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Cats and cannabinoids: past, present and future

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Abstract

The use of cannabinoids from hemp, which is classified as a cultivar of *Cannabis sativa* with up to 0.3% delta-9-tetrahydrocannabinol by USA federal definitions, is becoming increasingly popular in veterinary medicine. Owners frequently ask about their utility in a variety of conditions, including predominantly osteoarthritis, behavioral management, cancer, dermatitis and seizure disorders. Cannabinoid clinical utility, particularly cannabidiol (CBD) in dogs, is gradually emerging, while evidence for its use in cats remains limited. Several newer publications around the pharmacokinetics of CBD and cannabidiolic acid in cats show dramatic differences in bioavailability, elucidating that not all formulations are similar regarding serum or plasma concentrations. To date, although the pharmacokinetics look favorable, there are a handful of clinical studies on feline acute/chronic pain states and fear/anxiety/stress, alongside some pre-clinical studies where there is a potential for clinical translation. These limited studies, combined with positive owner and veterinary practitioner anecdotes, suggest there may be more opportunities for further pilot investigations to refine dosing and product selection for more randomized, placebo-controlled studies across several morbidities in the future.

Keywords: Cannabidiol; CBD; CBDA; bioavailability; cannabidiolic acid; pharmacokinetics; endocannabinoid system

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Introduction

Since the USA federal legalization in 2018 of *Cannabis sativa* L with delta-9-tetrahydrocannabinol (THC) concentrations up to 0.3% by dry weight, also known legally as industrial hemp, there has been a burgeoning cannabinoid market focused primarily on cannabidiol (CBD). This legal change has resulted in a surge of pet products containing CBD (and other cannabinoids) marketed as nutraceuticals (animal supplements), claiming to support many physiological processes. Legal nutraceuticals have strict labeling requirements that cannot claim to treat, cure or mitigate a disease. Conversely, many products fall into the illegal, unapproved drug category, not always because of the compounds in the product but when nutraceutical labels or marketing make claims to treat, cure or mitigate a disease without Food and Drug Administration (FDA) approval.[1]

The literature about clinical use of cannabinoids in cats remains limited, while there is an ever-growing body of work that favors the addition of cannabinoids in dogs. This review, however, aims to explore non-intoxicating cannabinoids in cats.

The endocannabinoid system and endocannabinoidome

CBD was first isolated in 1940 and largely ignored once THC was discovered in 1964.[2,3] Subsequently, the endocannabinoid system (ECS) was identified in the late 1980s

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Table 1 Natural physiological agonists and antagonists to cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) in mammals

Endogenous ligand	CB1 receptor activity	CB2 receptor activity
Anandamide (AEA)	Agonist (highly selective)	Weak agonist
2-Arachidonoylglycerol (2-AG)	Agonist	Agonist
2-Arachidonoyl dopamine (NADA)	Agonist (selective)	Weak agonist
2-Arachidonoyl glycerol ether (Noladin ether) (2-AGE)	Agonist (selective)	Weak agonist
Virodhamine	Antagonist	Agonist

after the discovery of cannabinoid receptor 1 (CB1), followed by cannabinoid receptor 2 (CB2) in the early 1990s. Although CB1 receptors are primarily located in the nervous system and serve as the main binding sites for THC, CB2 receptors are inducible and more widely distributed throughout peripheral tissues. Since the discovery of THC and CBD, hundreds of additional phytocannabinoids have been described.[4] The ECS is now recognized as a conserved system across the mammalian kingdom, playing a key role in maintaining homeostasis by regulating neurotransmission and interacting with other physiological receptor systems.[5]

In a brief review of the CB1 receptor, when an action potential reaches the presynaptic terminal during neurotransmission, it triggers the release of neurotransmitters such as gamma-aminobutyric acid, glutamate, dopamine or acetylcholine into the synaptic cleft. This release can activate signaling pathways that stimulate the production of fatty acid derivatives, such as endocannabinoids, from membrane lipids. These derivatives often act in a retrograde fashion to modulate neurotransmission and synaptic plasticity, but can also interact with other receptors and ion channels.[6–8] The fatty acids listed in Table 1 are ligands for the CB1 and CB2 receptors.[6–8]

In the nervous system, CB1 receptors are found on the presynaptic axons. When agonized by these fatty acid moieties, they allow for hyperpolarization of the presynaptic terminal, limiting neurotransmitter release on demand and acting as a homeostatic control. CB1 receptor activity specifically regulates neurotransmitter release as a feedback mechanism, whereas CB2 receptors are less involved in direct neuronal signaling within the central nervous system, yet are inducible and are present during injury and/or inflammation. Because this system fluctuates constantly, fatty acids are required to be soluble in the lipid bilayer. The postsynaptic neuron has at least two described hydrolase enzymes – fatty acid amide hydrolase (FAAH) and monoacylglycol lipase (MAGL) – that rapidly eliminate the head group from the fatty acid for metabolism or recycling. The hydrolyzing enzymes specifically target endocannabinoids such as anandamide (FAAH) and 2-arachidonoylglycerol (MAGL), reinforcing their role in regulating this signaling pathway.[9]

This process underlies the primary mechanism for 'endocannabinoid tone', in which endocannabinoids not only act through CB1 and CB2 receptor signaling but also interact with other channels and receptor systems. This broad network, which continues to expand, is referred to as the 'endocannabinoidome'.[10]

CBD is the primary cannabinoid that the industry isolates from hemp. There has been a resurgence in understanding the mechanisms by which CBD may have actions within the 'endocannabinoidome' at the level of the nervous system and other tissues. CBD is non-intoxicating because of its inability to bind to the CB1 orthosteric binding site of the receptor. Instead, its affinity is at the allosteric binding site and can even dampen and, in some cases, reverse the effects of agonists, known as a non-competitive negative allosteric modulator.[11] Similarly, there is little to no activation of the CB2 receptor at physiological concentrations. However, at high concentrations, CBD can act as a partial agonist and can activate or inhibit other receptors and channels, along with several other phytocannabinoids.[12]

