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Scientific Validation of Cannabidiol for Management of Dog and Cat Diseases

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Abstract

Cannabidiol (CBD) is a non-psychotropic phytocannabinoid of the plant *Cannabis sativa* L. CBD is increasingly being explored as an alternative to conventional therapies to treat health disorders in dogs and cats. Mechanisms of action of CBD have been investigated mostly in rodents and in vitro and include modulation of CB1, CB2, 5-HT, GPR, and opioid receptors. In companion animals, CBD appears to have good bioavailability and safety profile with few side effects at physiological doses. Some dog studies have found CBD to improve clinical signs associated with osteoarthritis, pruritus, and epilepsy. However, further studies are needed to conclude a therapeutic action of CBD for each of these conditions, as well as for decreasing anxiety and aggression in dogs and cats. Herein, we summarize the available scientific evidence associated with the mechanisms of action of CBD, including pharmacokinetics, safety, regulation, and efficacy in ameliorating various health conditions in dogs and cats.

1. INTRODUCTION

CBD: cannabidiol

The cannabidiol (CBD) pet market is expected to increase by $3.05 billion during 2021–2025, with a compound annual growth forecast to reach nearly 30% (1). As recreational marijuana has been legalized in some US states and other countries, CBD has gained popularity among people and their pets. However, along with this expansion into the pet market, concerns remain about CBD's legality, safety, and efficacy in veterinary patients.

A survey conducted online in the United States reported that nearly 60% of pet owners give or were giving CBD to their dogs, and 12% to their cats, most commonly for treating conditions like osteoarthritis (OA), seizures, cancer, or anxiety (2). From these, 64% found it helps with pain reduction, 50% that it aids with sleep, 49% that it reduces anxiety, and 30% that it reduces convulsions. Pet owners opt for cannabis products for their pets because they are natural and generally perceived as a cost-effective treatment option for pain. Thus, cannabis supplements might be preferred over conventional medications (3). Although CBD is promising as an adjunct therapy for various conditions, and people have been providing it as a supplement to their pets, data about its efficacy and long-term safety are limited.

We conducted a literature search to understand what is known to date about CBD uses, pharmacokinetics, tolerability, and efficacy in canine and feline patients. Articles included in this review were obtained from the databases ScienceDirect, PubMed, and Google Scholar and contained one or a combination of the following keywords: cannabis, dog, cat, CBD, cannabidiol, safety, pharmacokinetics, anxiety, epilepsy, anti-inflammatory, and analgesic.

2. CBD FORMS AND LEGALITY FOR DOGS AND CATS IN THE UNITED STATES

The CBD used in dog and cat supplements is derived from hemp (*Cannabis sativa*), which is required to contain tetrahydrocannabinol (THC) levels below 0.3% in the whole plant. CBD can be supplemented either as full or broad spectrum or as an isolate (3), which may be extracted using petroleum-based solvents, ethanol, or supercritical CO_2 (4). Full spectrum refers to a minimally processed whole hemp plant after decarboxylation and distillation, which has a CBD content of 10–25% and contains more than 100 phytocannabinoids (PCs) along with terpenes, flavonoids, fatty acids, and other phytochemicals (4, 5). When it is further distilled to remove THC and concentrate CBD to 25–80%, the extract is referred to as broad spectrum (4). Finally, the CBD isolate contains the pure CBD molecule at a concentration >95%.

The pet food industry is regulated at the federal level by the Food and Drug Administration (FDA) and at the state level most commonly through the adoption of standards and regulations set forth by the Association of American Feed Control Officials (AAFCO). Regulations appear to be inconsistent between federal and state agencies (6). Although animal caretakers have used hemp for centuries, the Marihuana Tax Act of 1937 placed taxes on all sales of cannabis and its products, which restricted its market. In 1970, these products were placed under the Controlled Substances Act (CSA) as a Schedule I drug (7). Hemp was also included in this category, although its THC content is low to negligible. The 2014 Agricultural Act (also known as the 2018 Farm Bill) defined hemp as any part of *C. sativa* with a THC content below 0.3%, which allowed the use of industrial hemp for research in states that permitted cannabis farming. The 2014 Agricultural Act also removed hemp and its derivatives with THC below 0.3% from the CSA of 1970 (marijuana remained in their control). Cannabis products with a THC content >0.3% are still considered a Schedule I controlled substance (8).

Some reports have noted inconsistencies in pet CBD supplements that are available in the market, such as misleading or untested claims, violations of good manufacturing practices, lower

amounts of CBD than what was stated on the label, and/or THC above the allowed limit (0.3%) (9, 10). Unfortunately, many cannabis products are marketed in the United States with unsubstantiated claims of efficacy (6). To legally sell CBD products, safety in the intended species and efficacy of therapeutic claims must first be approved by the FDA (6). Some CBD or cannabis-derived products have been approved for use in humans, such as a purified form of CBD called Epidiolex® (6), prescribed for certain forms of epilepsy.

Despite the FDA's guidance prohibiting CBD use in supplements or the introduction of CBD into human or animal food that is marketed across state lines, veterinary products that contain cannabis with THC less than 0.3% are being sold as supplements and are available for purchasing online or at retail stores. Thus, in 2019, the FDA declared that CBD is not a generally recognized as safe (GRAS) substance. Another study also found that of 29 CBD pet products tested, 4 were contaminated with heavy metals, although all had THC below 0.3% (11). Bonn-Miller et al. (12) analyzed 84 non-FDA-approved CBD products from 31 countries and reported that CBD supplemented in oil appeared to have the most variation in human products, with high batch-to-batch inconsistency. To date, clear regulatory guidance from the FDA is lacking due to the need for more studies on the safety of CBD (4). Because hemp and its derivatives have no clear definitions as a food additive by AAFCO and CBD is not considered GRAS by the FDA, it can currently be sold as a supplement in most states, provided it does not cross state lines and no claims of medical efficacy are made. For the most part, hemp-derived products cannot be included as an ingredient in pet foods (7).

