

HEMP – ITS USE IN PREVENTION AND TREATMENT OF DISEASES OF COMPANION ANIMALS

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ABSTRACT

Hemp (*Cannabis sativa* L. subsp. *sativa*) is a rich source of cannabidiol (CBD) and tetrahydrocannabinol (THC). In this plant predominant is CBD, which is devoid of psychogenic properties. Hemp has quite a wide range of uses, ranging from cosmetology to the food and pet-food industries. CBD has many pharmacological effects, including antipsychotic, anxiolytic, sedative, antiepileptic, anti-inflammatory, analgesic, antiemetic, antidiabetic and anti-ischemic effects. All these effects can be convincingly explained by the observations regarding the mechanism of action of CBD. However, it is not known in what dose hemp would cause the above-mentioned effects. Although CBD oil may have therapeutic potential, the scientific evidence supporting its use in animals is currently limited, and there are few well-controlled studies, most of which focus on companion animals.

Key words: animals, cannabidiol, *Cannabis sativa* L. subsp. *sativa*, diseases, pharmacological effects

INTRODUCTION

Currently, there is more and more information about *Cannabis* and its chemical composition. There are many results from studies not only on humans and laboratory animals, but also the number of studies on the use of cannabinoids in dogs is constantly increasing. The family Cannabaceae, the genus *Cannabis*, the species *Cannabis sativa* L., including two subspecies: *C. sativa* subsp. *sativa* and *C. sativa* subsp. *indica* (the vernacular taxonomy of ‘sativa’ and ‘indica’ respectively) [McPartland 2018].

Cannabis sativa L. is a species cultivated for a very long time because of its three main characteristics [Andre et al. 2016]:

1. the presence of fibers that can be used in the textile industry or for non-textile purposes (in the automotive, construction, composite, etc. industries), which are also used by the paper industry,
2. presence of oil in seeds,
3. the presence of hallucinogenic substances.

Cannabis sativa L., is a dioecious plant whose both male and female produce a resinous substance that contains cannabinoids. Within the species, there are vari-

ous taxa in the rank of subspecies or varieties, cultivated or growing wild in different climatic zones. The best known are *Cannabis* and fibrous (common) hemp. Hemp (*Cannabis sativa* subsp. *sativa*) was known already in antiquity [Rupasinghe et al. 2020].

Hemp (Fig. 1), or *Cannabis* (Fig. 2), is an annual cycle angiosperm plant, belonging to the Cannabaceae family. The terms ‘hemp’ and ‘*Cannabis*’ are synonymous, but usually hemp refers to the plant as a vegetable, textile fiber, or raw material for construction or in the gastronomic field; the term *Cannabis* is preferred instead when it is intended to emphasize its therapeutic or psychoactive connotation. From a botanical point of view, however, the plant is the same: *Cannabis sativa* L. (*sativa* = “useful”), with all its subspecies and varieties [Pollio 2016, Della Rocca and Di Salvo 2020].

There are many research results not only in humans and laboratory animals, but the number of studies on the use of cannabinoids in dogs is also steadily increasing. Hemp is a rich source of cannabidiol (CBD) and tetrahydrocannabinol (THC). However, many people wonder about the legality, safety, and effectiveness of *Cannabis* products in treating animal diseases. Therefore, this review analyzes the latest scientific findings on the nutri-

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tional composition of Cannabis, together with the results of research on the nutritional implications also for animal diseases.



Fig. 1. Hemp/'Sativa' (*Cannabis sativa* subsp. *sativa*) [Anderson 1980]



Fig. 2. Hemp/'Indica' (*Cannabis sativa* subsp. *indica*) [Anderson 1980]

HISTORICAL OVERVIEW

The interest in hemp is not a new phenomenon. Humans have been cultivating both Cannabis and hemp for more than 5000 years for a variety of uses, including, paper, fiber, clothing, and medicine. Hemp has been valued for a long time for its use in industry and ancient medicine practices. The therapeutic applications of the medicinal compounds produced by this plant have received increased attention in conventional medicine over recent years [Hazzah et al. 2020]. The human Cannabis market (both hemp and marijuana) has experienced dramatic growth, and projections estimate the industry will continue this impressive expansion, from roughly \$12.581 billion in 2018 to a projected market of \$36.903 billion by 2024 [Wood 2019].

