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Cannabidiol and the possibilities of its use in veterinary medicine of dogs and horses: A brief review

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Abstract: In connection with the use of cannabinoids for therapeutic purposes in human medicine, there is increased attention for their use in veterinary medicine, particularly by the owners of companion animals and horses. Therefore, veterinarians are expected to face this interest and have the corresponding knowledge on these substances. Presently, it is not possible to use medical marijuana (in terms of the dried cannabis flowers) for veterinary purposes in many countries, but there is increasing evidence that isolated cannabinoids also have beneficial effects (namely cannabidiol – CBD). Thus, this review summarises the possible therapeutic implications of CBD within the scope of evidence-based medicine, particularly in dogs and horses in association with the treatment of pain, epilepsy and anxiety in order to provide veterinarians with a concise overview of scientific findings in this field.

Keywords: cannabidiol; cannabinoids; dogs; horses; pain treatment

List of abbreviations

ALP = alkaline phosphatase; **AUC** = area under the curve; **CB_1** = cannabinoid receptor type 1; **CB_2** = cannabinoid receptor type 2; **CBD** = cannabidiol; **C_{max}** = maximum drug concentration in plasma; **CYP** = cytochrome P-450; **EMA** = European Medicines Agency; **FAAH** = fatty acid amide hydrolase; **GABA** = gamma-amino butyric acid; **GPR18** = G-protein coupled receptor 18; **5-HT_{1A}** = serotonin receptor type 1A; **5-HT_{2A}** = serotonin receptor type 2A; **5-HT_{3A}** = serotonin receptor type 3A; **LC-MS** = liquid chromatography-mass spectrometry; **NMDA** = *N*-methyl-D-aspartate; **THC** = **Δ^9**-tetrahydrocannabinol; **TRPV1** = transient receptor potential cation channel; subfamily A member 1; **PPARα** = peroxisome proliferator-activated receptor α; **PPARγ** = peroxisome proliferator-activated receptor γ; **T_{max}** = time to achieve maximum drug concentration; **$T_{1/2}$** = biological elimination half-life

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Introduction

Cannabidiol (CBD) is a drug classified as a cannabinoid (or more specifically a phytocannabinoid), which means that it is a cannabis-specific substance found only in hemp (*Cannabis sativa* L.). More than 140 phytocannabinoids have been described till this time.

The precise chemical structure of CBD isolated from hemp oil was identified in 1963 (Mechoulam and Shvo 1963). This identification enabled the research of its pharmacological mechanisms in living organisms on a molecular level, which finally contributed to the significant clarification of the possible therapeutic effects associated with CBD use.

Cannabidiol is a lipophilic substance with large distribution volume (32 l/kg in humans). It binds to plasma proteins and is widely distributed to the periphery. It is quickly redistributed to the brain and fat tissue and it also binds to erythrocytes (Ohlsson et al. 1986; Gaston and Friedman 2017). Metabolisation is particularly on the level of oxidative reactions catalysed by cytochrome P-450, (CYP)3A4 and also CYP2C19 (Jiang et al. 2011; Stout and Cimino 2014).

The mechanism of the CBD action is rather complex, where the main principle consists in the negative allosteric modulation of cannabinoid CB_1 receptors which results in the decreased efficacy of agonists acting on these receptors (e.g., endogenous cannabinoid anandamide or Δ^9-tetrahydrocannabinol – THC). Other important mechanisms of CBD involve antagonism/inverse agonism on cannabinoid CB_2 receptors and antagonism on the cannabinoid receptors GPR18. There are, nevertheless, also reports that CBD additionally acts as an inverse agonist/antagonist on cannabinoid CB_1 receptors and a negative allosteric modulator on cannabinoid CB_2 receptors (Peng et al. 2022). It has been shown that CBD acts as an agonist on serotonergic receptors 5-HT_{1A}, a partial agonist on subtype 5-HT_{2A} and a non-competitive antagonist on subtype 5-HT_{3A}. It may also stimulate the adenosine receptors A1, GABAergic $GABA_A$ receptors and nuclear receptors PPARγ. In addition, it activates the α1 and α1β subunits of the glycine receptors. CBD has a partially agonistic effect on dopamine D_2 receptors (Peng et al. 2022). The antagonistic activity of CBD on sigma-1 receptors (σ1R) disrupts their functional association with the NR1 subunit of NMDA receptors and, finally, it can act as a non-selective inhibitor of voltage dependent sodium channels. There is also a beginning debate about possible non-receptor mechanisms (e.g., an increase in the anandamide levels, which is thought to be in context to the CBD inhibitory effect on the inactivating hydrolase FAAH) (Laprairie et al. 2015; Morales et al. 2017; Preedy 2017; Ghovanloo et al. 2018; Rodriguez-Munoz et al. 2018).

