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Cannabidiol-based natural health products for companion animals: Recent advances in the management of anxiety, pain, and inflammation

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ABSTRACT

Recent advances in cannabidiol (CBD) use in canines and felines for anxiety management, pain management, and anti-inflammatory effects were reviewed using a literature search conducted with the following keywords: CBD, anxiety, inflammation, pain, dogs, cats, and companion animals. For decades, research on CBD has been hindered due to the status of cannabis (*C. sativa* L.) as an illicit drug. Limited safety data show that CBD is well-tolerated in dogs, with insufficient information on the safety profile of CBD in cats. Upon oral supplementation of CBD, elevation in liver enzymes was observed for both dogs and cats, and pharmacokinetics of CBD are different in the two species. There is a significant gap in the literature on the therapeutic use of CBD in cats, with no feline data on anxiety, pain, and inflammation management. There is evidence that chronic osteoarthritic pain in dogs can be reduced by supplementation with CBD. Furthermore, experiments are required to better understand whether CBD has an influence on noise-induced fear and anxiolytic response. Preliminary evidence exists to support the analgesic properties of CBD in treating chronic canine osteoarthritis; however, there are inter- and intra-species differences in pharmacokinetics, tolerance, dosage, and safety of CBD. Therefore, to validate the anxiety management, pain management, and anti-inflammatory efficacy of CBD, it is essential to conduct systematic, randomized, and controlled trials. Further, the safety and efficacious dose of CBD in companion animals warrants investigation.

1. Introduction

Originated in Central Asia and now globally cultivated, cannabis (*C. sativa* L.) thrives in temperate and tropical temperatures and can grow up to five meters tall (Barbagallo et al., 2019). Cannabis, as a multi-purpose plant, has been documented throughout history in many cultures, including ancient China (Unschuld, 1986; Zuardi, 2006), India (Kalant, 2009), medieval Persia (Gorji and Ghadiri, 2002), and later in Europe (Kalant, 2001) as a source of grain (Li, 1974a), fibre for paper (Li, 1974b; Temple, 1986), textile (Chang, 1963; Cheng, 1963), rope and thread (Cheng, 1963), oil (Fleming and Clarke, 1998; Schultes et al., 1974), narcotics (Fleming and Clarke, 1998; Schultes et al., 1974), and medicine (Mikuriya, 1969; Unschuld, 1986; Zuardi, 2006). Additionally, the cannabis plant is reported to have a wide array of therapeutic benefits in many conditions and disorders (Carter, 2020; Rupasinghe et al., 2020), including epilepsy (Perucca, 2017; Stockings et al., 2018), anxiety (Bonaccorso et al., 2019; Wright et al., 2020), inflammation (Nichols and Kaplan, 2019; Pellati et al., 2018), pain (Hill et al., 2017; Tamba et al., 2020), nausea and vomiting (Limebeer et al., 2012), nervous system disorders (Fagan and Campbell, 2014), multiple sclerosis (Russo et al., 2015), glaucoma (Alexander, 2016), gastrointestinal disorders (Martínez et al., 2020) and cancer (Pellati et al., 2018; Rupasinghe et al., 2020). In the early 20th century, however, due to attitude change, cannabis was first classified as a restricted drug and eventually became prohibited as an illegal drug in North America (Carter, 2020). Although cannabis is recently legalized in Canada in 2018 and eleven states of the USA as well as the District of Columbia over the years (Carter, 2020), the use of cannabinoids remains illicit in many countries due to their psychoactive effects and addictive potential (Landa et al., 2016). As a result, the medicinal properties of cannabis remain underexplored.

C. sativa contains more than 100 different active molecules called

Abbreviations: 2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; ABHD6, α-β-hydrolase domain 6; AEA, anandamide; CB1, cannabinoid receptor 1; DAG, diacylglycerol; DAGL, diacylglycerol lipase; FAAH, fatty acid amide hydrolase; MAGL, Monoacylglycerol lipase.