As mentioned above, the 'endocannabinoidome' refers to the promiscuity of endogenous and exogenous cannabinoids that can activate or inhibit several other receptors, including the transient receptor potential channels (TRP), which have many receptor subtypes, such as A1, M8, and V1 and V2 classification. The multiplicity of receptors and/or channels beyond CB1 and CB2 receptors that cannabinoids can also modify include activation and inhibition of what are called orphan G protein-coupled receptors (GPRs) such as GPR3, 55 and 118, which are found in the nervous system and other tissues and lead to calcium influx variations among other potentially therapeutic physiological sequelae.[13–16] Similarly, non-THC phytocannabinoids may also interact with specific calcium channels, in a similar way to gabapentin, making it a possible synergistic treatment. In practices that use CBD formulations regularly in addition to medications such as gabapentin, practitioners already know to counsel owners about the potential for lethargy when the two are used concomitantly.[17,18]

A more common receptor system on which CBD and its precursor cannabidiolic acid (CBDA) act is 5-hydroxytryptamine (5HT), otherwise known as serotonin, and more specifically with the 5HT1A and 1B receptors that are found primarily in the brain.[19,20]

Cannabinoids also have anti-inflammatory properties, with multiple mechanisms of action. Like nonsteroidal anti-inflammatory drugs, the acidic forms of phytocannabinoids, such as CBDA and cannabigerolic acid (CBGA), downregulate cyclooxygenase (COX) 1 and 2, and may also act as mild direct inhibitors of the COX-2 isoenzyme, leading to a reduced production of inflammatory prostaglandins.[21,22] In addition, phytocannabinoids are potent antioxidants that neutralize reactive oxygen species, reducing oxidative stress and inflammatory responses.[23] They also can suppress proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)-6 and IL-1 beta, which contribute to chronic inflammatory conditions such as arthritis and inflammatory bowel disease or chronic inflammatory enteropathy.[24] Their immune-modulatory effects can reduce the activation of macrophages and microglia, critical drivers of inflammation, shifting immune responses from pro-inflammatory to anti-inflammatory. These actions are thought to be driven by agonist activities to the peroxisomal proliferation activation receptors (PPAR), mainly the alpha and gamma subtypes where CBD and CBDA have an affinity for this receptor, inhibiting the transcription and translation of inflammatory genes.[25]

In addition, CBD has the potential to specifically inhibit FAAH, which delays the degradation of the anti-inflammatory endocannabinoid anandamide, allowing for slightly longer retention at the synapse and modifying endocannabinoid tone.[9]

Phytocannabinoids and their biosynthesis

Over 100 cannabinoids have been identified in the cannabis plant, depending on the strain and cultivar.[26] The biosynthetic pathway and formation of phytocannabinoids of any functional quantity center around four cannabinoids: CBGA, CBDA, cannabichromenic acid (CBCA) and tetrahydrocannabinolic acid (THCA). These natural precursor acids are the primary phytocannabinoids made in the plant. These acids are not well recognized or studied because of the extraction process that occurs for most products, leading to decarboxylation of the acid moiety on the olivetolate acid ring, which leads to the formation of the more recognized CBD, THC, cannabichromene (CBC) or cannabigerol (CBG). Depending on the plant synthase activity, CBGA will convert into CBDA, THCA or CBCA, which, when extracted under high heat, decarboxylate into CBD, THC and CBC, and are featured prominently in extracts from hemp (Figure 1). If a *C sativa* plant is classified as marijuana, the end primary cannabinoid product is Δ-9-THC. As a result of ever-evolving extraction efficiencies and methods, the number of cannabinoid acids maintained in a final product is expanding.

Comparative metabolism studies of cannabinoids

The metabolism of cannabinoids appears to be variable across species.[27] The metabolism of phytocannabinoids involves distinct phase I and phase II enzymatic activities, leading to the production of various metabolic end products. In rodents and humans, it is well established that the primary metabolites of THC and CBD (the most extensively studied cannabinoids) undergo carboxylation and glucuronidation, facilitating their elimination via renal or enterohepatic pathways.[28,29]

CBD is metabolized predominantly into 7-hydroxy-CBD (7-OH-CBD) through the cytochrome P450 (CYP450) enzyme system, particularly CYP3A4 and CYP2C19 in many species. This metabolism primarily includes processes such as 7-hydroxylation and further oxidation to form 7-carboxy-CBD (7-COOH-CBD), which is subsequently glucuronidated to enhance water solubility and promote excretion.[28,29] THC metabolism similarly involves rapid hydroxylation at the C11 position, producing 11-hydroxy-THC (11-OH-THC), a metabolite with enhanced psychotropic activity. This active metabolite, however, is quickly oxidized to 11-carboxy-THC (11-COOH-THC) and then glucuronidated for disposal, following a pathway similar to that of CBD.[25]

There is limited detailed information on phytocannabinoid metabolism in species other than rodents or humans. Recent studies suggest that differing CYP450 isoform activities and glucuronidation are prominent in dogs, with CYP1 isoenzymes inducing 6-hydroxylation and carboxylation of cannabinoids. In addition, CBDA appears to be metabolized primarily through direct glucuronidation.[30]

In cats, data on cannabinoid metabolism are sparse, with most insights derived from studies on liver microsomes from a single cat.[27] Similar to dogs, in cats cannabinoids undergo differential hydroxylation via the CYP450 system, primarily resulting in 8-hydroxylation of THC to form 8-OH-THC.[27] Formation of 11-OH-THC occurs, but less significantly, as it was not detectable in a recent feline pharmacokinetic analysis of a whole hemp extract.[27,31] This metabolic profile may contribute to reduced neurotoxicity of THC in cats compared with some other species. For CBD, metabolism in cats involves more extensive 6-hydroxylation and 4-carbon hydroxylation of the pentyl tail, rather than the strong 7-hydroxylation and subsequent carboxylation observed in rodents and humans.[27] Preliminary pharmacokinetic studies in cats suggest that 7-OH-CBD and 7-COOH-CBD, the primary metabolites in humans and rodents, are formed minimally or not at all in cats depending on dose, while escalating doses of THC resulted in relatively low 11-OH-THC in cats.[27,32,33]

To date, the metabolism of the two most studied cannabinoids, THC and CBD, remains poorly understood in cats, with significant gaps in pharmacokinetic data.