The main general documented therapeutic effects of CBD

Since the involvement of CBD in many receptor systems it is not surprising that its described effects are also very miscellaneous and can be seen on both preclinical and clinical levels. The main ones are listed here:

Anxiolytic effect – it has been shown that previous treatments with CBD significantly decreased the anxiety and restlessness. CBD blocked the anxiety induced by the THC and substantially reduced the anxiety in general in both animal models and humans (de Mello Schier et al. 2014; Masataka 2019).

Antiepileptic effect – a double blind, placebo-controlled study was carried out with 120 human patients where the effects of CBD were observed on convulsion attacks in Dravet syndrome (serious epileptic syndrome typically manifesting in childhood and associated with seizures resistant to treatment and high mortality rate). Cannabidiol was given as a supplement to the standard epileptic treatment. The study showed that the CBD decreased the frequency of the convulsions in the participating children and adolescents suffering from Dravet syndrome for a period of 14 days (Devinsky et al. 2017).

A case report published in the scientific journal *Epilepsia* described the use of CBD in a 5-year-old girl. The first seizure this child experienced was a prolonged status epilepticus at 3 months of age and treatment with "classical" anticonvulsant drugs was regarded as hopeless. After administration of a cannabis extract with a high content of CBD, the girl showed reduced seizure frequency from nearly 50 convulsive seizures per day to 2–3 nocturnal convulsions per month (i.e., > 90% reduction in generalised tonic-clonic seizures), which also speaks unambiguously in favour of CBD use in such pathological conditions (Maa and Figi 2014).

https://doi.org/10.17221/127/2021-VETMED

A positive attitude towards CBD use in seizures associated with Lennox-Gastaut syndrome (symptomatic epilepsy caused by brain injury or malformation with manifestation up to 5 years of age) or Dravet syndrome was assumed in 2019 also by the European Medicines Agency (EMA).

Analgesic effect – cannabidiol exerted analgesic effects in various animal models (inflammatory pain, arthritis-related pain) (De Gregorio et al. 2019; Mlost et al. 2020).

Other reported CBD effects in animal models involve: anti-inflammatory and antioxidant properties (Atalay et al. 2019), a positive effect on autoimmune diseases including diabetes and rheumatoid arthritis (Lehman et al. 2016; Gusho and Court 2020) or a promising therapeutic potential in oncological conditions (Daris et al. 2019; Seltzer et al. 2020).

CBD in veterinary medicine

Expanding the use of cannabinoids or medical cannabis in humans is logically associated with increasing interest in the curative approach in veterinary medicine also (particularly with the owners of companion animals and horses). The use of medical cannabis for veterinary purposes is not possible in many countries due to legislative restrictions; nevertheless, the use of CBD alone is feasible in general and it has already become a reality in fact.

In practice, a plethora of information on the effects of cannabinoids in animals is available, because substances primarily intended for administration in humans are tested in animal models within the pre-clinical research (Landa et al. 2016). With respect to the clinical use of cannabinoids in veterinary medicine, the number of reliable sources is, however, much smaller. The first scientific works dealing with the possible use of cannabinoids in veterinary medicine are oriented particularly towards CBD.

Research carried out in the USA focused on the veterinarians' knowledge level, views and experiences related to the use of cannabinoids in the medical treatment of dogs showed that most participants expressed support for use of CBD products in animals (Kogan et al. 2019a). Similar results were seen in a study focused on Canadian dog owners. The participating owners administered cannabis products for the treatment of pain, inflammation, and anxiety to dogs, and accounted that these preparations are equally or even more effective than conventional medications (Kogan et al. 2019b).

PHARMACOKINETICS OF CBD IN DOGS AND HORSES

According to our knowledge, there is only a limited number of reliable data sources concerning pharmacokinetics of CBD in animals, but some specifications are at hand, particularly for dogs and horses. The bioavailability following the oral administration in dogs is rather low (13–19%), probably due to the large first-pass effect. The distribution volume in dogs is approximately 100 l (Samara et al. 1988; Bartner et al. 2018).