3. ENDOCANNABINOID SYSTEM AND PHYTOCANNABINOIDS

3.1. Endocannabinoid System

Although cannabis has been used for centuries, the endocannabinoid system (ECS) was discovered only recently in the early 1990s after identification, cloning, and characterization of the cannabinoid receptor 1 (CB1) present in the brain (13, 14). This was followed by the discovery of a second receptor (CB2), initially hypothesized to be peripheral because it was not found in the human brain (14, 15). The CB1 receptor is expressed on most central nervous system cell types but at variable levels (16). Although CB2 receptors are expressed at a lower level in neurons in the brain than CB1, they are also expressed moderately in glial cells, including microglia, during pathologies related to degeneration and inflammation (17, 18). The ECS is present in nearly all animals, including primitive invertebrates like the sea urchin, nematodes, and mussels and more evolved animals like mammals (7). The ECS is composed of endocannabinoids (ECs), G protein–coupled receptors called EC receptors (CB1 and CB2), and enzymes that degrade and recycle ECs (9). ECs are a large family of fatty acids that contain either an amide or ester group, which are involved in the activation of cannabinoid receptors to regulate homeostasis in regard to brain function, immunity, and other physiological functions (14).

CB1 receptor distribution varies across species and is present in both the central nervous system and the periphery, whereas CB2 is more abundant in intestinal and immune system cells (9). ECs are released postsynaptically and act on presynaptic receptors CB1 and CB2, causing a rapid inhibitory modulation of neurotransmitters responsible for promoting various biological processes like pain, inflammation, immunity, bone growth, and anxiety (19). Thus, ECs promote homeostasis through modulation of stressful physiological responses (20). The most studied and potent ECs are anandamide (21) and 2-arachidonoyl glycerol (9, 22). ECs have different affinities for each receptor, are produced as needed by enzymes in the postsynaptic neuronal membranes, and have a short half-life because they are quickly hydrolyzed by the enzymes fatty acid amide hydrolase (23) and monoacylglycerol lipase (9). ECs are also important modulators of synaptic

transmission. Although early evidence indicated a role of ECs in retrograde synaptic function (see 24 for a review), evidence also indicates that ECs can signal in a nonretrograde manner (25).

3.2. Phytocannabinoids Present in Hemp

Cannabis is an Asian herb that can be divided into marijuana with high THC content and hemp (*C. sativa*; low THC content <0.3%) (6). This review focuses on hemp extracts because they have been the target of veterinary studies due to their high concentration of CBD and low to nondetectable levels of psychoactive THC.

Nearly 150 PCs are found in hemp (26), mainly in the resin produced by glandular hairs of the plant (27). PCs are naturally occurring terpenophenolic compounds present in cannabis plants (28). The main constituents include CBD, THC, cannabigerol (CBG), cannabichromene (CBC), and their acidic forms, which may be enzymatically degraded and transformed into other PCs due to heat, atmospheric oxygen, and light activation (26). Other known subclasses of PCs include cannabinol (CBN), Δ-8-THC, cannabicyclol (CBL), cannabinodiol (CBND), cannabielsoin (CBE), and cannabitriol (CBT) (27). From all subclasses of PCs, the two most abundant and studied are THC and CBD. Although structurally very similar (26), CBD and THC have different mechanisms of action. Whereas THC is a partial CB1 and CB2 receptor agonist with direct interaction, CBD has a lower affinity for both receptors with indirect negative allosteric modulation of CB1 (9). CBD's minimal agonism of the CB receptors might account for its negligible psychotropic effect (29). CBD also interacts with other receptors and systems besides the cannabinoid receptors (29), which are discussed in separate sections of this review.

The acidic or carboxylated forms of PCs were found to be more abundant in hemp than their neutral forms (26, 30), which currently are assumed to derive from these acid forms through mostly nonenzymatic decarboxylation (26). CBG is the precursor of both CBD and CBC through C–C and C–O bond formations, respectively (26). Other cannabinoids may develop from CBD, including cannabinol that is formed from a sequence of C–O bond formation and aromatization (26). The mechanisms of action of cannabinoids are described in different sections of this review, with a major focus on CBD.

3.3. Perceptions of Pet Owners and Veterinarians Regarding the Use of Products Containing Cannabinoids

Due to increased knowledge regarding the therapeutic potential of CBD products in humans, along with recent legalization in some states, more pet owners are exploring options for providing cannabinoid products for their pets (31). Pet owners' and veterinarians' perceptions of CBD use are generally positive, although many veterinarians do not feel knowledgeable enough about the therapeutic and toxic effects of cannabinoid products (32).

Kogan et al. (2) evaluated consumer perceptions on the use of hemp products for companion animals. They used an anonymous online survey from a commercial website that specialized in hemp products for animals. This survey received 632 responses regarding the type of hemp products pet owners purchased, the reason for the purchase, and the value of hemp products for the health of their pet. Results indicated that 58.8% were currently supplementing hemp products for their dog, with 77.6% using these products for medical and behavioral conditions diagnosed by their veterinarian. CBD was used most commonly to treat seizures, cancer, anxiety, and arthritis. Only 11.93% (out of 570 respondents) administered hemp products for their cat. The survey results indicated that the perceptions of the therapeutic benefits of hemp products for both dogs and cats were mostly positive. Relief from pain, better sleep, decreased anxiety, and reduced inflammation were the most common benefits reported. The most common side effects reported for both

dogs and cats were sedation (~20% for both dogs and cats) and increased appetite (~16% for both dogs and cats). The most common reasons for discontinuing hemp products were ineffectiveness and expense.

