Chapter 25

Perspectives on the Deworming Effect of *Cannabis sativa* in Companion and Production Animals

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ABSTRACT

Parasitic diseases are considered the most prevalent and important health problems in companion and production animals, causing zoonotic problems, a high mortality rate, feed efficiency rate and costs incurred for their treatment and control. Therefore, the use of different deworming drugs in the veterinary field is common. In previous works, it has been indicated that an effective anthelmintic drug should have a good range of action to achieve a high cure rate with a minimum dose, in addition to not presenting toxicity to the host and being economical. However, the treatment of parasitic diseases is complex because of current drug resistance. Currently, different studies have been carried out using alternative treatments, such as the use of plants that have medicinal properties. In this way, medicine based on herbal medicines could become a precursor in the conversion of local knowledge into global knowledge, using medicinal plants with a factor of sustainable development in people and animals from various parts of the world. Some plants have healing properties. They naturally synthesize and accumulate some molecules such as alkaloids, volatile oils, vitamins, and minerals in some regions of the leaves, fruits, seeds, and rhizomes. This situation can be useful for improving clinical treatments. The medicinal properties of plants have been applied in treatments for parasitic infections in humans and various animal species. A range of plants have been reported in the literature for their anthelmintic importance. Several studies present results aimed at showing that certain plant species have nutritional value, but also show results related to the reduction of parasitosis in some animals. Therefore, this chapter discusses some perspectives of the medicinal effect and dewormer of *Cannabis sativa* in animals, as an alternative for resistance to dewormers in animals.

KEYWORDS
Cannabinoids, Deworming, Medicinal, CBD, THC

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INTRODUCTION

Cannabis belongs to the (*Cannabaceae* family), this family brings together different species, these plants occur annually, they can be female or male with distinctive leaves with fingers that show serrations and unisexual flowers. *C. sativa* is the only specie identified of (*Cannabis sativa* L, 2019), on the other hand, the definition of hemp is usually used for *C. sativa* cultivars that are grown with other fines such as industrial or pharmacological fines, but the Marijuana is related to crops whose purpose is the pharmacological preparation associated with medicinal or recreational uses (Johnson, 2019). Cannabis is composed of >500 substances, made up of 120 terpenes and sesquiterpenes and >110 (phyto) cannabinoids, within these are shown; The classic cannabinoids are Cannabidiol (CBD, CBN) and tetrahydrocannabinoid (THC). that have been given importance in their pharmacological use (Russo, 2011), for example, Synthetic or plant-based THC (△9-THC) and other cannabinoids are used for the treatment of some clinical signs such as nausea, spasticity, neuropathic pain, epilepsy, glaucoma, multiple sclerosis, and eating disorders associated with cancer treatments (Allan et al., 2008; Alexander, 2016).

Some studies indicate the deworming effect that this plant may have, however, its effect in its entirety has not been fully explored. The high prevalence reports of groups of helminth parasites that present resistance to anthelmintics, the residual drug products in animal products and the high cost of anthelmintics available on the market have made studies focus their attention on research on medicinal plants. As an alternative to the unwanted effects of anthelmintics. Therefore, the objective of this chapter is to analyze some perspectives on the medicinal and deworming effect of *Cannabis sativa* in animals, as a response to the problem of resistance to dewormers in animals.

Chemical Composition of *Cannabis sativa*

This finding led to the review of endogenous coordinators that activated them, called endocannabinoids. Currently, the definition of cannabinoids includes phytocannabinoids, endocannabinoids and synthetic analogues. An example of the different components of each group is presented in Fig. 1.

