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The Treatment of Osteoarthritis in Dogs with CBD Oil: A Literature Review

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1 List of Abbreviations

- OA: Osteoarthritis
- NSAIDs: Non-steroidal anti-inflammatory drugs
- ADAMTS*:* Disintegrin and metalloproteinase with thrombospondin-like motifs
- TNF: Tumour necrosis factor
- MMP: matrix metalloproteinase
- COX: Cyclooxygenase enzyme
- THC: Tetrahydrocannabinol
- CBD: Cannabidiol
- CBN: Cannabinol
- CBG: Cannabigerol
- CNS: Central nervous system
- *C. sativa*: *Cannabis sativa*
- GABA: Gamma-aminobutyric acid
- CB1 and 2: Cannabinoid receptors 1 and 2
- ECS: Endocannabinoid system
- FDA: US food and drug administration

2 Introduction

Osteoarthritis (OA) is the most common joint disorder in animals and has debilitating effects on those suffering from it [1]. OA is a significant cause of pain in dogs, humans, and many other species, and affects their quality of life as it is a progressive and degenerative disease [2]. It is estimated that approximately 90% of dogs above 5 years of age are affected by OA with the prevalence increasing proportionally with age, with many possibly going undiagnosed and associated pain unnoticed [3]. Therefore, it is valuable to explore the effectiveness of traditional treatments and to explore newer therapies that could be used either independently or in combination with traditional treatments [2].

Standard treatments such as, NSAIDs are commonly prescribed and used long term, but these tend to have some side effects especially when used over extended periods of time such as, gastrointestinal upset and renal toxicity [4]. As a result, there is growing interest in alternative therapies that can alleviate pain and inflammation with less or no side effects such as, a group of substances called nutraceuticals which have been described as naturally occurring biologically effective nutritional supplements that can result in health benefits, with several of these products on the market and being used to relieve arthritic symptoms [5]. Glucosamine and chondroitin sulphate are supplements that have been shown to contribute to cartilage formation and repair, reduce inflammation, slow cartilage deterioration and reduce painful swelling in joints [3]. Another nutraceutical used as complementary treatment along with other therapies for OA, are polyunsaturated fatty acids (PUFAs), these compounds can be found within the green-lipped mussel, along with glucosamine and chondroitin sulphate, and has been evaluated as a complementary therapy for dogs with OA [5].

Cannabinoids, which are also nutraceuticals, have become increasingly popular in recent years, both in people and animals, mostly due to their potential use as an analgesic for chronic pain [2]. The shift in popularity of CBD reflects a trend in society and is shown by the economic changes of the agricultural hemp sector. Consumer curiosity has also helped see a rise in its popularity [6]. Much information about the effects of CBD is documented as it a substance primarily meant for human administration therefore, is tested on animals regularly in pre-clinical research but, the use of CBD in veterinary practice and research is less documented with a more limited pool of research papers and clinical trials in comparison to human research [7].

3 Osteoarthritis

3.1 Osteoarthritis in general

In both human and veterinary medicine osteoarthritis is the most common joint disorder and as a result leads to subsequent decrease in mobility and functionality in the affected individual [1]. Arthritis is a commonly occurring chronic disease in humans and animals such as dogs, cats and horses [8]. Dogs tend to suffer more frequently with arthritis due to excessive exercise/ running, injury or genetic predisposition [9]. Osteoarthritis (OA) is a significant cause of pain in many dogs [2] and it is a debilitating chronic illness causing pain and discomfort to the affected individual [10].

OA is a multi-factorial disease and is not as simple as wear and tear of the joints, it is the abnormal remodelling of the joints driven by an inflammatory process, resulting in pain, deformity and loss of function [11]. Pain is the body's normal or physiological response to injury, infection and genetic changes, which can be divided into acute and chronic processes [12]. Common risk factors such as age, gender, previous injury, obesity and genetic predisposition have been identified, alongside mechanical factors like malalignment of the joint or abnormal joint shape [11].

In a study of 148,741 dogs across England from 93 different clinics, it was found that purebred dogs had a higher prevalence of degenerative joint disease than other dogs, suggesting an inherited element of the disease [3]. Large breeds such as German Shepherds, Huskies and Labrador Retrievers are more commonly affect than smaller breeds [9]. In canines OA is more likely to occur in joints with already underlying pathologies such as, hip dysplasia, elbow dysplasia, cruciate ligament disease, patella luxation or limb malformations [2].

OA is commonly occurring in horses and has been estimated that up to 60% of lameness cases are related to OA, with equine degenerative arthritis being first described in 1938 and the metacarpophalangeal joint, or fetlock, being the most commonly affected joint for spontaneous OA in racehorses followed by the carpal, or knee, joints [13].

OA is the slowly progressing degeneration of the cartilage, hypertrophy of the bone and changes of the synovial membrane which will lead to pain, stiffness of the joints and decreased flexibility [9]. OA can have metabolic and molecular triggers which cause

anatomical and/or physiological changes within the joint(s), these changes are recognised in the characteristic radiographic changes such as joint space narrowing, subchondral cysts and osteophyte formation [10].

Many different animal models of OA have been conducted in order best illustrate the pathology of the disease, including spontaneous cases in aging animals such as mice and guinea pigs as well as enzymatically or chemically induced models in mice, rats and dogs [8]. For animal models of OA, the stifle joint is regularly used along with, the fetlock and middle carpal joints in horses and the temporomandibular joint, or jaw, in mice [10].

This disease consists of four progressive stages. In stage one, small bone spurs develop, while the cartilage starts to break down which causes inflammation and pain. Then in stage two there is mild erosion of the bone, due to cartilage break down, which causes osteophytes or bone spurs to develop which affect normal joint movement. In stage three it is now considered moderate OA, and the cartilage is now very thin between the bones and causes grinding between the adjacent bones which causes more severe symptoms and inflammation. Finally in the fourth and final stage, this is considered severe OA where the joint space has significantly narrowed, the cartilage is almost absent and joint mobility is severely affected [9].

Figure 1 is showing the signalling pathways and structural changes cause by OA with *A* being a healthy normal joint and *B* being the so-called "diseased" joint. Several abnormalities in the function of these components have been found to promote OA in the joint such as when inflammation occurs this causes cytokines to be release like interleukins, TNF and disintegrin which further triggers the complex pathology of OA [10]. There can also be changes seen in muscles around the joint(s), nerves, bursa and local fat pads that may contribute to the symptoms of OA [11].

(Abbreviations: *ADAMTS:* disintegrin and metalloproteinase with thrombospondin-like motifs, *I:* Interleukin, *MMP*: matrix metalloproteinase, *TNF*: tumour necrosis factor, *IFN*: interferon, *IGF*: insulin-like growth factor, *TGF*: transforming growth factor, *VEGF*: vascular endothelial growth factor [10]).

The release of cytokines such as, interleukins (IL-1, IL-4), and TNF, degrading enzymes like ADAMTS and MMPs from chondrocytes, osteoblasts and synoviocytes, triggers the complex process of OA [10]. MMPs are highly efficient at degrading collagen type 2 and once the collagen network is degraded it appears that it can reach an irreversible stage [11].

When this occurs, the chondrocytes become hypertrophic and lose their ability to form new cartilage, while the subchondral bone undergoes abnormal remodelling causing the formation of subchondral cysts and osteophytes in an attempt to correct the joint instability [10]. There is evidence of an age-related decrease of cells in the superficial zone of cartilage, along with increased production of free radicals mediated by mechanical injury or response to cytokines which may contribute to cell death [11].

