Volume 7 • Issue 5 • May 2021

feline focus

The International Society of Feline Medicine
Journal for Veterinary Nurses and Technicians

State of the art
Use of cannabinoids in cats

A closer look at...
Hepatic disease

A day in the life...
Ophthalmology clinic

Spotlight on science
Research news

isfm Vet Nurses and Technicians

icatcare.org/felinefocus

Cannabinoids in cats: use and misuse

The use of cannabinoids in human medicine has been controversial owing to their association with recreational marijuana use. Interest in using these compounds as medicine for both humans and animals goes back thousands of years, but only recently has their use been examined by medical scientists and practitioners, as the stigma lessens with publication of both preclinical and clinical studies. In this article we take a shallow dive into the basics of what phytocannabinoids are and their potential therapeutic impacts in feline patient populations.

Stephen Cital RVT SRA RLAT VCC CVPP VTS-LAM(Res Anesthesia)

Liz Hughston MEd RVT VCC VTS(SAIM)(ECC)

Stephen Cital is the co-founder of the Veterinary Cannabinoid Academy and is a laboratory manager in the department of neurobiology at Stanford University, USA. He holds multiple certifications focused on anaesthesia and analgesia, and lectures on these topics along with cannabis in veterinary medicine internationally. Stephen is the executive director for the Academy of Laboratory Animal Veterinary Technicians and Nurses.

Liz Hughston is the co-founder of the Veterinary Cannabinoid Academy and practises as a relief veterinary technician in the San Francisco Bay Area, USA. Liz was certified as a veterinary technician specialist in both small animal internal medicine and emergency and critical care in 2012. She is president of the National Veterinary Professionals Union, past president of the Academy of Internal Medicine for Veterinary Technicians and is on the Editorial Advisory Board of dvm360.

Phytocannabinoids are molecules found in numerous plant species that elicit physiological effects on a system within all mammals known as the endocannabinoid system (ECS). Recent research has expanded the impact of these compounds outside of the 'classic' ECS system in what is known as the endocannabinoidome. While these molecules are found in many different plants there is one plant genus most famous for its robust production of these compounds: *Cannabis sativa L*.

When discussing sources of plant-derived cannabinoids, there are some fundamental distinctions one must make on the topic of medical cannabis, and even specific terminology that should be used. The first distinction is between a 'marijuana' plant vs a 'hemp' plant (Figure 1). The hemp plant has much lower levels of delta-9-tetrahydrocannabinol (THC) (less than 0.3% by dry weight per US Federal law) and has found favour

Key point

Cannabinoids may provide therapeutic benefits in a wide range of feline conditions, from seizure control to cancer treatment.

Figure 1: The hemp plant is used in the manufacture of food and clothing as well as the production of medical cannabinoids

Hemp vs marijuana

Cannabinoids can be derived from either the hemp plant or the marijuana plant.

Cannabinoid products derived from the hemp plant, will contain less than 0.3% THC (the cannabinoid responsible for psychoactive effects).

Cannabinoid products derived from the marijuana plant contain more than 10% THC.

among veterinary professionals since there is a reduced risk of THC 'toxicity' or intoxication.[1,2] THC is the most common of only a few phytocannabinoids that bind to the orthosteric, or 'active', site of the cannabinoid type 1 (CB_1) receptor within the ECS. Other cannabinoids, such as cannabidiol (CBD), bind to an allosteric site on the ECS receptors and do not cause intoxication. Both THC and CBD are the most studied and used phytocannabinoids to date but are only two of over 100 phytocannabinoids that have been identified in cannabis plants.[3]

THC

Although the authors feel there is a legitimate use for THC in veterinary patients, especially in cats, which have a seemingly higher tolerance to THC and its intoxicating effects, we will focus on CBD dominant products for the rest of this article.