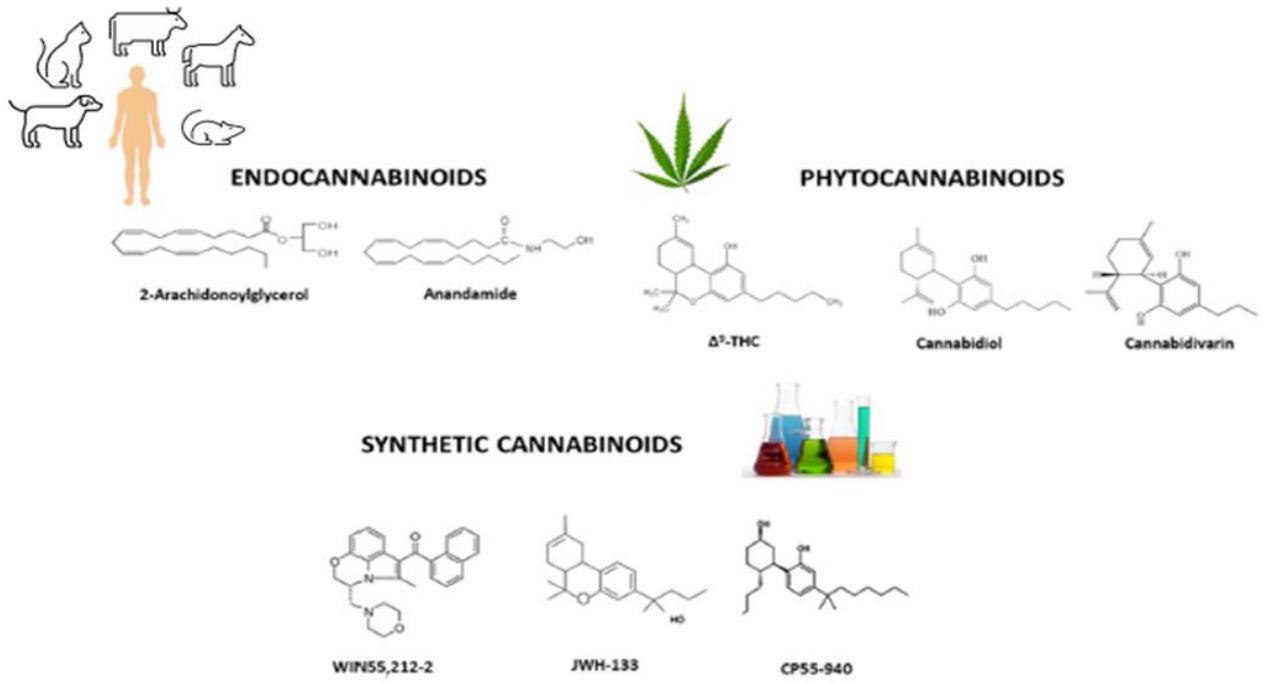

Fig. 1: Representation of the compounds of the main molecules present in THC, tetrahydrocannabinol, endo, phytocannabinoids and synthetic cannabinoids.

General use of Cannabinoids in Animals

Cannabidiols (CBD) have increased in popularity because of legalization in some of US States and other countries and are now recommended by human and veterinary doctors. Despite this, there are still concerns about the legislation, toxicity and benefits of CBD in veterinary patients because clinical experiments are scarce. When an online questionnaire was conducted in the United States, the results reported that almost 60% of pet owners included CBD in their treatments for dogs, and 12% in their cats, as a management for osteoarthritis, seizures, cancer or anxiety. (Kogan et al., 2016). Of the total sample, 64% found benefits for pain threshold management. 50% of owners reported that it helped their pets rest better, 49% that it reduced anxiety, and 30% that it reduced seizures in their pets. Therefore, it can be concluded that pet owners choose cannabis products for their pets because they are natural and generally perceive them as a maintenance therapy for pain management (Wallace et al., 2020). Some studies for the general use of cannabinoids in animals have confirmed the evidence of their functioning and effectiveness; in general, these compounds have been used in dogs, cats, horses, mice, non-human primates, and bovines. Below are the most common applications in veterinary medicine:

Pain Management

Various studies indicate that this plant has a system with physiological functions, including an analgesic action (Walker et al., 2002). This conclusion is based on preclinical trials that documented the presence of receptors for these substances, as well as the enzymes necessary for the synthesis and degradation of endocannabinoids in peripheral and central structures related to pain control. These studies also demonstrated the antinociceptive and antihyperalgesic effects of endocannabinoids in various models of transient (physiological), inflammatory and neuropathic pain (Iversen et al., 2002).