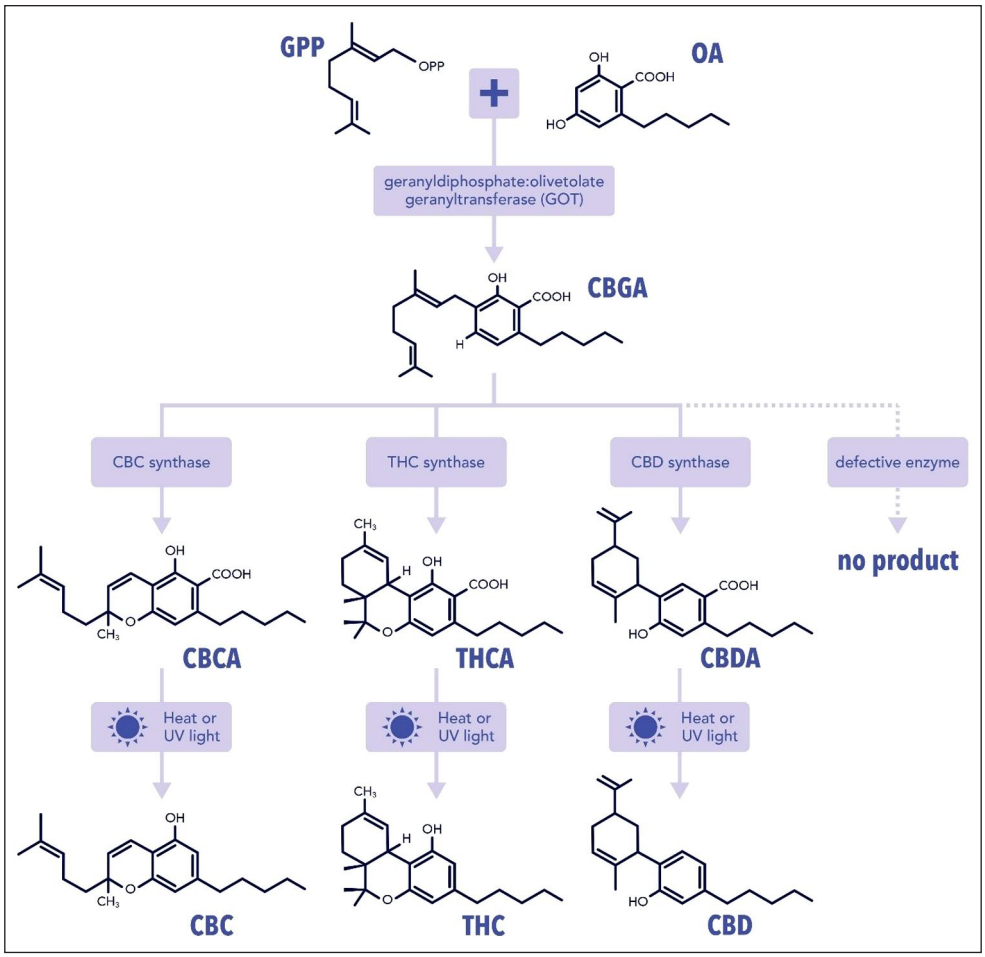

Figure 1 Depiction of major cannabinoid production in typical *Cannabis sativa* cultivars showing the formation of cannabigerolic acid (CBGA) from geranyl diphosphate (GPP) and olivetolic acid (OA). Based on synthase activity, CBGA will become either cannabidiolic acid (CBDA), tetrahydrocannabinolic acid (THCA) or cannabichromenic acid (CBCA) as native cannabinoids to the plant. When heat extracted or exposed to ultraviolet light, decarboxylation occurs to form the neutral cannabinoids cannabidiol (CBD), delta-9-tetrahydrocannabinol (THC) or cannabichromene (CBC)

Further research is needed to elucidate these metabolic pathways and their potential implications for therapeutic use in feline species.

Cats and CBD: an emerging area of study

Cats and anatomy of the receptors

As stated above, the receptor biology around targets of cannabinoids is well established in rodents and now in dogs, particularly around healthy nervous system tissue as it relates to the density and distribution of CB1 and CB2 receptors.[34]

Unfortunately, in the cat there has been no systematic examination of brain anatomy through immunohistochemistry to understand the distribution of receptors involved in the 'endocannabinoidome'. It is expected to be comparable to that in the dog, because of similar clinical signs of predominantly ataxia, incontinence and recumbency during toxic exposure, yet cats may be less sensitive to similar exposure based on lesser metabolism to 11-OH-THC.[33]

The distribution of 'endocannabinoidome' receptors in other organ systems in the cat has been identified by extensively examining the skin and gingiva and oral mucosa (healthy and diseased) as well as healthy ovary and oviduct, bladder (through agonist action) and gastrointestinal (GI) tract.[35–39]