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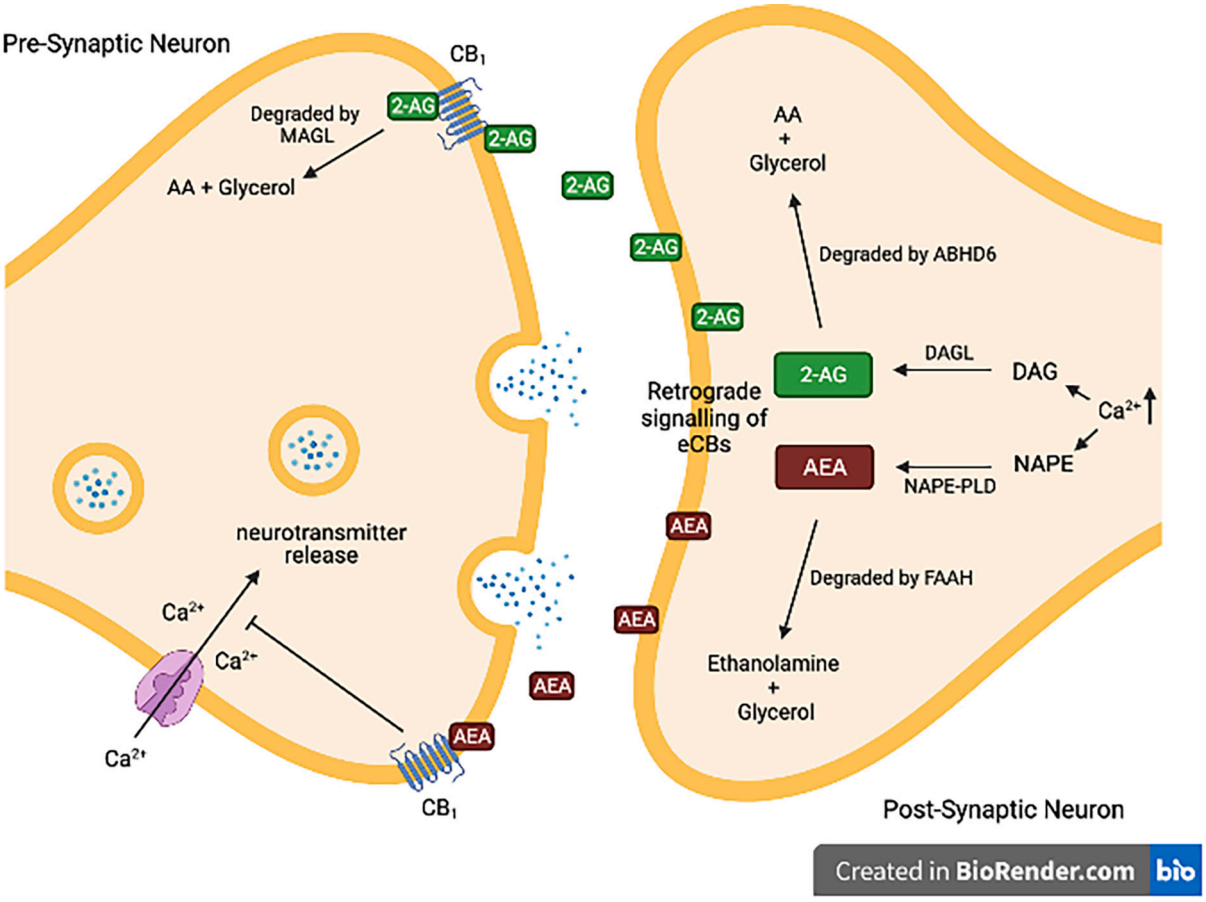

Fig. 1. The endocannabinoid system. Endocannabinoids, AEA and 2-AG, are synthesized on demand, where they travel from post-synaptic neuron to pre-synaptic neuron and bind to CB_1 through retrograde signaling. This inhibits the calcium-controlled neurotransmitter release by inhibiting calcium channels. Following CB_1 activation, AEA is enzymatically degraded post-synaptically by FAAH, and 2-AG is degraded by MAGL pre-synaptically and by ABHD6 post-synaptically. Adapted from "Cannabinoids in health and disease: Pharmacological potential in metabolic syndrome and neuroinflammation" by Mastinu et al. (2018) and Murataeva et al. (2014).

cannabinoids ("phytocannabinoids"), and the two main phytocannabinoids are the most abundant 9-Δ-tetrahydrocannabinol (THC) and the second most abundant cannabidiol (CBD) (Carter, 2020). THC is responsible for the psychoactive effects of cannabis, where the consumption of THC induces euphoria and alters sensory perception (Reddy and Golub, 2016). It is categorized as a recreational/addictive compound that is specially regulated in some countries (Abuhasira et al., 2018). The transient acute effects of THC vary between individuals (Freeman et al., 2019) and can include a dose-dependent increase in heart rate (Martin-Santos et al., 2012), increase appetite, reduce anxiety at low doses but increase anxiety at high doses (Tambaro and Bortolato, 2012), decrease alertness (Zuurman et al., 2008), and disrupt emotional processes, executive function and reward function (Bloomfield et al., 2019; D'Souza et al., 2004; Volkow et al., 2016). On the other hand, CBD is recognized as a non- or minimally-psychoactive molecule (Shannon et al., 2019).

CBD research has been hindered for decades due to its legal status. In recent years, renewed interest prompted an explosion of research investigating the safety and efficacy of CBD for various conditions in murine models and human studies. Sold as a herbal supplement, strong evidence supports the benefit of CBD in controlling refractory seizures, while acute and chronic CBD exert promising potential for managing anxiety and schizophrenia, respectively (White, 2019). Other preliminary efficacies of CBD include treatment for various neurological disorders, pain, depression, and insomnia (Shannon et al., 2019). In the USA, Epidiolex® (99% CBD; 0.1% THC) is approved for the treatment of drug-resistant seizures associated with Lennox-Gastaut and Dravet Syndrome in patients over two years of age (U.S. Food and Drug Administration, 2018). In Canada, CBD is classified as a Schedule II drug, and veterinarians cannot prescribe any medical cannabis or CBD products for pets due to the potential side effects and unproven effectiveness (Kogan et al., 2019a). However, CBD oils, capsules, and treats are marketed for dogs and cats.