A survey conducted in Slovenia with 408 respondents found similar results (33). These authors used a 5-point Likert scale (1 = strongly disagree and 5 = strongly agree) to understand participants' perceptions toward CBD for their pets. On average, pet owners strongly agreed (4.45) that CBD supplementation for dogs and cats should be legal. They also agreed that CBD is effective for treating various health conditions (3.86), that it is natural and thus more suitable for treating health conditions than synthetic medicines (3.62), and that they would recommend it for their friends' pets (3.78). Slovenians surveyed disagreed that there is not enough scientific data supporting the efficacy of CBD for treating various veterinary conditions (3.45, reserved scale). Conversely, when looking at pet owners who had never used CBD for their pets, a national online survey conducted in the United States found that the main reason for not using CBD was the lack of information on safety and efficacy (34). From the 1,238 survey responses, 71% had never given a CBD product to their pet, and only 11% of these would not be interested in trying it. Findings in this survey support that the majority (65%) of pet owners that had used or were using CBD for their pets perceived an improvement in their conditions, and 24% were unsure (34). That study showed clear evidence that people who had been giving CBD to their pet for a longer period of time perceived it to be more efficacious than those who had just started supplementing it. When asked about side effects noted from CBD on a multiple-choice question, respondents answered either no (45%) or mild (lethargy and sleepiness; 24% each) effects. Less than 2% of respondents reported side effects like increased anxiety, inappetence, diarrhea, ataxia, or disorientation.

An important driver for CBD use in pets relates to the owner's own experience with these supplements. In Slovenia, 62% of owners who had used CBD for themselves were also giving it to their pet (33). When interviewing people with cats that presented behavioral problems, those who had used CBD for themselves also felt more comfortable supplementing it to their cat (35). In a mixed-methods study, Wallace et al. (3) found that the motivations for using CBD to treat chronic pain in human and dog patients were somewhat similar. Most individuals thought that hemp products were a good treatment option for both humans (45%) and dogs (44%); some thought it was the best option for pain (50% for humans; 56% for dogs); and close to 50% of respondents also reported they liked that it came from natural sources and that they preferred cannabis over traditional medicines for both themselves and their dogs. Human subjects used more marijuana/cannabis (THC > 0.3%) than they gave to their dogs (76% versus 26%, respectively), likely because of THC's known toxicity in canines, but both groups had used a similar proportion of hemp isolate (THC < 0.3%) and hemp broad or full spectrum (THC < 0.3%) (3). An apparent anthropomorphism phenomenon regarding CBD use in humans and pets has been described previously in other aspects of pet husbandry (36).

Veterinarian education about CBD and thereby cannabis product recommendations for their clients could play an important role in CBD's popularity and future sales, but this is not yet the situation. In a US national survey, only 12% of pet owners who had ever used CBD supplements for their pets reported having it recommended by a veterinarian (34). Kogan et al. (32) conducted an anonymous survey invitation using the Veterinarian Information Network that was sent to approximately 34,000 US veterinarians. From 2,130 veterinarians who chose to participate, 44% responded that they knew some about the therapeutic effects of CBD products in dogs, whereas 35% responded they did not know much. Knowledge about the reported toxic effects of CBD products in dogs was lower, with 30% knowing some and 44% not knowing much. Just over half (56%) of participants reported having clinical experience with CBD products via direct observation of what the client reported, and the most familiar products to these participants were

oil extracts/tinctures and biscuits/edibles. The most witnessed or reported side effects were sedation and increased appetite. Positive outcomes included analgesia for chronic and acute pain, decreased anxiety, and reduced seizure frequency/severity. This survey indicated that CBD products are being advised, recommended, or prescribed infrequently: 44.1% responded "never" or "rarely" advising it (28.9%). The most common reasons were the lack of knowledge and the need for more research. The use of CBD supplements by pet owners for treating the behavioral issues in companion animals is largely due to its potential calming effects (2, 34). From 356 participants interviewed that had used CBD for their pets at least once, 67% said it was for either anxiety or CBD's calming effect (34). Grigg et al. (35) evaluated cat owners' perceptions of prescription medications as well as herbal and nutritional supplements when dealing with behavioral problems. This study was the result of an online and anonymous survey of 448 respondents. Results showed that although most owners (97.8%) reported their cat having at least one behavioral problem, only 16 (3.6%) reported seeking help from a behaviorist, and only 3.3% had a veterinarian recommend they find help regarding their cat's behavioral issues. Approximately 50% were aware of the types of medications, supplements, and CBD products available. Further, 21.4% of owners responded "yes" and 57.4% responded "maybe" when asked whether they would give medications or supplements. Most common concerns were the negative side effects, including sedation and addiction. Overall, this study found that most cat owners observe behavioral issues but rarely seek help from their veterinarian. Most are open to the idea of different treatment options (only 21.2% participants responded "no" to giving their cat medication), but more education is needed from their veterinarian on understanding and treating behavior problems.

From all the surveys reported, there seems to be a common trend for pet owners to supplement their pets with CBD even with little information or knowledge available (34), especially if they have tried CBD for themselves and experienced positive results (33). Most pet owners have a positive perception of CBD's efficacy in treating conditions like anxiety and chronic pain; however, both veterinarians and pet owners still have some insecurity due to gaps in knowledge about the dosing efficacy and safety of CBD. Pet owners have reported that the most important features of CBD products are proven efficacy as a treatment option (37), affordability, and appropriate regulation with regard to safety and efficacy (38).

4. PHARMACOKINETICS AND SAFETY OF CBD

There have been many reports of cannabis poisoning in dogs and cats, due mostly to ingestion of human-grade marijuana products (39, 40). Common clinical side effects of marijuana intoxication include ataxia, disorientation, mydriasis, urinary incontinence, hyperesthesia, tremors, and vomiting (40). The side effects are thought to come from lipid-soluble THC ingestion, mainly through the activation of psychotropic CB1 receptors (39). Although Δ-9-THC has a high safety margin, with a lethal dose (LD50) in dogs estimated to be more than 3,000 mg/kg (31, 39, 41), deaths have occurred after ingestion of food products containing highly concentrated THC butter (39).

Pet cannabis products vary greatly from those meant for human consumption, as they are made from hemp (*C. sativa*) and thus contain very low to nondetectable levels of THC. Most safety and pharmacokinetic (PK) studies have used hemp extracts, oils, or chewables containing CBD, with low levels of other cannabinoids and THC levels below 0.3% (**Supplemental Table 1**). Further, CBD doses tested in most safety or tolerability studies in dogs ranged from 1 to 20 mg/kg of body weight (BW) daily. Although they are different cannabinoids, the CBD tested is usually 500 to 3,000 times lower than the estimated lethal dose of THC.