Skin immunohistochemistry reveals CB1 and CB2 receptors localized to the epithelial compartments of cats (n = 5) and that immunolocalization appears to be enhanced in cats with eosinophilic dermatitis in the suprabasal compartment for CB1 and in the dermal compartment for CB2, including mast cells.[39] Localization of PPAR-alpha was also examined, with minimal expression in the epidermal and dermal compartments in normal cat skin, whereas it was markedly upregulated in the diseased hyperplastic

epidermis and the perivascular infiltrate, particularly mast cells.[39]

Similarly, immunohistochemistry was performed in the healthy GI tract, including the stomach, various portions of the small intestine and the large intestine.[38] A more comprehensive examination of the endocannabinoidome was performed, including CB1, CB2, PPAR-alpha, GPR55, 5HT1a and TRPA1. CB1 receptors were found throughout the GI tract at the level of the epithelium and goblet cells, myenteric plexus, enteroendocrine cells and smooth muscle layers of the GI tract. CB2 receptor immunostaining was similar to epithelial expression and goblet cell staining was less prominent; there was no goblet cell staining in the large intestine. Most notably, the CB2 receptor was found in macrophages and enteroendocrine cells in the lamina propria with minimal to no staining in the myenteric plexus. Staining of GPR55 was ubiquitous along the GI tract in the epithelium, enteroendocrine cells, immunocytes and enteric neurons. Immunostaining of PPAR-alpha was prominent in enteroendocrine cells, neuronal and glial components of the enteric nervous system, immunocytes and smooth muscle throughout the GI tract. TRPA1 receptor expression was again ubiquitous within the enteric nervous system and primarily goblet cells, while 5HT1a receptor expression was found in the laterobasilar portion of epithelial cells and smooth muscle of the blood vessels only.[38]

Similarly, the expression of the aforementioned receptors was explored in normal cats and cats with severe gingivostomatitis.[37] The immunohistochemistry results showed there was expression of CB1, 5HT1a and TRPA1 in the gingival epithelium, with no staining for CBR1 or GPR55 in normal gingival tissues.[37] The inflammatory cells within the submucosa of these tissues appeared to have slightly differential expression, with CB2, 5HT1a and GPR55 immunoreactivity. In all tissues, the receptor immunoreactivity was heightened in cats with gingivostomatitis showing induction of CB2 receptors.[37] All of these data related to receptor expression being heightened in the disease state suggest that there is potential for cannabinoids to be targets of these organ systems in inflammatory disease, which requires further elucidation.

Cats, pharmacokinetics and safety

With the increasing availability of low-to-zero-THC, phytocannabinoid CBD-rich nutraceuticals, there has been growing clinical interest and use – alongside a surge in recently published feline pharmacokinetic data.[31–33,40–43] These studies encompass CBD isolates, CBD-rich hemp products (commonly referred to as full-spectrum or broad-spectrum products) and the FDA-approved CBD isolate product Epidiolex. Each of these studies is notable for differences in product formulation and delivery vehicles, significantly influencing pharmacokinetics.

Vital pharmacokinetic parameters, such as maximal serum concentration (Cmax), time to reach maximal concentration (Tmax) and area under the curve (AUC), vary across these products and studies. Understanding these differences is crucial, as they can impact the therapeutic efficacy and safety of cannabinoid products. Each study will be discussed in the context of these parameters to highlight the variability and its potential clinical implications.

An initial study examined a limited pharmacokinetic screen utilizing only a four-point pharmacokinetic curve in cats, which utilized a full-spectrum CBD and CBDA-rich hemp product, whereby pharmacokinetics followed only the CBD.[40] Fasted cats were dosed with CBD (1 mg/kg PO) and CBDA (1 mg/kg PO) in a fish oil base, revealing a Cmax for CBD of 42 ng/ml in the blood and a Tmax of 2 h, with an AUC of 164 ng-h/ml, showing relatively poor pharmacokinetics when delivered in a fish oil base. It is important to note that hypersalivation and headshaking were observed as adverse events during administration, raising concerns about whether the cats received the full dose in this study.[40] The cats were then administered a CBD/CBDA-rich formulation twice daily for 3 months (2 mg/kg PO). Monthly monitoring revealed no adverse events during physical examinations or in the serial complete blood counts and serum chemistries conducted on the eight colony-housed cats.

Primarily related to safety, Kulpa et al[33] conducted a more complicated study to examine dose escalation in cats, utilizing a broad-spectrum product primarily consisting of CBD (18.3 mg/ml), THC (25 mg/ml) or a mix of both CBD and THC (8 mg:5.2 mg/ml). A total of 20 cats were divided into five groups receiving a dose escalation of CBD or THC in medium-chain triglyceride (MCT) oil, a CBD:THC formulation (in a 1.5:1 ratio) in sunflower oil, or vehicle control groups of MCT and sunflower oil. Cats received acute doses and were monitored for adverse events related to the treatments, with dose escalations every 3 days and intensive monitoring for 24 h after dosing. CBD dosing was in the range of 2.8–30.5 mg/kg, with the maximum THC level in the highest dose of CBD oil being 1 mg/kg. THC dosing was in the range of 3.8–41.5 mg/kg, while the CBD:THC mixture was in the range of 1.2–13 mg/kg CBD and 0.8–8.4 mg/kg THC.[33]

In this study, the only notable adverse events were diarrhea and vomiting, which were also recorded in the vehicle treatment group and were likely related to the carrier oil. Lethargy was observed more frequently in the CBD group compared with the MCT vehicle, although this showed an inconsistent pattern across the four cats. Interestingly, the adverse events associated with THC and the CBD:THC combination differed; the most commonly observed issues in these groups were lethargy, ataxia, nictitating membrane protrusion and muscle tremors. No significant adverse events were observed with 11

escalating doses of sunflower oil as a control. Adverse events were recorded from the initial dose and continued through all 11 dose increases, but their occurrence was inconsistent between the cats. The authors concluded that adverse events appeared to have a longer duration when comparing equal doses of THC when CBD was co-administered; this suggests a synergy or difference in THC metabolism leading to prolonged adverse events. The human literature supports that relatively higher doses of CBD combined with THC can increase the concentrations of 11-OH-THC, a major intoxicating metabolite of THC, potentially enhancing its psychotropic effects; this is consistent with findings in human pharmacokinetics.[44] In addition, dual treatment with CBD and THC in cats was associated with increased vocalization behaviors, a response not observed with THC or CBD alone, suggesting distinct effects of cannabinoid mixtures.[33]