The current legal landscape allows products that have been formulated from the hemp subtype to be easily obtained by animal caregivers through over-the-counter purchases, such as from retail outlets and online marketplaces.

Hemp is a rich source of CBD and tetrahydrocannabinol (THC). In this plant predominant is CBD, which is devoid of psychogenic properties [Żuk-Gołaszewska and Gołaszewski 2018, Elsohly and Slade 2005]. Hemp contains also hundreds of different active compounds and of these, more than 100 are cannabinoids which, depending on the compound, have either psychoactive or non-psychoactive effects. CBD is a non-psychoactive lipid cannabinoid. CBD has been used in human medicine to mitigate anxiety, improve appetite, relieve nausea, control seizures of certain types, and assist in the management of sleep disorders [Crippa et al. 2009, Abuhasira et al. 2018, Stockings et al. 2018]. A variety of CBD products are available throughout Europe for human and animal use [De Briyne et al. 2021].

The first mention of Cannabis' effects on dogs' dates back to the 19th century. While in India, an Irish physician noticed the widespread use of Cannabis in many ailments, although he was unable to find any record of the drug being used in Europe. From his observations, he concluded that there is sufficient evidence that Cannabis has, in small doses, remarkable power to stimulate the digestive organs as well as stimulate the brain. The drug's effect on pain relief was also apparent. Inspired by these observations, the doctor initiated his own animal research by giving the dog "majoon", an Arabic Cannabis candy, and reporting that the dog ate it with great pleasure and began to appear drunk. Similarly, another dog was given "churrus", a Nepalese Cannabis resin, and the aforementioned doctor reported that the dog became drowsy, napping at intervals, moving, wagging his tail as if he was very pleased, staggering back and forth, and his face assumed an expression of helpless drunkenness. In all cases, the animals recovered and after a few hours their behavior returned to normal [De Briyne et al. 2021].

LEGAL REGULATIONS

The use of hemp in animal nutrition is legal. At the request of the European Commission, the Panel on Additives and Products or Substances for Use in Animal Feed (FEEDAP EFSA) issued a scientific opinion on the safety of *Cannabis* genus for use as animal feed [EFSA 2011]. Different types of feed materials can come from hemp: hemp seed meal, hemp seed oil, and the whole hemp plant (including hemp husks, fresh or dried). The next products are hemp flour (ground dried hemp leaves) and hemp protein isolate from seeds. Hemp seeds and hemp cake can be used as feed materials for all animal species and EFSA's maximum incorporation rates into complete feed by species. Interestingly, research into the effectiveness of nutrition also shows that hemp and its derivatives can be included in the diet of livestock as a good source of crude protein and essential fats [Klir et al. 2019].

There are currently many companies on the EU market selling hemp-derived “nutritional supplements” for companion animals, some of which clearly appear to be therapeutic feed claims. It is against the law to make claims about therapeutic feeds on nutritional products. According to EU Regulations, products for which therapeutic claims are made must first be approved by the National Health Products Agency or EMA in order to become a drug and be legally manufactured and marketed. This provides scientific data on the effectiveness and safety of the products. Veterinarians cannot provide scientific advice on the effectiveness of a nutritional product in treating disease because it is not a drug and such claims are illegal, unproven and potentially dangerous.

In Poland, the variety of Cannabis is prohibited, with the exception of the cultivation of *Cannabis sativa* subsp. *sativa*, it should not be confused with the widely known drug medicinal Cannabis [Journal of Laws 2017]. In addition, in hemp the sum of THC content – one of the two most important active substances whose concentration determines the narcotic power of Cannabis – does not exceed 0.2% of dry matter. Hemp with THC content above this value is Cannabis. When used as stimulants, they can contain up to 20–30% THC [Journal of Laws 2017].

TESTS FOR A SAFE AND EFFECTIVE DOSE

Due to changes in legislation, the use of CBD is becoming more and more popular in both human and veterinary medicine [Kogan et al. 2017]. However, research into the long-term use of CBD is still needed. The use of hemp-based cannabidiol (CBD) rich nutraceuticals is increasing in dogs and cats for disorders related to anxiety, seizures, cancer and pain. To date, little information is available regarding appropriate dosing or long-term effects on serum composition or complete blood count. There is little data on the pharmacokinetics of single or long-term dosing in dogs and cats.