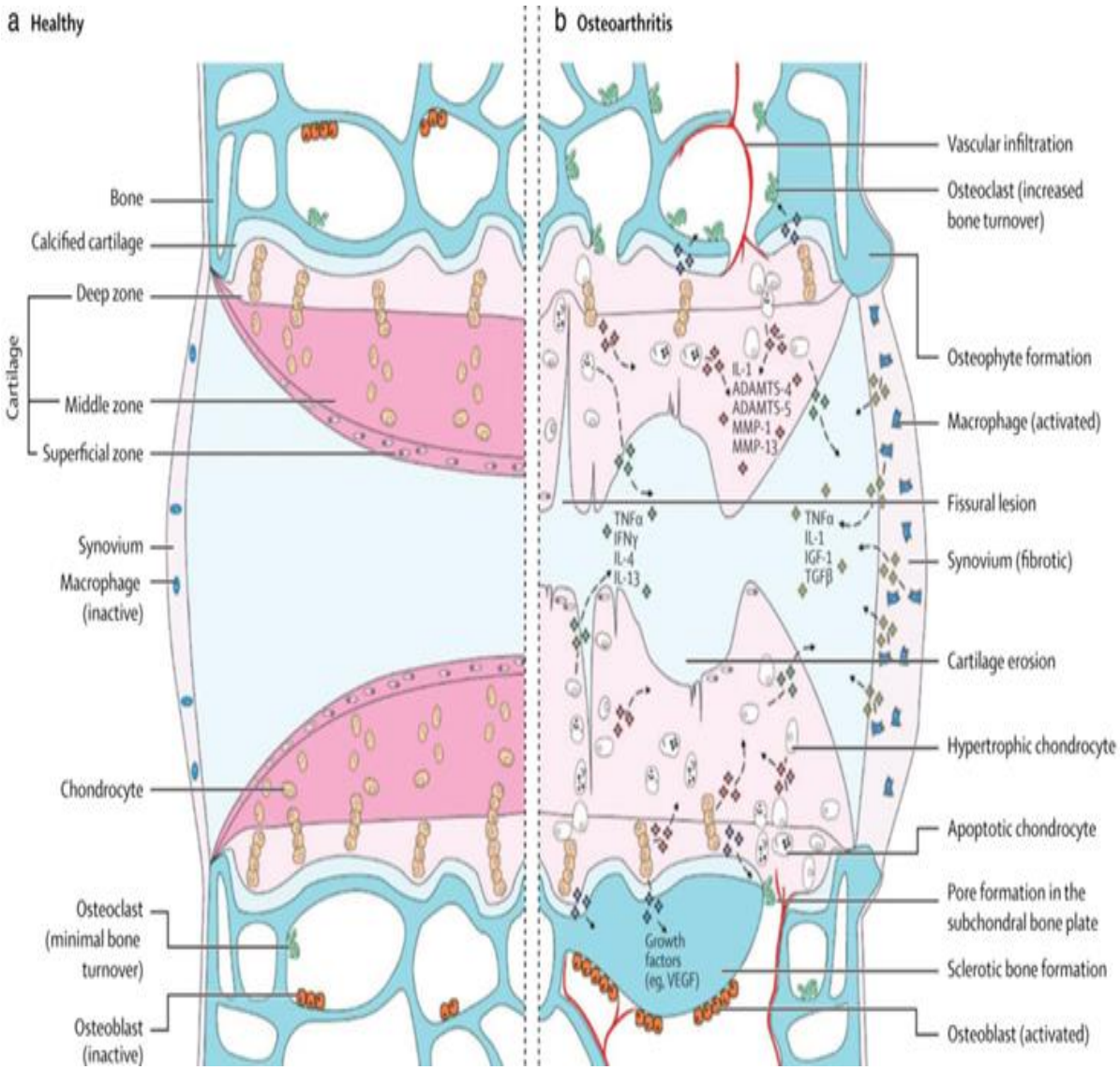

Figure 1. Signalling pathways and structural changes cause by the pathology of OA [10].

There are four components of the joint that participate in the pathology of OA. These are the meniscus, which is fibrocartilage composed of water, type 1 collagen and proteoglycans, this provides shock absorption and load bearing. The articular cartilage, which is hyaline cartilage composed of type 2 collagen and proteoglycans which provides a surface for movement of the joint. The subchondral bone gives support to the joint and is made up of mineralised type 1 collagen and the synovial membrane which produces synovial fluid that lubricates the joints and keeps the articular cartilage healthy [10]. When the cartilage is normal it provides a smooth surface with very low friction for efficient gliding movement during joint motion [11].

Accurate detection of pain in animals can be difficult, in some species more than others, as pain sensation is subjective and our animal companions cannot tell us directly, therefore pain should be assessed on an individual basis for each patient [14]. **Figure 2** shows an illustration of a knee joint with osteoarthritic changes and showing the main pathways of pain perception and the targets of certain drugs. Perception is how the brain interprets nociceptive inputs resulting in pain perception. Modulation is how the nociceptive stimulus is processed by the CNS. Transmission is the electrical impulse transmitted from peripheral sensory nerves to the CNS and transduction is the conversion of the nociceptive impulse into electrical impulse [2]. Dogs diagnosed with OA generally appear lethargic, stiff, have areas of muscle wastage, tend to lie down, or sit as soon as possible and have visible pain [9]. However, pet owners may note that their dogs differ from other dogs in regards to gait, vocalisation, socialisation, aggressiveness and panting but they don't consider these characteristics to be signs of pain as they believe them to be normal for their dog, which shows how chronic pain can often go unnoticed by owners [14].

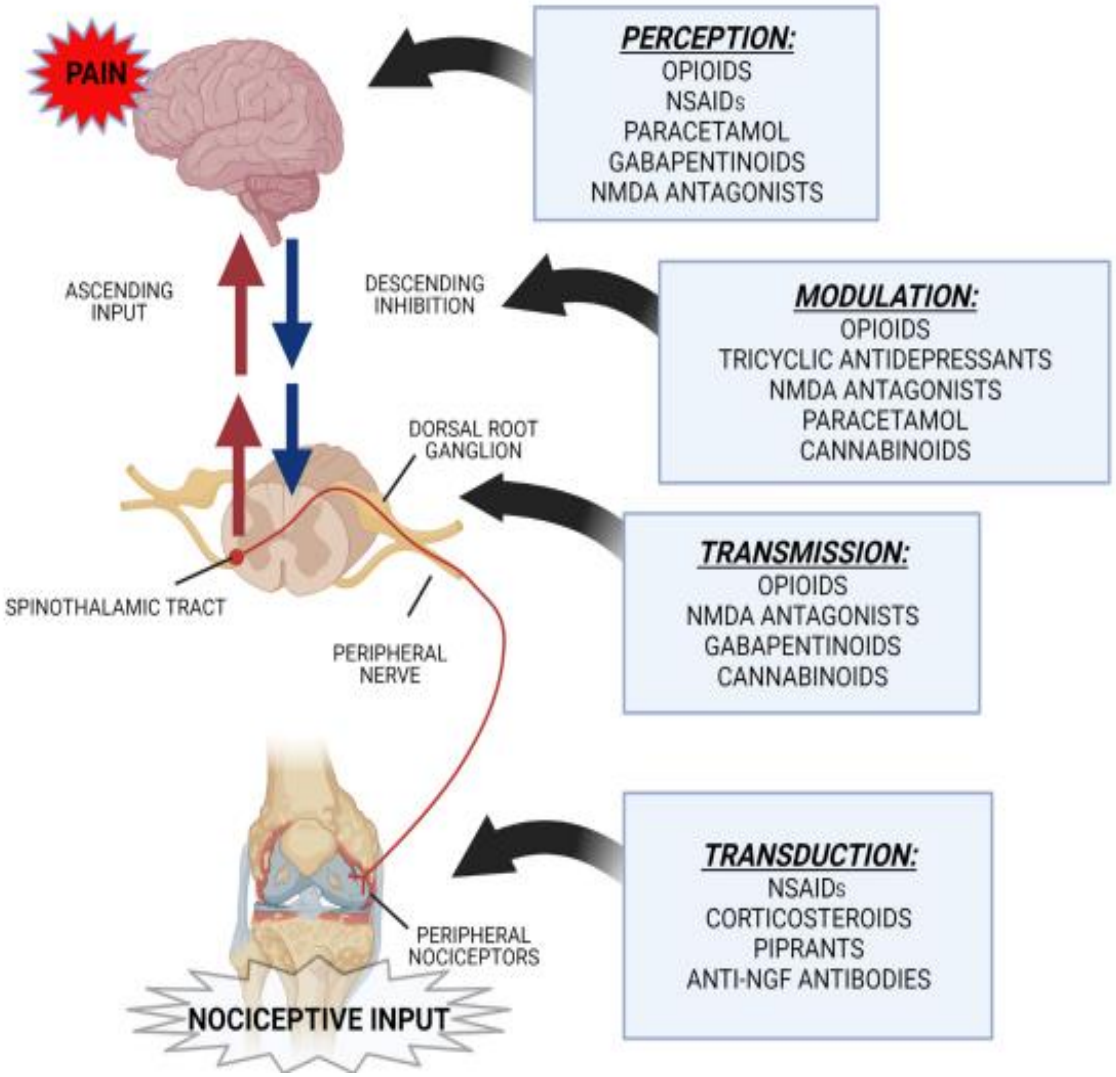

Figure 2. Main pathways of pain perception of OA and the targets of certain drugs [2].