The purpose of this article is to evaluate the potential of CBD-based natural health products for companion animals such as dogs and cats by reviewing recent advances in CBD treatment of anxiety, pain, and inflammation. The literature search was conducted using four databases, including Scopus, Web of Science, Google Scholar, and PubMed Central. The following keywords were used: CBD, anxiety, inflammation, pain, dogs, cats, and companion animals.

2. The endocannabinoid system and the pharmacodynamics of THC and CBD

The endocannabinoid system (ECS) is present in almost all animal species, including vertebrates and invertebrates (Silver, 2019). It is composed of three components: 1) endogenous ligands called endocannabinoids (eCBs), 2) G-protein coupled receptors called endocannabinoid receptors, and 3) enzymes that degrade and recycle the endocannabinoids (Silver, 2019) (Fig. 1). The two best-characterized endogenous endocannabinoids identified to date are anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), each having different affinities for the receptors (Papagianni and Stevenson, 2019). These are produced as needed by enzymes in the post-synaptic neuronal

membranes, where the production is initiated by a rising level of calcium ions (Hartsel et al., 2019). Delivered by the transport proteins, endocannabinoids bind to either of the G-protein coupled receptors located on pre-synaptic cell surfaces, such as the most-studied cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2) (Silver, 2019). Once the post-synaptic-released endocannabinoids acted on the pre-synaptic endocannabinoid receptors, the rapid inhibitory modulation of neurotransmitters then prompts for the essential biological processes, including neuronal plasticity, pain, anxiety, inflammation, neuroinflammation, memory, reward processing, immune function, metabolic regulation, and bone growth (Mackie, 2006). Following the brief activity, AEA is degraded by fatty acid hydrolase (FAAH) post-synaptically, and 2-AG is degraded by monoacylglycerol lipase (MAGL) pre-synaptically and by serine hydrolase α-β-hydrolase domain 6 (ABHD6) post-synaptically, as a part of endocannabinoid tone regulation (Murataeva et al., 2014; Silver, 2019). The modulatory function of the endocannabinoid system over other physiological systems has been recently reviewed (Di Marzo, 2018).

CB_1 receptors are primarily expressed in the central nervous system and peripheral nervous system, where they regulate neurotransmitter release, and to a lesser extent, in the cardiovascular, gastrointestinal, and reproductive tissues (Howlett et al., 2002). While the structure of the CB_1 receptor is similar throughout all mammalian species, the anatomical sites and density of the receptor differ between and within species (Hartsel et al., 2019). On the other hand, CB_2 receptors are mainly located in the cells of the immune system, specifically in leukocytes, spleen, and tonsils (Pertwee, 2001), where they mediate cytokine release (Howlett et al., 2002). In contrast to the similarity in CB_1 receptors across mammalian species, amino acid sequences of CB_2 receptors differ in humans, mice, rats, and dogs (Ndong et al., 2011). As well, canine CB_2 receptors exhibit 30 times less binding affinity when compared with human and rat CB_2 receptors (Ndong et al., 2011). Thus, these findings caution the direct extrapolation of rodent animal model outcomes in cannabinoid safety and efficacy, specifically those involving CB_2 receptors (Ndong et al., 2011).

The two major phytocannabinoids in cannabis, THC and CBD, are similar in their pharmacokinetic properties but display different pharmacodynamic properties (Greb and Puschner, 2018). THC directly interacts with CB_1 and CB_2 as a partial receptor agonist (Boggs et al., 2018). THC can act as both an agonist and antagonist at the CB_1 receptor (Freeman et al., 2019) to mediate its psychoactive effects, whereas the immunological and anti-inflammatory effects are thought to be related to CB_2 activation (Pertwee, 2008). On the other hand, CBD shows a lower affinity for both receptor subtypes and therefore interacts indirectly with the receptors by being a negative allosteric modulator at the orthosteric site of CB_1 and altering the potency and efficacy of the orthosteric ligand without activating the receptor (Freeman et al., 2019). As well, CBD antagonizes CB_1/CB_2 agonists, which allows for interaction with the receptors in the brain at low CBD concentrations (Pertwee, 2008). Apart from CB_1 and CB_2 receptors, CBD also exerts its effects through the interaction with other receptors, such as peroxisome proliferator-activated receptor-g (PPAR-g; anti-inflammatory; (Esposito et al., 2011)), a-3 glycine receptor (GLRA3; analgesic; (Xiong et al., 2012)), serotonin 5-HT_{1A} and 5-HT_{3A} receptors (antidepressant and anxiolytic; (de Mello Schier et al., 2014)), and vanilloid receptors (VR1; analgesic; (Bisogno et al., 2001; Greb and Puschner, 2018)). Although the full mechanism of action of CBD pharmacology has yet to be elucidated, it is clear that the non-psychotropic CBD exerts diverse effects on multiple systems in the body (Hurd, 2020) by demonstrating anti-epilepsy, anxiolytic, anti-inflammatory, and analgesic potentials via modulation of the endocannabinoid system (Izzo et al., 2009).

