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Review Article

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APPLICATION OF CANNABIDIOL (CBD) IN THE PHARMACOTHERAPY OF DOGS AND CATS

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Abstract. Cannabinoids are a group of organic chemical compounds that affect the endocannabinoid system. The endocannabinoid system (ECS) is a biochemical system responsible for regulating many physiological and cognitive functions. It consists of endogenous cannabinoids, enzymes that regulate the biosynthesis and biodegradation of endogenous cannabinoids and cannabinoid receptors (CB1, CB2). It regulates cognitive processes in the central nervous system, as well as the functioning of the immune system and the proper course of the inflammatory reaction. There are three groups of cannabinoids: endocannabinoids, phytocannabinoids, and synthetic cannabinoids. Phytocannabinoids are obtained mainly for medical purposes from hemp inflorescences (*Cannabis sativa*). There are over 100 cannabinoids that have been isolated from *Cannabis sativa* tissues, the most well-known of which are: tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol, cannabigerol, tetrahydrocannabivarin, cannabidivarin, cannabichromene. The widespread use of phytocannabinoids in medicine is limited by the possibility of undesirable psychoactive side effects, mainly due to one compound – THC. Unlike THC, CBD is devoid of psychogenic properties, which significantly affects the safety of therapy and does not generate legal problems. Hemp inflorescence extracts are successfully used in the treatment of many diseases in humans, although the use of hemp preparations in veterinary medicine has been unknown for many years. However, they have found documented use in the treatment of degenerative joint diseases, epilepsy, and behavioral disorders. This work aims to systematize and summarize the available knowledge on the use of cannabidiol in the treatment of canine and feline diseases.

Key words: CBD, cannabinoids, endocannabinoid system, pharmacotherapy.

INTRODUCTION

Cannabis sativa is a species of plant belonging to the hemp botanical class, *Cannabaceae* family. It is characterized by excellent adaptability, thanks to which it is found on all continents, except Antarctica (Chandra et al. 2017). It is a short-day plant, and naturally begins flowering in late summer in response to the lengthening of the night (Zielonka et al. 2020). The cannabis

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plant has been known to mankind for millennia mainly as a source of fiber from aboveground shoots, food from achenes, or as a drug extracted from female plants (Brand and Zhao 2017). Domestication of the species has resulted in changes in morphology, chemotypes, distribution and ecology of cultivated forms compared to related wild plants (Zielonka et al. 2020). Its introduction into medicine occurred in the early 19th century. The species has been indicated for the treatment of glaucoma pain, nausea, depression, and neuralgia (McGrath et al. 2019). *Cannabis sativa* contains numerous biologically active compounds, representing different chemical classes. Some of them belong to the primary metabolites, such as amino acids, fatty acids and steroids, while stilbenoids, lignanamides, terpenoids, flavonoids and cannabinoids are the secondary metabolites (Russo 2011).

In botany, there are three subgenera of *Cannabis sativa* L.:

– *Cannabis sativa var. sativa* – seed hemp,
– *Cannabis sativa var. indica* – indica hemp,
– *Cannabis sativa var. ruderalis* – wild hemp.

Indica hemp has naturally increased tissue THC content compared to other cannabis varieties and is used as a stimulant/drug (e.g. marijuana) or as a medicine with analgesic effects. Seed hemp is a monoecious, typically fibrous hemp that contains less than 0.2% psychoactive substances (THC) (Wakshlag et al. 2020). Wild hemp is widespread in Central and Eastern Europe, usually grows naturally and has a lower THC content than indica and even seed hemp. In practice, the subgenus *Cannabis sativa var. sativa* (abbreviated as Sativa) and *Cannabis sativa var. indica* (abbreviated here as Indica) are used for medicinal products or as a raw material for making medicines (Chandra et al. 2017; De Briyne et al. 2021).