Trace amounts of THC found in legal products sold or prescribed in the UK generally do not warrant concern for toxicity. There is no question as to the risk and occurrence of THC toxicity, but it should be noted there are no reported deaths that can be definitively attributed to THC or other phytocannabinoids directly. The suspected lethal dose of THC in dogs is >9 g/kg based on research conducted in the 1970s, a nearly impossible dose to achieve under normal use conditions.[4] A 2018 study investigating the susceptibility of cannabis-induced convulsions in rats and dogs reported no seizures in dogs given doses of THC and CBD around 25 mg/kg PO q12h, for over a year. However, central nervous system signs including ataxia, tremors and hypoactivity were observed.[5] In a more recent canine study with acute dosing up to 62

THC content rules

In the UK, legally sold commercial products must contain even less THC than what is found in US-defined hemp. This distinction is particularly important for recommendations made by veterinary professionals. Given the legal nuances that can change often, we encourage readers to review the Veterinary Medicines Directorate statement on veterinary medicinal products containing cannabidiol. (https://www.gov.uk/government/news/vmd-statement-on-veterinary-medicinal-products-containing-cannabidiol).

Endocannabinoid receptor system

The endocannaboid receptor system has been evolving since the dawn of multicellular species. The ECS is a system that comprises:

- naturally occurring ligands called endocannabinoids (produced endogenously by every organism with an ECS);
- catabolic and hydrolysing enzymes for these endocannabinoids;
- two primary receptors known as CB_1 and CB_2; and
- other endocannabinoid-like molecules.

The functions of the ECS are varied but its main purpose is to maintain homeostasis. The ECS is active throughout the day in all mammalian species, triggering feeding behaviour, sleep, immune response, memory formation and processing and other homeostatic processes. There seems to be an overlap between the ECS and other receptor systems, including opioid receptors, serotonin receptors and dopamine receptors. This more expansive view of the ECS includes the understanding that endogenous ligands as well as molecules from the cannabis plant both have affinity for various receptors, thereby inducing various physiological responses and broadening the therapeutic potential of phytocannabinoids.[6,7]

Key point

The word 'cannabinoid' is a given to molecules that bind to the CB_1 and CB_2 receptors within the mammalian body. These molecules can be derived from plants, produced within the body or synthesised in a laboratory.

Currently, there are a number of pharmaceutical companies researching the use of ECS enzyme inhibiting compounds to preserve endocannabinoids for various conditions, which may lead to lower effective doses of supplemental (phyto)cannabinoids in the future.

mg/kg of THC, the dogs had dose-related signs, but no fatalities occurred in the course of the study.[8] While these studies failed to include cats, we know from clinical experience and limited species-specific data that feline patients appear to have a higher tolerance for, and different absorption of phytocannabinoids compared with, their canine counterparts, therefore requiring higher or more frequent dosing in some circumstances.[9]

When it comes to THC use in practice there is no doubt as to its therapeutic potential; however, some of the most respected cannabinoid researchers have pivoted away from reliance on THC use in clinical practice as there is nothing therapeutically that the other non-intoxicating phytocannabinoids cannot do that THC can.[4] In fact, in vitro research using human cancer cell lines found that THC had proliferative effects on certain types of cancers but demonstrated anti-cancer effects on other types.[10-13]

Additionally, THC is one of a few phytocannabinoids that can downregulate the production of endocannabinoids, which may or may not be in the patient's best health interests. Levels of THC found in hemp (<0.3%) typically present little concern for intoxication, ECS downregulation or other adverse events.[14,15]

CBD

Cannabidiol (CBD) is the second most popular and studied phytocannabinoid at the moment. Safety data are favourable in many species, including cats.[9]