Epilepsy

Currently, there has emerged an appreciable approach towards phytocannabinoids developed for the treatment of some

neurological disorders, such as the specific case of epilepsy (Leo et al., 2016). The recent conclusions available to date allow us to propose the hypothesis that the endocannabinoid system (ECS) is of importance for the regulation of the activities of the nervous system in areas directly or indirectly damaged in patients with this disease. These experiments are supported by several investigations with a description of electrophysiological, biochemical and pharmacological brain anatomy (Capasso, 2017).

Behavioral Disorders

Several studies have highlighted the effectiveness of CBD as a therapy for some behavioral disorders in dogs (Morris et al., 2020; Corsetti et al., 2021). Additionally, it is important to consider veterinary data documenting the potential application of CBD as an effective complementary treatment for anxiety. A notable example is a study with a nine-year-old pug dog who had a history of anxiety and aggression (reactivity when seeing other dogs) since the age of two. After administering three doses of CBD (5mg twice daily with food) as part of an alternative therapy, reactivity decreased by up to 50%. Subsequently, the patient continued to show significant improvement with continued use of the cannabinoid (Krause, 2019).

Skin Diseases

CB1 and CB2 receptors are expressed in canine keratinocytes, showing greater immunoreactivity in dogs with allergy problems compared to healthy dogs (Chiocchetti et al., 2022). Furthermore, these canine skin cells express TRPV1 receptors (Barbero et al., 2018). Published studies have provided information on how cannabinoids can be used to control pruritus, using ALIAmides such as Adelmidrol®, a compound that may be beneficial for this condition. Cannabinoid receptor agonists, such as PEA, have been shown to attenuate inflammation in the skin of mice in a model of allergic contact dermatitis (Petrosino et al., 2018) and reduce skin lesions and pruritus in atopic dogs (Noli et al., 2015). In addition, great interest has been paid to the use of this plant because of its potential deworming effect on animals.

Perspectives on the Deworming Effect of *Cannabis sativa* in Animals

Promoting the benefits of medicinal cannabis in veterinary practice is important since it is a plant with scientific support regarding its use in problems such as resistance to deworming drugs worldwide. However, the usefulness of the medicinal plant for veterinary use is not common in many countries due to legal regulation; But CBD can be feasible and has become a widely used compound in the veterinary clinic; Everyday, there is more data available on the beneficial effects of cannabinoids in animals, because these substances intended mainly for administration in humans are tested for the first time in animal models (Landa et al., 2016). Therefore, in this section, the major results will be described regarding the deworming effect of *Cannabis Sativa* in the work carried out on humans and animals. At the end of the 1990s and during the period 2000-2010, the sequencing of complete human, animal and parasite genomes was carried out, which made it possible to identify new drugs to counteract pathogens. In addition to vertebrates, the order *Chordata*, such as the *Ascidian Ciona* intestinalis and the *Lancelet Bramchiostoma floridae*, have been reported to have binding mechanisms for these substances (Elphick, 2007). In addition, results are emerging on the effect of extracts on protozoa, helminths and even ectoparasites such as fleas and ticks (Anday and Mercier, 2005).

Deworming Effect on Protozoa

In laboratory tests using the ciliate model of *Tetrahymena pyriformis*, it was observed that △9-THC at concentrations of 3.2 to 24μM inhibited development, shape/size, and mitosis in cultures with synchronized division by blocking RNA synthesis and DNA (McClean and Zimmerman, 1976).