Supplemental Material >

Most veterinary studies on cannabinoid safety and tolerability are recent. CBD product sales rose following the descheduling of hemp from the Farm Bill in 2018, and interest has increased

among companies and researchers to understand what dose is safe, as well as efficacious, for dogs and cats with given conditions. Caution must be taken when extrapolating CBD safety and PK information across species, because significant differences may exist among cannabinoid receptors. For example, Ndong et al. (42) found that CBD had similar affinity to canine CB2 as to human and rodent CB2, but its potency is approximately 30 times lower in dogs than in the other species tested. Hence, tolerability studies of a given cannabinoid must be conducted in the intended species.

Several factors may affect drug pharmacokinetics. Pharmacokinetics encompass the relationship between drug absorption, distribution in the body, and metabolization (inactivation) (43). Drugs cross cell membranes mainly through passive diffusion, the rate of which is determined by molecular size, lipid solubility, affinity for binding to proteins, and degree of ionization (43). When administered orally, the most prevalent route of CBD administration to pets, the drug is absorbed mainly in the small intestine due to its large surface area. A drug has high oral bioavailability when its total absorption to the bloodstream is similar to what it would be if administered intravenously, because bioavailability refers to the ratio of the concentration–time curve (area under the curve) of a drug given orally to the area under the curve of the same drug at the same concentration given intravenously (43). Other factors that affect drug absorption include particle size and tablet configuration, its interaction with food particles, and variations in the gastrointestinal (GI) system of each patient (43).

For all the reasons that can affect drug absorption and metabolization, PK studies of CBD given orally to dogs have found large interindividual variation in parameters tested (**Supplemental Table 1**). Many studies used three to six animals due to challenges presented with timed blood collections, or because power calculations indicated this number of replicates was sufficient to detect a treatment difference. Thus, to decrease this variability, more dogs might be needed for future studies, although this can be logistically challenging. Also, PK parameters were expected to vary among studies given differing formulations, including the form or origin of CBD or the vehicle used. The form of CBD administered affected its absorption rate and bioavailability in a study with beagles testing CBD at equal doses as an infused oil, microencapsulated, and a transdermal cream. Their relative bioavailabilities were 100%, 54.7%, and 9.9% for the oil, capsule, and cream, respectively (44). In that study, CBD half-life was 2 h and 1.5 h when dogs were given the oil and capsule, respectively, and was nondetectable in dogs treated with the cream. Another study with beagles tested three other forms of a formula containing CBD and cannabidiolic acid (CBDA) at equal proportions (1 mg/kg each) (45). They found that the CBD-rich hemp extract soft chew had the highest plasma CBD peak (C_{max}) and that CBDA's C_{max} had a plasma peak more than twice that of CBD (45). Also, CBD's half-life of all supplements was higher than what was reported in Bartner et al.'s (44) work and approximated 4 h in the oil formulas (45).

Supplemental Material >

The effects of food on the PK of drugs have been demonstrated in a CBD and THC PK study (46). In this study, dogs in both fed and fasted states were dosed orally with a cannabis olive oil extract containing 0.037 mg/kg CBD and 1.5 mg/kg THC. Levels of plasma CBD were nondetectable, but THC time-to-peak plasma levels were much longer in fed than fasted dogs, and plasma concentration over time (area under the curve) was almost 3 times greater in fasted dogs. This indicates that food slowed and lowered THC absorption, probably due to the physical barrier the food bolus created between THC and the intestinal villi, and due to food particle interactions with THC. The THC absorption at the fed state could have been underestimated slightly because some was still present in dog plasma at 10 h, which was the last timed blood collection in the study. An important parameter that was similar between both fed and fasted states in dogs was the THC half-life, which would be expected because its metabolization rate should not be affected by the physical interference of the food. Although levels of plasma CBD were nondetectable (46), one

could extrapolate that it would behave similarly to THC in regard to its PK at a fasted versus fed condition, because the molecules are structurally very similar. CBD and THC have similar numbers of atoms, but CBD has a broken phenolic ring with an alcohol group instead of a closed ring with an ether (28).

CBD seems to accumulate in the body when administered long-term. One study looked at the PK of CBD after one month of dosing it at four different concentrations (plus a placebo) to four beagle dogs in each group once daily and found that the plasma concentrations of CBD increased over time (47). That would be expected because CBD is a molecule composed of aromatic rings and a hydrocarbon chain (48), which could be stored in adipose tissues.

Studies on CBD safety and tolerability seldom reported adverse events (AEs) with a single dose. These either were absent short-term at lower doses up to 4 mg CBD/kg/day (45, 49) or mostly consisted of mild GI discomfort, including loose stools and vomiting, when administered at doses above 10 mg CBD/kg/day (47, 50, 51).

Supplemental Material >

The most common consistently reported blood parameter abnormality in all studies on CBD safety or tolerability was increased levels of the enzyme alkaline phosphatase (ALP; **Supplemental Table 1**). ALP is a membrane-bound glycoprotein divided into four isozymes expressed at the intestine, placenta, germ cells, or tissue-nonspecific (liver/bone/kidney) in humans (52). In domestic animals, only two isoenzymes were found: a tissue-nonspecific (including from liver, bone, kidney, and placenta) or an intestinal (53) isozyme. The increase in ALP might be due to increased liver function, because CBD and other cannabinoids both are metabolized by and inhibit many cytochrome isozymes in the human liver, especially P450 (8). However, ALP is involved in many physiological functions in different organs (53); therefore, whether the increased serum ALP is due to hepatic disturbance remains unknown.

The highest doses of CBD and THC assessed in beagle dogs were up to 64.7 mg/kg and 52.4 mg/kg, respectively, in a 10-dose escalation study (47). Dogs tolerated the CBD infused in medium-chain triglyceride (MCT) oil reasonably well, with only mild AEs, whereas the MCT oil with predominant THC had more frequent AE episodes, including 2 moderate and 1 severe AE. The formula that contained 1.5 CBD:1 THC had the most AEs, with 18 moderate and 3 severe events, and had to be stopped at the fifth dose. Interestingly, the plasma concentrations of both CBD and THC were similar at 6 h and 24 h when dogs were administered the ninth dose (~52 mg/kg CBD and ~35 mg/kg THC) (47).

