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CBD 101:

Wholesale to the vet market

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The idea of using CBD for a wide range of medicinal purposes in both human and veterinary medicine has gained extensive popularity in the last several years. This article will function as a brief review of definitions, pharmacology, and some recent studies into the use of CBD for various conditions in veterinary medicine.

What is CBD?

First, there are many definitions that can become confusing in discussions regarding CBD. Cannabidiol (CBD) is one of several cannabinoids found in the cannabis plant. The two major cannabinoids found in the cannabis plant are cannabidiol (CBD) and tetrahydrocannabinol (THC). THC is the principal

psychoactive component of the plant, while CBD does not have psychoactive properties. Another class of compounds found in cannabis are terpenoids, or terpenes, which are volatile aromatic compounds responsible for the taste and smell of the plant. Terpenes can also help determine how a plant extract will act on a chemical level, and can act synergistically with CBD in what is known as the 'entourage effect'. Terpenes, just like CBD and THC, vary drastically across different strains of the cannabis plant.

What are CBD extracts?

Both marijuana and hemp are the same plant, with the cultivars that are referred to as hemp grown for their non-drug uses. The Farm Bill of 2018 has legally defined 'industrial hemp' as cannabis

containing no more than 0.3% THC by dry weight. Therefore, hemp strains are high in CBD, and are what is used primarily to source CBD extracts. There are three major types of CBD extracts: full spectrum, broad spectrum, and isolate. Full spectrum refers to an extract that contains the full profile of cannabinoids and terpenes found in that plant. This type of extract would provide the highest level of the entourage effect. This extract will also contain THC, albeit a very small amount, and not enough to produce a psychoactive response when used at proper dosages. Broad spectrum isolates are full spectrum isolates with the THC removed. This extract avoids the THC (important for humans undergoing routine drug testing) while still maintaining the spectrum of molecules needed to deliver the entourage effect. Finally, the CBD isolate is exactly what it sounds like, an isolate of pure CBD without any other molecules. With a pure CBD isolate, you will lose the benefit of the entourage effect. Some companies will add terpenes back into their isolate to gain back some of this effect; this product is not the same as a broad spectrum product.

As with all nutraceuticals and products that fall into the category of 'supplements', there is no regulation regarding quality control. The market has been flooded with products claiming to contain CBD, with independent testing then confirming the product contains little to none of the advertised components. As with any other nutraceutical, selecting a product from a company that does rigorous quality control, clinical studies, and offers a consistent, reliable product is critical to treatment success. Additionally, cannabis is unique in that each specific strain of the plant has a different molecular profile, so the ratio of CBD to terpenes and other molecules will vary. These variations can alter their therapeutic impact, so consistency of the plant extract for any given product is also important.

How does CBD work?

In short, it is very complicated, and many mechanisms remain to be discovered and completely explained. Cannabinoid receptors are located throughout the body as part of the endocannabinoid system. This system is involved in many physiological processes, including pain sensation, appetite, mood and memory and in general helps maintain internal homeostasis. There are two main cannabinoid receptors, CB1 and CB2. CB1 is expressed mainly in the brain and CNS, and also in the lungs, liver and kidneys. CB2 is expressed mainly in the immune (T cells, macrophages,

B cells) and hematopoietic system, and is also found in the peripheral nervous system. CB2 receptors help mediate pain relief and inflammation. The receptor is a G-protein coupled receptor. THC is known to work mainly through the CB1 receptor, leading to its psychoactive effects. CBD, on the other hand, has been found to work through a myriad of receptors and signaling pathways, and does not activate CB1, thus avoiding the psychoactive effects. Some of the effects of CBD appear to be inhibiting endocannabinoid reuptake, increasing activity of serotonin 5HT receptors, and activating transient receptor potential cation channels. CBD also downregulates cyclooxygenase expression and stimulates transcription and translational activity via the peroxisome proliferation receptor. Essentially, CB2 activation can inhibit proinflammatory cytokine production and the subsequent release of anti-inflammatory cytokines. Several studies have demonstrated that CBD can down regulate cytokine and chemokine production, as well as upregulate T-regulatory cells, which will in turn modulate inflammatory response. Experimental models have also shown that CBD (and THC) can induce T lymphocyte apoptosis, which could mediate inflammation caused by T-cell activation. CB2 activation by CBD has also been shown to stimulate the release of endogenous opioids (such as beta-endorphin), which then mediates local pain relief by binding mu-opioid receptors. CBD also acts on a myriad of other molecular targets, including receptors, enzymes, ion channels, and transporters.

How should CBD be administered to animals?

The elimination half life of CBD in dogs in several studies has been shown to be about four hours, necessitating q12 dosing for maximum efficacy. Another study looked at different delivery methods for the CBD extract, determining that oral CBD infused oil gave the best absorption profile, followed by oral microencapsulated beads, and the transdermal application. CBD undergoes extensive first-pass metabolism; in spite of this, oral administration appears to have better systemic uptake than transdermal administration. More recent studies have examined oral transmucosal dosing, which appears to have even better absorption than oral administration for gastric absorption.

Studies in cats have been very limited, with one study noting adverse reaction to administration (salivation and head shaking) of a fish oil infused product, and absorption in these cats was less than the dogs in the study. Clinical efficacy in specific disease conditions have not been examined in cats.