3.2 Overview of treatment options

OA is a long-term disease and its management in pets can be challenging for vets and pet owners alike. Treatments can be costly, and it takes patience and persistence to find the most appropriate treatment for the individual. This includes medications such as opioids, NSAIDs, nutraceuticals, physical rehabilitation, weight loss and nutritional intervention [3]. Management plans for OA in dogs involves both non-invasive and invasive approaches, with the objective being to minimise joint pain, reduce inflammation and slow the degenerative process of the articular cartilage to therefore, improve the animal's quality of life [9].

Non-steroidal anti-inflammatory drugs have been the first-line treatment for canine OA pain for many years [2]. Examples of commonly used NSAIDs in veterinary practice include carprofen, meloxicam and firocoxib [15]. NSAIDs are efficacious but may not provide adequate pain relief in cases of OA and can have potential side effects that preclude its use such as, kidney, gastrointestinal and liver pathologies [4]. Conventional NSAIDs work by inhibiting the enzyme cyclooxygenase (COX), which cause the production of prostaglandins from arachidonic acid. There are two types of COX enzymes, COX-1 and COX-2 [2]. Prostaglandins are produced by cells and their proinflammatory properties result in pain, fever and increased platelet clumping [9]. Many medicines available on the market for dogs, for example NSAIDs, have limitations such as side effects, particularly in risk patients [5]. The unwanted side effects elicited by NSAIDs are caused by the inhibition of COX-1, which results in gastrointestinal signs like, vomiting, diarrhoea and, in severe cases, gastrointestinal ulceration. Also, renal effects such as decreased glomerular filtration rate and, in severe cases, renal toxicity [2]. COX-1 produces prostaglandins that support platelet clumping and protect the stomach, whereas COX-2 produces prostaglandins that are responsible for pain and inflammation [9]. As a result, there is a preference for drugs that are more selective COX-2 inhibitors, such as the highly COX-2 selective drugs, coxibs [2].

Tramadol, a drug in the class of opioids, is widely used for pain management in dogs but evidence in literature described tramadol has mixed results for canine OA [15]. Tramadol exerts its analgesic effects via multiple mechanisms. It is a mu-opioid agonist and inhibits the reuptake or serotonin and noradrenaline [2]. NSAIDS and tramadol are commonly used clinically in veterinary medicine, however, there is little research about the clinical efficacy of this combination for the treatment of OA in dogs [15]. With a limited number of clinical studies evaluating the clinical efficacy of tramadol for the treatment of OA in dogs it is difficult to come to a definitive conclusion on it clinical effectiveness [2].

Corticosteroids are thought to decrease pain and reduce inflammation in OA management, but their use is controversial in OA due to the well documented side effects of long-term corticosteroid use, such as poor wound healing and increased risk of skin infections [2]. Steroids inhibit the production of arachidonic acid, which stops inflammation and the production of prostaglandins, similarly to NSAIDs [9].

In 2020, a new canine specific monoclonal antibody called bendivetmab or Librela was released onto the market after approval from the European Medicines Agency. Librela is

licensed in the UK as a once-a-month subcutaneous injection for dogs over 1 year for the alleviation of pain associated with OA in dogs and shows great promise in providing an alternative treatment option for dogs with chronic OA [2].

With the era of modern medicine in full motion, there are now countless opportunities for research of many different treatment options of different diseases. Non-medicinal therapies are becoming increasingly popular, mostly as complementary therapies such as, glucosamine supplements, CBD oil and green-lipped mussel preparation [5]. Due to recent interest in alternative therapies for pain relief many owners have been using hemp products rich in cannabinoids [4]. Glucosamine sulphate may be effective for arthritis treatment as sulphate is needed to produce cartilage and as the body ages the production of glucosamine slows down, making it an important supplement to aid the treatment joint issues [9]. A greater understanding of the biology and pain mechanisms associated with OA has led to an increasing number of treatment options for dogs with OA over the past decade, hopefully this will continue to improve the welfare of dogs suffering from this condition [2]. Chronic pain is dogs is becoming increasingly recognised as a significant problem and it is challenging to find fully efficient treatment for canine osteoarthritis-related pain [16].

4 Understanding CBD oil

4.1 Utilisation of hemp in history

Cannabis has been documented throughout history in many cultures such as ancient China, India, Persia and Europe and has had many purposes such as a source of grain, fibre for paper, rope and thread, oil and medicine [16]. Herbal cannabis has been used for medical purposes for thousands of years. Nowadays, the medical usefulness of cannabinoids has been more intensively explored [17].

In the mid-19th century, much research was conducted in search of active natural medicinal products, where many alkaloids were isolated in pure form from plants such as, morphine. However, many of the terpenoids, which are non-polar molecules with low solubility in water [18], the class in which cannabinoids belong to, were not isolated until later [19]. In 1964, Dr Raphael Mechoulam discovered tetrahydrocannabinol or THC, the first cannabinoid to be identified. This paved the way for much groundbreaking work in this field that led to the discovery of CBD and other cannabinoids and the endocannabinoid system [20]. **Figure 3** is showing some of the important cannabinoids [21]. Cannabinoids can be divided into three major categories based on their origin: endocannabinoids, phytocannabinoids and synthetic cannabinoids [1].

Cannabidiol or CBD is the non-psychoactive isomer of the well-known compound that is psychoactive, THC [22]. CBD was first isolated and characterised structurally in 1940 and was found to be chemically unstable at room temperature and can isomerize into cannabinoids in acidic environments [23]. Cannabigerol (CBG) is the precursor of THC and CBD, and it appears to react with the receptors of the endocannabinoid system and other receptors outside of this system [18]. CBD can be converted into THC via an acid-catalysed reaction and this sensitivity to acidic environments has led to a hypothesis that CBD may convert to THC under gastric conditions, but this has been debated in literature and there has been no evidence of this in the human gut [23]. In 1988, the two cannabinoid receptors, type 1 and type 2 were discovered. These receptors belong to a family of seven transmembrane Guanosine binding protein-coupled receptors, and these are an important part of the signalling pathway called the ‘endocannabinoid system’ [12].

CBD has been shown to exert potent anti-inflammatory and antioxidant effects [19]. The psychotropic effects of cannabis are mainly mediated by CB1 receptors and are found in

many parts of the body such as, the brain, other organs like the liver and reproductive tract as well as, other tissues like adipose tissue and immune cells [12]. Preclinical and clinical studies have suggested the anti-nociceptive effect of CBD and CBD combined with other compounds in several pain-related diseases. However, analgesic effects of CBD can vary depending on the dose and route of administration [24]. In lower vertebrates, CBD has been reported to have immunomodulatory, anti-nociceptive and anti-inflammatory effects, making it an attractive option for dogs with OA [4]. A recent study of the clinical safety of CBD in cats and dogs found a decrease in veterinary pain assessment and need for other analgesics [1]. One study suggested that cannabinoids could protect against the effects if immune-mediated and inflammatory allergic disorder in dogs and the apparent analgesic effect of hemp oil may be due to the downregulation of cyclooxygenase enzymes, influencing nociceptive signalling and/or inflammation [4].

