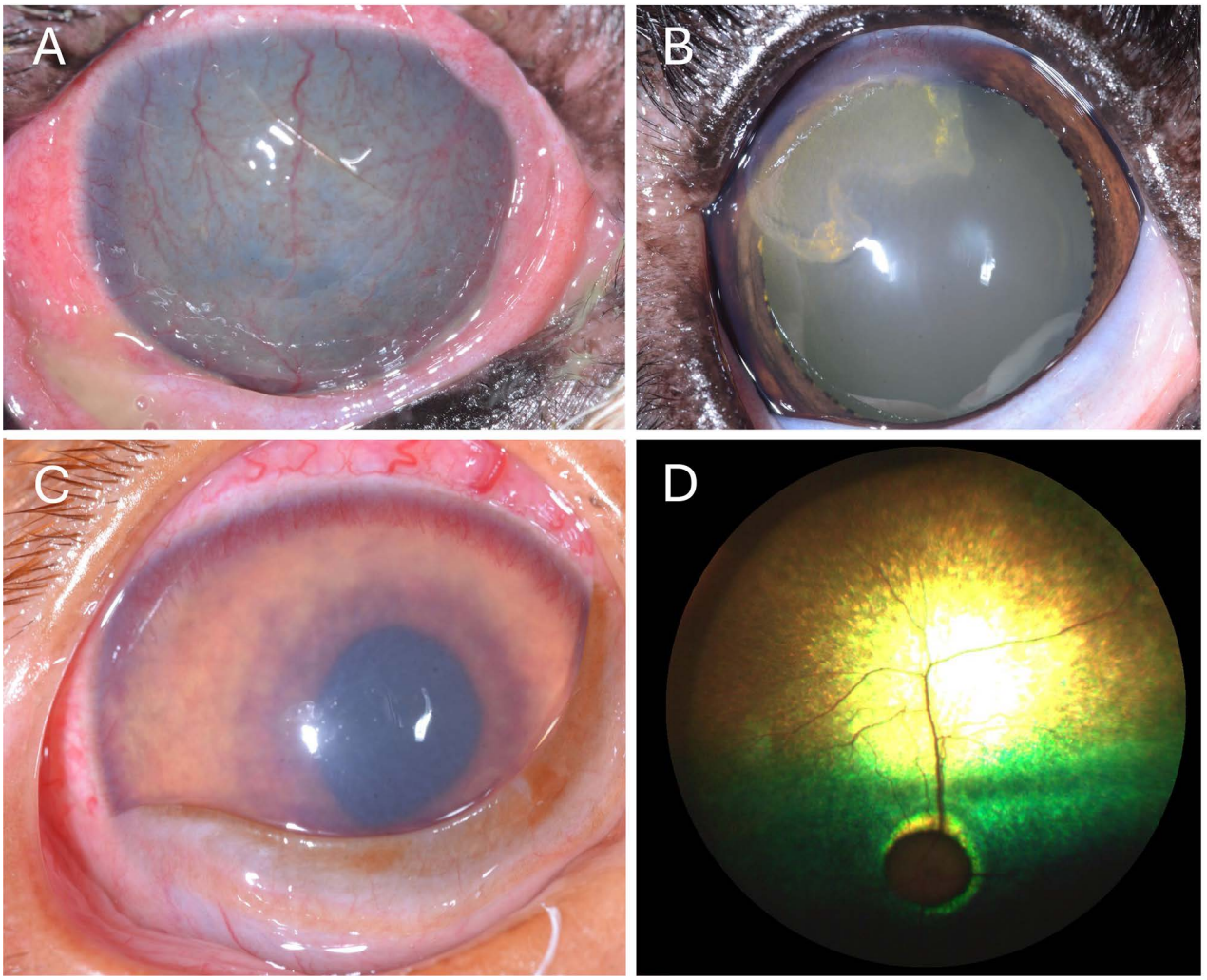

Figure 2—Images of ophthalmic diseases where cannabidiol treatment has been proposed as being beneficial in humans, lab animals, and/or dogs. A—Keratitis. Cannabidiol has been shown to have an anti-inflammatory and antinoxious effect on corneal inflammation. B—Indolent corneal ulcerations. Cannabidiol has been shown to increase healing and to have an antinoxious effect on corneal ulcerations. C—Anterior uveitis. Cannabidiol is thought to have an anti-inflammatory effect for posterior uveitis in lab animals, but no studies have shown cannabidiol to be effective for anterior uveitis. D—Retinal atrophy. Cannabidiol has shown positive neuroprotective effects in animal models, but no studies have been performed in dogs.