A summary of the selected pharmacokinetic parameters for canines can be seen in Table 1. They are based on a single oral administration of CBD at a dose of 2 mg/kg (Deabold et al. 2019).

Concerning pharmacokinetics in horses, Collins et al. (2019) carried out a study with eighteen Quarter Horse geldings. These horses were randomly assigned to three treatment groups where they were administered CBD single doses 50 mg (n_1), 100 mg (n_2), and 250 mg (n_3) in the form of pellets. In this study, the serum CBD concentrations were below the lower limit of detection in all the animals in group n_1 and in five of the six animals in group n_2. The maximum concentrations

Table 1. The main pharmacokinetic parameters in dogs

Pharmacokinetic parameter in dogs	Value
AUC (ng/ml/h)	1 297
C_{max} (ng/ml)	301
T_{max} (h)	1.4
$T_{1/2}$ (h)	1

AUC (area under the curve) = area under the plasma drug concentration-time curve defines the actual body exposure to the drug after administration of a dose (expresses the bioavailability of the substance); C_{max} = maximum plasma concentration of the drug after a single administration; T_{max} = the time required to reach the maximum plasma concentration (T_{max} and C_{max} describe the rate of absorption); $T_{1/2}$ = biological elimination half-life (the time required for the plasma concentration of a drug to fall to half of its value; it characterises the rate of the drug elimination)

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were detected in one animal from group n_2 and in five of the six horses from group n_3 two hours after administration. Similar results concerning the maximum concentration were reported by Jones et al. (2018).

Davis (2019) studied the pharmacokinetics of a CBD oil after the transmucosal administration in healthy horses. Thirteen animals were given CBD oil at a dose of 0.1 mg/kg. The cannabinoid in the serum was quantified by liquid chromatography-mass spectrometry (LC-MS) and a summary of the selected pharmacokinetic parameters from this study can be seen in Table 2.

CLINICAL USE OF CBD IN DOGS

It has been shown that the expression of cannabinoid receptors in the brain is larger in dogs than in humans and, therefore, dogs are more sensitive to cannabinoids in general (Freundt-Revilla et al. 2017). The main domain of possible CBD use in dogs is, without any doubt, pain treatment.

A randomised placebo-controlled, veterinarian, and owner blinded, cross-over study was conducted at the Cornell University (Ithaca, USA) with osteoarthritic dogs. Within this study, beagles received each of two treatments: CBD oil (2 mg/kg) or placebo oil every 12 hours. The treatment was administered orally and each treatment lasted for 4 weeks with a 2-week washout period. The owner questionnaires and baseline veterinary assessment were completed before initiating the treatments and at weeks 2 and 4. The Canine Brief Pain Inventory and Hudson Activity Scores showed a significant decrease in pain and an increase in activity ($P < 0.01$) with the CBD oil. The veterinary assessment showed decreased pain during the CBD treatment ($P < 0.02$), i.e., an increase in the quality of life was seen. The owners reported no side effects in the dogs. The serum chemistry showed an increase in the alkaline phosphatase (ALP) during the CBD treatment (Gamble et al. 2018).

Table 2. The main pharmacokinetic parameters in horses

Pharmacokinetic parameter in horses	Value
AUC (ng/ml/min)	247.1
C_{max} (ng/ml)	27.2
T_{max} (h)	2.9
$T_{1/2}$ (h)	15.2

AUC (area under the curve) = area under the plasma drug concentration-time curve defines the actual body exposure to the drug after administration of a dose (expresses the bioavailability of the substance); C_{max} = maximum plasma concentration of the drug after a single administration; T_{max} = the time required to reach the maximum plasma concentration (T_{max} and C_{max} describe the rate of absorption); $T_{1/2}$ = biological elimination half-life (the time required for the plasma concentration of a drug to fall to half of its value; it characterises the rate of the drug elimination)