The CBD literature on cats is scarce. There is one publication of a 24-h PK and short safety study of cats dosed at fast with CBD and CBDA at equal concentrations of 2 mg/kg each (dosed once at the PK and twice over 12 weeks for safety assessment) (54) (**Supplemental Table 1**). The researchers duplicated this in dogs and found that cats had a much lower CBD plasma peak and total absorption than dogs. Cats also did not seem to tolerate CBD as well as dogs, as they presented with more frequent AEs, most of which were mild, including head shaking and excessive licking. Interestingly, GI signs, including soft stools, were present in dogs but not in cats. However, dogs only had few episodes of soft stools, and the study (54) lacked a negative control, so it might have been unrelated to the drug. Deabold et al. (54) used soft chews to supplement CBD to dogs, which may have helped lower the incidence of soft feces when compared to other studies using an oil (47, 50). A second safety and tolerability study of cannabinoids administered to cats at escalating doses found an increased incidence of diarrhea with MCT oil formulations compared to a sunflower oil formulation (no differences when comparing CBD with THC on the MCT oil), indicating that the oil vehicle affected the GI system (55) (**Supplemental Table 1**). They also found some neurological, constitutional (nonspecific clinical signs that could have various potential causes, like lethargy and hypothermia), and ocular AEs in cats administered CBD, THC, and CBD:THC at escalating

doses up to 30.5, 41.5, and 13:8.4 mg/kg, respectively, but all these events were considered mild. Conversely, dogs administered THC and a combination of THC:CBD at escalating doses up to 52.4 and 13.4:9.2 mg/kg, respectively, had a few moderate and severe AEs (47), indicating that cats might tolerate THC better than dogs. However, other longer-term studies are needed to elucidate the tolerability of different levels of CBD, THC, and CBD:THC mixtures in both dogs and cats.

5. CBD PHYSIOLOGICAL EFFECTS AND POTENTIAL TREATMENT FOR RELATED CONDITIONS

5.1. Anti-Inflammatory and Analgesic Effects

Evidence indicates that cannabinoids have anti-inflammatory effects (56). The anti-inflammatory mechanisms of cannabinoids are generally attributed to CB2 activation, as it has immunosuppressive and anti-inflammatory actions. The CB2 receptor is a G protein–coupled peripheral receptor for cannabinoids (15). One of its proposed immunosuppressive mechanisms is by decreasing expression of selected proteins that are released by macrophages (57). The CB2 receptor is expressed on most leukocytes (57) and also microglia (for a review, see 58). Whereas CBD has predominantly anti-inflammatory effects, some cannabinoids, including THC, may exhibit pro-inflammatory effects (59).

CBD's anti-inflammatory properties have been studied predominantly in rodent models and their mechanism of action examined in cell cultures (60). In canines, recent studies have shown mixed results regarding CBD's efficacy as an adjunct therapy for managing inflammatory conditions like OA. Mejia et al. (61) found that CBD administered at 2.5 mg/kg twice daily, either in conjunction with non-steroidal anti-inflammatory drugs or not, did not improve objective measures of pain in client-owned dogs that suffered from OA compared to the placebo. The authors found some improvement in both the placebo and treatment groups, which was attributed to either caregiver's placebo effect (61, 62) or possible anti-inflammatory properties in the hemp seed oil that was used as the vehicle. This was the only study to use objective outcome parameters. Conversely, Verrico et al. (63) found a significant reduction in pain (perceived by the owner) combined with increased mobility in large dogs with OA when given CBD for 4 weeks at doses ranging from 0.5 to 1.2 mg/kg. This effect was observed when using either naked or encapsulated CBD (liposomal CBD), without additional anti-inflammatory drugs. Similarly, Gamble et al. (49) reported decreased pain and increased activity in client-owned dogs administered 2 mg/kg CBD twice daily for 4 weeks. Brioschi et al. (64) also found that CBD administered for 12 weeks at 2 mg/kg twice daily significantly reduced the Pain Severity Score in OA dogs when compared to OA dogs not administered CBD. However, all dogs in Brioschi et al.'s (64) study and most dogs in Gamble et al.'s (49) study were administered anti-inflammatory drugs during the clinical trial, indicating a beneficial effect of CBD when combined with anti-inflammatory drugs. A regimen of anti-inflammatory therapy could include a lower dose of anti-inflammatory drugs when combined with CBD, but further studies are warranted.

Some studies have also investigated the role of CBD in other health conditions and responses of dogs that could be useful when assessing the application of potential anti-inflammatory effects. For instance, Morris et al. (65) reported a decrease in daily scratching in adult healthy canines when fed CBD for 21 days compared to non-CBD dogs. Of note, although inflammation is an important component of pruritus in dermatological disorders, pruritus may also be part of noninflammatory conditions (66). Immunoreactivity of receptors CB1 and CB2 has been demonstrated immunohistochemically in skin samples of healthy dogs, in the epidermis, and in cells in the dermis, including perivascular cells, as well as in fibroblasts (67). This immunoreactivity was stronger

in the skin of dogs with atopic dermatitis. Whether an increase in CB2 reactivity is a protective mechanism is not clear, but a potential to address cannabinoid signaling pathways as a therapeutic approach for inflammatory dermatological problems also exists.