A long-term study by GW Pharmaceuticals treated dogs and rats for 39 weeks with a CBD isolate at 10–100 mg/kg PO. There were mild elevations in liver enzymes (alkaline phosphatase [ALP] up to eight-fold and alanine transaminase [ALT] had only minor increases) and notable hepatocellular hypertrophy, both of which are also commonly seen with steroid use.[16] What is important to remember, given these results, is that doses used in clinical practice are seldom greater than 10 mg/kg/day. More recently, a 12-week study was published showing the safety of using a CBD/CBDA product in healthy dogs and cats. CBDA is the acidic form of CBD, found in raw, unheated, undried cannabis.[9] Acidic forms of CBD and THC have been shown to be cyclooxygenase inhibiting, making them potent anti-inflammatory agents.[17,18] The study concluded that a dose of 2 mg/kg PO q12h, is safe and well tolerated. However, one cat did have a transient spike in ALT at week 4 of the study, which could not be directly correlated to the CBD product.[9] All other chemistry values in the dogs and cats remained within normal limits.[9]

From a clinical standpoint, it is important to remember the significance and species-specific differences between these two liver enzymes. ALP elevations alone in dogs are typically of little clinical concern without elevations of other liver enzymes, whereas ALP elevations in cats is of concern. ALT elevations in cats without other elevations of liver enzymes are generally of little concern but should be monitored.[21,22]

In the most comprehensive study to date looking at the safety and tolerability of CBD and THC dosing in cats, researchers were able to achieve dosing up to 30.5 mg/kg of CBD and 41.5 mg/kg THC with only mild adverse effects.[23] This study was conducted in healthy cats, with a structured dose increase over time. While we do not encourage cannabis dosing at the high levels identified in this study, it does give us an additional level of comfort with the suggested dosing currently used clinically by these authors and others.

Varying response to cannabinoids

The variance in response to cannabinoid products is heavily reliant on multiple factors known collectively as the endocannabinoid system tone.[19,20] The tone of the ECS is dependent on:

- the disease or injury being treated and its severity;
- production of endocannabinoids;
- production of catalysing or hydrolysing endocannabinoid enzymes;
- the number of ECS receptors and the activity of the endocannabinoidome;
- the gene variant of the receptors (Akt, CB_1, CB_2, etc); and
- the formulation of the product being used and its dose.

Clinical veterinary cannabis studies

There is a growing list of relevant studies for practical use of phytocannabinoids in dogs. Unfortunately, there are few in cats. However, there is a large and ever-growing community of veterinary professionals that do use these compounds in feline patients with success.

Osteoarthritis
Seven studies looking at the efficacy of different CBD products for increasing the comfort levels of dogs with osteoarthritis have been published. All of the studies concluded that CBD has a minor to significantly favourable impact on decreasing pain scores and increasing quality of life for dogs. Dosages in these studies ranged from 0.25 to 2.5 mg/kg PO q12h. In most of these studies, ALP became elevated in a percentage of the canine participants. However, these were not considered to warrant clinical intervention. The researchers suggested the elevations were related to CBD liver metabolism, also supported by human and rodent studies.[24,25]

The bone healing properties of CBD have been investigated in rodent models; ALP in these subjects increased as bone density increased over the course of CBD treatment.[26] Knowing that osteoarthritis is an under-diagnosed problem in feline patients, the authors are hopeful that research on using CBD in cats will be forthcoming.

Seizure disorders
A pilot study conducted in dogs, found that a dose of 2.5 mg/kg q12h did not meet the study goal of a 50% decrease in seizure activity. However, there was an average 33% decrease in seizure activity in those dogs that responded to CBD therapy, which shows great promise.[27] A longer-term study with a higher CBD dose is currently underway.