3. Pharmacokinetics and safety of CBD

Before the Cannabis prohibition due to its psychoactive properties, the uncontrolled medicinal uses of cannabis date back for centuries throughout history, even for thousands of years by the Chinese medicine (Di Marzo, 2018). However, only until recently, cannabis was recognized as a potential medical treatment or therapy for various conditions and diseases of humans (Hartsel et al., 2019). Specifically, the idea of using CBD-infused pet products is increasing in popularity among pet owners, and the cannabinoid pet treat industry is booming (Greb and Puschner, 2018) but is underregulated (Wakshlag et al., 2020a). With the recent countrywide legalization of recreational use of cannabis in Canada as well as in some states of the USA (Carter, 2020), pet owners are turning towards the non-traditional therapeutic supplement for their marketed potential in anxiety, seizures, and pain management (Kogan et al., 2019a). As such, veterinarians are receiving increased inquiries about the use of cannabis for the treatment of canine ailments and mental issues (Kogan et al., 2019b).

In the USA and certain EU countries, even though cannabis-derived veterinary medicine products cannot be prescribed, approved human cannabis-derived medicinal products may be allowed for off-label use in animals (De Briyne et al., 2021). On the other hand, Canadian veterinarians remain prohibited from authorizing the use of cannabis products for pets (De Briyne et al., 2021; Wallace et al., 2020). However, companies are marketing their treats for alleviation of anxiety, arthritis, pain, inflammation, nausea, epilepsy, etc., and even cancer for companion animals ("Canna-Pet® CBD Treats for Dogs,", 2021). While emerging preliminary evidence suggests that CBD supplementation (up to 4.5 mg/kg body weight (BW)/day) does not alter the daily activity and even exhibited potential antipruritic in healthy dogs (Morris et al., 2021) and anti-aggressive effects in shelter dogs (Corsetti et al., 2021), due to decades of its illegal status, fundamental research on the safety, efficacy, and pharmacokinetics of CBD in animals has been scarce, and conclusive clinical studies in companion animals are lacking (Greb and Puschner, 2018; Hartsel et al., 2019).

Recently, a handful of studies explored CBD pharmacokinetics and safety in dogs (Bartner et al., 2018; Deabold et al., 2019; Gamble et al., 2018; McGrath et al., 2018; Vaughn et al., 2020; Wakshlag et al., 2020b). The effects of CBD on dogs are reported to be dose-proportional (Bartner et al., 2018), where the higher the dose and plasma concentration, the more efficacious. At the dosage of 2 mg/kg twice daily, oral CBD has a short half-life ($t_{1/2}$) ranging from 1 to 4.2 h, maximal serum concentration (C_{max}) ranging from 102 to 301 ng/mL, and time to reach maximal serum concentration (t_{max}) ranging from 1.4 to 1.5 h (Deabold et al., 2019; Gamble et al., 2018). When comparing three forms of delivery methods, namely oral microencapsulated oil beads, oral CBD-infused oil or CBD-infused transdermal cream applied to the pinnae, the authors reported incomplete transdermal absorption and low plasma concentration in dogs given the CBD-infused transdermal cream (Bartner et al., 2018). In fact, oral CBD-infused oil exhibited the best pharmacokinetic profile with the highest C_{max} and systemic exposure (Bartner et al., 2018). However, low bioavailability of oral CBD administration has been previously reported (Samara et al., 1988), potentially due to the first-pass effect (drug metabolized in the liver before it reaches the systemic circulation).

In terms of safety, CBD supplementation in the canine is generally well-tolerated with very few mild adverse events (Gamble et al., 2018; McGrath et al., 2018), where the number and type of adverse events (gastrointestinal, constitutional, and neurological) are closely matching that of the placebo (Vaughn et al., 2020). However, elevated alkaline phosphatase (ALP) associated with CBD supplementation is observed across many studies (Gamble et al., 2018; McGrath et al., 2019; McGrath et al., 2018; Vaughn et al., 2020), which may be an indication of hepatic injury and altered function, including damaged liver cells, obstructed bile ducts, active bone formation, hyperparathyroidism, vitamin D deficiency or untreated celiac disease, etc. (Sharma et al., 2014). However, the observed elevation of ALP after CBD administration could also be due to hepatic microsomal enzyme induction by CBD and/or THC without causing actual liver damage. Therefore, in future research, real liver damages need to be observed.