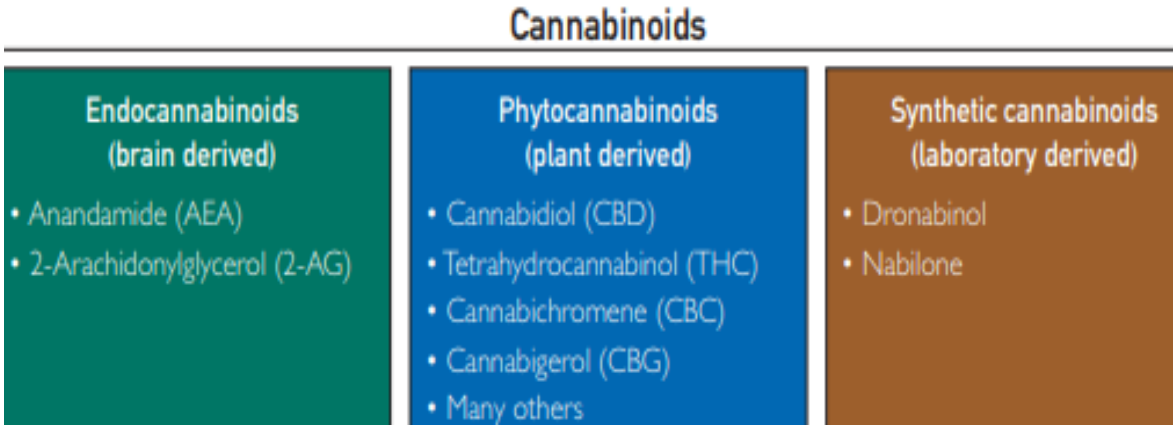

Figure 3. Some of the important cannabinoids [21].

4.2 The hemp plant (*Cannabis sativa*)

The hemp plant, often called the cannabis plant, has two main subspecies, *ssp. indica* and *ssp. Sativa.* They are differentiated by their physical characteristics. The *indica* plants are shorter with broad dark green leaves and have higher CBD content compared to the *sativa* plants in which THC content is higher. The *sativa* strains are usually taller, with thin leaves and a pale green colour [25]. Cannabis is the dried parts of female plants of the *indica* subspecies, and the female plant typically produces hundreds of small flowers in clusters at the top of the plant. Within these buds the psychoactive components of the plant are

contained [18]. *Cannabis sativa* first originated in Central Asia but is now globally cultivated, it thrives in temperate and tropical temperatures, and can be grown in almost every soil type, and can grow up to five meter in height [18].

Essentially, CBD is a concentrated extract made from cannabis flowers or leaves that is dissolved in oils such as, sunflower, hemp or olive oil [22]. The leaves and flowers of the Cannabis plant are the parts that are harvested and used. These contain many different cannabinoids, but the major known active components are THC, cannabinol (CBN) and cannabidiol (CBD) [26]. The highest concentration of the psychoactive compounds found in cannabis are found in the buds which are the flowering tops of the female plant, compared to the seeds and stalk which contain lower concentrations of these compounds [18].

While the plant is alive cannabinoids are synthesised and accumulate as cannabinoid acids but when the plants are dried, stored and heated these compounds decarboxylise into their more known and used forms such as, CBD and THC [25]. The cannabis plant produces an estimated number of 500 chemical compounds, which includes primary metabolites such as, amino acids, vitamins and fatty acids. Secondary metabolites include terpenoids, (like flavonoids and stilbenes), glycoproteins and dibenzyls. These compounds have analgesic, anti-inflammatory and many also have antioxidant properties [27]. Terpenes are the largest group of phytochemicals found in cannabis and are responsible for the odour and flavour of different cannabis strains. These are physiologically active secondary metabolites [28].

4.3 Mechanism of action of CBD

In the 20th century the mechanism of action of CBD began to be uncovered after the discovery of the active substances in cannabis, namely the phytocannabinoids [29]. In the 1990s the endocannabinoid system (ECS) was discovered, it was a previously unknown normal body system, consisting of cannabinoid natural neurotransmitters and endocannabinoid target receptors in multiple organs, such as the brain [17]. The endogenous endocannabinoid system has two main components, anandamide and 2-arachidonylglycerol, which regulate the sensitivity of serotonin, dopamine, GABA and glutamate in the central nervous system. This shows that cannabinoids have the ability regulate both physiological and pathological processes, for example, pain, energy metabolism and immune response [23].

CBD possesses sedative, anti-convulsive, anti-inflammatory and anti-psychotic properties, however, it does not have the typical intoxicating side effects shown by THC. CBD uses gamma-aminobutyric acid A (GABA-A) and adenosine A1 receptor dependant mechanisms to mediate neuronal inhibition and anti-epileptic effects [20]. The ECS is known to play a role in pain modification and inflammation involving CB1 and CB2 receptors that are widely distributed in the body, including the synovium of joints [4]. CB2 receptors are mainly located in immune cells, such as macrophages and mast cells, where they can act to inhibit the production of proinflammatory cytokines, thus helping reduce inflammation in OA [1]. The ECS is involved in different disease states and important regulatory function, from chronic inflammation, regulating homeostasis in the gut, in anxiety and migraines [21]. THC is the main psychoactive component in cannabis and its main effects are against CB1 receptors, also it has known effects on pain, digestion, emotions and appetite enhancement [12].

CBD is a non-psychotropic compound that exerts antinociceptive and anti-inflammatory effects and acts as a non-competitive allosteric antagonist of CB receptors. These properties make CBD an attractive analgesic option for treatment of dogs with OA. CB1 receptors have high expression levels in areas associated with nociceptive perception, such as the thalamus and amygdala, the midbrain grey matter cells and the substantia gelatinosa or the spinal cord [20]. The psychotropic effects of cannabis are mainly mediated by CB1 receptors and are found in many parts of the body such as, the brain, several organs like the liver and reproductive organs and different tissues for example, adipose tissue and immune cells [12].

Figure 4 represents the pathogenesis of pain following inflammatory disease or nociceptive stimulus, the different cytokines involved in the process, the descending supraspinal modulation and neurotransmitters and the retrograde endocannabinoid signalling mediated by the synapse. Endocannabinoids are produced from the postsynaptic terminals where there is neuronal activation from a stimulus. Natural and synthetic cannabinoids act in the same way as the two major endocannabinoids shown in the illustration: 2-arachidonolglycerol (2-AG) and anandamide (AEA). Endocannabinoids readily cross the membrane and travel in retrograde to the CB1 receptors where they are activated in the presynaptic terminals.

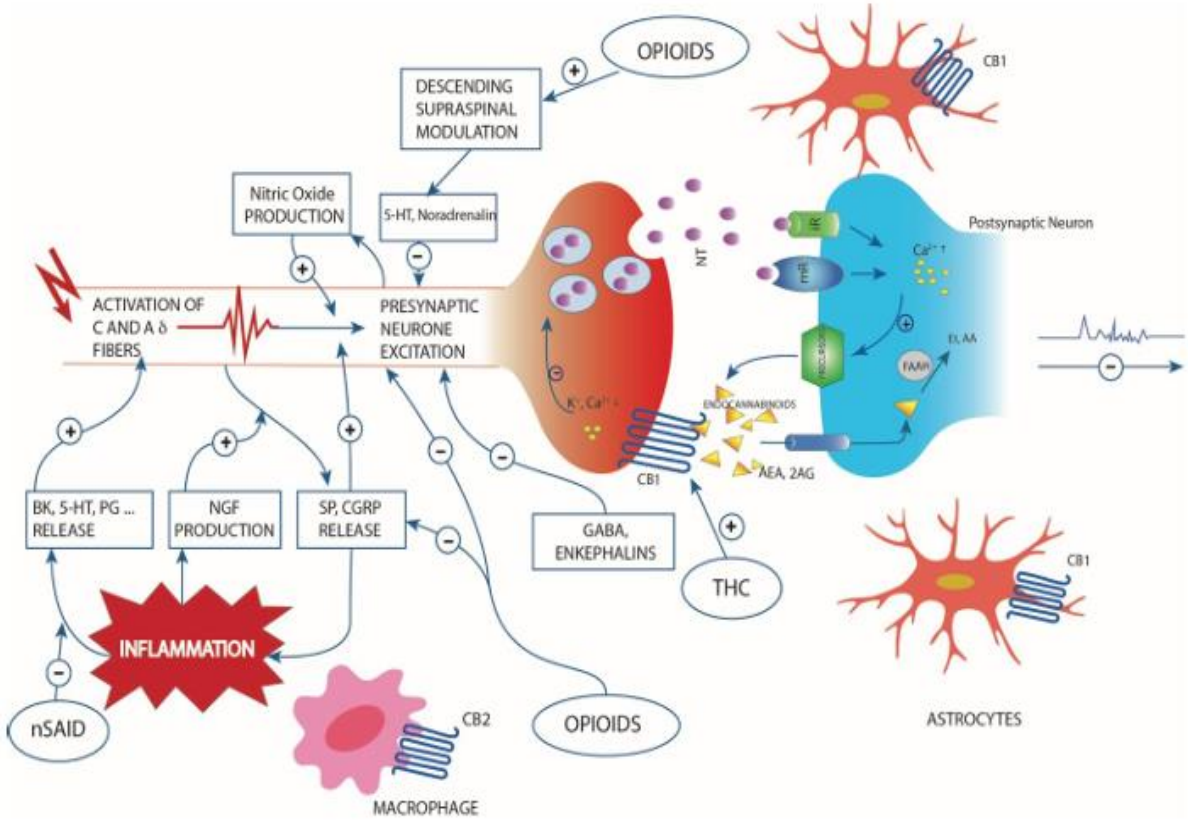

Figure 4. Shows a simplified illustration of the pathogenesis of pain and its interaction with opioids, THC and NSAIDs [12].