The LD50 (the lethal dose that would cause death in 50% of test animals) has not been established for CBD in dogs, but it appears to

Receptor Name	Location	Receptor Effect	
CB1	Brain, spinal cord, lung, liver, kidney	Inhibits release of glutamate and GABA, psychoactive	Main target of THCCB2
CB2	Peripheral nervous system, immune cells	Mediate cytokine release, anti-inflammatory, anti-nociceptive	One of many targets of CBD

Terpene name	Aroma/odor	Other plants that contain this terpene	Proposed Benefit
Linalool	Floral, rose, woody	Lavender, citrus fruit, birch tree, hops	Antianxiety, sedative
Myrcene	Celery-like, herbaceous, woody	Bay leaf, hops, thyme, lemon grass, mango	Analgesic, sedative, relaxation
α - Pinene	Cool, fresh, herbal, piney	Conifers, rosemary	Alertness, possible memory retention
β - Pinene	Green hay, piney, spicy, woody	Conifers, hops, citrus tree	Anti-inflammatory, bronchodilator
Terpinolene	Fresh, lemon peel, sweet	Tea tree, conifers, cumin, sage, rosemary, lilac	Antibacterial, antifungal, possible sedative
α - Bisabolol	Coconut, fruity, nutty	Chamomile, figwort	Anti-bacterial, anti-inflammatory
β - Caryophyllene	Clove, dry, spicy, woody	Clove, rosemary, hops	Antimicrobial, anti-inflammatory, neuroprotective
α - Humulene	Bitter, floral, peppery, woody	Hops, sage, spicebush, ginseng, mint	Anti-bacterial, anti-inflammatory
D- Limonene	Citrusy, sweet	Citrus fruit, conifers, mint	Anti-bacterial, mood elevation, stress relief

be very safe. Even for the THC component of cannabis extracts, a dose 1000 times that necessary to induce hallucinatory effects is not lethal to dogs.

What are the potential uses for CBD in animals?

Many therapeutic targets have been suggested for CBD in humans and animals, ranging from the treatment of chronic pain and inflammation, to anxiety, migraines, and seizures. Preliminary studies have been undertaken in animals in just the last two years looking at treatment of specific diseases conditions, since the Farm Bill in 2018 legalized hemp (with significant restrictions) that have allowed scientific studies to take place. While most CBD remains schedule I, specific hemp-derived products have been removed from schedule I. The first CBD-derived drug for humans (Epidiolex) received FDA approval in June 2018; this drug is for the treatment of seizures associated with two rare and severe types of epilepsy. A pilot study looking at CBD and the treatment of osteoarthritis pain in dogs showed statistically significant improvements in pain and activity scores after four weeks of treatment. Dogs received 2mg/kg of CBD oil every 12 hours. No clinical side effects were noted, but some mild elevations in ALP were noted in the CBD group during treatment. This study was performed with the veterinary CBD product 'ElleVet'.

Another study looked at CBD as an adjunctive treatment for intractable epilepsy in 26 client owned dogs. Dogs were given CBD-infused oil at 2.5mg/kg q12 for the 12 week study period, and compared to placebo dogs. At the end of the study, the CBD

treated dogs had a significant reduction in seizure frequency compared to the placebo group, but there was no difference in the proportion of responders (placebo vs CBD) when compared between the two groups. It was speculated that the dose of CBD in this group was too low to achieve an adequate response.

Other areas of interest that warrant further investigation include chronic inflammatory diseases, such as canine atopic dermatitis, chronic neuropathic pain syndromes, and anxiety syndromes. It is well documented in the human literature that stress and anxiety exacerbate many chronic disease conditions, and especially in pruritic dermatologic conditions, stress perpetuates itch and vice versa. An adjunctive treatment that could offer treatment for inflammation as well as anxiety could have exciting implications in the field of veterinary dermatology.

What are the side effects of treatment with CBD?

Generally, due to the non-psychotropic nature of CBD, side effects reported in humans have been fairly minor. Commonly reported adverse effects in human trials included somnolence, loss of appetite, and diarrhea. Diarrhea was also noted as an uncommon adverse event in a pharmacokinetic study. In the epilepsy trial, ataxia was reported in a small number of dogs. In the osteoarthritis trial, no observable side effects were reported. In both trials, elevations in serum alkaline phosphatase became elevated in the CBD treatment groups. This is likely to be due to the induction of the cytochrome P450 system, known to occur from CBD metabolism. In humans, CBD is a potent inhibitor of

CBD Veterinary Pharmaceutical Pricing Comparison

Company	Product	Formulation	Size	CBD Strength	Price	Cost/mg
ChronoZoo (DermaZoo)	HempZoo	Full Spectrum	30 ml	1,500 mg	\$29.99	\$0.020
Travco (Nutramax)	Chronoquin	Full Spectrum	60 ml	1,200 mg	\$79.99	\$0.067
Rx Vitamins Inc.	HempRx	Whole Hemp Extract	30 ml	450 mg	\$50.00	\$0.11
Rx Vitamins Inc.	HempRx Forte	Whole Hemp Extract	60 ml	1,800 mg	\$120.00	\$0.06
Ananda Pets	Vets choice	Full Spectrum	30 ml	300 mg	\$59.99	\$0.20
Alpha Tech Pet	Vediol	Hemp Oil	60 ml	300 mg	\$100	\$0.33

CYP enzymes, which could lead to decreased metabolism of other drugs similarly metabolized, and could have the potential for significant drug interactions. This should be kept in mind when adding CBD treatment to existing pharmaceutical treatment, and monitoring of liver enzymes may be warranted.

Where do we go from here?

Studies evaluating the effects and potential therapeutic uses of CBD in both humans and animals are ongoing. Optimal formulation of the product (ratio of CBD to terpenes, etc) and optimal dosing in regard to disease condition remain to be elucidated. Overall, relative safety of administration appears to be favorable, and with further study, CBD seems to have potential in veterinary medicine.

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