receptor potential vanilloid-1 is a nonselective cation channel that is activated by high temperatures.[29] Activation of TRPV1 has been correlated with corneal and retinal diseases such as corneal ulcerations and glaucoma due to the release of the neuropeptide substance P from corneal cold sensing neurons and its presence in retinal ganglion cells, respectively.[30,31] Different receptors that have been suggested as being important for THC and CBD activity are reviewed in **Table 1**.

Intraocular Pressure and Tear Production

The ability of THC to decrease intraocular pressure (IOP) makes it a potential antiglaucoma treatment option.[21] The ocular hypotensive property of THC is due to its ability to decrease aqueous humor (AH) formation from ciliary body epithelium and to increase AH outflow through the trabecular meshwork.[32,33] Activation of CB_1R and GRP receptors in both ciliary body and trabecular meshwork has been accepted as the reason for THC's ocular hypotensive property, but the involvement of the cannabinoid receptors on AH production/outflow and IOP is not completely understood.[32,33] Although THC can significantly decrease IOP in all species, it is not recommended by the American Glaucoma Society as an antiglaucoma drug due to the psychoactive and intoxicating effect if used systemically, as well as the short effectiveness of this drug, which means multiple treatments (systemically and topical) to keep the IOP low.[21,34]

A study by Fischer et al[35] evaluated the effect of topical THC 2% ophthalmic solution on IOP and AH flow rate in clinically normal dogs. The study found that THC significantly reduced the IOP with 12.54 ± 3.18 mm Hg in the THC group versus 13.88 ± 3.36 mm Hg in the control group (AM) and 11.69 ± 3.94 mm Hg versus 12.13 ± 2.99 mm Hg (PM), respectively, after 9 treatments twice a day. The authors noted that the IOP varied substantially among individuals, and no significant differences were found for aqueous humor flow rate.[35] No follow-up studies regarding THC as a treatment for glaucoma in dogs have been published. The recommendation from the American Glaucoma Society of not using THC as an antiglaucoma treatment, as described above, should also be followed by the veterinary society.[34] Using topical THC as an antiglaucoma treatment in dogs is not recommended, especially when adding the risk for systemic absorption from using topical ophthalmic THC on dogs and therefore the potential for systemic toxicity and death.

Varied results for CBD's effect on IOP in humans, mice, rats, rabbits, and dogs have been published with studies[16,20,36] showing that CBD can either decrease, increase, or have no effect on IOP. A study[37] regarding CBD's effect on IOPs in normotensive research beagles showed no effect of oral dosing with CBD at 2 different CBD doses (5 and 10 mg/kg, PO, once a day) over a 36-week treatment time. This study also showed no effect of CBD on tear production (measured with Schirmer tear test-1). The previous study[37] did find detectable CBD in tears at both doses following the 36-month treatment with CBD. The mechanism of action for CBD on IOP is not completely understood.[20,33] Studies[5,36] have shown that CBD could influence AH production and outflow through the ciliary body and trabecular meshwork. It has been proposed that CBD has an antagonistic effect on CB_1R and an agonistic effect on GRP18 receptors. This antagonistic versus agonistic effect

Table 1—Most common receptors that have been associated with cannabinoid interaction on ocular tissue.