While CBD alone did not elicit significant side effects, when administered in combination with THC, dose-dependent severe adverse events (Vaughn et al., 2020) and neurological signs (hyperesthesia/proprioceptive deficits) were observed (Chicoine et al., 2020), suggesting that when administered in synergy, CBD potentiated instead of antagonized the psychoactive and physiological effects of THC (Vaughn et al., 2020). The same elevation in ALP observed in CBD supplementation alone is also reported in CBD and THC synergistic supplementation (Vaughn et al., 2020). Vaughn and colleagues postulated that the interaction between CBD and THC might be due to the fact that CBD modifies the effect of THC through changes in absorption, distribution (pharmacokinetics), and/or CBD modifies the effect of THC via additive, synergistic, or antagonistic effects (pharmacodynamic) (Vaughn et al., 2020).

To date, only two studies reported CBD pharmacokinetics in healthy cats (Deabold et al., 2019; Kulpa et al., 2021). In the escalating dose study (2.8 mg/kg – 30.5 mg/kg), Kulpa et al. (2021) reported an average t_{max} of 3.3 h and C_{max} of 250 μg/mL at the dose of 25 mg/kg CBD oil. On the other hand, a single-dose CBD pharmacokinetics study showed a lower t_{max} of 2 h and C_{max} of 43 ng/mL (Deabold et al., 2019) at a much lower dose of CBD oil of 2 mg/kg twice daily. With only two feline studies performed with small sample sizes and different study designs (single-dose vs escalating doses; type of carrier oil used), feline CBD pharmacokinetics data remain insufficient. However, both studies reported overall good tolerances of CBD oil in cats, with only mild and rare adverse effects such as hypersalivation (Kulpa et al., 2021), emesis (Kulpa et al., 2021), excessive licking and headshaking during administration (Deabold et al., 2019) and normal liver markers in the majority of the healthy cats studied (Deabold et al., 2019). Overall, the safety profile of CBD supplementation in healthy cats is severely inconclusive. Interestingly, when comparing single-dose CBD pharmacokinetics in cats and dogs, Deabold et al. (2019) reported a short $t_{1/2}$ of 1.5 h and 1 h, C_{max} of 43 ng/mL and 102 ng/mL and t_{max} of 2 h and 1.4 h, for cats and dogs, respectively (Deabold et al., 2019), at the dosage of 2 mg/kg twice daily. The authors pointed out inter-species differences in pharmacokinetics with cats showing lower oral absorption kinetics and longer retention time, where C_{max} was 7-times lower in the cats compared to that of the dogs, suggesting different feline and canine dosing recommendations.

CBD distributes rapidly in the system due to its lipophilic property (Samara et al., 1988). In fact, human pharmacokinetics data demonstrated increased CBD absorption by 4–5 folds when consumed with food (Millar et al., 2018; Taylor et al., 2018). Moreover, being lipophilic in nature, long-term CBD accumulation in the tissues and toxicity are potential concerns (De Briyne et al., 2021). In the healthy animal population, preliminary pharmacokinetic results generally indicate the safety of CBD use. However, some research has demonstrated that CBD exerts immunosuppressant effects that are therapeutic for autoimmune diseases, noting that CBD use is risky in immunocompromised animals (Greb and Puschner, 2018; Rieder et al., 2010). Oral CBD oil seems to be the most favorable delivery system, although the first-pass effect may play a role. It is worth noting that while multiple reports of hepatic enzymes during short-term CBD oil administration have been made, there are currently no toxicokinetic data on the chronic use of CBD in companion animals. This prompts the need for more well-designed, randomized, controlled trials for the evaluation of pharmacokinetics, safety, and long-term effects of CBD oil and cream use, specifically in terms of accumulation in tissues and hepatic toxicity.

4. Anxiety management and calming

Anxiety is defined as an emotional response towards the anticipation of a potential threat or an impending danger (Papagianni and Stevenson, 2019). Physiologic signs of anxiety can include tachycardia, tachypnea, vasomotor changes, trembling or paralysis, increased salivation or sweating, anorexia, and gastrointestinal disturbances, and behavioral signs such as immobility, pacing, circling, restlessness can also be displayed (Sherman and Mills, 2008). Dogs experience many kinds of anxieties, with the most common being general fearfulness towards unfamiliar people, dogs, the environment, separation anxiety, and noise aversions (e.g., fireworks and thunderstorms) (Tiira et al., 2016). Currently, several different veterinary drugs used to treat different types of anxiety in companion animals include benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors, etc. (Hammerle et al., 2015). However, due to potential undesirable side effects, companion animal owners prefer to reduce drug use and show interest in the management of anxiety using natural products (Morris et al., 2020).