CB1 receptors will then inhibit neurotransmitter (NT) release via inhibiting calcium influx which terminate the pain signals being transduced. Inflammation leads to the production of biochemical compounds namely, bradykinin (BK), serotonin (5-HT) and prostaglandins (PG) and the up-regulation of nerve growth factor (NGF) which mediates pain. **Figure 4** also shows how opioids, THC and NSAIDs act on the nervous system when there is pain and inflammation [12].

(Abbreviations: ionotropic (iR), metabotropic (mR), Fatty acid amide hydrolase (FAAH), ethanolamine (Et), substance P (SP), calcitonin gene-related peptide (CGRP)) [12].

4.4 Pharmacokinetics of CBD in dogs and medicinal effects

Some drugs, including cannabinoids, are affected by the metabolism of the liver and gut enzymes (first-pass effect), and they have certain pharmacokinetic requirements to be

absorbed and have a better effect. Therefore, they need different administration routes than systemic oral delivery such as, transdermal, nasal and transmucosal. Via these routes the drug can be taken up directly into the bloodstream and avoid the first-pass effect [12]. The bioavailability of oral administration of CBD in dogs was found to be quite low at 13-19%, most likely due to the large first-pass effect [7].

According to one study conducted, it was deduced that the CBD half-life of elimination median was 4.2 hours, with a range from 3.8 to 6.8h, for a 2mg/kg dose and 4.2h, ranging from 3.8-4.8h, for the 8mg/kg dose, in their study [4]. In the same study, they found the median maximal concentration of CBD oil was reached after 1.5h for 2mg/kg dose and 2h for the 8mg/kg dose [4]. Unfortunately, the oral bioavailability of CBD was found to be poor probably due to the high first pass effect in the liver or gastrointestinal degradation, however this can be avoided via oral transmucosal administration [30].

At this time the evaluation of the pharmacokinetics of commercially available hemp products has not been assessed but there are several studies about different aspects about CBD oil and its effects [4]. A recent study in dogs has shown that an oil-based delivery of CBD is the preferred method of absorption, compared to transdermal which seems to be less effective as infused oils [30]. Another study that was conducted showed that there is a short half-life of CBD in cats and dogs with cats showing far lower oral absorption or rapid elimination, showing that dosing may be different in the two species [31]. One study found oral transmucosal CBD administration to be well tolerate with mild or absent side effects, as well as no relevant chances in the measure blood cell count and serum biochemical analysis [30].

5 Current research on CBD and osteoarthritis

5.1 Existing studies and clinical trials

Until recent years the use of cannabinoids in veterinary medicine was mainly restricted to experiments that mostly focused on the toxicity of CBD or for pre-clinical studies that focused on human medicine [29]. Now, the use of CBD products is increasing for cats and dogs but to date there is little data about the appropriate dosing or long-term effects on serum chemistry or total blood counts and about the pharmacokinetics of once off or long term dosing in cats and dogs [31]. There is no gold standard for measuring chronic pain in dogs, often blood tests and x-rays are completed and can indicate joint disease in dogs but it is hypothesised that both vet and owners evaluations of the dogs movement, behaviour and demeanour may provide more useful information [14]. Even though cannabinoids have been used for centuries in humans and animals for the treatment of symptoms associated with chronic pain, little scientific evidence is available [1].

At Cornell University, Ithaca, USA Lauri-jo Gamble and her colleagues [4] conducted a double-blind; where both the vet and owner were unaware of what each dog was given; clinical study. Where 16 dogs, that had confirmed OA with radiographic evidence, were given 2mg/kg CBD oil orally twice a day or the same volume of olive oil as a placebo for a 4-week time frame. The dogs that were included in the study were evaluated for lameness by a visual detection of lameness and palpation of painful joint(s) that would then be x-rayed to prove OA and had signs of pain reported by the owners. The ages of the participants ranged from a 3-year-old Bernese Mountain dog to a 14-year-old border collie, with the majority of dogs being older than 8 years old [4].

At the beginning of the trial, at 2 weeks and at 4 weeks, the vet evaluated each dog using a pain scoring system, also the owner's provided information about their perception of the dog's pain level. Pharmacokinetics of this study found the CBD half-life was a median of 4.2h for a dose of 2mg/kg, ranging from 3.8-2.8h [4].

Results showed the dogs treated with CBD had a decrease in pain scores and increase in activity. Also, the owners reported no side effects although, lab results showed an increase in alkaline phosphatase (ALP) was reported in 9 dogs receiving CBD treatment, which is a liver enzyme, which is quite sensitive to show hepatobiliary changes but is not specific [4].

At the Colorado State University Teaching Hospital in the USA Sebastian Mejia and his colleagues [1] conducted a randomized, double-blind, placebo-controlled clinical trial. 27 dogs with naturally occurring OA of the carpus, elbow, shoulder, tarsus, stifle or hip joint of any breed or sex were eligible to participate. 23 dogs completed the study. The dogs had to be above 15kg and over 3 years old. Their condition was confirmed with radiographs, observed lameness and using a pain score system. Dogs were excluded from the study if they had palpable instability of the shoulder of stifle joints, neoplasia, evidence of neurological disease or had any intra-articular injections within 6 months prior to the study. The ages of the dogs ranged from a 4-year-old newfoundland to a 14-year-old mixed breed dog, with most dogs being above the age of 8 [1].

Baseline data was collected for 4 weeks before then they all received either CBD for 6 weeks followed by the placebo for another 6 weeks or the placebo followed by the CBD for a further 6 weeks. Given the short half-life of less than 4 hours of the product, the was no washout period between the placebo and CBD treatments. The patients were given cold pressed hemp seed oil with chicken flavouring, to try to hide the smell of CBD, that contained <0.3% THC. The oil was dosed at 2.5mg/kg orally every 12 hours or the placebo of the same amount. Gait analysis was performed every 3 weeks after the beginning of treatment using a pressure-sensitive walkway in trot, or at walk if they were unable to trot [1].

Side effects of vomiting in 2 dogs and slightly increased liver enzymes were noted in 14 of the dogs receiving the CBD oil, but not the placebo. The dogs with increased ALP levels had repeat blood tests 6 weeks after the trial and it was found that the ALP levels decreased to within the reference range. The overall conclusion was that the small sample size makes it difficult to make a definitive conclusion and that more research is needed before recommending CBD for clinical use [1].

In 2020, Lori Kogan and her colleagues [32] conducted a 90-day clinical trial to assess the effect of full-spectrum hemp extract and hemp seed oil on dogs with chronic pain. 37 dogs with chronic osteoarthritis, for at least 3 months duration, were included in the study. 32 completed the study. The average age of the dogs was 10.9 years old, ranging from a 2-year-old Rhodesian ridgeback to 16.6 years old Scottish terrier. The dogs had pain assessment check-ups every 2 weeks during the 90 days and the owners kept informal activity logs of the dog's daily movement [32].