			Ophthalmic relation	
Receptor	**Abbreviation**	**Function**	**Tissue**	**Action**
Cannabinoid receptor type 1 and 2	CB_1R and CB_2R	Regulates neuronal transmission and physiological processes such as pain, inflammation, memory, and feeding behavior	Conjunctiva and cornea	Increase healing and decrease pain
			Ciliary body	Decreases aqueous humor production (decreases IOP)
			Trabecular meshwork	Increases aqueous humor outflow (decreases IOP)
			Retina	Neuroprotection
G protein–coupled receptor	GRP	Regulates physiological responses to hormones, neurotransmitters, and environmental stimulants	Ciliary body	Decreases aqueous humor production (decreases IOP)
			Trabecular meshwork	Increases aqueous humor outflow (decreases IOP)
			Retina	Neuroprotection
Transient receptor potential vanilloid-1	TRPV1	This receptor is activated by heat, protons, proinflammatory cytokines; this receptor is associated with pain and inflammation	Cornea	Inhibition will decrease corneal inflammation and pain
			Retina	Inhibition will decrease retinal inflammation and act as a neuroprotector
Serotonin $5HT_{1A}$ receptors	Serotonin $5HT_{1A}$	This is a neurotransmitter and a peripheral inflammatory mediator	Cornea	Inhibition will decrease corneal inflammation and pain
			Retina	Inhibition will decrease retinal inflammation and act as a neuroprotector

IOP = Intraocular pressure.

on the cannabinoid receptors can be the reason different studies[5,33] have shown differences in CBD's effect on IOP. The American Glaucoma Society issued a statement in 2019 that specified that it does not support the treatment of pediatric glaucoma patients with cannabinoids (THC and CBD) due to a lack of studies that show a positive effect of medical cannabinoids on IOP and preserving ganglion cells function in pediatric patients with glaucoma.[38]

Cornea

Newer studies[39–41] have found CBD to have antinociceptive and anti-inflammatory effects on corneal tissue. Cannabidiol is thought to decrease major proinflammatory cytokines such as tumor necrosis factor-α, IL-1β, and IL-6, as well as inhibit leading vascular growth factors such as VEGF.[41,42] A study[39] has proposed that CBD's antinociceptive and anti-inflammatory effect is not related to CB_1R and CB_2R but due to its ability to be an inhibitor of TRPV1, as well as serotonin $5HT_{1A}$ receptors. Serotonin $5HT_{1A}$ is a key neurotransmitter that contributes to pain and inflammation and is found in corneal epithelial cells. Activation of serotonin $5HT_{1A}$ will lead to activation of NF-κB signaling, which is a central mediator of inflammation.[43,44]

Using CBD as a topical ophthalmic treatment has been challenging. Cannabidiol has a low solubility and bioavailability as well as being highly lipophilic, which is a challenge when it comes to CBD's ability to penetrate the hydrophilic stromal layers of the cornea.[41,45] Nanocarriers have been investigated and have shown some promising results regarding decreasing corneal inflammation and pain, but it still seems to be a challenge to find an effective nanocarrier that can lead topical CBD deeper into the layers of the cornea and intraocular tissue by corneal penetration.[41] Other challenges with CBD as a topical treatment for corneal inflammation are its ability to be cytotoxic toward corneal epithelial and endothelial cells, as well as having a low pH that can cause ocular surface irritation.[36,41] These challenges are still under investigation and there is no FDA-approved topical ophthalmic CBD product on the market.

An abstract[46] regarding systemic CBD's effect on experimentally induced anterior uveitis in dogs showed that dogs treated with systemic CBD did not develop corneal ulcerations as a complication to their aqueous paracentesis procedures, whereas the group of dogs treated with topical prednisolone acetate 1% ophthalmic suspension had 50% of the eyes (4 out of 8 eyes) develop corneal ulceration. This result could indicate a potential positive effect of systemic CBD on ocular surface health in dogs, especially since Jost et al[37] showed that systemic CBD is detectable in canine tears. Topical prednisolone acetate is known to increase risk of corneal ulceration and to have a negative healing effect on corneal epithelial cells.[47,48] The use of this topical steroid could have been the reason why 50% of the dogs developed corneal ulcerations in the prednisolone acetate group. Future studies will need to evaluate for a potential positive correlation between systemic CBD and its effect on inflammatory corneal diseases such as keratoconjunctivitis sicca, chronic superficial keratitis, and corneal ulcerations.[49]