The first report of the medicinal use of cannabis for treatment (more specifically, for epilepsy) dates back to 2900 BC, yet it was not until 1839 that Irish physician William O'Shaughnessy described the medicinal properties of cannabis, most notably its ability to inhibit seizures, in a forty-page treatise (Della Rocca and Di Salvo 2020). Even then, he was already conducting research on the potential uses of hemp on animals. However, it was not until 1964 that Gaoni and Mechoulam described the structure of tetrahydrocannabinol (THC), the most important substance responsible for the psychoactive effects of cannabis extracts, or the "high" effect (De Briyne et al. 2021).

Cannabinoids are organic compounds with a specific chemical structure, characterized by their effects on the body's endocannabinoid system (ECS). The ECS is a biochemical system involved in the regulation of many biological processes, and thus significantly contributes to the maintenance of homeostasis. The ECS regulates such physiological processes as lipid and carbohydrate metabolism (by affecting the activity of adipocytes, hepatocytes, and the endocrine part of the pancreas), embryonic implantation, pre- and postnatal development, the proper work of the immune system, and the course of the inflammatory response. Importantly, it also determines normal cognitive and behavioral processes, exerting effects on memory, motivation, motor activity, hunger and satiety sensation and even pain sensation (Zielonka et al. 2020). The biological components of the ECS are endogenous cannabinoids (dominated by anandamide and 2-arachidonylglycerol), enzymes that regulate the biosynthesis and biodegradation of endogenous cannabinoids (phospholipases, NAPE-PLD, DAGL, FAAH, MAGL), and cannabinoid receptors: CB1 and CB2. Both are metabotropic receptors coupled to the Gi protein, so they are considered inhibitory receptors. As for where they are expressed in the body, the CB1 receptor is characteristic mainly of the nervous system, where it is found in both its central (cerebral cortex, limbic system, cerebellum, amygdala, spinal cord) and peripheral parts; while CB2 receptors are mainly coupled to the immune system – they are found in lymphoid organs (spleen, bone marrow, lymph nodes) and in many types of white blood cells. In addition to endocannabinoids, CB receptors and enzymes of the endocannabinoid system can be affected by exoge-

nous compounds: synthetic or isolated from plant tissues – these are called phytocannabinoids (Biernacki and Skrzydlewska 2016).

Phytocannabinoids are mainly found in the tissues of the cannabis plant *Cannabis sativa* (occasionally, a phytochemical affecting the ECS is also found in other plants). This is a group of more than 100 highly lipophilic terpenophenolic compounds, isolated from the approximately 400 compounds that make up this plant, found in large quantities especially in the resin (Chandra et al. 2017). However, they occur there in the form of pharmacologically inactive cannabinoid acids. Only their decarboxylation, usually by heating or lowering the pH, leads to their activation (Burstein 1999; Marcu 2016). Of these, only one compound, delta-9-tetrahydrocannabinol (Δ9THC), is characterized by psychoactive properties and for this reason is used recreationally, most often as an illicit drug (Russo 2011). All the rest of the phytocannabinoids lack this effect, despite their significant and generally beneficial effects on the body. Cannabidiol (CBD) is no exception – the cannabinoid found in the highest amounts in most cannabis varieties (Chandra et al. 2017). This compound, despite the fact that it probably has no affinity for cannabinoid receptors, has biochemical effects on other levels – it is, among others, an activator of voltage-gated calcium channels (TRPA1, TRPV1 and 2), a blocker of T-type calcium channels, an agonist of serotonin 5HT1a receptors, an inhibitor of lipoxygenases, a modulator of phospholipase A2, an inhibitor of anandamide reuptake (Biernacki and Skrzydlewska 2016). For this reason, it exerts a number of beneficial pharmacological effects that are not accompanied by the psychoactive effects characteristic of THC. Its beneficial effects on the body, which are almost devoid of any side effects, are often used in human medicine, where this compound has found application in the treatment of seizures and epilepsy, spasticity in the course of multiple sclerosis (MS), neuropathic pain, or even inflammation of various etiologies, among others (Russo 2011). Due to its strong lipophilicity, it is used in the form of oil solutions (so-called CBD oils) of various concentrations (some as high as 30%), applied most often sublingually. Epidiolex® is a 10% CBD oil, registered in the US for the treatment of certain childhood drug-resistant epilepsies. Its use in human medicine has been a subject of interest for several years and is still on an upward wave (De Briyne et al. 2021).