Epileptic patients generally require higher doses compared with those needed for other conditions such as pain.[28] Anecdotally, the authors have seen great success using CBD for seizure disorders in combination with other anti-epileptic drugs (AEDs). In fact, many owners are able to significantly decrease traditional AED dosages. Compared with traditional AEDs, tolerance to CBD is not a frequently observed phenomenon; however, in a recent human study, around 30% of patients did develop what appeared to be a CBD tolerance. Dosages were increased with a good response.[29]

Oncology
In vivo studies using CBD in veterinary oncology treatment are currently ongoing. There are two studies examining the efficacy of CBD products for treating transitional cell carcinoma in dogs and a broader quality-of-life study. Cell culture studies have been conducted with great promise for in vivo application. Canine glioblastoma, canine lymphoma, canine mammary carcinoma and osteosarcoma cell lines are all responsive to CBD. The data suggests potential synergy and enhanced cancer targeting when CBD is used in conjunction with two chemotherapeutic agents, doxorubicin and vincristine.[30–32] Effective dosages of phytocannabinoids (based on scaled dosing from cell-line work) appear

Monitoring cannabis therapy

Liver enzymes should be monitored for patients that will be on a CBD or other cannabis product long term (ie, longer than 3 months). Testing should include measurement of ALP, aspartate aminotransferase (AST) and ALT at a minimum. The addition of gamma-glutamyl transferase and C-reactive (CRP) protein may be considered in addition. CRP measurement may be an interesting way to gauge success by assessing whether there has been a decrease in inflammatory markers.

to be greater than 5 mg/kg PO q12h, but patients can benefit from symptomatic relief at much lower doses.

There is one published feline case study from Thailand where the veterinarian used a full spectrum CBD product at a dose of 0.7 mg/kg/day PO to treat a large ocular sarcoma. Over a period of a few weeks the mass shrank and eventually fell off. While exciting, this case report had many limitations but is one of the first published case reports available.[33]

In a study from 1984, 57 cats were used as a model for the possible anti-emetic effects of THC against cisplatin induced nausea and vomiting. The cats were given various doses of THC by mouth, intramuscularly or intravenously. The authors acknowledged that dosing refinement was needed given some of the untoward behavioural effects observed; however, the results demonstrated better emetic latency and decreased emetic activity.[34]

Human studies have found more effective responses to chemotherapy treatment and an improved quality of life when phytocannabinoid products are used.[35–37] The use of phytocannabinoids decreases nausea and increases appetite in both people and rats receiving chemotherapy.[38,39]

Cognitive health/anxiety
Animal models using CBD as a treatment modality for anxiety or panic attacks are supported by studies placing a prey species in front of a predator species, as well as conditioned escape responses in mice and rats. According to these studies, anxiety or panic attacks could be related to the flight and freezing defensive responses elicited by threats; expression of these responses was decreased in both models.[28,40,41] There is one published canine study (with many confounding limitations) that found no advantage in using CBD as an anxiolytic for exposure to an acute stress-inducing environmental stimulus.[42] Experienced feline practitioners have

Common drug interactions

Benzodiazepines
Benzodiazepines commonly potentiate the sedative effects of cannabinoid products, even in those containing zero THC. Animals may appear extremely lethargic or have clinical signs similar to THC intoxication. If excessive sedation is seen, the authors recommend a significant decrease (at least 25%) in the dosage of either the phytocannabinoid product or benzodiazepine. Dose titration, both increases and decreases, over time may be warranted for the small percentage of animals that experience these clinical signs.

Gabapentin, acepromazine, tramadol, phenobarbital
In some patient's, transient lethargy, inappetence, abnormal behaviours and, in severe cases, urinary incontinence may be observed when given concurrently with gabapentin, acepromazine, tramadol and phenobarbital. Dose titration over time may be warranted for the small percentage of animals that experience these signs.

Trazodone (and other selective serotonin reuptake inhibitors [SSRIs])
Theoretically, the potential of serotonin syndrome exists. However, this has not been described in animals or humans administered the combination of cannabis products and SSRIs.

Non-steroidal anti-inflammatory drugs
Use of cannabinoid products appears to be safe with concurrent use of non-steroidal anti-inflammatory drugs.

hailed CBD as a novel, yet effective, treatment for cats with chronic feline idiopathic cystitis.