Pharmacokinetically, the only assessment of serum cannabinoids in the study by Kulpa et al[33] was conducted after the ninth dose and beyond, so a comprehensive pharmacokinetic evaluation could not be performed. However, the study indicates that administering broad-spectrum CBD at doses of 25 mg/kg results in serum concentrations peaking at 250 ng/ml at 2–4 h, with no observed adverse effects in the cats. Interestingly, when comparing the ninth doses of CBD and THC, administered at only 10.9 mg/kg and 6.9 mg/kg, respectively, the serum concentrations were similar, if not greater, than when a CBD-predominant formulation was given at the 25 mg/kg dose. This suggests that various cannabinoid mixtures or products may have different effects on absorption that need to be recognized. This indicates that the method of administration or combinations of cannabinoids may play a significant role in pharmacokinetics. Most importantly, serum biochemistry and complete blood counts did not show significant changes from the study initiation to the 6–7-week endpoint in this population.[33]

A secondary pharmacokinetic study was conducted to evaluate the same whole hemp CBD/CBDA product used in the initial study by Deabold et al[40] discussed earlier.[31] Considering differences in delivery vehicles, the dosing was adjusted to administer approximately 1.4 mg/kg of CBD and 1.1 mg/kg of CBDA to eight adult colony cats. This study was the first to assess CBDA pharmacokinetics in cats, and showed profound differences between CBD and CBDA absorption.[31] The 24-h pharmacokinetics revealed the CBD Cmax to be approximately 282 ng/ml, with a Tmax of 2 h and an AUC of 908 ng-h/ml, while CBDA absorption was remarkably better with a Cmax of 1011 ng/ml, Tmax of 1.6 h and AUC of 2639 ng-h/ml. A complete blood count and physical examination before and after revealed no abnormalities or adverse events related to this dosing, which was every 12 h for the 1-week duration, in which serum CBD and CBDA were then reassessed 6 h after the last dose (the 13th dose over 1 week), with serum concentrations averaging approximately 50 ng/ml for CBD and 100 ng/ml for CBDA. This was approximately half of the predicted steady-state concentrations based on typical five-dose pharmacokinetics calculated using pharmacokinetic software. The discrepancy between predicted and actual concentrations suggests that longer-term dosing is needed to fully understand absorption and retention during chronic use. It also indicates that hepatic disposal may be upregulated and that tissue retention remains unknown.

Considering the differences in pharmacokinetics observed across products and vehicle delivery, Rozental et al[41] performed a seminal study to understand dose escalation and pharmacokinetics. In this study, a purported CBD isolate was tested on two different groups of four cats. Each group underwent three treatment cycles, with 2-week washout periods between pharmacokinetic assessments. The doses administered were in the range of 2.5–80 mg/kg, resulting in a linear dose–response relationship for absorption kinetics.

For comparative purposes, a typical dose of 2.5 mg/kg resulted in a Cmax of only 18 ng/ml, a Tmax of 2.0 h and an AUC of 84 ng-h/ml. These results indicate inferior absorption kinetics compared with findings from other studies (Table 2). No changes were observed in physical examinations, behavior or complete blood counts after a single dose, either before or after treatment. However, a decrease in creatinine and blood urea nitrogen levels was noted from before to after treatment, although the cause of this change remains unclear.

Although these acute treatment studies provide valuable insights into dosing and pharmacokinetics, few long-term studies have been conducted. Recently, a two-part, long-term study was conducted using a CBD isolate in sunflower oil at a dosage of 4 mg/kg daily over a 1-month and then a 6-month duration.[42] The study monitored 19 cats, with three later dropped, leaving eight on placebo and eight receiving treatment. The first phase lasted 1 month to assess pharmacokinetics, followed by a 2-month washout period. A second trial then involved 20 cats – 16 of which had participated in the first study – with 10 receiving a placebo and 10 receiving treatment. In total, 17 cats completed the trial. This second phase extended over 6 months, during which adverse events and health parameters were closely monitored.

Pharmacokinetic assessments were conducted at 0, 1, 2 and 4 h to capture peak concentrations during the first week; similar measurements were taken in the second week, where the nadir serum concentration was evaluated 24 h after the last dose. All cats were administered the CBD with food, of which there were few refusals. Serum concentrations in week 1 peaked at 2 h, with concentrations of approximately 240 ng/ml at the initiation of the study and 425 ng/ml at the 2-week interval. Nadir

Table 2 Summary of pharmacokinetic studies performed in cats across eight publications for cannabidiol (CBD) (cannabidiolic acid (CBDA)) concentrations focusing on maximal concentration (Cmax), time to maximal concentration (Tmax) and area under the curve (AUC), vehicle utilized, fed or fasted state and isolate/broad/full-spectrum products