The dogs initially received a cold-pressed hemp seed oil infused with full-spectrum hemp extract, cultivated in Colarado, USA, 4 times a day at a dose of 0.25mg/kg for 3 days and then afterwards twice daily. Full-spectrum extract includes cannabinoids (CBD, CBD etc), flavonoids and terpenes. The dose of CBD was increased by 0.5 to 0.75mg/kg after each reassessment of pain until the patient's pain score was 0 to 1 on a scale of 10 with the primary goal of achieving adequate comfort without inducing sedation, which is a known side effect of CBD ingestion. The patients pain severity was scored using a 0 to 10 scale with 10 being the worse possible pain. Some of the dogs were given gabapentin alongside the CBD oil but once their comfort level was stable, they reduced the gabapentin dosages of the 23 dogs taking gabapentin 10 of them were able to discontinue its use and 11 were able to be given reduced doses while being given CBD concurrently [32].

This study found that all the dogs that completed the study had a decrease in pain score, overall ranging from 0/10 to 2/10. 7 dogs had no change in their pain score but were given gabapentin alongside the CBD, so their comfort was kept at the same level and did not decrease because of the additional CBD supplementation. Among the 30 dogs they found that the dose needed to achieve a positive effect ranged from 0.3 to 4.12 mg/kg twice daily doses. They found an overall increase in alkaline phosphatase enzyme levels which suggest the need for further safety studies to determine the long-term effects particularly on the liver [32].

Figure 5 showing an example of a pain index scoring system, based on dogs with chronic hip dysplasia, which is used in studies to score patients before and after treatments to see the effects and to ascertain the comfort of the animal for animal welfare purposes [14]. Pain score assessment was used in the studies mentioned above conducted by [4], [1] and [31]. Different types of scales have been used to assess pain in dogs, however, there is little data on specific changes in behaviour and demeanour associated with chronic pain in dogs [14].

Question topic	Scores for dogs with CHD		Scores for control dogs		
	Median	Range	Median	Range	*P value*
Positive behavior					
Appetite	0	0–3	0	0–2	0.59
Mood*	1	0–3	0	0–1	< 0.001
Frequency of contact with human family members	1	0–2	0	0–2	0.086
Frequency of tail wagging	1	0–3	0	0–2	0.013
Activity	1.5	0–4	1	0–3	0.052
Play and games*	1	0–4	0	0–1	< 0.001
Negative behavior					
Excessive panting	1	0–4	0	0–2	< 0.001
Licking of lips	0	0–4	0	0–3	0.97
Vocalization (audible complaining)*	1	0–3	0	0–1	< 0.001
Vocalization when stretching hind legs caudally	2	0–4	0	0–1	< 0.001
Aggressiveness towards humans	0	0–3	0	0–2	0.88
Aggressiveness towards other dogs	2	0–3	1	0–3	0.47
Aggressiveness towards dogs in its own pack	1	0–4	1	0–2	0.09
Submissiveness in the pack	1.5	0–4	2	0–4	0.27
Locomotion					
Walking*	1	0–3	0	0–1	< 0.001
Trotting*	1.5	0–4	0	0–1	< 0.001
Pacing	1	0–4	2	0–4	< 0.001
Galloping*	1	0–4	0	0–1	< 0.001
Jumping*	2	0–4	0	0–1	< 0.001
Climbing stairs	2	1–4	0	0–1	< 0.001
Descending stairs	2	0–4	0	0–2	< 0.001
Laying down*	2	0–4	0	0–1	< 0.001
Getting up*	2.5	0–4	0	0–1	< 0.001
Difficulty moving after rest*	2	0–4	0	0	< 0.001
Difficulty moving after major activity*	3	1–4	0	0–1	< 0.001
Chronic pain index (sum of answers to 11 questions)	19	7–35	2	0-5	< 0.001

*Question selected for inclusion in chronic pain index. Values of $P < 0.05$ were considered significant.

Figure 5. An example of a pain index scoring chart for dogs with chronic hip dysplasia [14]

Kelly A. Deabold and her colleagues [31] conducted a study about the single-dose pharmacokinetics and preliminary safety assessment on 8 healthy dogs and 8 healthy cats. In the dog study, 8 purpose-bred beagles with a median age of 3.2 years old, ranging from 11 months to 5 years old participated in the study. They were given ElleVet Mobility Chews (ElleVet Sciences; Portland, ME, USA) at a dose of 2mg/kg CBD twice daily for 84 days, all dogs were fasted from the prior day and were not fed until 8 hours after the initial dosing. Before the trial started and every 4 weeks a blood sample was taken via the jugular vein of each dog for full blood counts and serum chemistry tests. For the cats, 8 purpose-bred domestic shorthaired cats were used in the study where they were given CBD-infused fish oil at 2mg/kg dosage, and they were fasted from the previous day and were not fed for 6 hours after the initial dosing. Blood was collected in the same way as the dogs at the same time frames and sent for the same lab tests [31].

The animals were observed for side effects for the duration of the study such as vomiting, loose stool, pain or distress. Complete blood count results for the dogs showed no deviations from normal and the serum chemistry showed no statistically significant results including ALP levels and only one cat showed elevated ALT levels but there was a significant increase in Blood Urea Nitrogen over time. Some loose stool was noted among the 8 dogs 44 times and vomiting was recorded 6 times and, in the cats, the main side effects were excessive licking and head shaking also, some vomiting and salivating were observed. In conclusion they found that dogs appear to absorb CBD better than cats and due to some adverse effects in cats more research should be conducted about the safety of CBD in these animals [31].

A pilot study was conducted by Elisa Martello and her colleagues [33] about the effects on joint pain and mobility of a new dietary supplement. The participants of the study had x-rays of their joints, and the veterinarian confirmed clinical signs of OA in at least one joint. A total of 8 dogs completed the study of 30 days. The dogs ages ranged from 5 to 14-years-old and all of them were considered medium to large sized dogs with their weights ranging from 20 to 50kg, apart from one small dog weighing 7.4kg. Dogs were excluded if they had evidence of other diseases, based on their clinical history and blood test results, had acute pain, recent trauma or surgery on any joint in the last 6 months or if they had been given any medication or diet supplements in the last 2 weeks before enrolment into the study [33].

They administered orally a new diet supplement produced by Candioli Pharma, an Italian company, for a total of 30 days. The tablet consisted of 99% pure cannabidiol in powdered form and the dogs were given 2.4mg per 15kg of body weight. The dogs underwent a vet and owner evaluation of their pain on day 1, day 15 and day 30 of the trial. The owners were given a total of 11 questions about the dog's mood, lameness, willingness to move, play and jump and they had to score them from 0 to 4. Where 0 and 1 indicate normal movement and behaviour and score from 2 to 4 indicate a more severe pain score. They also scored how easy the tablet was to administer to the dog, how palatable and its effectiveness, all using a score from 0 to 3. The supplement was well tolerated with no vomiting or diarrhoea noted and they found it was quite palatable too. They found a reduction in pain score from the first to the last evaluation [33].

In 2018, Stephanie McGrath and her colleagues [34] conducted a study about the side effects associated with CBD oil in dogs. Their study aimed to evaluate the safety and side effects of CBD in healthy dogs by giving them higher doses than used in clinical scenarios. A

participant group of 30 healthy intact male beagles participated in the study. Their ages ranged from 4 to 5 years old and weighed on average 13kg, ranging from 9.5 to 16.2kg [34].

Before taking part in the study, they had physical exam conducted by a neurologist or a resident in neurology, lab tests including urinalysis and chemistry panels and bile acid assays. All of the dogs were transported to an on-site research facility and were housed in a single run and fed the same maintenance food once daily. They divided the dogs randomly into 3 groups for 3 different CBD administration methods, which were all given twice daily. Group 1 had CBD-infused transdermal cream applied to the pinnae, group 2 were given oral CBD oil beads in a capsule and the third group received CBD infused oil. These 3 groups were further divided into subgroups were the A group received 10mg/kg/day of CBD, and the B group received 20mg/kg/day of CBD [34].

All of the participants had a general health assessment twice a day and underwent a physical exam weekly for the duration of the 6-week study. At weeks 2,4 and 6 each dog had samples collected and these underwent chemistry panels, bile acid assays and urinalyses. The bile acid tests were done to determine if the CBD affected the cytochrome p450 enzyme activity in the liver and compare it to how it does in humans. It was mentioned that phytocannabinoids are extensively metabolised by cytochrome p450, but CBD inhibits cytochrome p450 potently [34].