Feline cognitive dysfunction (FCD) is also a point of concern for many owners with geriatric cats in the home. Typical manifestations of FCD include changes in social interaction, disorientation, changes in sleep–wake patterns, litter tray avoidance and excessive vocalisation. In a paper published in 2020, researchers suggested that CBD may help both human and feline patients suffering from cognitive dysfunction. This study recommended using cats with FCD as a potential model for testing the clinical efficacy of CBD for treatment of cognitive dysfunction.[43]

Dermatological
Preliminary results from three canine studies have shown around a 50% decrease in itch scoring for dogs with atopy lesions (data to be published). Topical and systemic forms of CBD have anecdotally been used with success in cats. There is one study assessing ECS receptor activity in feline patients with hypersensitivity dermatitis. This study demonstrated ECS activity by means of receptor proliferation, suggesting the possible use of phytocannabinoid products in this feline patient population.[44]

Gastrointestinal/oral mucosa
Receptor identification studies in gastrointestinal and oral mucosal tissues from cats demonstrate

What to look for in a cannabis product

Always ask for a certificate of analysis (CoA) for any cannabis product you or your clients are thinking about purchasing. This is a third-party, independent laboratory analysis of the product. While there are issues with testing facilities and standardisation, this is currently the only way to evaluate the quality of a product. If a company cannot or will not provide you with a CoA, the authors recommend not purchasing their product.

The CoA should include:
- a breakdown of all cannabinoids present in the product. We have good evidence that whole-plant (also known as full-spectrum or broad-spectrum) products are more effective than products that contain only CBD (such products are termed 'isolates' and may require much higher doses to achieve the desired effect);
- the CBD:THC ratio in the product;
- terpene analysis;
- heavy metal testing;
- herbicide/fungicide insecticide testing;
- microbial testing;
- mycotoxin testing; and
- residual solvent testing.

The company should also provide the following information:
- the amount of CBD per ml;
- a complete ingredient list. Check for dangerous ingredients such as xylitol or other flavourings; and
- the extraction method used.

Key point

A company should provide all of the information listed here without hesitation and immediately upon request. As the market matures, purchasing a product that is backed by positive scientific studies using the product will be advisable.

densities of ECS receptors that suggest a potential therapeutic benefit of using CBD as a treatment modality for diagnoses such as irritable bowel disease and gingivostomatitis.[45,46] Human studies show good efficacy against chronic forms of colitis.[47–49] Other studies have looked at the protective effects of certain phytocannabinoids, specifically for gastrointestinal mucosal lesions secondary to acute pancreatitis in rat models.[50,51]

Renal disease

Human patients have been using phytocannabinoid products to alleviate chronic renal disease related symptoms for years with great success and no adverse effects described in the literature thus far.[52] Rodent data suggest a future potential for therapeutic disease management.[53,54] This may be a great option for stimulating appetite and keeping the often geriatric kidney failure patient comfortable if the use of non-steroidal anti-inflammatory agents are a concern.

Conclusions

Just like in human medical cannabis circles, the veterinary cannabis industry will continue to evolve, developing specific cannabinoid and terpene profiles for various ailments or ECS support. As scientists, consumers and animal lovers, we must pressure cannabis/hemp manufacturers to produce products following good manufacturing guidelines, using safe ingredients for animals, with transparency around what is in their products. To that end, manufacturers should suggest dosing regimens based on science instead of conjecture. It is critical to note that dose extrapolation from one tested product to the next will not necessarily provide the same efficacy nor have the same safety profile. Conclusions of a specific study, using a specific cannabis product, must be viewed in context, considering the wide array of cannabinoid and terpene profiles on the market. We must also urge local governments, to adopt legislative language to allow veterinary professionals to discuss, recommend and, in some cases, prescribe cannabis products for their patients. Lastly, we must encourage veterinary professionals at all levels to educate themselves on this topic.

References

1 Wakshlag JJ, Cital S, Eaton SJ, et al. **Cannabinoid, terpene, and heavy metal analysis of 29 over-the-counter commercial veterinary hemp supplements.** *Vet Med (Auckl)* 2020; 11: 45–55.