Publication	CBD (CBDA) source	Fed or fasted	Vehicle	Dose	Cmax	Tmax	AUC
Deabold et al[40]	Full spectrum	Fasted	Fish oil	CBD 1 mg/kg	43 ± 9	2 ± 0	164 ± 49
Kulpa et al[33]	Broad spectrum	Fasted	MCT or sesame	CBD 25 mg/kg; 10.6 mg/kg CBD + THC	236 ± 193 (25 mg/kg CBD); 483 ± 281 (10.6 mg/kg CBD + THC)	3 h (25 mg/kg CBD); 4 h (10.6 mg CBD + THC)	NA
Wang et al[31]	Full spectrum	Fasted	Paste	CBD 1.3 mg/kg; CBDA 1.1 mg/kg	465 ± 220 (CBD); 1011 ± 495 (CBDA)	2 ± 0.6 (CBD); 1.6 ± 1.1 (CBDA)	909 ± 528 (CBD); 2639 ± 1285 (CBDA)
Rozental et al[41]	Isolate	Fasted	MCT oil	CBD 2.5 mg/kg	17.8 (3.2–45.3)	2.0 (2.0–4.0)	83.5 (8.1–165.9)
Coltherd et al[42]	Isolate	Fasted	Sunflower oil	CBD 4 mg/kg	420 week 2 estimate; 225 initial estimate	1.6 h initial estimate; 2.0 h week 2 estimate	155 (95% CI 97–214) initial; 247 ng/ml (95% CI = 188–306) week 2
Jukier et al[43]	Isolate	Fed and fasted	Sesame oil	CBD 5 mg/kg	Fasted: 269 ± 334 Fed: 465 ± 220	Fasted: 2.6 ± 1.6 Fed: 4.7 ± 2.1	Fasted: 921 ± 1003 Fed: 2650 ± 1118
Lyons et al[32]	Full spectrum	Fasted	Olive oil	CBD 2 mg kg; CBD 5 mg/kg	111 ± 79 (CBD 2 mg/kg); 214 ± 183 (CBD 5 mg/kg)	2.9 ± 1.7 (CBD 2 mg/kg); 2.7 ± 0.8 (5 mg/kg)	344 ± 183 (CBD 2 mg/kg); 1293 ± 970 (CBD 5 mg/kg)

Data are mean ± SD or median (range)
CI = confidence interval; MCT = medium-chain triglyceride; NA = not available; THC = delta-9-tetrahydrocannabinol

concentrations of approximately 16.5 ng/ml at the end of the 4-week treatment, with AUCs of 621 ng-h/ml and 987 ng-h/ml at weeks 0 and 2, respectively, were seen. No adverse behavioral or physical examination findings were reported. At the 4-week time point, however, one cat in the placebo group displayed hematuria and elevations in alanine transaminase (ALT) and aspartate transaminase (AST). In contrast, two cats in the CBD group also displayed abnormal elevations in ALT (two-fold change) and AST and were eliminated from the longer-term 6-month study because of suspected cholangiohepatitis.[42]

The 6-month study examined monthly serum biochemistry, complete blood counts, resting bile acids, and levels of CBD and related metabolites in serum, feces and urine, using the same CBD isolate in a sunflower oil vehicle as in the 1-month study above. During the 6-month study, one cat was removed by week 4 owing to behavioral issues. Two cats were shown to have elevations in ALT (one placebo and one CBD treatment) and were deemed to have infectious hepatitis. Over the 6 months, the remaining cats showed no differences in physical examination findings or behavior or blood parameters between groups. Serum CBD nadir concentrations across weeks 4–26 showed some gradual accumulation of CBD, which peaked by week 18 at an average of 28 ng/ml; after 4 weeks of washout from week 26, by week 30, there was no evidence of CBD in the bloodstream. No CBD or metabolites of CBD could be detected in urine; at the same time, fecal samples showed a snapshot of 45–451 µg/g in feces, suggesting relatively poor absorption yet adequate safety for chronic administration in cats.

The most recent study examined the only FDA-approved CBD isolate product, Epidiolex, which can be used as an extra-label source of CBD for veterinarians.[43] However, this product is not off-patent and could be cost-prohibitive to most clients and veterinarians. The study examined the administration of 5 mg/kg CBD to nine cats in a fed vs fasted state, in a crossover design, for comprehensive 24-h pharmacokinetics. The average Cmax in the fasted state was 269 ng/ml, while in the fed state it was 463 ng/ml. The average Tmax in the fasted state was 2.7 h, while in the fed state it was 4.6 h. The mean AUC in the fasted state was 921 ng-h/ml, while in the fed state it was 2621 ng-h/ml. These data clearly demonstrate that CBD absorption is improved in the fed state, suggesting that dosing should occur with a food matrix. However, specific feed amounts cannot be determined, as the study notes that cats were fed their regular diets without quantifying relative consumption. It is only known that both kibble and canned food were offered, and some portion was consumed shortly before treatment.

A final pharmacokinetic study utilizing a full-spectrum hemp product with a CBD:THC ratio of 20:1 was examined for 24-h pharmacokinetics.[32] Two groups of six cats were provided different doses, with one group receiving 2 mg/kg

of CBD and 0.1 mg/kg of THC and the other group receiving 5 mg/kg of CBD and 0.25 mg/kg of THC in an olive oil base after fasting and allowing food consumption 2 h after treatment. The mean serum Cmax was 111 ng/ml at 2 mg/kg dosing and 214 ng/ml at 5 mg/kg dosing, with Tmax being similar at 2.5 h in both groups. The AUC was also proportional to the dose, at 344 ng-h/ml at 2 mg/kg dosing and 1293 ng-h/ml at 5 mg/kg dosing. For THC, the mean Cmax was 17.1 and 27.9 ng/ml at 2 and 5 mg/kg dosing, respectively, with a similar Tmax to CBD. More importantly, the evaluation of metabolites of THC, including the more psychotropic metabolite 11-OH-THC, was below the limit of quantification. The traditionally examined metabolites 7-OH-CBD and 7-COOH-CBD could not be detected; however, the 6-OH-CBD metabolite was detectable in some cats. This suggests that cats have different metabolic pathways, as shown in in vitro hepatic microsome studies.[27] These pathways require further examination in cats, as they could influence pharmacodynamic response.[32]