A randomised, double-blind, placebo-controlled study was performed on large dogs (> 20 kg) in Sunset Animal Hospital (Houston, TX, USA). The dogs were included in the study if they received an affirmative diagnosis of osteoarthritis by a veterinarian and demonstrated signs of pain according to an assessment by their owners, detectable lameness on a visual gait assessment, and painful joint(s) upon palpation. All the other medications were discontinued at least 2 weeks before the enrolment, and the dogs did not receive any medications during the 4-week study period apart from the study medication (naked or liposomal CBD). Before the beginning of treatment and at day 30, the dogs were evaluated by the study veterinarian (assessment of locomotion). Furthermore, the owners also evaluated dogs before the treatment and at weeks 4 and 6 (Helsinki Chronic Pain Index). The symptomatology was not significantly changed following the administration of the placebo or the 20 mg/day naked CBD; however, the administration of liposomally encapsulated CBD (20 mg/day) or naked CBD (50 mg/day) significantly decreased the pain and increased mobility (i.e., an improvement in the quality of life in the tested dogs quantitated by both the owner and veterinarian). The effect was statistically significant at least 15 days after cessation of the therapy (Verrico et al. 2020).

A study conducted in the Veterinary Teaching Hospital at the University of Milan (Lodi, Italy) included twenty-one dogs of different breeds, age, body weight and gender suffering from osteoarthritis. This study evaluated the efficacy of oral transmucosal CBD in addition to a multimodal pharmacological treatment for chronic osteoarthritis-related pain. The dogs were randomly divided into two groups: in group n_1, oral transmucosal CBD (2 mg/kg every 12 h) was added to the therapeutic protocol (anti-inflammatory drug, gabapentin, amitriptyline), there was no CBD administration

https://doi.org/10.17221/127/2021-VETMED

in group n_2. The dogs were evaluated by the owners (Canine Brief Pain Inventory). It was shown that severity of the pain was significantly lower in group n_1 with the co-administration of CBD. The authors concluded that such a co-administration can be more useful in reducing the other administered drugs' dosage, which subsequently minimises the severity and incidence of the associated side effects (Brioschi et al. 2020).

A ninety-day pilot clinical trial carried out at the Colorado State University involved 37 dogs diagnosed with chronic maladaptive pain resulting from osteoarthritis which tested the effects of a CBD-rich hemp oil extract on this pathological condition. Thirty-two dogs completed the study and of these, 30 showed improved pain support. Twenty-three dogs were taking gabapentin at the beginning of the study and 10 of them were able to completely quit the intake of this drug. Moreover, with the CBD oil supplement it was possible to reduce the daily dose of gabapentin in an additional 11 dogs (Kogan et al. 2020).

In contrast to the previous findings, there is a report which does not speak in favour of the CBD effects on pain treatment (Mejia et al. 2021). These authors conducted a prospective, double-blinded, crossover, placebo-controlled study which involved twenty-three dogs with naturally occurring osteoarthritis of the appendicular joints. Baseline data were acquired for a period of 4 weeks, followed by random allocation to either a placebo group or a treatment group with cannabidiol for 6 weeks, followed by 6 weeks with the opposite treatment. For the evaluations, an objective gait analysis, the activity counts and clinical metrology instruments were used. No differences were found between the groups at any time point for any of the recorded outcome measures.

Beside pain treatment, beneficial effects of cannabidiol have been described in dogs for the treatment of epilepsy. Scientists at Colorado State University (Fort Collins, CO, USA) assessed the effect of orally administered CBD in addition to a conventional antiepileptic treatment on the seizure frequency in dogs with intractable idiopathic epilepsy. The dogs were randomly divided into two groups. Group n_1 was given CBD-infused oil (2.5 mg/kg, p.o.) twice daily for 12 weeks in addition to the existing antiepileptic treatments, group n_2 (placebo) was administered non-infused oil under the same conditions. Despite that the proportion of responders was similar between the groups, a significant reduction in seizure frequency was observed in the dogs that received CBD. As with the use of CBD for pain treatment, the owners did not report any adverse behavioural effects. The laboratory tests showed a significant increase in the serum alkaline phosphatase activity (McGrath et al. 2019).

Finally, in addition to the studies listed above, there are data from veterinarians in the form of case studies which document the possible use of CBD as a suitable alternative remedy for treatment of anxiety. As an example, we can describe a case study of a nine-year old pug. This dog had a history of anxiety and dog aggression (reactivity when seeing other dogs) that began at the age of two. The reactivity improved by approximately 50% following three doses of CBD (5 mg twice daily with food) and the dog continued to show significant improvement with the continued use of cannabidiol (Krause 2019).