2 Brutlag A and Hommerding H. **Toxicology of marijuana, synthetic cannabinoids, and cannabidiol in dogs and cats.** *Vet Clin North Am Small Anim Pract* 2018; 48: 1087–1102.

3 Morales P, Hurst DP and Reggio PH. **Molecular targets of the phytocannabinoids: a complex picture.** *Prog Chem Org Nat Prod* 2017; 103: 103–131.

4 Thompson GR, Rosenkrantz H, Schaeppi UH, et al. **Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys.** *Toxicol Appl Pharmacol* 1973; 25: 363–372.

5 Whalley BJ, Lin H, Bell L, et al. **Species-specific susceptibility to cannabis-induced convulsions: species-specific effects of cannabis extracts.** *Br J Pharmacol* 2019; 176: 1506–1523.

6 Silver RJ. **The endocannabinoid system of animals.** *Animals (Basel)* 2019; 9: 686.

7 Tsuboi K, Uyama T, Okamoto Y, et al. **Endocannabinoids and related N-acylethanolamines: biological activities and metabolism**. *Inflamm Regen* 2018; 38: 28.

8 Vaughn D, Kulpa J and Paulionis L. **Preliminary investigation of the safety of escalating cannabinoid doses in healthy dogs.** *Front Vet Sci* 2020; 7: 51.

9 Deabold KA, Schwark WS, Wolf L and Wakshlag JJ. **Single-dose pharmacokinetics and preliminary safety assessment with use of CBD-rich hemp nutraceutical in healthy dogs and cats.** *Animals (Basel)* 2019; 9: 832. DOI: 10.3390/ani9100832.

10 Śledziński P, Zeyland J, Słomski R, et al.