This paper aims to systematize and summarize the available knowledge on the use of cannabinoid oils in the treatment of canine and feline diseases. The authors wish to disseminate knowledge about cannabidiol preparations and clarify the possibilities of their application in the treatment of dogs and cats.

CBD FORMULATION IN VETERINARY MEDICINE

In humans, it is known that active substances administered by vaporization have the greatest bioavailability. It is difficult to imagine such a route of administration in animals, which, however, does not exclude the need for work on special inhalers, which are a modified versions of the ones used to administer, for example, anti-asthmatic drugs to cats. To date, studies have also been conducted on the possibility of using cannabis extracts via the transdermal route, although the number of such studies is so far insufficient to develop a standard method of administering cannabinoids by a route other than oral (Huestis 2007).

Until recently, veterinarians and owners of animals treated with CBD had to source oils intended for the “human” market, due to the fact that strictly veterinary oils were simply not available on the market. Recently, the situation has changed, and in addition to the multitude of isolates and extracts in various compositions intended for humans, oils for animals are also available. There are 3 types of oils divided according to their composition: isolates, containing CBD as the only substance dissolved in oil, most often hemp or MCT (coconut and sometimes – palm, containing medium-chain fatty acids). “Full spectrum” extracts contain a plant extract

that, in addition to CBD, contains smaller amounts of other cannabinoids (including THC), as well as a whole range of terpenoids, flavonoids, alkaloids, stilbenoids and lignanamides found in hemp tissues (Huestis 2007; Wakshlag et al. 2020). “Broad spectrum” extracts, on the other hand, differ from the previous ones in the absence of THC in their composition, and this type of preparation is the most favorable solution both pharmacologically and legally. This is due the fact of the so-called “entourage effect” observed in the 1990s – a synergistic effect between the action of cannabinoids and other phytochemicals present in cannabis (Wakshlag et al. 2020). This phenomenon determines a different effect of CBD after simultaneous administration of compounds accompanying it naturally in the plant, (mainly terpenoids and flavonoids) than after the same dose of pure CBD in isolate form. That is why “broad spectrum” preparations are considered to be the most effective; they also do not pose legal problems related to the presence of THC. There are important organoleptic differences between isolates and extracts – cannabinoids themselves are odorless and tasteless compounds, while terpenoids and flavonoids present in extracts contribute to their characteristic “hemp-like” taste and aroma, unlike isolates, which are neutral in this regard. Sometimes, unfortunately, this creates problems related to the reluctance of animals to take the oil, with some cats showing a particularly strong aversion (Wakshlag et al. 2020). Therefore, a rational solution would seem to be to enrich such a preparation with a compound that improves palatability, encouraging the cat to take a dose – such as valerian or catnip extract. Unfortunately, we probably do not have such preparations on the market. However, there are preparations enriched with the flavor of bacon, peanuts, or based on olive, salmon or cod oils, which are readily accepted by animals (cod-liver oil – a source of valuable unsaturated fatty acids, vitamins A and D). Depending on the composition of the “non-cannabinoid” component of the oil and the proportion of additives, manufacturers dedicate separate preparations to dogs and cats, although universal ones, simply designed for pets, are also popular.

It is suspected that there may be synergism (even hyperadditive) between CBD and the fatty acids in the oils (Russo 2011). This hypothesis, particularly with regard to the anti-inflammatory effects of CBD, is based on ample evidence that appropriate doses and proportions of polyunsaturated fatty acids (PUFAs) in the diet of dogs and cats can lower existing inflammation. Therefore, a CBD oil enriched with high amounts of PUFAs would be an interesting formulation, potentially qualifying it as a treatment for inflammation (Della Rocca and Di Salvo 2020; Karlik 2020).