The summary table (Table 2) shows the diverse absorption kinetics between products, which may depend on the cannabinoid profile, and whether the product is an isolate vs broad/full spectrum. It is evident that full-spectrum products appear to portray better absorption kinetics in general and that CBDA is absorbed superiorly to CBD, based on the research by Wang et al,[31] which is similar to other species, including humans.[45,46] The work by Kulpa et al[33] did not undertake pharmacokinetics, since they examined the timing of absorption only after the ninth dose in an escalating dose trial.[33] However, it was evident that when THC was present in nearly equal proportions to CBD, the absorption of CBD was nearly twice as high at half the dose compared with a CBD-rich extract containing only minor cannabinoids. This suggests an interplay between cannabinoids that may influence absorption and retention.[33] The work by Jukier et al[43] was the only one to distinctly compare fed vs fasted states, showing that oral CBD consumption in the fed state was superior to the fasted state, which aligns with findings from studies in rodents, primates and humans.[40]

Cats and clinical uses

Unfortunately, to date, there have been few studies on the use of CBD in cats, with only four placebo-controlled and blinded clinical trials to study the efficacy of CBD-rich hemp products.[47–50] The first such study examined the effects of a CBD-rich complex nutraceutical (additional vitamin B6, B3, hemp oil and terpenes) on cats with feline chronic gingivostomatitis.[47] That study evaluated multiple parameters, such as dental lesion scoring, owner pain/comfort surveys, heart rate and blood pressure, complete blood counts, serum chemistry and serum cannabinoid concentrations, collected at completion of the trial on day 15. Cats (mean age 5.7 years) were dosed at 4 mg per cat with 2.5 g of a powdered CBD formulation mixed in 2 ml of water and provided to the cat orally, with treatment starting 2 h before dental extractions (mean number of extractions: 19 in the CBD group, 22 in the placebo group). These cats then continued oral dosing every 12 h, until day 15 at follow-up examination, in a blinded manner. No significant alterations were observed in the complete blood count, serum chemistry, heart rate or blood pressure between the groups examined. There was a significant difference in the Systemic Disease Activity Index, which incorporates owner perception, while the unvalidated Composite Oral Pain Scale showed no difference between the groups of cats, which could be related to the inadequacy of the scoring methods.[51] Overall, although not statistically significant ($P = 0.12$), the body weight increased in cats treated with CBD and decreased in placebo-treated cats. This study did not evaluate changes from baseline but instead compared group differences based on body weight at the two time points. Use of rescue analgesia during the 2-week trial did not differ between groups. Serum cannabinoid concentrations were relatively low, with no cat exceeding 35 ng/ml CBD, and many registering below 10 ng/ml. This suggests probable subtherapeutic dosing, as the average administered dose was approximately 1 mg/kg body weight, delivered as a powdered formulation in an aqueous base. It should be noted that the product used contained additional vitamins and essential fatty acids, which were absent from the placebo (a cellulose-based powder), further complicating interpretation and introducing potential confounding variables.

A second study was recently performed in a blinded, placebo-controlled manner, examining the effects of CBD as part of a pre-anesthetic protocol and for pain relief after ovariohysterectomy.[48] Cats were provided with a CBD isolate product at 2 mg/kg in an olive oil-based vehicle or a placebo of olive oil, 60 mins before premedication using dexmedetomidine and meperidine, followed by propofol induction. Multiple physiological parameters were followed intraoperatively, including blood pressure, heart rate and oxygen saturation, with no changes shown across both groups during the procedure. Sedation was scored pre- and postoperatively via a descriptive numerical scale (scale range = 0–16 points), alongside two pain scoring systems, namely the Glasgow Feline Composite Measure Pain Scale (GCMPS-Feline) and the UNESP-Botucatu Multidimensional Composite Pain Scale. The GCMPS-Feline included behavioral categories (scale range = 0–16 points) and facial expression changes (scale range = 0–4 points). Pain scale cutoffs were determined as thresholds for rescue analgesia, allowing for monitoring of morphine use postoperatively as well as fentanyl for analgesia during the surgical procedure. Intraoperatively, it was found that 4/12 cats in the placebo group required fentanyl rescue analgesia, while none in the CBD group required rescue. Sedation and pain scores did not differ

between the two groups using the three measures, and morphine treatment was not different between groups. When examining each time point, there was a decrease in pain scores on 2/3 pain scales at 0.5 h after extubation; conclusions regarding the study deemed the treatment safe as a preoperative treatment. This treatment protocol is thought-provoking, based on known pharmacokinetics and the utility of a single CBD dose for analgesia. Further studies examining the pharmacokinetics of this product and possibly higher dosing were suggested, particularly since most of the parameters assessed in the study would have been well past the time point of maximal serum concentration using a single preoperative dose. Interestingly, a similar study in dogs utilizing the same dose of CBD as in this feline study displayed positive results in relation to pain.[52] This highlights that not all CBD products may be equal and that when recommending or dispensing CBD-rich hemp products, it is important for practitioners to have a working knowledge of documented positive clinical outcomes, with supporting data regarding absorption or pharmacodynamics.

A third recent study examined the effects of CBD on anxiety in cats.[49] The cats were treated with 4 mg/kg of a broad-spectrum CBD-rich hemp extract in sunflower oil or placebo sunflower oil. The cats were all neutered males that were randomized and treated for 2 weeks, then crossed over to the second treatment for 2 weeks. They were evaluated using a modified Secure Base Test, related to separation and reintroduction, as an assessment of the anxiety associated with a bout of separation. This scoring system was assessed after owners were with the cat in a new area for an extended period of time; they then left for 2 mins and were then reintroduced to the room in a chair. The cat's avoidance, direct contact or whether the cat was in near proximity to the owner was assessed. Results suggested that cats in the placebo group spent, on average, 2.5 s longer in proximity to their owner, while cats in the CBD treatment group had 2 s more direct contact, within an observation interval of 100 s. These differences appear to be of little clinical relevance in the context of a single acute 4 mg/kg dose and separation-related behaviors. Genuine behavioral issues require clinical evaluation and appropriate treatment protocols involving both acute and chronic dosing, rather than relying on tests of this nature in behaviorally normal cats.