The plant and its derivatives also inhibited the development and formation of cysts of the parasite *Naegleria fowleri*, the cause of primary amoebic meningoencephalitis (Pringle et al., 1979). It is important to note that laboratory experiments focused on these pathogens have not been effective in designs where the central nervous system is affected. On the other hand, research in a murine model supplemented with a dose of THC (40 mg/kg i.p.) and then parasitized intranasally with *A. Culbertsoni*, had a greater number of positives than the untreated ones (Marciano-Cabral et al., 2001). Additionally, evidence has been presented showing the use of this plant as a treatment against malaria. In mice with brain infection by murine malaria, a dose of CBD (30mg/kg for 7 days) and the antimalarial artesunate (day 5 p.i.) were used; shortages and anxiety problems before or after deworming led to an increase in the survival of animals (Campos et al., 2015). In another study, mice freely fed leaves and seeds of the plant showed a slight effect on parasites, but a significant reduction in clinical signs, suggesting that the plant could induce a state of tolerance to malaria with asymptomatic carriage. In people or animals that consume it daily (Akinola et al., 2018). Research results have identified hemozoin as a product of hemoglobin digestion by *P. falciparum*, as a target for THC and CBD, compounds that have potential antimalarial activity (De Sousa et al., 2021).

Toxoplasmosis is a disease that has as its etiology a complex, *Toxoplasma gondii,* most cases are asymptomatic, but if the disease becomes chronic, it can lead the parasite to the Central Nervous System, having neuropsychiatric signs and behavioral disorders, complicating it with epilepsy and schizophrenia. (Milne et al., 2020). In the laboratory, tests were carried out on mice infected with acute or chronic toxoplasmosis; THC caused a decrease in seizures, while synthetic substances such as JZL184 (MAGL inhibitor), ACEA (CB1 agonist) and AM630 (CB2 antagonist) eliminated effects that can induce seizures and the agonist AM251 (CB1 antagonist) and HU308 (CB2 antagonist) had greater effects. These data indicate a benefit to eliminate neurological alterations caused by the parasitic load in the nervous

system (Ghanbari et al., 2020).

The most important protozoan diseases are caused by the genus *Trypanosoma* and *Leishmania*. Chagas disease is caused by *T. cruzi*. This pathology is a public health problem that can cause diseases related to the heart, in addition to megacolon and megaesophagus, it also causes serious problems of the nervous system (Pérez-Molina and Molina, 2018). The cannabinoid (+) WIN55,212 has been used, presenting good results, with high levels of reduction in the parasitosis of cardiac myoblasts; However, in vivo experiments with infected mice showed increased heart rate, inflammation, and increased parasitosis without any beneficial effect on heartworms. These data indicate that cannabinoids could have a negative effect on cardiac repair, suggesting their therapeutic usefulness in chronic infections of this type (Croxford et al., 2005). In experimental *African trypanosomiasis*, therapeutic experiments in rats revealed effective therapeutic results of *C. sativa* in an aqueous presentation used as an extract (Nok et al., 1994).

Giardia intestinalis (*G. intestinalis*) is an important parasite that causes diarrhea in humans and animals worldwide. This type of organism releases extracellular vesicles (EV) that influence its pathophysiology. New characteristics of *G. intestinalis* EV production have been described, where its ability to release two different populations of EVs is observed: large extracellular vesicles (LEV) and small extracellular vesicles (SEV). Proteomic analysis showed differences in proteins relevant to infection and host-pathogen interactions between the two EV subsets, including cytoskeletal and antioxidant stress response proteins in LEV. Recent experiments evaluate the effect of two inhibitors of EV release in mammalian cells, identified as peptidylarginine deiminase (PAD) and cannabidiol (CBD), on *Giardia* EV release. The results indicated that both inhibitors could effectively reduce EV release, and the PAD inhibitor specifically affected LEV release and reduced parasite adhesion to host cells in vitro. These findings suggest that LEV and SEV play different roles in the host-pathogen interaction and that treatment with VE inhibitors, such as this plant, could be a new therapeutic approach for chronic giardiasis (Gavinho et al., 2020).