The endocannabinoid system plays an intimate role in the regulation of stress responses. Chronic environmental stress downregulates CB_1 receptors, which in turn reduce levels of AEA and increase levels of 2-AG, where decreased AEA levels are associated with the progression of stress response and increased anxiety behavior (Morena et al., 2016). Apart from the cannabinoid receptors, recent lines of evidence point to the influence of CBD on various other receptors, including the serotonin $5\text{-}HT_{1A}$ receptor and transient receptor potential vanilloid type 1 receptors (De Gregorio et al., 2019; Papagianni and Stevenson, 2019). Serotonin (5-HT) is an associated neurotransmitter in pain, depression, and anxiety (Bardin et al., 2000; Lesch et al., 1996). $5\text{-}HT_{1A}$ receptors are widely distributed in the brain, especially in commonly stress- and anxiety-related structures such as raphé nuclei, hippocampus, prefrontal cortex, amygdala, and hypothalamus (Chalmers and Watson, 1991). In murine studies, anxiolytic effects of CBD at doses of 5–60 mg/kg were found to be mediated through the activation of CB_1 and CB_2 receptors (Fogaça et al., 2018; Hartmann et al., 2019), as well as $5\text{-}HT_{1A}$ receptors (De Gregorio et al., 2019; Hartmann et al., 2019).

There are currently no data available on CBD use in cats for anxiety, while the only canine study on CBD and anxiety reported that CBD at 1.4 mg/kg BW/day did not exert anxiolytic effects (Morris et al., 2020). While CBD oil administration in shelter dogs has been shown to reduce aggressive behavior towards humans (Corsetti et al., 2021), anxiolytic evidence has not been observed in dogs supplemented with CBD oil (Corsetti et al., 2021) or CBD-infused treats (Morris et al., 2020). However, rodent and human studies on the effect of CBD in alleviating anxiety showed mixed results. Clinical evidence from recent randomized, double-blind, and controlled trials has demonstrated that short-term oral CBD alleviated public speaking-induced anxiety (Appiah-Kusi et al., 2020; de Faria et al., 2020) and social anxiety (Masataka, 2019). Also, CBD showed promising results in managing anxiety-related comorbidities in various diseases and conditions, including psychiatric illnesses, neurofibromatosis type 1 (Hegazy and Platnick, 2019), Dravet syndrome (Patra et al., 2020), fragile X syndrome (Zieba et al., 2019), and Crohn's disease (Klier et al., 2020), etc. However, Wildes et al. (2020) reported opposing findings that as frequencies and or percentage of CBD oil use increased, anxiety or depression in adults prescribed opioids for persistent pain worsened in their study. Furthermore, few mice studies found intraperitoneal injections of CBD at doses ranging from 5 to 20 mg/kg BW produce limited (Shallcross et al., 2019; Zieba et al., 2019) to no anxiety-alleviating effects (Kasten et al., 2019), and a dose of 20 mg/kg BW was even found to be anxiogenic (Schleicher et al., 2019).

While some pre-clinical and clinical studies have demonstrated the potential anxiolytic effects of CBD administration (Bitencourt and Takahashi, 2018), a recent comprehensive review article concluded that there is not enough evidence that CBD is effective in treating anxiety (Black et al., 2019). The variability in the study results can be due to the difference in animals/subjects, sample size, trial length, dosage, and method of delivery. In addition, while some murine models and human studies have produced promising results, research has also demonstrated inter-species differences in cannabinoid receptor number and location between humans and dogs (Hartsel et al., 2019; Silver, 2019); therefore, recommendations on CBD use for anxiety treatment cannot be based solely off on rodent models and human studies. High-quality large-

scaled, randomized, and placebo-controlled trials for CBD use in companion animals are necessary to be able to correctly analyze the effectiveness, safety, and risks of medical CBD.

5. Pain management

The common types of pain experienced by companion animals include acute, chronic, cancer, and neuropathic pain (Allweiler, 2020). Signs of pain can be physical (changes in heart rate, breathing pattern, movement, posture, or reflexes) or behavioral (anorexia, lethargy, unusual restlessness, anxiety, mood or personality changes, irritability and licking, biting, or rubbing the site of pain) (Allweiler, 2020). Since the analgesic techniques in animals often follow guidelines developed for human medicine (Livingston, 2010), the same challenge of undesirable side effects associated with current pain management drugs exists (Ferraz et al., 2020). Traditional drugs (Ferraz et al., 2020) such as nonsteroidal anti-inflammatory drugs (NSAIDS; non-selective and COX-2 selective inhibitors), acetaminophen, opioids, and corticosteroids can cause injuries to various organ systems, including renal (Harirforoosh et al., 2013), cardiovascular (Harirforoosh et al., 2013; Poetker and Reh, 2010), gastrointestinal (Harirforoosh et al., 2013; Poetker and Reh, 2010; Rayar et al., 2017), hepatic (Marcondes-Alves et al., 2019), and ophthalmic dysfunction or damage (Poetker and Reh, 2010), as well as psychiatric and morphological changes (Poetker and Reh, 2010). Moreover, opioids pose a risk of addiction, respiratory depression, and even death (Benyamin et al., 2008). As a result, there is merit in exploring the potential of CBD for pain management as it is recognized as non-addictive, non-psychoactive, and well-tolerated in most research.