Uvea

There are few research studies published regarding CBD's anti-inflammatory effect on uveal tissue. Posterior uveitis is a common ophthalmic disease in humans and can have devastating blinding outcomes.[50] Therefore, the focus on CBD's effect on uveitis has mainly been on posterior uveitis in laboratory animals. A rat study[51] showed that CBD has an anti-inflammatory effect on endotoxin-induced posterior uveitis by decreasing TNF-α in retinal tissue. A study (MdL Henriksen, DVM, PhD, DACVO, College of Veterinary Medicine, North Carolina State University, unpublished data, 2024) regarding systemic CBD's effect on ophthalmic short-term and long-term complications following phacoemulsification in diabetic dogs did not show a difference between the CBD group versus the control group. The study (MdL Henriksen, DVM, PhD, DACVO, College of Veterinary Medicine, North Carolina State University, unpublished data, 2024) found an elevation of the liver enzyme ALP in the group of dogs treated with systemic CBD (10 mg/kg, PO, twice daily), which seems to be a common finding in canine CBD studies.[52,53] Corsato Alvarenga et al[53] found that a long-term (36-week) treatment of 5 mg/kg, PO, once daily was better tolerated than a treatment of 10 mg/kg, once daily, but ALP was elevated in both groups compared to the control. The impact of this ALP elevation is not known and should be investigated further. In the meantime, any dogs treated with systemic CBD should be monitored for changes in ALP and other liver parameters that could indicate systemic complications from the treatment, regardless of which systemic CBD dose that is being used.

Retina and Optic Nerve Head

Cannabidiol is thought to have a neuroprotective effect on retinal and optic nerve tissue.[54,55] Studies in diabetic rats[47,54] have shown that CBD, as an antioxidant, protects against retinal degeneration and diabetic retinopathy by decreasing the glutamine synthetase through its interaction with CB_1R. The same group[55] of researchers also found that CBD's antioxidant properties will block the activation of p38 MAPK. The formation of p38 MAPK, a mitogen-activated protein kinase, is a response to tissue stress and blood-retinal barrier breakdown causing posterior uveitis with increased proinflammatory cytokine formation, such as TNF-α and VEGF.[56] By blocking p38 MAPK with CBD, studies have shown that TNF-α and VEGF formation is also blocked. This leads to the consideration that CBD has an anti-inflammatory and neuroprotective effect on retinal tissue.[55,56] As mentioned, serotonin $5HT_{1A}$ and TRPV1 are expressed in retinal tissue and an inhibition of

these receptors decreases retinal inflammation seen in retinal diseases such as glaucoma.[30,57] Since studies[58,59] have shown that CBD is able to inhibit these 2 inflammatory receptors, future studies should aim to evaluate CBD's anti-inflammatory effect on retinal tissue by blocking serotonin $5HT_{1A}$ and TRPV1, as seen in other clinical studies of neurologic tissue. No studies in dogs with retinal diseases have been performed to date. Studies of CBD's effect on dogs with retinal diseases such as glaucoma, sudden acquired retinal degeneration syndrome, and progressive retinal atrophy would help us understand if treatment with systemic CBD could have a positive neuroprotective effect on retinal and optic nerve tissue.

In conclusion, there is a growing interest in using CBD to treat medical diseases in dogs. Cannabidiol is being investigated for its anti-inflammatory, antinociceptive, and neuroprotective effect in ophthalmic diseases and disorders in various species. There are only a few CBD studies in dogs regarding its effect on ophthalmic tissue and diseases. For now, it seems that CBD does not have an effect on IOP in normotensive dogs, but systemic CBD will be excreted into the tears of normal, healthy dogs. Systemic CBD may have a positive effect on ocular surface health through its excretion into the tear film, but studies have not been able to prove a positive anti-inflammatory effect of systemic CBD on intraocular inflammation. No studies have examined CBD's effect on retinal and optic nerve tissue in dogs. Treatment with systemic CBD is known to elevate ALP in dogs, and blood work should be monitored carefully in dogs. More research regarding CBD and its effect on ophthalmic diseases in dogs is needed before we can say if CBD is safe to use and has any effect on the canine eye. Finally, an important take-home message from this review is that THC is toxic for dogs and should not be used for any reason.