To meet pets’ taste preferences, manufacturers also offer “CBD treats” – in the form of so-called “bites”, containing flavor-attractive blends of fats (sheep, salmon) and additives such as powdered spirulina or garlic. More recently, we can treat reluctant animals with encapsulated CBD oil, as well as in the form of lozenges (containing vitamins, protein, fiber and micronutrients in addition to CBD) (Morris et al. 2020). Such a lozenge can be given whole or crushed and added to a bowl of food. It is also possible to apply CBD in paste form, but those intended for humans generally come in doses too high for use in animals (sometimes above 50%) (McGrath et al. 2019). However, CBD pastes designed for the veterinary market have recently become available, with a much lower CBD content, and with a convenient graduated dispenser so that the correct dose can be applied.

The most typical concentration of CBD in veterinary preparations is between 2–5%. The most common doses used in veterinary medicine are in the range of 2–10 mg/kg. P.O. For example, in most publications, the commonly accepted therapeutic dose for the treatment of seizures in the dog is about 2.5 mg/kg b.w. p.o. every 12 h. The research was conducted on a group of dogs consisting of breeds such as: mixed-breed dogs, Golden Retrievers, Pug, Newfoundland, Wirehaired Pointing Griffon, Vizsla, Shetland Sheepdog, Australian Shepherd, Boxer, Dogo Argentino, and Labrador Retriever (McGrath et al. 2019).

CBD – PHARMACOKINETICS AND CLINICAL APPLICATION

Studies on the fate of cannabidiol in dogs (Table 1) show that the oral oil form has better availability than transdermal preparations (Mozaffari et al. 2021). However, CBD given via the oral route also undergoes many processes that reduce the efficiency of CBD extracts. Drugs containing CBD undergo the first-pass effect. That means, that after absorption in the large intestine, they go through the portal vein to the liver, where a significant percentage of the dose is metabolized, as a consequence, only a small amount of the medicinal substance reaches the general circulation, resulting in low bioavailability for tissues. However, due to its high lipophilicity, it is efficiently distributed and can accumulate in tissues with a high fat content. The effect of CBD is dose dependent. As we can see at a dose of 20 mg/kg, the plasma concentration of the drug is around 846 ng/kg. The maximum therapeutic effect occurs approximately 2 hours after administration. The half-life is 2 to 4 hours, so in order to maintain the effects of CBD, it must be administered several times a day (Child and Tallon 2022).

In most publications, the commonly accepted therapeutic dose of pure CBD isolate for the treatment of seizures in the dog is about 2.5 mg/kg every 12 h, while when using cannabis extract it is 2 mg/kg (McGrath et al. 2019). Some differences in the dosage amount of CBD alone or CBD administered in hemp extract may be related to the occurrence of entourage effect, and overall, it is not entirely clear whether CBD alone will be as effective as administering hemp extract standardized to CBD. In humans, CBD is recommended to be administered with food, or at least in the presence of fat, so perhaps the same recommendations should apply to dogs and cats.

Table 1. The most important pharmacokinetic parameters of cannabidiol (Gamble et al. 2018)

Parameter	Value
C_{max} – maximal concentration (single dose of CBD)	
dosage 2 mg/kg b.w.	102 ng/ml
dosage 8 mg/kg b.w.	591 ng/ml
dosage 10 mg/kg b.w.	625 ng/kg
dosage 20 mg/kg b.w.	846 ng/kg
T_{max} – time to reach C_{max}	
dosage 2 mg/kg b.w.	1,5 h
dosage 8 mg/kg b.w.	2 h
T1/2 – half-life in the body	2–4 h
Vd – volume of distribution after I.V. administration of 45 mg dosage	6,9–10,4 l/kg

In veterinary medicine, the use of CBD is still the subject of scientific research, and despite a number of clinical trials and the granting of numerous patents describing the use of CBD in the treatment of dogs and cats, so far no veterinary medicinal product using this substance has been registered. This does not change the fact that CBD is used supportively in the treatment of several disease entities. Currently, the scientific literature is dominated by reports on the efficacy of CBD primarily in the treatment of osteoarthritis, epilepsy, anxiety/aggression and pruritus in skin atopy, primarily in dogs (Kogan et al. 2019; Landa et al. 2021). These studies also indicate that CBD is well tolerated in dogs and cats and does not interact with phenobarbital.