Throughout the 6-week study, they found gastrointestinal upset to be the most common adverse effect and that all of the dogs in the study developed diarrhoea and 6/30 had one episode of vomiting each. The dogs that vomited had received CBD orally in the capsule or oil, but they determined there was no correlation between the vomiting and the dose given. They suspected that the episodes of diarrhoea were secondary to the CBD treatments, also other contributing factors such as moving to the new housing facility and new diet could have been stressors. In the group receiving the transdermal cream on the pinnae, all of the dogs, except one, developed an erythematous pinna at weeks 2 and 4, one other dog receiving CBD orally also developed these symptoms. Other adverse clinical signs noted were ocular discharge in 10/30 dogs, nasal discharge in 10/30 dogs, salivary staining of the feet or ventral abdomen in 5/30 dogs and salivation during administration of CBD oil formulation at both concentrations. There were no clinically significant abnormalities detected in the bile acid tests for any dogs during the 6 weeks. They found the only clinically significant bloodwork abnormality to be the elevation of ALP in 11 dogs, these were the dogs receiving the oral

CBD oil and CBD capsules but none of the dogs receiving the transdermal dose had elevations of ALP [34]. **Figure 6** illustrates the clinically significant elevated ALP levels seen in some dogs throughout the study [34].

Overall, they concluded that the products were well tolerated clinically, however, the episodes of diarrhoea and elevations in ALP levels warrant further research and discussion. It was mentioned that the lack of a control group and short duration of the study were limitations of the study and that a longer study would help understand the effects of CBD on the canine liver [34].

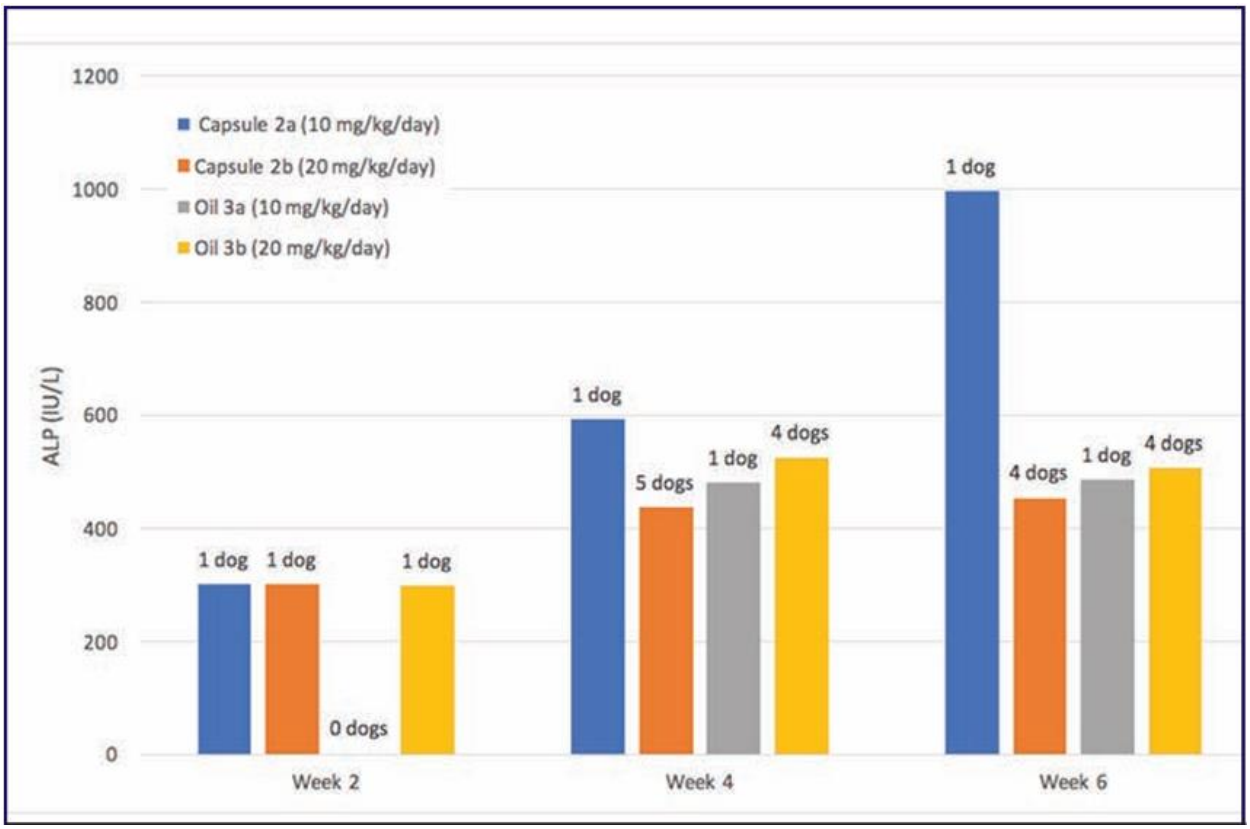

Figure 6. The number of dogs with clinically significant elevations of ALP levels during the study [34].

6 Comparative analysis

6.1 Traditional treatments

Traditional treatment of OA in dogs typically includes NSAIDs, which do not address underlying causes of pain. They work against prostaglandins that are produced in response to pain and inflammation. Also, corticosteroids, often referred to as steroids, are very effective in reducing pain and inflammation and are a common choice for the treatment of OA related pain in dogs [9]. Commonly, the most used drugs for the treatment of OA are limited to those that are proven to be safe and effective. Therefore, these drugs tend to be the most extensively reviewed products. However, there is a constant search to find new and improved treatments, with non-pharmaceutical treatments often explored and embraced despite the lack of approved safety or efficacy [15].

NSAIDs tend to be the primary treatment for OA currently with common side effects being reported such as gastrointestinal upset and glomerular filtration decrease which is proven by the increase in BUN (blood urea nitrogen), creatinine or phosphorus seen in the blood tests [4]. All NSAIDs have potential side effects, the most common include gastrointestinal signs such as vomiting, diarrhoea and in severe cases, gastrointestinal ulceration and renal toxicity [2]. In one review of 35 canine models of OA and 29 clinical trials they found that 35 of the 64 had adverse effects caused by NSAIDs [4]. Acetylsalicylic acid is an NSAIDs that is commonly prescribed for OA as it is relatively inexpensive. However, studies have shown that it can decrease chondrocyte production of collagen and proteoglycans and can enhance cartilage degeneration [9]. The coxibs are a class of NSAIDs which are highly selective for COX-2 which reduces their side effects caused by other NSAIDs. When COX-1 is inhibited the typical NSAIDs side effect are seen, such as gastrointestinal upset [2]. Several clinical studies have reported that NSAIDs don't provide complete pain relief or disease modifying effect and refractory cases are common [33]. Paracetamol is not licensed on its own for use in dogs in the UK but is licensed in combination with codeine phosphate for the treatment of acute pain of traumatic origin, as a complementary treatment in painful conditions and for postoperative analgesia [2].

Steroids are the most used drug in veterinary medicine and are a popular choice in the treatment of OA as they inhibit the production of arachidonic acid which blocks the production of prostaglandins resulting in less pain and inflammation. However, long term

steroids can cause many side effects including, weight gain, osteoporosis, diabetes, gastrointestinal bleeding and cataracts [9]. The use of steroids in OA management is controversial due to the risks of long-term use. A recent clinical trial found an improvement of comfort in dogs following an intra-articular injection of triamcinolone hexacetonide, compared to the control group who received a placebo [2].

A combination of NSAIDs and tramadol have been used in veterinary practice even though there are no published clinical trials about the clinical efficacy of this combination for the treatment of canine OA [15]. There is evidence that the use of tramadol in clinical scenarios has mixed results, there are a limited number of clinical studies investigating its efficacy for the treatment of canine OA, so it is difficult to conclude its usefulness for this disease [2]. Although no clinical trials have confirmed a safe dosage range, tramadol is typically administered at a dosage of 2 to 5mg/kg orally every 8 to 12 hours [15].