Concerning the safety of CBD use and the occurrence of possible adverse effects, there are consistent reports on an increase in the liver enzymes (McGrath et al. 2019; Mejia et al. 2021). Other described adverse effects involved minimal ptyalism (Brioschi et al. 2020) and vomiting (Mejia et al. 2021), but CBD appears to be well tolerated in dogs in general (McGrath et al. 2018).

There is, nevertheless, one very recent case study which rather surprisingly documents pad sloughing and rapidly progressive cutaneous and mucosal ulceration within five days of administering an oral CBD oil product. These signs developed in a 4-year-old castrated male Labrador Retriever treated for anxiety (cannabidiol 0.3 mg/kg *per os*, once daily). The sloughing of all the metacarpal and metatarsal, and most digital pads was seen and, moreover, ulcers and erythema were noted on the rostral tongue, lip folds, prepuce, anorectal junction, left inferior palpebra and both medial pinnae. The histopathological findings and cutaneous symptoms were consistent with Stevens-Johnson syndrome. All the changes completely resolved after the hemp oil withdrawal and a 12-day course of cephalexin and prednisone (including complete re-epithelisation). Although CBD is the active substance in the used product, other compounds cannot be discounted as possible contributors (Simpson et al. 2020).

Moreover, this report remains completely unique and the authors themselves termed the described symptoms as a "probable" adverse drug reaction.

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CLINICAL USE OF CBD IN HORSES

Compared to dogs, there is a significantly smaller number of scientific sources concerning CBD use in horses, however, some information can be found even for this animal species.

Chiocchetti et al. (2021) studied the localisation of well-established and putative cannabinoid receptors in the equine dorsal root ganglia using immunohistochemical methods. It was found that the neurons showed immunoreactivity for CB_1, CB_2, PPARα, TRPA1 and 5-HT_{1A}. Moreover, the neuronal satellite glial cells showed immunoreactivity for the CB_2, PPARα, TRPA1 and 5-HT_{1A} receptors. The authors concluded that the expression of the receptors in this localisation could be of particular relevance for future functional studies assessing the effects of cannabinoids in horses to treat pain.

Ellis and Contino (2021) published a case study in the journal *Equine Veterinary Education* concerning a 4-year-old Quarter Horse mare with a 5-week history of strong sensitivity to touch near the withers/shoulder region. An insect bite was considered as a possible cause. Conventional therapeutic approaches (dexamethasone, gabapentin, magnesium/vitamin E, prednisolone and aquapuncture with vitamin B12 did not produce any improvement in the clinical signs. The horse was given pure crystalline CBD (250 mg by mouth twice daily), which is known to have anti-inflammatory and antinociceptive effects. The condition significantly improved after 36 h, and the dose of the CBD was decreased by one half after 60 days. However, this reduction resulted in a recurrence of the clinical signs after one day. The dose was, therefore, adjusted to the initial level and it was gradually decreased during a period of 2 months without the repeated presence of increased sensitivity. The maintenance dose was 150 mg once a day and the owner described a 90% improvement (Ellis and Contino 2021).

Recently, a patent application was published concerning use of CBD to decrease stress and anxiety in horses (US 10,624,936 B2). Denapoli and Denapoli (2020) described the calming effects of CBD in 7 horses of different ages and sex in this application, where the administration of cannabidiol at a dose of 50 mg and 100 mg dramatically improved the behaviour associated with stress or anxiety.

In the matter of safety, CBD has been referred to as generally well-tolerated substance in horses (Collins et al. 2019; Davis 2019; Draeger et al. 2020).

Conclusion

It is clear from this brief review that research into CBD use in dogs or horses is, for the time, limited by the small number of animals or methodologies used, the results should be interpreted carefully and further research is required to obtain more robust data. This conclusion is also supported by other authors who dealt with the possible use of CBD in animals (Mercer and Davis 2021; Wessmann et al. 2021). The reports mentioned in this review, nevertheless, represent the first attempts for scientific documentation of CBD effects in veterinary medicine and their conclusions convincingly suggest the therapeutic potential of CBD for some animal species. A large advantage of CBD use is that preparations containing cannabidiol can be sold freely and, therefore, they could play an important role in the introduction of cannabinoid substances to veterinary medicine – at least as an interesting alternative or complementary medicine to conventional therapeutic approaches or as a supplement to them.

Conflict of interest

The authors declare no conflict of interest.

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