TNF-α: tumor necrosis factor α

LPS: lipopolysaccharide

NF-κB: nuclear factor κB

The molecular mechanisms by which CBD exerts an anti-inflammatory effect are complex and likely multifactorial. Evidence for their cellular actions has been derived from cell culture and rodent studies. Some of the anti-inflammatory effects of cannabinoids include suppression of B-cell proliferation, inhibition of excessive mast cell maturation, and expression reduction of cytokines [tumor necrosis factor α (TNF-α), interleukin (IL)-12, IL-1, IL-6, IL-10] and chemokines [chemokine (C-C motif) ligand 2 (CCL2, aka MCP-1), CCL5 (aka RANTES), C-X-C motif chemokine 10 (CXCL8, aka IL-8)]. In an ex vivo inflammatory model of lipopolysaccharide (LPS)-stimulated whole dog blood, CBD at 50 and 100 μg/mL significantly reduced IL-6 and TNF-α production when compared to controls (68). Researchers also observed a reduction in nuclear factor κB (NF-κB) and cyclooxygenase-2 expression in the CBD-treated group. In another study, CBD decreased the production and release of IL-1β, IL-6, and interferon (IFN)-β from LPS-activated BV-2 microglial cells (69). Massimini et al. (70) used DH82 canine macrophage cells and CPEK canine keratinocyte cells to mimic an in vitro model of atopic dermatitis using Th1/Th2 inflammatory cytokines. They showed that a combination of polyphenols and CBD significantly reduced the expression of chemokines including CCL2 and CCL17 in both cell lines. In human THP-1 cells that were differentiated into macrophages and subsequently stimulated with LPS, higher concentrations of CBD exhibited cytotoxicity, but lower concentrations of CBD had an anti-inflammatory effect, including a decrease in TNF-α, IL-1β, RANTES (regulated upon activation, normal T-cell expressed and presumably secreted), and IL-6 (71). CBD has a very low affinity for CB1 and CB2 receptors but acts as an indirect antagonist of their agonists. Although one would assume that this would cause CBD to reduce the effects of THC, it may potentiate THC's effects by increasing CB1 receptor density or through another CB1-related mechanism. It may also extend the duration of the effects of THC by inhibiting the cytochrome P-450–3A and 2C enzymes. CBD may also act on G protein–coupled receptor 55 (GPR55) in the brain, likely as an antagonist. The evidence for such is the activation of GPR55 by its agonist O-1602, resulting in increased IL-12 and TNF-α production in LPS-activated monocytes, which was blocked by CBD. In human coronary artery endothelial cells, CBD significantly attenuated the high-glucose-induced activation of NF-κB and also the transendothelial migration of monocytes (72).

Studies in rodent models have also revealed some potential mechanisms by which CBD might exert an anti-inflammatory effect. Weiss et al. (73, 74) found a robust anti-inflammatory effect following administration of CBD in non-obese diabetic mice (NOD mice), including reduction of serum IFN-γ and TNF-α. Administration of CBD also reduced IL-12 produced by splenocytes and elevated the anti-inflammatory IL-10 in 11- to 14-week-old NOD mice. In a mouse model of spinal cord injury, mice that received CBD for 10 weeks following the injury had a significant decrease in pro-inflammatory cytokines and chemokines associated with T-cell differentiation when compared to controls (75). Qi et al. (76) demonstrated that CBD oral spray significantly reduced tongue inflammation in a mouse model of oral ulcers, possibly by inhibiting NLR family pyrin domain containing 3 (NLRP3) inflammasome activation. Similarly, CBD attenuated the activation of NLRP3-inflammasome in a mouse model of nonalcoholic steatohepatitis induced by a high-fat/high-cholesterol diet (77).

Studies of the anti-inflammatory effects of CBD in humans are scarce. Morissette et al. (78) assessed the anti-inflammatory effect of CBD in patients with cocaine use disorder. The trial consisted of a 10-day detoxification phase followed by a 12-week outpatient follow-up during which subjects were given 800 mg/day CBD. Circulating levels of IL-6, vascular endothelial growth factor, cluster of differentiation CD14+CD16+, monocytes, and a subtype of natural killer cells

decreased significantly when compared with subjects receiving placebo. Hobbs et al. (79) examined the anti-inflammatory effects of CBD in an ex vivo model in blood collected from 10 healthy adults. There was an increase in TNF-α in peripheral blood mononuclear cells that were collected at baseline and subsequently stimulated with LPS, and this increase was significantly attenuated in cells that were exposed to CBD.

These studies indicate that the anti-inflammatory effects of CBD include their ability to decrease pro-inflammatory cytokines/chemokines, including attenuation of NF-κB and inflammasome-mediated signaling pathways. Other signaling targets of CBD include transient receptor potential vanilloid (TRPV) channels, serotonin receptors, and also G protein–coupled receptors (80). Whether these mechanisms mediate the anti-inflammatory effects of CBD in canines is not known but is a possibility.

Effects of CBD (or other cannabinoids) to alleviate nociception may also be mediated through its action on the opioid receptors. Interestingly, oral administration of *Lactobacillus acidophilus*, a probiotic, in patients with intestinal bowel syndrome increased CB2 and μ-opioid receptors in intestinal cells, resulting in analgesic functions in the gut (81). CBD also acts as a positive allosteric modulator of μ- and δ-opioid receptors (82). A similar mechanism was also reported previously for THC, which can act as a positive allosteric modulator of μ-opioid receptor (83). Further, a brainstem circuit that contributes to the pain-suppressing effects of morphine and is also required for the analgesic effects of cannabinoids has also been described (84).

5.2. Anticonvulsant Potential

Idiopathic epilepsy (IE) is a condition with low prevalence in dogs (85) but with serious consequences if untreated. It is a neurological disorder caused by different factors that affects the brain along with cognitive and psychiatric comorbidities (86). Epilepsy is characterized mainly by recurrent and unpredictable epileptic seizures, which are defined as "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (86, p. 470). The goal of treating epilepsy is to reduce or mitigate these seizures. However, refractory epilepsy is still poorly controlled in approximately 35% of humans, despite the availability of therapeutics (87). No single drug can control all epilepsy cases due to the nature of diverse etiologies (88). In 2018, the FDA approved Epidiolex®, a commercial product with 99%-pure CBD extract, to treat rare forms of pediatric epilepsy (87). In the same year, the US Drug Enforcement Agency placed Epidiolex® in Schedule V of the CSA, facilitating its commercialization. The interest in using CBD to treat epilepsy in humans has opened opportunities to fund and support more studies in animals, although interspecies data extrapolation must be exercised with caution (89).

As described previously in this review, CBD modulates many physiological and neurological responses in the body. Regarding epilepsy, the mechanism(s) of action of CBD are not fully elucidated. At least part of CBD's anticonvulsant activity may be due to GABAergic modulation (88). Some studies also found that some of CBD's anticonvulsant effects could be through EC signaling potentiation, either by inhibiting EC hydrolysis or by increasing calcium mobilization to interact with specific receptors (88, 90, 91). Moreover, CBD at high doses exerts neuroprotective effects that may help treat or alleviate deleterious consequences of chronic epilepsy (92).