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References

1. Cannabis, marijuana and cannabinoids – what you need to know. National Center for Complementary and Integrity Health (NIH). Accessed July 22, 2024. https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know
2. Crocq MA. History of cannabis and the endocannabinoid system. *Dialogues Clin Neurosci.* 2020;22(3):223–228. doi:10.31887/DCNS.2020.22.3/mcrocq
3. O'Shaughnessy WB. On the preparations of the Indian hemp, or Gunjah. *Prov Med J Retrosp Med Sci.* 1843;4(5):363–369.
4. Gieringer DH. The origins of cannabis prohibition in California. Schaffer Library of Drug Policy. Revised May-July 2012. Accessed April 11, 2024. https://www.druglibrary.org/schaffer/history/California_Marijuana_Law_History/California_Marijuana_Law_History_TOC.html
5. Aebersold AS, Song ZH. The effect of cannabidiol on aqueous humor outflow and trabecular meshwork cell signaling. *Cells.* 2022;11(19):3006. doi:10.3390/cells11193006
6. State Medical Cannabis Law. National Conference of States Legislature (NCSL). Accessed July 15, 2024. https://www.ncsl.org/health/state-medical-cannabis-laws
7. Matthews AL, Hickey C. More US states are regulating marijuana. See where it's legal across the country. CNN. 2023. Accessed April 11, 2024. https://www.cnn.com/us/us-states-where-marijuana-is-legal-dg/index.html
8. H.R.2 - An act to provide for the reform and continuation of agricultural and other programs of the Department of Agriculture through fiscal year 2023, and for other purposes. Congress.gov. Accessed July 15, 2024. https://www.congress.gov/bill/115th-congress/house-bill/2
9. The Agriculture Improvement Act of 2018 (2018 Farm Bill)-old. USDA. Accessed July 15, 2024. https://www.fs.usda.gov/managing-land/farm-bill-old
10. Malone T. CBD, marijuana and hemp: what is the difference among these cannabis products, and which are legal? MSU Today. April 6, 2021. Accessed August 24, 2024. https://msutoday.msu.edu/news/2021/cbd-marijuana-and-hemp
11. FDA regulation of cannabis and cannabis-derived products, including cannabidiol (CBD) 2024. FDA. Accessed April 11, 2024. https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd
12. Cannabis overview. National Conference of States Legislature (NCSL). Accessed July 15, 2024. https://www.ncsl.org/civil-and-criminal-justice/cannabis-overview
13. Hall A. CBD statistics, data, and use. Forbes Health. 2024. Accessed May 2, 2024. https://www.forbes.com/health/cbd/cbd-statistics/
14. Mikulic M. Total U.S. cannabidiol (CBD) product sales 2014–2022. Statista. Accessed May 2, 2024. https://www.statista.com/statistics/760498/total-us-cbd-sales/
15. Khalsa JH, Bunt G, Blum K, Maggirwar SB, Galanter M, Potenza MN. Review: cannabinoids as medicinals. *Current Addict Rep.* 2022;9(4):630–646.
16. Aebersold A, Duff M, Sloan L, Song Z. Cannabidiol signaling in the eye and its potential as an ocular therapeutic agent. *Cell Physiol Biochem.* 2021;14(1–2):1–4.
17. Afflitto GG, Aiello F, Scuteri D, Bagetta G, Nucci C. CB1R, CBNR and TRPV1 expression and modulation in in vivo, animal glaucoma models: a systemic review. *Biomed Pharmacother.* 2022;150:112981.
18. Mackie K. Cannabinoid receptors: where they are and what they do. *J Neuroendocrinol.* 2008;20(suppl 1):10–14.
19. Console-Bram L, Brailoiu E, Brailoiu GC, Sharir H, Abood ME. Activation of GPR18 by cannabinoid compounds: a tale of biased agonism. *Br J Pharmacol.* 2014;171(16):3908–3917. doi:10.1111/bph.12746
20. Wang MTM, Danesh-Meyer HV. Review: cannabinoids and the eye. *Surv Ophthalmol.* 2021;66(2)327–345.
21. Donaldson CW. Marijuana exposure in animals. *Vet Med.* 2002;97(6):437–438.
22. Johnstone G. Marijuana poising in dogs. American Kennel Club. 2023. Accessed April 11th 2024. https://www.akc.org/expert-advice/health/marijuana-poisoning-in-dogs/
23. Henry JG, Shoemaker G, Prieto JM, Hannon MB, Wakshlag JJ. The effect of cannabidiol on canine neoplastic cell proliferation and mitogen-activated protein kinase activation during autophagy and apoptosis. *Vet Comp Oncol.* 2021;19(2):253–265.