A study of [Deabold et al. 2019] showed that cats exhibit significantly lower CBD absorption kinetics after oral administration or a rapid elimination, suggesting that dosing may vary between dogs and cats. The same studies showed that there were no changes in the physical examination and few changes in blood parameters and serum chemistry, suggesting the relative safety of oral supplementation with CBD over 12 weeks. One out of eight cats showed a sustained increase in serum levels of the enzyme alanine aminotransferase (ALT) beyond the reference range, and the cats often exhibited excessive licking and head shaking following administration of the oil. Based on these and other recent data, CBD-rich hemp nutraceuticals appear to be safe for healthy adult dogs, while cats need more work to fully understand usefulness and absorption.

Due to many doubts about the optimal dose of CBD, which would have beneficial therapeutic effects, more and more research in this area is currently carried out. For example, a study of [Gamble et al. 2018] osteoarthritis using hemp extract showed that CBD was beneficial for dogs given a dose of $2 \text{ mg} \cdot \text{kg}^{-1}$ body weight (BW). In addition, a dog seizure study showed efficacy with $2.5 \text{ mg} \cdot \text{kg}^{-1}$ BW, the effective serum concentrations were $200\text{--}800 \text{ ng} \cdot \text{ml}^{-1}$. However, no optimal delivery methods have been identified. More work is needed to better understand how food affects CBD absorption and pharmacokinetics. Scientists have concluded that hemp-based CBD appears to be safe in healthy dogs and cats. However, side effects were seen in both cats and dogs, including mild clinical signs, moderate elevations in liver enzymes and mild variations in blood counts. However, the study was uncontrolled, and it is unclear if these effects are due to delivery agents compared to CBD. Moreover, the study was small and limited in scope and duration. Further insight can be obtained by testing CBD in a wider population and considering animals of different ages and with a variety of diseases. Researchers also suggest that further safety and efficacy studies in animals are warranted [Gamble et al. 2018].

Other studies regarding the selection of the appropriate dosage of CBD for dogs have been conducted by [Vaughn et al. 2021]. In a randomized, blinded, placebo-controlled study, dogs were randomly assigned to weight and gender balanced groups and received a CBD extract of 1, 2, 4, or $12 \text{ mg} \cdot \text{kg}^{-1}$ BW or a placebo oil formulation once daily for 28 days. Outcome variables were assessed through daily health observations, veterinary examinations, blood counts, and serum chemistry analysis.

Repeated administration of CBD was shown to be well tolerated in dogs, with no clinically significant changes in measured safety scores. Veterinary investigations did not reveal any clinically significant abnormalities. Adverse events were mild in severity. Compared to the administration of the placebo preparation, administration of CBD at a dose of $12 \text{ mg} \cdot \text{kg}^{-1}$ BW resulted in a greater number of side effects, mainly manifested by excessive salivation and a much higher activity of serum alkaline phosphatase. Total systemic exposure to CBD increased dependent on the dose. Repeated daily oral administration of CBD resulted in a dose-dependent increase in total systemic exposure to CBD and a 24-hour trough plasma concentration in healthy dogs. Choosing the right dose still requires appropriate research to help identify the optimal amount of CBD necessary to achieve the desired effects [Vaughn et al. 2021].

PAIN AND OSTEOARTHRITIS

Today, more and more people are using Cannabis preparations to treat chronic pain in themselves or their dogs.

The results of study [Wallace et al. 2020] suggest that people choose Cannabis products because they are natural and are a possible solution to dealing with chronic pain when conventional medications are not always effective. Most people report that these products meet their pain relief expectations. However, more careful assessments are necessary to understand both the objective biomedical and the subjective socio-emotional benefits of Cannabis products to effectively treat pain in patients and dogs. In addition, objective facts about Cannabis products are needed to effectively treat pain in humans and dogs. It is recommended that both doctors and veterinarians work towards feeling more comfortable by proactively raising the topic of Cannabis use through additional training and education [Wallace et al. 2020].

The search for alternative painkillers is necessary, for example in the case of osteoarthritis. This is because routine treatment with non-steroidal anti-inflammatory drugs, while effective, may not provide adequate pain relief from osteoarthritis (OA) and may have potential side effects that preclude its use, especially in geriatric patients with certain comorbidities, such as kidney or gastrointestinal disorders.