6.2 CBD treatment

Cannabinoids have a complex mechanism of action but have potential to be used as analgesics for patients with chronic pain [2]. In several chronic pain models, it has been shown that CBD may exert some analgesic and anti-inflammatory effects [24]. Clinical trials conducted so far about the use of CBD oil in dogs with OA, have had mixed results with most having low samples sizes, some without a placebo control group and others with participants on concurrent treatments like NSAIDs [2]. CBD was proven to be safe with only mild side effects such as, ataxia, sedation, nausea or headache in humans [24].

Despite the small sample size, a study showed that CBD oil increased the comfort and activity in the home environment in the dogs with OA [4]. The increase in liver enzyme levels after the treatment of CBD could be due to the induction of cytochrome-P450 enzyme which is involved in the oxidative metabolism in the liver, this suggests potential hepatotoxic effects. However, in a study of 30 dogs that were administrated up to four times the 2mg/kg standard dose, the ALP levels were increased in 11 dogs and other liver enzymes and bile acids remained in reference ranges [1]. In one study, they found the outcome of treatment with CBD oil to be decreased pain scores, improved mobility and improved quality of life [35]. There is a need for an extensive safety study of the clinically applicable dose of CBD to evaluate the long-term effects on the canine liver and gastrointestinal system [34].

One study reported that pet owners have used cannabis to treat behaviour disorders such as separation anxiety in addition to other issues such as irritable bowel syndrome, seizures and management of pain [35].

Another study in the USA found that 85% of vets rarely or never lean towards the use of cannabis, while 91% never or rarely prescribe cannabis products for patients, with lack of knowledge being the underlying reason for these choices, however, with more clinical trials and changing laws this study only outlines views from that time [19]. A recent survey showed that pet owners endorse hemp-based products due to the widespread information about its improvement of numerous diseases when hemp products were used medicinally such as pain, inflammation, anxiety and pruritus [4]. The awareness of cannabis-based treatments has been increasing among pet owners and veterinarians [34]. A study about the consumers' perception of hemp products for animals, found that the most common reason for the consumer to try a hemp product was, they liked the idea that the product came from natural sources [35].

7 Regulatory and safety considerations

7.1 Regulatory status of CBD

The discussion about the legal status of CBD circulates around the question of whether CBD is a medicine or a natural food supplement, the difference being medicinal products are considered unsafe until proven safe, compared to food supplements that are first considered safe unless proven otherwise [22]. Cannabis has three kinds of legalisation in different countries: for medical, recreational or research use [18]. Until recent years, the restrictions on cannabis research for veterinary patients have severely hindered the progress of clinical investigations of the medical usefulness of hemp products [35].

CBD is becoming increasingly popular in both human and veterinary medicine, in the United States legislation now allows use of hemp and hemp-based products if they contain less than 0.3% THC [35]. Currently there are several companies selling nutraceutical products that are rich in cannabinoids for pets, however little scientific evidence regarding safe and effective oral dosing exists [4]. In the US, several companies are producing products like, biscuits, edibles and capsules, containing non-psychoactive cannabinoids which are available on the market for pet owners in some states such as, California, Oregon and Washington [35]. While herbal cannabis has not met rigorous standards for the FDA for medical approval, the food and drug administration which oversees drug approval in the US, specific well-characterised cannabinoids have met those standards [17]. CBD is usually derived from fibre-type varieties of cannabis, such as Hemp, although in many countries the cultivation of such plants is allowed it is strictly controlled by regulations [22].

In Europe the cultivation of certain cannabis varieties may be granted provided they are registered in the EU's "Common Catalogue of Varieties of Agricultural Plant Species" and the THC content doesn't exceed 0.2% in the dried flowers. In Canada it can contain up to 0.3%, while Switzerland allows up to 1% THC [22]. In 2018 in the United States the FDA approved the use of one drug, called Epidiolex, which contains CBD as the active ingredient, for use for the treatment of severe epilepsy in humans, this begs the question; if it is safe for human use why has it not been promoted as treatment for animals with severe medical issues [18]. In Italy Cannabis use is illegal but exclusively for personal use has been decriminalised with strict sanctions and in Romania is legal to use cannabis derivatives for medicinal purposes only in humans while there is ongoing research into cannabis use for Alzheimer's

disease, Parkinson's disease and Tourette's syndrome [18]. Currently, there is no licensed use of CBD for dogs in the UK and veterinarians should be aware of the legal position regarding prescribing these medications [2].

7.2 Safety concerns

The risks of CBD are not directly related to the pure CBD compound itself, but more with products of unknown composition and quality, in particular products containing contaminants or potentially mislabelled or misleading labels [22]. CBD can be associated with adverse drug effects along with having the potential for pharmacokinetic and pharmacodynamic drug-drug interactions, therefore given its use among patients with complex conditions and treatment regimens, awareness of potential safety issues with CBD is needed [36]. Different strains of cannabis products have differing amount of CBD and other cannabinoids so this makes interpreting the outcome of some studies difficult as industrial hemp extract components may differ to available products in a largely unregulated market [4]. Unlike pharmaceuticals which have strict FDA regulations for health claims, there are few regulations about the health claims of nutraceuticals so their safety must be assured in advance. Extensive and independent testing must be reported about a nutraceutical before health professionals recommend it to their patients [9].

Apart from addiction there are some other negative effects of cannabis such as cognitive function after long term use, mostly studied in adolescent people. Mainly cannabis has been shown to have transient symptoms such as incoherence and memory disturbance in humans [35]. There are several studies reporting gastrointestinal signs and elevated liver enzymes in canine participants receiving CBD treatments [34] [32] [31].

8 Conclusion

8.1 Summary of findings

To conclude, as there is no cure for this disease the main objective is to slow the progression of OA, reduce pain and improve the quality of life. As shown in my earlier section, an overall theme from the current research about CBD oil and its potential use in dogs with OA, is that there is a need for more clinical trials and research, particularly about the long-term effects and potential side effects in dogs. Especially as multiple studies have shown increased levels of ALP suggesting potential liver toxicity. Although shown in the above research, there is much potential for the use of CBD oil as there are some promising results for decreasing of pain levels and increase in activity of the dogs in these studies. Therefore, I believe it is worth investing more time and research into this area.

I think it is interesting to note that in the studies mentioned there is a trend where youngest dog in the study was a large, Rhodesian ridgeback, or giant breed, Newfoundland and Bernese Mountain dog, which adds to the idea that there is a genetic element of OA. It is interesting to note that most dogs in the mentioned studies were above 8 years old which deems them all geriatric dogs, this could affect the results slightly as older animals could have underlying diseases or slower metabolisms which could affect the outcomes of the studies. In dogs with underlying illnesses such as, kidney insufficiency, CBD seems to be a promising alternative to NSAIDs which are known to aggravate problems in patients with this existing illness.

OA is such a common disease, even in this modern era of veterinary medicine, therefore, I believe it's important that there is constant need for new research in this area. While evaluating current treatments and exploring newer treatment options for these patients to better manage and understand this disease. I think further exploration of this topic is needed particularly about the long-term effects of CBD and potential side effects. Ideally, there would be more clinical trials with a larger sample size for more accurate and interpretable results.

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Thesis progress report for veterinary students

Name of student: Nicola Holland

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Name and title of the supervisor: Dr. Cserhalmi Dániel, associate professor, head of Department

Department: Department of Botany

Thesis title: The Treatment of Osteoarthritis in Dogs with CBD Oil: A Literature Review

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2024	02	09	Discussing the major chapters of the thesis	
2.	2024	03	01	Literature consultation on osteoarthritis	
3.	2024	03	22	Literature consultation on CBD	
4.	2024	04	25	Literature consultation on CBD	
5.	2024	05	17	First draft consultation	

Grade achieved at the end of the first semester: 5

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2024	08	30	First revision	
2.	2024	09	19	Discussing comparative treatment session	
3.	2024	10	18	Second draft consultation	

4.	2024	11	08	Second revision	
5.	2024	11	15	Final editing	

Grade achieved at the end of the second semester: 5

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

ÁLLATORVOSTUDOMÁNYI EGYETEM Növénytani Tanszék 1787 BUDAPEST

.....

signature of the supervisor, tanszékvezető

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in 2024.11.19.