In the treatment of osteoarthritis in dogs, CBD was used at a dose of 2 mg/kg every 12 h for 4 weeks in 16 dogs. The study found a decrease in pain and an increase in activity of the dogs, and no side effects of the therapy, but 9 of the 16 dogs had an increase in liver alkaline phosphatase activity (Brioschi et al. 2020).

In an experiment on the treatment of epilepsy, 12 dogs received CBD at a dose of 2.5 mg/kg every 12 hours for 12 weeks as an adjunct to anti-epileptic treatment. The study also included a placebo group (14 dogs) receiving only conventional antiepileptic drugs. In the CBD group, there was a 33% (median) decrease in the frequency of epileptic seizures, although the >50% decrease in epileptic activity was the same in both groups (McGrath et al. 2019).

CBD was also used as an adjunctive analgesic treatment in dogs with osteoarthritis. Patients received a dose of 2.5 mg of CBD every 12 h as an adjunct to anti-inflammatory therapy, gabapentin and amitriptyline. All pain indices assessed in this study were better in patients receiving CBD than in patients without CBD, and the quality-of-life index also improved. This would suggest that CBD may have beneficial effects for so-called multifactorial pain therapy in dogs (Brioschi et al. 2020).

However, the effectiveness of CBD as an anxiety-reducing agent in dogs could not be confirmed in clinical trials. The results of the study conducted did not show any anti-anxiety effect of this substance, although it is possible that this study used too low of a dose of CBD (1.4 mg/kg every 12 h). Somewhat contradictory to this clinical study is the fact that CBD is often used by pet owners to calm or lift anxiety tension, e.g. during travel or New Year's Eve, which is reported to provide very beneficial effects (Morris et al. 2020).

2,130 veterinarians participated in a survey on the effectiveness of CBD use in dogs in the US market. The results of this survey are very interesting, as they show that CBD is most often used to treat chronic pain (out of 1019 patients, CBD was very helpful in 34% of patients and somewhat helpful in another 57% of patients), anxiety (out of 883 patients, CBD was very helpful in 22% of patients and somewhat helpful in 65% of patients), acute pain (out of 708 patients, CBD was very helpful in 23% of patients and somewhat helpful in 60% of patients) and seizures (out of 612 patients, CBD was very helpful in 22% of patients and somewhat helpful in 56% of patients) (Kogan et al. 2019).

It cannot be ruled out that ongoing large-scale research on cannabis extracts will lead to recommendations for the use of a completely different cannabinoid, the effects of which may not have been fully understood to date. A candidate for such a substance, for example, is palmitoyl ethanolamide (PEA), which is an analog of the endocannabinoid anandamide. It is already known that PEA is produced during inflammation and when tissues are damaged. It increases the release of anandamide from various inflammatory cells, and studies show promise for its use in the treatment of pain, inflammation and pruritus associated with eosinophilic syndrome in cats, as well as in mast cell-related disorders and skin diseases in dogs.

SIDE EFFECTS AND RISK OF CBD INTOXICATION

According to published studies on CBD toxicity in dogs, long-term CBD administration resulted only in an increase in blood alkaline phosphatase levels (twofold, relative to reference values). The use of a dose of 10 mg/kg b.w. P.O., however, poses a risk of adverse neurological symptoms, so lower doses tend to be recommended (Brioschi et al. 2020). The most frequently notified adverse effect was sedation (Kogan et al. 2019). Severe psychosomatic symptoms occurred primarily when CBD was administered in combination with THC and were similar to marijuana intoxication. They usually took the form of lethargy and central nervous system depression, unsteadiness and excessive agitation (Kogan et al. 2019; Della Rocca and Di Salvo 2020; Mejia et al. 2021).

Most studies published to date on the use of CBD in dogs and cats under controlled clinical conditions have found no signs of intoxication. In pharmacokinetic studies, CBD used in doses up to 4.5 mg/kg, i.p. did not cause any adverse effects on the behavior of dogs (signs of intoxication or appearance of psychotic symptoms). However, it is known that at a dose of 10 mg/kg, there is a higher risk of adverse neurological symptoms.