24. Inkol JM, Hocker SE, Mutsaers AJ. Combination therapy with cannabidiol and chemotherapeutics in canine urothelial carcinoma cells. *PLoS One.* 2021;16(8):e025559.
25. Rozental AJ, Weisbeck BG, Corsato Alvarenga I, et al. The efficacy and safety of cannabidiol as adjunct treatment for drug-resistant idiopathic epilepsy in 51 dogs: a double-blinded crossover study. *J Vet Intern Med.* 2023;37(6):2291–2300.
26. Patikorn C, Nerapusee O, Soontornvipart K, et al. Efficacy and safety of cannabidiol for the treatment of canine osteoarthritis: a systematic review and meta-analysis of animal intervention studies. *Front Vet Sci.* 2023;10:1248412.
27. Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB_1 and CB_2 receptor agonists in vitro. *Br J Pharmacol.* 2007;150(5):613–623.
28. Etemad L, Karimi G, Alavi MS, Roohbakhsh A. Pharmacological effects of cannabidiol by transient receptor potential channels. *Life Sci.* 2022;300:120582.
29. Tsuji F, Aono H. Role of transient receptor potential vanilloid 1 in inflammation and autoimmune diseases. *Pharmaceuticals.* 2012;5(8):837–852.
30. Sappington RM, Sidorova T, Ward NJ, Chakravarthy R, Ho KW, Calkins DJ. Activation of transient receptor potential vanilloid-1 (TRPV1) influences how retinal ganglion cell neurons respond to pressure-related stress. *Channels.* 2015;9(2):102–113.
31. Li F, Yang W, Jiang H, et al. TRPV1 activity and substance P release are required for corneal cold nociception. *Nat Commun.* 2019;10(1):5678. doi:10.1038/s41467-019-13536-0
32. Cairns EA, Baldridge WH, Kelly MEM. The endocannabinoid system as a therapeutic target in glaucoma. *Neural Plast.* 2016;9364091:1–10.
33. Miller S, Daily L, Leishman E, Bradshaw H, Straiker A. Δ9-Tetrahydrocannabinol and cannabidiol differentially regulate intraocular pressure. *Invest Ophthalmol Vis Sci.* 2018;59(15):5904–5911.
34. Jampel H. American glaucoma society position statement: marijuana and the treatment of glaucoma. *J Glaucoma.* 2010;19(2):75–76.
35. Fischer KM, Ward DA, Hendrix DVH. Effects of a topically applied 2% delta-9-tetrahydrocannabinol ophthalmic solution on intraocular pressure and aqueous humor flow rate in clinically normal dogs. *Am J Vet Res.* 2013;74(2):275–280.
36. Senapati S, Youssef AAA, Sweeney C, Cai C, Dudhipala N, Majumdar S. Cannabidiol loaded topical ophthalmic nanoemulsion lowers intraocular pressure in normotensive Dutch-belted rabbits. *Pharmaceutics.* 2022;14(12):2585.
37. Jost HE, Spitznagel K, Alvarenga IC, et al. Long-term effect of oral cannabidiol administration to healthy adult dogs and tear production, intraocular pressure and tear concentrations. *Vet Ophthalmol.* 2023;27(4):357–366.
38. Grossman AL, Javitt MJ, Moster SJ, Grajewski AL. American glaucoma society position statement on cannabinoid use in pediatric glaucoma patients. *Ophthalmol Glaucoma.* 2019;2(6):365–366.
39. Thapa D, Cairns EA, Szczesniak AM, Toguri JT, Caldwell MD, Kelly MEM. The cannabinoids Δ^8THC, CBD, and HU-308 act via distinct receptors to reduce corenal pain and inflammation. *Cannabis Cannabinoid Res.* 2018;3(1):11–20. doi:10.1089/can.2017.0041
40. Rebibo L, Frusic-Zlotkin M, Ofri R, Nassar T, Benita S. The dose-dependent effect of a stabilized cannabidiol nanoemulsion on ocular surface inflammation and intraocular pressure. *Int J Pharm.* 2022;617:121627. doi:10.1016/j.ijpharm.2022.121627