Endogenous endocannabinoids AEA and 2-AG are one group of the body's first responders to tissue injury, where these molecules activate cannabinoid receptors, which regulate neuroimmune interactions and modulate pain by various methods (Silver, 2019). AEA suppresses pain by 1) activating CB_1 for inhibition of pain signals at the synapse, 2) becoming directly transformed by COX-2 enzyme into pain-relieving prostamides, and 3) activating CB_2 and other receptors for the interference of inflammation (Hill et al., 2017; Silver, 2019). On the other hand, 2-AG is involved in the descending modulation of pain during acute stress (Hill et al., 2017). Thus, further understanding the specific function of AEA and 2-AG will help to understand the efficacy and applications of phytocannabinoids in the management of pain.

Murine models have reported anti-nociceptive effects of CBD by various methods of delivery, including subcutaneous (De Gregorio et al., 2019), intraperitoneal (Genaro et al., 2017), transdermal (Hammell et al., 2016), and intra-arterial (Philpott et al., 2017). The pain-relieving action of CBD seemed to be dose-dependent as reported in experimental models of post-operative pain, arthritis, and osteoarthritis (OA) pain (Genaro et al., 2017; Hammell et al., 2016; Philpott et al., 2017). However, Britch et al. (2017) produced conflicting results and reported that intraperitoneal CBD alone had no anti-nociceptive effects in a model of healthy Sprague-Dawley rats.

To date, there are a total of five studies on CBD supplementation in managing chronic canine pain (Gamble et al., 2018; Kogan et al., 2020; Martello et al., 2019; Mejia et al., 2021; Verrico et al., 2020), and none in feline pain, whether acute or chronic. CBD supplementation is delivered by oral administration of CBD oil (Gamble et al., 2018), ingestion of CBD-enriched tablets (Martello et al., 2019), CBD-enriched hemp oil delivered on food (Kogan et al., 2020) and ingestion of naked and liposomally-encapsulated CBD (Verrico et al., 2020) at doses of 0.3–4.12 mg/kg body weight alleviated osteoarthritic (OA) pain in client-owned dogs and improved quality of life. Kogan et al. (2020) even reported that in dogs on gabapentin, a drug used for treating neuropathic pain, the additional CBD supplementation allowed a third of the dogs to wean off the drug, and another one-third of the dogs were able to have their doses reduced. In addition, it was reported that a wide range of doses (0.3–4.12 mg/kg body weight) was needed to achieve the analgesic effects in chronic canine OA pain, where some responded to small doses of CBD while others required larger doses for the same effect (Kogan et al., 2020), suggesting different pain tolerance in dogs and different dosage requirements (Allweiler, 2013). However, in contrast to the other studies, Mejia et al. (2021) did not observe any OA pain relief using CBD treatment in their double-blinded, crossover, placebo-controlled study but noted elevation in liver enzymes and vomiting as side effects.

With only a handful of randomized, placebo-controlled, and double-blinded canine studies conducted, there is insufficient information to make a conclusion on CBD use in pain management for dogs. Even though most preliminary results suggest that CBD is well-tolerated in dogs, with the multiple cases of elevated serum ALP during CBD treatment in both healthy dogs and OA dogs, it is crucial that the long-term safety of CBD in dogs is evaluated, especially regarding hepatotoxicity. Overall, data on CBD use for pain management in dogs are limited and weak, and randomized, placebo-controlled trials are needed to determine dosage, efficacy, and safety of administration of CBD alone or in combination with other pain medication while taking into consideration of breed and individual differences.

6. Anti-inflammatory effects

Inflammation is a complex physiological defense mechanism activated in order to re-establish homeostasis when the body is challenged by microbial infections, tissue injury, or other harmful conditions (Nascimento Menezes et al., 2019). It is characterized by the four basic signs of redness, fever, pain, and swelling (Rayar et al., 2017), mediated by pro-inflammatory agents such as cytokines, chemokines, etc. (Nascimento Menezes et al., 2019). Although it is mostly a protective mechanism, chronic inflammation can also lead to the development and progression of many diseases and conditions (Hartsel et al., 2019). Among the mediators participating in the inflammation process, prostaglandins (PG) remain the major target of anti-inflammatory therapy. The mechanism of action of NSAIDs lies in the inhibition of PG biosynthesis. NSAIDs are non-selective or selective inhibitors of cyclooxygenase (COX), the key regulatory enzyme of PG biosynthesis (Ong et al., 2007). Steroids are inflammatory modulators and increase anti-inflammatory agents (Rhen and Cidlowski, 2005), which could lead to some adverse events. As a result, the anti-inflammatory effects of medicinal plant extracts such as CBD are gaining more attention.