Studies by Gamble et al. [2018] showed that the terminal half-life of oral CBD was 4 to 5 hours, suggesting that it was bioavailable with a dosing regimen of at least $2 \text{ mg} \cdot \text{kg}^{-1} \text{ BW}$ twice daily [Gamble et al. 2018]. After an initial finding of no neurological effects at the dose of $2 \text{ mg} \cdot \text{kg}^{-1} \text{ BW}$, the dose administered was increased to $8 \text{ mg} \cdot \text{kg}^{-1} \text{ BW}$ to evaluate the potential neurological effects. It has been shown that absorption may be greater and more consistent due to the oil-based vehicle, which may be due to the lipophilic nature of CBD, so food delivery may be preferable [Samara et al. 1988]. Dogs with osteoarthritis receiving a high-CBD hemp extract ($2 \text{ mg} \cdot \text{kg}^{-1} \text{ BW}$) have been shown to be perceived as relaxed and more active, which may be indicative of pain relief. No side effects appeared to be observed in the dogs participating in the pharmacokinetic study at doses of 2 and $8 \text{ mg} \cdot \text{kg}^{-1} \text{ BW}$, or in dogs treated with OA for one month. However, there have been a few cases of increases in alkaline phosphatase that could be related to treatment [Gamble et al. 2018].

CANCER

CBD has been tested for its direct anti-cancer properties alone and in combination with standard cancer treatments, yielding encouraging results [Henry et al. 2020]. Studies investigating the antiproliferative and cell death responses associated with in vitro treatment of a canine cancer cell line with CBD alone and in combination with conventional chemotherapeutic agents, and exploring major proliferative pathways potentially involved in response to CBD treatment. CBD has been shown

to significantly reduce cancer cell proliferation in dogs. Overall, CBD is effective in inhibiting cell proliferation and rapidly inducing autophagy and apoptosis in cancer cell lines, and more clinical research is needed to understand its effectiveness and interactions with traditional chemotherapy [Henry et al. 2020].

SKIN DISEASES

The therapeutic potential of *C. sativa* subsp. *sativa* extracts and related cannabinoids can be used successfully in a variety of widespread skin diseases including acne, atopic dermatitis, psoriasis, pruritus and pain. Cannabinoids exhibit potential anti-inflammatory, antioxidant, anti-aging and anti-acne effects through various mechanisms. CBD has photoprotective, antioxidant and anti-inflammatory effects at the skin level. Animal models and pilot clinical trials have supported the use of cannabidiol in inflammatory skin conditions. One of the most promising uses of CBD is for treating seborrheic disorders [Martinelli et al. 2021].

ANTIMICROBIAL EFFECT

It has been shown that essential oils extracted from *C. sativa* subsp. *sativa* fibers exhibit antimicrobial activity, and the degree of this effect depends on the variety [Novak et al. 2001]. *C. sativa* has been reported to have antibacterial activity [Leizer et al. 2000]. CBD has been identified as a component of hemp oil effective against gram-positive bacteria and yeasts. In studies [Ali et al. 2012] *Cannabis sativa* subsp. *sativa* seed oil has been tested for its antimicrobial activity. CBD oil showed marked antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*, moderate activity against *Escherichia coli* and high against *Pseudomonas aeruginosa*. This may be an interesting discovery, useful in therapy with standard antibiotics against a given microorganism [Ali et al. 2012].

EPILEPSY

Recently, a frequently discussed topic is the introduction of CBD could help alleviate the symptoms of epilepsy in dogs and reduce the frequency of seizures. The studies of [Morrow and Belshaw 2020] compared the mean monthly seizure frequency in the 16-week pre-study period with the 12-week study duration, with response to treatment defined as at least a 50% reduction in the mean number of seizures per month. Serum biochemical analysis was also performed and serum concentrations of the anti-epileptic drug and CBD were measured at the start of the study and then four, eight and 12 weeks later. Eight out of nine dogs treated with CBD was shown to show a reduction in the mean monthly seizure frequency

compared to 16 weeks prior to treatment. There were no significant drug-related adverse events or behavioral changes [Morrow and Belshaw 2020].