Furthermore, quite often, an increase in plasma alkaline phosphatase (ALP) levels has been described, which may be due to the stimulation of microsomal enzyme activity in the liver by CBD. Dogs receiving CBD showed an increase in alkaline phosphatase activity, while 2 dogs from the study group appeared to be non-compliant (McGrath et al. 2019).

The survey of US veterinarians' use of CBD described above found that the most common side effect of this therapy was patient sedation (51.2% of cases). Other side effects were far less common and included increased appetite (17%), increased anxiety (12.8%), bradycardia (11.9%), as well as vomiting, anorexia, diarrhea and increased thirst (less than 10%) (Kogan et al. 2019).

CONCLUSIONS

Cannabidiol (CBD) as a drug or a potential active ingredient in the nutrition of dogs and cats became the subject of great interest in global markets a dozen years ago, and this interest, combined with the increase in the number of hemp crops, also found its way to Europe. As a result, a lot of interest by potential producers and users of CBD-containing preparations has been evident in Europe for several years, but this has not translated into their registration in dog and cat nutrition. However, perhaps in the near future the potential interest in the use of CBD for the treatment of certain diseases (pain therapy, epilepsy etc.) or behavior modification in dogs and cats will lead to the registration of this substance as a veterinary medicinal product – in a specific dose and for a specific indication. Nowadays, the predominant reports in the scientific literature are that CBD is effective primarily in the treatment of osteoarthritis, epilepsy, anxiety/aggression, and pruritus in skin atopy, mainly in dogs.

Regardless of the many unknowns, there is no doubt that hemp can be a source of many active substances with therapeutic effects for dogs and cats, although further laboratory and clinical studies are needed to standardize their use in practice.

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ZASTOSOWANIE KANNABIDIOLU (CBD) W FARMAKOTERAPII PSÓW I KOTÓW

Streszczenie. Kannabinoidy to grupa organicznych związków chemicznych wpływających na układ endokannabinoidowy (ECS), który jest układem biochemicznym odpowiedzialnym za regulację wielu funkcji fizjologicznych i poznawczych. Składa się z endogennych kannabinoidów, enzymów regulujących biosyntezę i biodegradację endogennych kannabinoidów oraz receptorów kannabinoidowych (CB_1, CB_2). Reguluje procesy poznawcze w ośrodkowym układzie nerwowym, a także funkcjonowanie układu odpornościowego i właściwy przebieg reakcji zapalnej. Wyróżniamy trzy grupy kannabinoidów: endokannabinoidy, fitokannabinoidy i kannabinoidy syntetyczne. Fitokannabinoidy pozyskuje się głównie do celów medycznych z kwiatostanów konopi siewnej (*Cannabis sativa*). Do kannabinoidów pozyskiwanych z tkanek *Cannabis sativa* należy ponad 100 związków chemicznych, a do najlepiej poznanych należą: tetrahydrokannabinol (THC), kannabidiol (CBD), kannabinol, kannabigerol, tetrahydrokannabiwarin, kannabidiwarin, kannabichromen. Powszechne stosowanie fitokanabinoidów w medycynie ograniczone jest przez możliwość wystąpienia niepożądanego efektu psychoaktywnego, za który odpowiada głównie jeden związek, THC. W przeciwieństwie do THC, CBD jest pozbawiony właściwości psychogennych, co znacząco wpływa na bezpieczeństwo terapii i nie generuje problemów natury prawnej. Wyciągi z kwiatostanów konopi siewnych są z powodzeniem wykorzystywane w leczeniu wielu chorób u ludzi, natomiast zastosowanie preparatów konopnych w weterynarii od wielu lat było nieznane. Znalazły one jednak udokumentowane zastosowanie w leczeniu chorób zwyrodnieniowych stawów, epilepsji czy zaburzeń behawioralnych. Praca ma na celu usystematyzowanie oraz podsumowanie dostępnej wiedzy na temat stosowania kannabidiolu w leczeniu chorób psów i kotów.

Słowa kluczowe: CBD, kannabinoidy, układ endokannabinoidowy, farmakoterapia.