Anthelmintic Effect on Helminths

Nematodes, cestodes and trematodes, are parasites with distinctively defined shapes. In several regions, farmers have used *cannabis* as an anthelmintic (Roulette et al., 2016). Extracts from this plant have demonstrated nematicidal activity against plant pathogens, such as Meloidogyne incognita (Mukhtar et al., 2013). In addition, studies have been carried out in animals infected with the intestinal nematode *Nippostrongylus brasiliensis,* whose life cycle is like that of hookworms harmful to humans. The data indicate that inhibition of the CB1 receptor with the synthetic molecule AM6545 promoted an increase in parasite load and egg production, as well as a decrease in the Th2 cytokine IL-5. Interestingly, transcriptomic analyzes integrated with mass spectrometry and qPCR in the advancing stages of *N. brasiliensis* revealed that this and other worms can produce their own endocannabinoids (eCBD), peaking in their infectious larval form. These findings suggest that parasite-produced endocannabinoids, a previously undescribed group of CBDs, play a role in the host immune response, which could facilitate parasite expulsion (Batugedara et al., 2018).

Antiparasitic Effect on Ticks

Ticks, parasitic arachnids of the order *Ixodida*, feed on the blood of host mammals and birds, which represents a concern for both the livestock industry and the health of pets and their owners. Although tick-borne diseases are a significant concern, there is a paucity of information on how certain molecules derived from these parasites may interact with cannabinoid receptors (Schön, 2022). It has been suggested that *Cannabis sativa* extracts from the leaves and roots may have a relevant suppressive effect on egg hatching and total larval mortality, with an effective dose of 40mg/mL against *Riphicephalus (Boophilus) Microplus*, an important tick. in public health. Application of a 45% extract to larvae-infected cattle has been reported to reduce tick burden 96 hours after application. It has been suggested that acetylcholinesterase (AChE) from *R. microplus* could be a likely target. Bioinformatic predictions indicate that CBD could be a potent inhibitor of this enzyme, which positions it as a promising compound for future research in the control of ectoparasites (Nasreen et al., 2020).

Conclusions

Compounds of plant origin offer a wide range of benefits for human and animal health, making them promising alternatives for the treatment of parasitic diseases. These compounds include macrocyclic lactones, terpenes and polyphenols. The plant, known as hemp, marijuana or ganja, is distinguished from most plant species by its various industrial products and phyto-medicinal compounds, highlighting phyto-cannabinoids such as THC and CBD. CBD is a phyto-cannabinoid present in hemp, and more than 140 phyto-cannabinoids have been identified with medicinal properties for the treatment of various diseases. Although the use of cannabinoids in parasitic infections is promising due to their in vitro activities, more research in animal models and vectors is needed to fully understand their efficacy and safety. For example, THC has been observed to aggravate certain parasitic brain infections, such as *Acanthamoeba* spp., rather than improving the outcome. Furthermore, studies in murine models of malaria suggest that regular cannabis users could become asymptomatic carriers of the disease, which represents a public health problem. It is important to consider that synthetic cannabinoids could be harmful in chronic Chagas disease, compromising cardiac homeostasis and contributing to heart failure, the main cause of death due to *Trypanosoma cruzi*. Furthermore, the sandfly vectors of *Leishmania* spp. could spread parasites tolerant or resistant to phyto-cannabinoids if they have constant access to *Cannabis sativa* plants for food. Recent studies also suggest that several nematodes produce their own endocannabinoids, which could help soil-transmitted

helminths evade and suppress host immune responses. Therefore, these concerns should be addressed in future research. Although the use of known phyto-cannabinoids and synthetic cannabinoids in parasitic diseases requires further exploration, it represents an interesting area of research that shows potential in veterinary applications due to their antiparasitic properties.

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