Whether CBD is effective in reducing epileptic episodes in dogs with IE is inconclusive (93), and to date there are more clinical reports than controlled clinical studies. In 2019, Mogi & Fukuyama (94) published a case report in which CBD was given to 3 dogs with epileptic seizures for 8 weeks each, at different doses of 0.51, 1.25, and 5 mg/kg/day. The owner who administered the lower dose to a large dog found an increase in sleep time and a decrease in barking and seizures. The small dog at the middle dose had no changes, whereas the small dog at

the higher dose had clear improvement, showing less aggression during the treatment and only one convulsive episode during the 8 weeks. Although not a controlled study with replicates in a research setting, it was an important contribution to the design of future studies.

Two relevant controlled clinical trials explored the effect of CBD in dogs with IE (95, 96). A 3-month randomized blinded study found that dogs with IE that received whole hemp extract (THC < 0.3%) infused hemp oil at 2.5 mg/kg CBD twice daily in conjunction with other epilepsy drugs had a reduction of seizure frequency by 33% compared to the control group (96). Some study limitations included the small sample size of dogs who completed the trial and the fact that the data could have been analyzed as repeated measures over time to detect individual changes (93). Garcia et al. (95) conducted a double-blinded placebo controlled cross-over clinical trial in which dogs with IE received a CBD/CBDA-rich hemp extract at an approximate dose of 2 mg/kg twice a day for 3 months, in addition to 3 other antiepileptic drugs. Similarly, McGrath et al. (96) found a reduction in the total number of seizures (8.0 ± 4.8 placebo versus 5.0 ± 3.6 CBD/CBDA), as well as seizure days (5.8 ± 3.1 placebo versus 4.1 ± 3.4 CBD/CBDA), when dogs were administered the hemp extract. Additional studies are needed to strengthen the use of CBD or hemp extract in dogs with IE. Despite that, a survey of 297 pet owners with epileptic dogs showed that nearly half of these people were using different supplements to help reduce seizures or control side effects of other medications, and close to 40% of these supplements contained CBD (97). CBD is promising as an adjunct therapy for epileptic dogs, and its use is expected to increase as more studies are conducted on dosing, efficacy, and long-term safety.

5.3. Anxiolytic and Behavioral Effects

The humanization of companion animals, a phenomenon known as anthropomorphism, has led to some distress on dogs' and cats' welfare (36). Anxiety and other behavioral pathologies are examples of conditions for which awareness and interest have increased with anthropomorphism. Fear and aggression are normal physiological responses to a stress or danger, but these may be pathological and lead to chronic anxiety if excessive, persistent, or triggered by normal daily activities (20, 98). Given the variation among individuals, and the difficulty of assessing behavior at home or at the clinic, knowledge about the ontogeny, etiology, and epidemiology of behavioral conditions is lacking (99). Further, a survey found that aggression and anxiety are factors that lead pet owners to relinquish their dogs to shelters (100), resulting in welfare concerns for the affected dogs, emotional impacts on owners, and financial consequences for shelters. Thus, effective therapies must be established for these dogs.

Although there is a need for more scientific evidence that CBD is a therapeutic option to treat behavioral problems in dogs, like fearfulness and anxiety, pet owners perceive the calming and antianxiety effects of CBD favorably (34, 101). Approximately half of pet owners who have given CBD to their dogs to reduce fear or anxiety think it is effective (34, 101), even though doses given are inconsistent (34).

CBD's antianxiety and calming effects have been investigated in rodents and in mechanistic studies in vitro. The mechanisms by which CBD modulates different receptors are complex and are summarized briefly here, as an in-depth analysis is beyond the scope of this article. Evidence indicates that CBD interacts with several receptors known to regulate fear- and anxiety-related behaviors, specifically CB1, the serotonin 5-HT1A receptor, and TRPV1 (20). CBD acts as an indirect agonist of CB1 and may reduce fear (20, 102) and provide negative feedback to stress responses, with the potential to prevent anxiogenic consequences of chronic stress (20). The anxiolytic and panicolytic effects of activation or allosteric modulation of 5-HT1A receptors by CBD are still not understood fully and seem to depend on the brain region and location of 5-HT1A receptors on pre- or postsynaptic neurons (103). Research in rodent models has shown that the

anxiolytic effects of CBD depend on 5-HT1A neurotransmission, and Campos et al. (104) propose that this occurs via allosteric interactions with the binding site on the 5-HT1A receptor. Additionally, sequencing of the canine 5-HT1A receptor gene has revealed that the amino acid composition of the 5-HT1A receptor in the dog is highly similar to the human 5-HT1A receptor (92% homology) and the mouse 5-HT1A receptor (89% homology), with several regions reaching 100% amino acid homology across the three species (105). These similarities indicate that the effects of CBD on 5-HT1A receptors in dogs may be similar to those seen in mouse models, although further investigation into CBD's interaction with the canine 5-HT1A receptor is necessary. Finally, the TRPV1 receptor can be activated by noxious stimuli like capsaicin in sensory neurons but is also expressed in many brain regions related to the control of stress responses (106, 107). Campos et al. (106) suggest that TRPV1 receptors in the dorsolateral portion of the periaqueductal gray are activated by CBD and promote anxiolytic-like effects.

Animal studies on anxiolytic effects of CBD have shown mixed results. CBD seems to have a bell-shaped curve for managing anxiety, as it seems to be anxiolytic at moderate but not low or high levels (20, 108, 109). Doses between 2.5 and 10 mg/kg in rats (21) and a higher dose of 20 mg/kg in mice have been found to be anxiolytic (110, 111). CBD at 10 and 20 mg/kg reduced anxiety measures most efficiently; however, other studies found that intraperitoneal CBD at 10 mg/kg given for 14 days was anxiogenic (112). CBD also mitigates THC's anxiogenic effects (109). The acidic form of CBD, CBDA, has also been tested in mice for disrupting expression of cued fear and generalized anxiety behavior (113). Interestingly, this study found that only CBD disrupted cued fear memory expression, and only CBDA normalized the trauma-induced generalized anxiety–related behavior (113).