The current state and future perspectives of cannabinoids in cancer biology. *Cancer Med* 2018; 7: 765–775.
11 Hart S, Fischer OM and Ullrich A. **Cannabinoids induce cancer cell proliferation via tumor necrosis factor converting enzyme (TACE/ADAM17)-mediated transactivation of the epidermal growth factor receptor**. *Cancer Res* 2004; 64: 1943–1950.
12 Ghasemiesfe M, Barrow B, Leonard S, et al. **Association between marijuana use and risk of cancer: a systematic review and meta-analysis.** *JAMA Netw Open* 2019; 2: e1916318.
13 Baram L, Peled E, Berman P, et al. **The heterogeneity and complexity of cannabis extracts as antitumor agents.** *Oncotarget* 2019; 10: 4091–4106.
14 De Fonseca FR, Gorriti MA, Fernández-Ruiz JJ, et al. **Downregulation of rat brain cannabinoid binding sites after chronic delta 9-tetrahydrocannabinol treatment.** *Pharmacol Biochem Behav* 1994; 47: 33–40.
15 Hirvonen J, Goodwin RS, Li C-T, et al. **Reversible and regionally selective downregulation of brain cannabinoid CB_1 receptors in chronic daily cannabis smokers.** *Mol Psychiatry* 2012; 17: 642–649.
16 Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000PharmR.pdf (accessed February 8, 2021).
17 Takeda S, Misawa K, Yamamoto I, et al. **Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis.** *Drug Metab Dispos* 2008; 36: 1917–1921.
18 Takeda S, Okazaki H, Ikeda E, et al. **Down-regulation of cyclooxygenase-2 (COX-2) by cannabidiolic acid in human breast cancer cells.** *J Toxicol Sci* 2014; 39: 711–716.
19 Chanda PK, Gao Y, Mark L, et al. **Monoacylglycerol lipase activity is a critical modulator of the tone and integrity of the endocannabinoid system.** *Mol Pharmacol* 2010; 78: 996–1003.
20 Guida F, Boccella S, Belardo C, et al. **Altered gut microbiota and endocannabinoid system tone in vitamin D deficiency-mediated chronic pain.** *Brain Behav Immun* 2020; 85: 128–141.
21 IDEXX Laboratories. **Alkaline phophatase.** https://www.idexx.es/files/8093-us-alp-interpretive-summary.pdf (accessed February 8, 2021).
22 IDEXX Laboratories. **Alanine aminotransferase.** https://www.idexx.es/files/8091-us-alt-interpretive-summary.pdf (accessed February 8, 2021).
23 Kulpa JE, Paulionis LJ, Eglit GML, et al. **Safety and tolerability of escalating cannabinoid doses in healthy cats.** *J Feline Med and Surg* 2021. DOI: 10.1177/1098612X211004215.
24 Mejia S, Duerr FM, Griffenhagen G, et al. **Evaluation of the effect of cannabidiol on naturally occurring osteoarthritis-associated pain: a pilot study in dogs.** *J Am Anim Hosp Assoc* 2021. DOI: 10.5326/JAAHA-MS-7119.
25 Gamble L-J, Boesch JM, Frye CW, et al. **Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs.** *Front Vet Sci* 2018; 5. DOI: 10.3389/fvets.2018.00165.
26 Kogan NM, Melamed E, Wasserman E, et al. **Cannabidiol, a major non-psychotropic cannabis constituent enhances fracture healing and stimulates lysyl hydroxylase activity in osteoblasts: cbd enhances collagen crosslinking and strength of the fracture callus.** *J Bone Miner Res* 2015; 30: 1905–1913.
27 McGrath S, Bartner LR, Rao S, et al. **Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy.** *J Am Vet Med Assoc* 2019; 254: 1301–1308.
28 Maroon J and Bost J. **Review of the neurological benefits of phytocannabinoids.** *Surg Neurol Int* 2018; 9: 91.
29 Kramer SU-SM. **Cannabidiol tolerance in children and adults with treatment-resistant epilspsy** https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/5013 (2018, accessed February 8, 2021).
30 Henry JG, Shoemaker G, Prieto JM, et al. **The effect of cannabidiol on canine neoplastic cell proliferation and mitogen-activated protein kinase activation during autophagy and apoptosis.** *Vet Comp Oncol* 2020; e12669.
31 Gross C, Ramirez D, Dickinson P, et al. **Cannabidiol induces apoptosis and perturbs mitochondrial function in both human and canine glioma cells.** *FASEB J* 2020; 34 Suppl 1: 1–1. DOI: 10.1096/fasebj.2020.34.s1.04176.
32 Omer S, Boothe D, Mansour M, et al. **Abstract PO-047: anti-proliferative effect of cannabidiol (CBD) against B and T-cell lymphoma.** In: Poster Presentations. American Association for Cancer Research; 2020.
33 Buranakarn V. **Sarcoma cancer treatment using extracted cannabis oil in a cat.**