A fourth study investigated the effects of a single oral dose of CBD isolate at 4 mg/kg body weight on stress measures in domestic cats (n = 40) during transport in a carrier, and interaction with a novel person in an unfamiliar environment.[50] The work employed a randomized, blinded crossover design, in which each cat served as its own control. Stress indicators included physiological parameters (serum cortisol, immunoglobulin A, glucose) and behavioral metrics (eg, latency to approach, heart rate variability) and were assessed before, during and after the stress paradigm.

Results demonstrated that although the stress paradigm significantly increased cortisol levels, no statistically significant differences existed between the CBD and placebo groups for any physiological or behavioral stress measures. These findings suggest that a 4 mg/kg dose of CBD does not mitigate stress responses in cats under the conditions tested. The study highlights the need for further exploration of CBD's pharmacokinetics, effective dosing and delivery matrices in cats, as well as consideration of individual temperament and coping mechanisms in anxiety.

As many of the studies of safety and efficacy were in young or healthy cats, two of the authors recently utilized a CBD/CBDA-rich, full-spectrum hemp product to treat previously diagnosed osteoarthritis in cats using a dose of 2 mg/kg every 12 h in 14 geriatric cats. Of these cats, 10 had routine bloodwork performed at the beginning and 4 weeks into treatment, as part of a clinical standard with no other pain medications. The mean Feline Musculoskeletal Pain Inventory score at the start of treatment was 14.6 ± 5.7, with drops in mean pain scores to 11.2 ± 5.3 and 10.1 ± 4.7 at 2 and 4 weeks, respectively. Non-parametric Friedman testing showed significant differences over time by 4 weeks ($P < 0.01$). More importantly, the mean age of this feline cohort was 14 ± 2 years (range 10–19). Both serum chemistry and complete blood count showed no alterations in any parameter across all liver or kidney health markers based on the Student's *t*-test (see Table 3). Clinically, two cats with International Renal Interest Society stage 2 chronic kidney disease and two with hyperthyroidism in this small cohort showed no changes in serum chemistry values during treatment. These pilot data offer some reassurance to feline practitioners that CBD-rich hemp appears safe for geriatric cats, aligning with recent case reports suggesting quality-of-life improvements in cancer and pain management.[53,54] Although these findings stem from non-placebo-controlled studies and are therefore open to criticism, short-term use appears to be safe.

Cats and cannabinoids: what does the future hold?

The use of cannabinoids in cats, particularly CBD-rich hemp products, is emerging in feline medicine. Although some data for pain management are encouraging, with some promising receptor biology and clinical use in gingivostomatitis, they are not universally positive with the dosing and formulations used, and we do not yet have adequate clinical investigation and appropriate dosing to fully understand how cannabinoids can be utilized for pain management. It is becoming clear that the use of CBD-rich hemp products within the confines

Table 3 Selected serum chemistry parameters of renal and hepatic health in cats (n = 10) treated with a cannabidiol/cannabidiolic acid-rich, full-spectrum hemp product at 2 mg/kg every 12 h for 4 weeks (ANOVA shows no significant differences)

Analyte	Reference interval	Week 0	Week 4	*P* value
Glucose (mg/dl)	71–145	167 ± 112	163 ± 121	0.91
SDMA (µg/dl)	0–14	14 ± 5	13 ± 3	0.59
Creatinine (mg/dl)	0.9–2.3	1.7 ± 0.6	1.7 ± 0.5	0.92
Serum urea nitrogen (mg/dl)	16–37	34 ± 11	34 ± 12	0.87
Total protein (g/dl)	6.3–8.8	7.5 ± 0.5	7.5 ± 0.6	1.00
Albumin (g/dl)	2.6–3.9	3.6 ± 0.4	3.6 ± 0.3	0.81
Globulin (g/dl)	3.0–5.9	3.7 ± 1.1	3.9 ± 0.7	0.43
ALT (U/l)	27–158	89 ± 54	71 ± 38	0.50
AST (U/l)	16–67	26 ± 12	25 ± 9	0.52
ALP (U/l)	12–59	36 ± 13	39 ± 17	0.69
GGT (U/l)	0–6	1 ± 1	1 ± 1	0.17
Bilirubin (m/dl)	0–0.2	0.1 ± 0.0	0.1 ± 0.0	0.35
Cholesterol (mg/dl)	91–305	215 ± 63	199 ± 59	0.48
Total T4 (µg/dl)	0.8–4.7	3.1 ± 2.2	2.6 + 1.6	0.66

Data are mean ± SD unless otherwise indicated
ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transferase; SDMA = symmetric dimethylarginine; T4 = thyroxine

of 2–4 mg dosing orally once to twice a day is a safe dosage to employ for clients wanting to mitigate pain or treat other ailments in their cats. Other uses, such as atopic dermatitis and seizure management, have yet to be explored in feline medicine, as in canine medicine, but they will likely be fruitful endeavors. A key concern is the need for oral dosing and the highly variable pharmacokinetic profiles seen across different products in cats. This highlights the fact that efficacy may vary significantly between formulations and highlights the importance of exploring alternative routes of administration. As is often the case with oral medications, cats commonly resist treatment – especially with full-spectrum products containing cannabinoids, terpenes and other active compounds – likely because of taste aversion. Further research in this area is urgently needed.

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