CB_2 receptors are present on the surface of many immune cells, and various experimental models have demonstrated the immunomodulatory effects of the endocannabinoid system (Hartsel et al., 2019). CBD attenuates inflammation by 1) suppressing pro-inflammatory cytokines and chemokines such as TNF-α, GM-CSF, IFN-γ, IL-10, and IL-6, etc., 2) limiting immune cell infiltration, 3) inducing T-cell apoptosis, 4) inhibiting T-effector cell proliferation, and 5) promoting T-regulatory cell proliferation (Henshaw et al., 2021; Nascimento Menezes et al., 2019; Silver, 2019). From the recent rodent models reviewed, topical, intraperitoneal, and intra-arterial CBD attenuated experimentally induced multiple sclerosis (Giacoppo et al., 2015), arthritis (Hammell et al., 2016), spinal cord injury (Li et al., 2018), colitis (Pagano et al., 2016), and OA (Philpott et al., 2017). In an experimental model of arthritis, topical CBD application reduced joint swelling as well as the thickening of the synovial membrane in a dose-dependent manner (Hammell et al., 2016). In a model of colitis, pure CBD administered through both intraperitoneal injection and oral gavage did not attenuate colitis, but a high CBD-containing extract reduced inflammation damage (Pagano et al., 2016). Furthermore, local treatment of intra-arterial CBD in OA rats was found to alleviate acute transient joint inflammation.

There are currently no canine or feline data available on CBD use and treatment of inflammation. While the promising results from the rodent studies further strengthen the knowledge on the anti-inflammatory effects of CBD, these results cannot be directly extrapolated, and species-specific differences in cannabinoid receptors call for the need for canine and feline-specific studies to understand the anti-inflammatory benefits

Table 1
The strengths, weaknesses, opportunities, and threats (SWOT) analysis for the potential use of CBD in companion animals for the management of anxiety, pain, and inflammation.

Strengths	Weaknesses
• The use of CBD for certain human conditions such as drug-resistant seizures has been approved by the US FDA. • Some evidence for potential application of CBD on companion animals; for example, chronic canine osteoarthritis pain.	• Lack of strong scientific evidence for safety, bioavailability, and specific efficacious activities of CBD in companion animals. • Canine side effects include elevated ALP, diarrhea, and emesis. • Feline side effects include elevated ALP, excessive licking, head shaking, emesis, and hypersalivation.
Opportunities	**Threats**
• Non-prescription use of CBD in humans has been legalized in some countries. • Off-label use of human cannabis-derived products in animals by veterinarians is allowed in some countries. • Consumer demand for natural health products for companion animals is increasing. CBD-incorporated treats are already in the market of some countries. • Conditions-specific health claims for CBD can be established in the future once scientific evidence is established.	• Reported interspecific variations and inconsistent data of CBD on experimental mice models and limited reports on companion animals. • Government regulatory requirements are demanding the commercialization of natural health products, including CBD-based products in veterinary applications.

of CBD in companion animals.

7. Conclusion

While the use of medicinal cannabis in both humans and animals dates back for centuries, scientific evidence of CBD efficacy is scarce due to its illegal drug status for decades, and cannabis remains a controlled substance in many parts of the world. The strengths, weaknesses, opportunities, and threats (SWOT) analysis for the potential use of CBD in companion animals are summarized in Table 1. In the few pharmacokinetics and safety trials performed in healthy dogs, short-term CBD use appeared to be well-tolerated by dogs with minimal side effects. Limited feline CBD pharmacokinetics data revealed interspecies differences in pharmacokinetics between dogs and cats, suggesting different feline and canine dosing recommendations. Information on CBD use in managing inflammation is not available in both dogs and cats, and limited preliminary data exist for the effect of CBD on the management of canine anxiety and pain. In human and rodent studies, mixed results were obtained for the CBD efficacy in managing these conditions. Many studies produced weak evidence, and not enough randomized controlled trials are carried out. The differences in study designs, including subject/animal selection, sample size, trial length, formulation, dosage, and method of delivery, contributed to the varied experimental outcomes. A significant gap in the literature evaluating the long-term effects of CBD safety and efficacy exist. In the reported studies, several different doses of CBD have been used; notably, the safety trials have used much higher doses than the efficacy trials. Therefore, a clear establishment of appropriate doses for dogs and cats is still required. Until the risks of chronic CBD use are established, more large-scale, randomized, and controlled trials are needed in dogs and cats to evaluate the safety, potential efficacy, interaction with other treatments, and health benefits of CBD supplementation. In recent years, a growing interest has also been developed in investigating the potential use of other endocannabinoid system modulators such as synthetic cannabinoids. As our understanding expand on the role of endocannabinoids and phytocannabinoids in modulatory functions of mammalian physiology, the development of efficacious synthetic cannabinoids in the management of anxiety, pain, and inflammation of companion animals and humans could become an interesting area of research in the future.

Declarations

The authors declare no competing interests.

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