A meta-analysis on human studies concluded that the evidence on cannabis-based products' effects on anxiolysis is incomplete, because most studies had a small sample size along with some inconsistencies (114). Studies in humans found that CBD alone reduced anxiety with intermediate doses between 300 and 600 mg (approximately 4 to 8 mg/kg for an average 75-kg human) (114–117). In dogs, there is no established dose for treating anxiety and fear disorders. The few studies available have focused mainly on the short-term effects of CBD on aggressiveness and fear. A research study on shelter dogs found that CBD (dose calculated to be ~3.75 mg/kg) administered to dogs for 45 days could reduce aggressiveness toward humans but not behaviors related to stress (118). A second study assessed the effect of CBD supplementation on reducing acute fear triggered by fireworks in dogs supplemented with 1.4 mg/kg/day for 7 days and found no effect of CBD alone on reducing fear-induced stress (119).

In healthy research (kenneled) dogs, CBD supplemented up to 4.5 mg/kg/day (split into two treats given within 30 min of each meal) did not alter their amount of daily activity for 14 days measured by an activity tracker, including activity points, activity duration, resting, running, walking, head shaking, and sleep quality (65). There was only a tendency to decrease pruritus in these dogs. Hence, the studies conducted so far found no anxiolytic or calming effect in dogs at the doses, frequencies, and lengths tested, and no data are available to support the use of CBD for anxiety or aggressiveness in cats. In other species of veterinary interest, few published reports explore CBD's modulation of behavior. One study demonstrated decreased reactivity to a novel object test in horses that received 100 mg CBD per day for 6 weeks relative to horses that received a placebo; however, this study had limitations regarding the small sample size (treatment $n = 9$), differences in management between horses, and use of only gelding horses (120). Nevertheless, the decreased reactivity seen by Draeger et al. (120) provides some evidence for the efficacy of CBD on reducing fear-related behavior in veterinary species.

Other botanical components in hemp, called terpenes, are known to potentialize the calming effect of CBD in animals. This synergistic action is known as an entourage effect, and it happens

when a dominant molecule is supported by other plant molecules (121). Terpenes include more than 400 aromatic molecules, such as limonene, α-pinene, β-caryophyllene, and linalool, present in several botanicals, including lavender and citrus essential oils, propolis, and hemp. Several studies have reported anxiolysis from inhalation and consumption of some individual terpenes in mice (122–125). This entourage effect likely happens in dogs and cats as well but still needs scientific validation. Thus, full or broad hemp extracts, which contain terpenes, are expected to be more effective in reducing anxiety in companion animals than purified CBD alone.

5.4. Potential of CBD as Adjunct Therapy for Treating Cancer

The literature regarding CBD as a potential treatment for canine or feline cancer is scarce, but CBD could exert both antiemetic and antineoplastic effects (20). CBD may reduce symptoms associated with cancer as well as inducing cell apoptosis and decreasing cell migration in vivo (126).

No in vivo studies assess the antitumor effects of CBD in either dogs or cats; however, preliminary in vivo studies in mouse models have demonstrated some efficacy. CBD reduced the formation of polyps in a murine model of colon cancer (127) and reduced lung metastasis (128). These findings support the potential for CBD's use in rodent models of cancer; however, further studies in naturally occurring cancers would be useful to fully understand the potential applications and effects of CBD on tumor growth.

Several in vitro studies on canine tumor cell lines have demonstrated cytotoxic effects of CBD on cancer cells (129) and reduced tumor cell proliferation and viability when treated with CBD (126, 130). The mechanisms by which CBD may inhibit canine tumor cell proliferation are understood poorly. Proposed mechanisms include impairment of mitochondrial function (129) and induction of apoptosis and autophagy (130). Henry et al. (130) showed synergistic effects of CBD and conventional chemotherapeutic doxorubicin, as well as CBD and vincristine, on reducing cell proliferation in five different canine cancer cell lines. Interestingly, they also saw reductions in canine cancer cell proliferation at a lower dose of CBD in whole hemp extract (0.67–10 μg/mL) relative to a CBD isolate (2.5–10 μg/mL), which they hypothesize may be due to the entourage effect of other PC components enhancing the antiproliferative effects of CBD (130). Inkol et al. (126) also demonstrated a possible synergism of CBD and the conventional chemotherapeutics mitoxantrone and vinblastine in reducing the viability of canine urothelial carcinoma cells. In vitro studies have demonstrated antineoplastic effects of CBD in a variety of canine tumor cell types, and these effects could be enhanced when combined with certain chemotherapeutic agents.

6. CONCLUSIONS

Some evidence supports a beneficial role for CBD for adverse conditions including OA and seizures in companion animals. Nevertheless, more randomized and controlled studies are needed to advance the use of CBD in pets, especially when CBD content is varied, products are often combined with other PCs and adjuvants, and various routes of administration are used. Short-term safety and PK studies with CBD have shown it to be well tolerated, with a consistent elevation in the ALP enzyme with continuous use of oral CBD and only mild AEs like GI symptoms and lethargy. Administration of THC and a mixture of THC and CBD to both dogs and cats led to more frequent and severe AEs, some neurological. Dogs seem to be less tolerant to THC than cats, as they were reported to present with moderate and severe AEs after being administered THC orally. There also seems to be pharmacological interaction between THC and CBD that potentializes their effect and duration in the blood stream. Studies evaluating the effects of long-term administration of CBD in companion animals will provide valuable information

on the therapeutic role of CBD in veterinary medicine. The cellular mechanisms of CBD and the receptor systems on which it acts are areas of further investigation. This could potentially contribute to a better understanding of the pharmacological effects of CBD and can lead to identifying other health conditions in pets where the use of CBD could be beneficial. Evidence from science-based studies on the efficacy of CBD will help provide a framework to local, state, and federal regulatory agencies to formulate policy to enable veterinarians to prescribe CBD for pets.

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