BEHAVIOR

CBD interacts with the body through the endocannabinoid system (ECS). In animals, this system is a biological system that interacts with both endogenous cannabinoids and exogenous plant molecules mainly derived from hemp. In mammals, the ECS is very complex and modulates a variety of body responses [Silver 2019]. Through two main receptors, it is involved in the anti-inflammatory process, in managing anxiety, in immune functions and in reducing pain [Khasabova et al. 2008, Gray et al. 2015]. This system is also involved in maintaining the homeostasis of various organs and in modulating the nervous and immune systems.

Stress is a mental, physiological or emotional state characterized by a factor that changes the homeostasis of the living organism. In mammals, the response to a stressor, which may be physical or emotional, such as infection or anger, involves reactivity of the hypothalamic-pituitary-adrenal axis, resulting in an increase in circulating glucocorticoids, which may result in stress-related disorders [Costantini et al. 2012]. That is why, when necessary, it is so important to use measures that can relieve stress. The aim of study by [Corsetti et al. 2021] was to determine whether CBD influences stress-related behavior in shelter dogs. Dogs given CBD oil showed reduced aggressive behavior towards humans. Other behaviors indicative of stress, such as displacing activities and stereotypes, did not decrease. Despite some insignificant results, these findings suggest that more research is worth doing to further investigate the effects of CBD on dog behavior. This would certainly be valuable as the potential to improve dog welfare in shelters is invaluable.

SIDE EFFECTS

In some cases, the use of CBD may have negative effects. An example is the behavior of dogs. Exposure to Cannabis, synthetics, and CBD oil has been shown to increase arousal and irritable aggression [Brutlag and Hommerding 2018]. The use of these products can also sometimes reduce the effectiveness of your training. Dog trainers with customers using CBD oils reported that dogs exhibit dry mouth and drowsiness, which are known side effects of CBD that can interfere with training and behavior modification work [Means and Wismer 2018, Prinold 2019]. Another example is the case of a dog showing signs of exfoliation and rapidly progressive ulceration of the skin and mucous membranes within five days of oral administration of CBD oil. Histopathological findings combined with skin manifestations were consistent

with Stevens-Johnson syndrome. All changes completely resolved upon discontinuation of hemp oil in combination with cephalexin and prednisone therapy [Simpson et al. 2020].

CONCLUSION

CBD products for pets are non-intoxicating and can be very favorable for dog's health. There are many scientific publications on the importance of Cannabis in veterinary medicine. The literature review presented in this article indicates that the most promising effects of CBD are obtained mainly in the prevention and supportive treatment of pain, osteoarthritis, cancer, and skin diseases. CBD also has a beneficial antimicrobial effect and relieves anxiety and stress. When choosing hemp supplements for pets, it is essential to know the amount of CBD and the purity of THC. Dosage calculation must be very accurate to ensure safety and efficacy in consultation with your veterinarian. Given the current state of knowledge, it is necessary to continue research both in terms of the effective action of CBD and in combination with other biologically active compounds obtained from Cannabis.

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KONOPIE – ZASTOSOWANIE W ZAPOBIEGANIU I LECZENIU CHOROÓB ZWIERZĄT TOWARZYSZĄCYCH

STRESZCZENIE

Konopie (*Cannabis sativa* L. subsp. *sativa*) stanowią bogate źródło kannabidiolu (CBD) i tetrahydrokannabinolu (THC). W tej roślinie dominuje CBD, który pozbawiony jest właściwości psychogennej. Konopie mają dość szeroki zakres zastosowań, od kosmetologii po przemysł spożywczy i karmę dla zwierząt. CBD ma wiele efektów farmakologicznych, w tym działanie przeciwpsychotyczne, przeciwłękowe, uspokajające, przeciwpadaczkowe, przeciwzapalne, przeciwbólowe, przeciwwymiotne, przeciwcukrzycowe i przeciwniedokrwienne. Wszystkie te efekty można przekonująco wytłumaczyć obserwacjami dotyczącymi mechanizmu działania CBD. Nie wiadomo jednak, w jakiej dawce konopie mogą wywołać wyżej wymienione efekty. Chociaż olej CBD może mieć potencjał terapeutyczny, dowody naukowe potwierdzające jego stosowanie u zwierząt są obecnie ograniczone i istnieje kilka dobrze kontrolowanych badań, z których większość koncentruje się na zwierzętach towarzyszących.

Słowa kluczowe: *Cannabis sativa* L. subsp. *sativa*, choroby, działanie farmakologiczne, kannabidiol, zwierzęta