41. Nguyen Tran V, Strnad O, Suman J, et al. Cannabidiol nanoemulsion for eye treatment – anti-inflammatory, wound healing activity and its bioavailability using in vitro human corneal substitute. *Int J Pharm.* 2023;643:123202.
42. Solinas M, Massi P, Cantelmo AR, et al. Cannabidiol inhibits angiogenesis by multiple mechanisms. *Br J Pharmacol.* 2012;167(6):1218–1231.
43. Liu T, Zhang L, Sun S. NF-κB signaling in inflammation. *Signal Transduct Target Ther.* 2017;2:17023.
44. Hao S, Shi W, Liu W, Chen Q, Zhuo M. Multiple modulatory roles of serotonin in chronic pain and injury-related anxiety. *Front Synaptic Neurosci.* 2023;15:1122381.
45. Grifoni L, Vanti G, Donato R, Sacco C, Bilia AR. Promising nanocarriers to enhance solubility and bioavailability of cannabidiol for a plethora of therapeutic opportunities. *Molecules.* 2022;27(18):6070.
46. Henriksen MdL, Terhaar HM, Davey E, et al. Clinical findings in dogs treated with oral cannabidiol (CBD) versus prednisolone acetate 1% ophthalmic suspension for experimentally induced uveitis. ACVO Annual Meeting Abstract. *Vet Ophthalmol.* 2021;24. doi:10:1111/vop.12945
47. Petroutsos G, Guimaraes R, Giraud P, Pouliquen Y. Corticosteroids and corneal epithelial wound healing. *Br J Pharmacol.* 1982;66(11):705–708.
48. Hendrix DVH, Ward DA, Barnhill MA. Effects of anti-inflammatory drugs and preservatives on morphologic characteristics and migration of canine corneal epithelial cells in tissue culture. *Vet Ophthalmol.* 2002;5(2):127–135.
49. Whitley RD, Hamor RE. Chapter 19: diseases and surgery of the canine cornea and sclera. In: Gelatt KN, ed. *Veterinary Ophthalmology.* 6th ed. Wiley; 2021:1082–1172.
50. Sudharshan S, Sudha GK, Jyotirmay B. Symposium: current approach in the diagnosis and management of posterior uveitis. *Indian J Ophthalmol.* 2010;58(1):29–43.
51. Liu EK, Khalifa Y, Al-Shabrawey M, et al. Anti-inflammatory effects of cannabinoids in endotoxin-induced uveitis. *Invest Ophthalmol Vis Sci.* 2005;46:972.
52. Bartner LR, McGrath S, Rao S, Hyatt LK, Wittenburg LA. Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. *Can J Vet Res.* 2018;82(3):178–183.
53. Corsato Alvarenga I, Wilson KM, McGrath S. Tolerability of long-term cannabidiol supplementation to healthy adult dogs. *J Vet Intern Med.* 2024;38(1):326–335.
54. Liou GI, Ola MS, Caldwell RB, El-Remessy AB. Neuroprotective effect of cannabidiol involve inhibition of glutamine synthetase nitration in diabetic retina. *Invest Ophthalmol Vis Sci.* 2006;47:4828.
55. Liou GI, Tang Y, Hanson E, et al. *Neuroprotective effect of cannabidiol in endotocin-induced retinal inflammation. Invest Ophthalmol Vis Sci.* 2007;48:4954.
56. El-Remessy AB, Al-Shabrawey M, Khalifa Y, Tsai N, Caldwell RB, Liou GI. Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes. *Am J Pathol.* 2006;168(1):235–244.
57. Masson J. Serotonin in retina. *Biochimie.* 2019;161:51–55.
58. De Gregorio D, McLaughlin R, Luca P, et al. Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain. *Pain.* 2019;160(1):136–150.
59. Barata L, de Hoz-Rivera M, Romero A, et al. Role of 5HT1A receptors in the neuroprotective and behavioral effects of cannabidiol in hypoxic-ischemic newborn piglets. *J Front Pharmacol.* 2022;13:925740.