Int J Innov Res Sci Eng Technol 2020; 3: 35–40.
34 Karl P. **Antiemetic properties and plasma concentrations of delta-9-tetrahydrocannabinol agsinst cisplatin vomiting in cats.** In: Agurell S, Dewey WL and Willette RE (eds). The cannabinoids: chemical, pharmacologic and therapeutic aspects. Philadelphia; Elsevier; 1984, pp 869–870.
35 Scott KA, Dalgleish AG and Liu WM. **Anticancer effects of phytocannabinoids used with chemotherapy in leukaemia cells can be improved by altering the sequence of their administration.** *Int J Oncol* 2017; 51: 369–377.
36 Miyato H, Kitayama J, Yamashita H, et al. **Pharmacological synergism between cannabinoids and paclitaxel in gastric cancer cell lines.** *J Surg Res* 2009; 155: 40–47.
37 Gazzerro P, Malfitano AM, Proto MC, et al. **Synergistic inhibition of human colon cancer cell growth by the cannabinoid CB_1 receptor antagonist rimonabant and oxaliplatin.** *Oncol Rep* 2010; 23: 171–175.
38 Tramèr MR, Carroll D, Campbell FA, et al. **Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review.** *Brit Med J* 2001; 323: 16–21.
39 Mortimer TL, Mabin T and Engelbrecht A-M. **Cannabinoids: the lows and the highs of chemotherapy-induced nausea and vomiting.** *Future Oncol* 2019; 15: 1035–1049.
40 Skelley JW, Deas CM, Curren Z, et al. **Use of cannabidiol in anxiety and anxiety-related disorders**. *J Am Pharm Assoc* 2020; 60: 253–261.
41 R de Mello Schier A, P de Oliveira Ribeiro NS, Coutinho D, et al. **Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of *Cannabis sativa*.** *CNS Neurol Disord Drug Targets* 2014; 13: 953–960.
42 Morris EM, Kitts-Morgan SE, Spangler DM, et al. **The impact of feeding cannabidiol (CBD) containing treats on canine response to a noise-induced fear response test.** *Front Vet Sci* 2020; 7: 569565.
43 Zadik-Weiss L, Ritter S, Hermush V, et al. **Feline cognitive dysfunction as a model for Alzheimer's disease in the research of CBD as a potential treatment — a narrative review.** *J Cannabis Res* 2020. DOI: 10.1186/s42238-020-00054-w.
44 Miragliotta V, Ricci PL, Albanese F, et al. **Cannabinoid receptor types 1 and 2 and peroxisome proliferator-activated receptor-α: distribution in the skin of clinically healthy cats and cats with hypersensitivity dermatitis.** *Vet Dermatol* 2018; 29: 316-e111.
45 Stanzani A, Galiazzo G, Giancola F, et al. **Localization of cannabinoid and cannabinoid related receptors in the cat gastrointestinal tract.** *Histochem Cell Biol* 2020; 153: 339–356.
46 Polidoro G, Galiazzo G, Giancola F, et al. **Expression of cannabinoid and cannabinoid-related receptors in the oral mucosa of healthy cats and cats with chronic gingivostomatitis.** *J Feline Med Surg* 2020; 21: 1165–1171.
47 Kunos G and Pacher P. **Cannabinoids cool the intestine.** *Nat Med* 2004; 10: 678–679.
48 Kienzl M, Storr M and Schicho R. **Cannabinoids and opioids in the treatment of inflammatory bowel diseases.** *Clin Transl Gastroenterol* 2020; 11: e00120. DOI: 10.14309/ctg.0000000000000120.
49 Holleran G, Scaldaferri F, Gasbarrini A, et al. **Herbal medicinal products for inflammatory bowel disease: a focus on those assessed in double-blind randomised controlled trials.** *Phytother Res* 2020; 34: 77–93.
50 Michalski CW, Laukert T, Sauliunaite D, et al. **Cannabinoids ameliorate pain and reduce disease pathology in cerulein-induced acute pancreatitis.** *Gastroenterology* 2007; 132: 1968–1978.
51 Sharafi G, He H and Nikfarjam M. **Potential use of cannabinoids for the treatment of pancreatic cancer.** *J Pancreat Cancer* 2019; 5: 1–7.
52 Park F, Potukuchi PK, Moradi H, et al. **Cannabinoids and the kidney: effects in health and disease.** *Am J Physiol Renal Physiol* 2017; 313: F1124–1132.
53 Barutta F, Bruno G, Mastrocola R, et al. **The role of cannabinoid signaling in acute and chronic kidney diseases.** *Kidney Int* 2018; 94: 252–258.
54 Janiak P, Poirier B, Bidouard J-P, et al. **Blockade of cannabinoid CB_1 receptors improves renal function, metabolic profile, and increased survival of obese Zucker rats.** *Kidney Int* 2007; 72: 1345–1357.

Further reading

- Cital S, Kramer K, Hughston L and Gaynor JS (eds). Cannabis therapy in veterinary medicine. New York: Springer Nature, 2021.