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## Effects on Pain and Mobility of a New Diet Supplement in Dogs with Osteoarthritis: A Pilot Study

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### Abstract

In this study, we have evaluated the efficacy of a new diet supplement in reducing chronic pain and improving mobility in a group of 10 dogs with Osteoarthritis (OA). OA is a common debilitating condition affecting humans and animals. Tablets containing a preparation of natural ingredients (Cannabidiol (CBD)-rich fraction, *Boswellia serrata* Roxb. in a Phytosome® delivery form and *Cucumis melo* L. extract) were administered for 30 days. Veterinary evaluations were performed and owners filled questionnaires on chronic pain (Helsinki chronic pain index-HCPI) three times during the study. The product was well tolerated and owners reported a good palatability and ease of administration. In terms of effectiveness, results of a Generalized Linear Mixed Model (GLMM) on HCPI highlighted a significant reduction of pain scores at the end of the study. Based on our observations, our new dietary supplement has beneficial effects in dogs with OA after the treatment.

**Keyword:** Pain; Diet supplement; *Boswellia serrata*; Cannabidiol (CBD); Osteoarthritis; Dog

### Introduction

Osteoarthritis (OA) is a degenerative and inflammatory condition, progressive and debilitating. It affects both humans and animals worldwide. More than 20% of the dogs >1 year of age are affected by OA. In normal joints, cartilage covers and protects the ending part of bones, promoting friction and absorbing impacts. The progressive joint destruction leads to

lameness, pain, mobility limitations and it compromises the overall quality of life [1]. In the absence of a definitive cure for this condition, the main goals for clinicians are the slowing down of disease progression, reduction of chronic pain and improvement of everyday activities. Together with the opinion of a specialist veterinarian, the ongoing monitoring of chronic pain in dogs with OA using validated owner questionnaires could be considered as a valid indirect measure of change in the inflammation status and a useful tool to set or modify therapies [2]. A multimodal approach is commonly used to treat OA in animals: physiotherapy, body-weight control, appropriate nutrition, anti-inflammatory drugs and analgesic [3]. It is worth making that clear that the most common drugs used to reduce inflammation in patients with OA, like non-steroidal anti-inflammatory drugs (NSAIDs), are not always completely effective or well tolerated and they have no disease-modifying effects. The long-term use of pharmacological agents should be considered with caution taking into account the ratio between benefits and risks [4,5]. In literature, several clinical studies reported that NSAIDs do not provide complete pain relief in dogs with OA and that refractory cases are common [6]. In the recent years, nutraceuticals, food or dietary supplements that offer health and medical benefits have been largely studied and used for treating both humans and animals affected by OA, reporting few or no side effects. Even if most of the available studies have limitations and bias, these new approach is opening large horizons for modifications in the management of musculoskeletal diseases that have a chronic progression such as OA in dogs [4,7]. For example, the gum resin extracted from the *Boswellia serrata* Roxb. possesses anti-inflammatory, anti-arthritis and analgesic activity and has been used in the traditional Ayurvedic medicine [8]. On wounding, *B. serrata*

yields a gummy oleoresin, which contains oils, terpenoids and polysaccharides. The resinous part of *B. serrata* is characterized by monoterpenes, diterpenes, a mixture of pentacyclic triterpene acids known as boswellic acid ( $\alpha$ ,  $\beta$ ,  $\gamma$ ), responsible for inhibition of pro-inflammatory enzymes [9,10]. In addition, boswellic acids were found to be able to significantly ameliorate the inflammation status by reducing the infiltration of leucocytes into the knee joint [9]. As a specific example,  $\beta$ -boswellic acid, the main triterpene from the resin, is able to modulate the inflammatory response of the cathepsin G [11] and to inhibit the microsomal prostaglandin E2 synthase-1 E1 (mPGES-1) [12].

In a recent review [13], relevant anti-inflammatory properties of another natural product, Cannabis (*Cannabis sativa* L.), was pointed out. In this review, it is stated that “the endocannabinoid system actively participates in the pathophysiology of osteoarthritis-associated joint pain”. In human medicine, several trials confirmed the efficacy of endocannabinoid agonists that target the peripheral Cannabinoid receptor type 2 (CB2), providing benefits in reducing inflammation and chronic pain in patients with chronic disease (i.e., arthritis). In Europe, Cannabidiol (CBD)-based oil products obtained from inflorescences of industrial hemp varieties are an article of commerce in several EU countries [14].

In addition to inflammation, significant oxidative stress is commonly observed in articular cartilage and synovium suffering from OA [1]. In fact, some diseases associated with aging in pets are often linked to this. In the recent years, the interest in the use of dietary anti-oxidant superoxide dismutase (SOD) in the therapeutic application has increased [15,16]. As an example, the product resulting from the lyophilization of melon fruit pulp and juice (cantaloupe melon, *Cucumis melo* L.) is naturally rich in the primary SOD. Studies have already demonstrated the antioxidant and anti-inflammatory properties in experiments *in vitro* and *in vivo* [17]. This natural supplement is already used as antioxidant in poultry and weaning pigs to overcome stress and to improve performance [17,18]. Anti-oxidants may also be beneficial in dogs with OA, improving joint function and reducing pain [17]. The aim of this study was to evaluate for the first time the synergistic effect of different active ingredients with proven anti-inflammatory activity in a group of dogs with OA in reducing joint inflammation and chronic pain. Specifically, we tested a new oral diet supplementation containing a Cannabidiol (CBD)-rich fraction obtained from industrial hemp extract oil and derived products, *B. serrata* Roxb. in a Phytosome® delivery form and *Cucumis melo* L. extract.

## Materials and Methods

### Animals included and recruitment

Client-owned dogs suffering from OA were recruited by two veterinarians between May and June, 2018 (Alessandria, Italy). A written informed consent was obtained from the dogs' owners who were fully aware of the study design. All procedures, treatments and animal care were in compliance with the guidelines of the Italian Minister of Health for the care and use of animals (D.L. 4 March 2014 n. 26). Inclusion criteria were the

following: confirmed radiographic and clinical signs of OA by a veterinarian orthopedic on at least one joint. Exclusion criteria are listed here: evidence of other diseases based on clinical history and blood test results, acute pain, recent trauma or surgery on any joint in the previous 6 months, neurological conditions, medications or diet supplements given in the two weeks before the enrolment in the study.

### Study design and the dietary supplement

We performed a pilot study where a new diet supplement produced by the Candioli Pharma S.r.l (Italy), was orally administered in dogs with osteoarthritis once daily for a total of 30 days. The dose per day was calculated according to the manufacture instruction and based on animal weight. The tablet preparation consists in a combination of natural ingredients containing mainly: Cannabidiol (CBD), Casperome® (Indena, Italy) and powdered melon fruit pulp and juice (*Cucumis melo* L.) extract. The CBD used in the supplement is a 99+% pure Cannabidiol crystalline (powdered) form isolate derived entirely from industrial hemp oil (*Cannabis sativa*) extracted from the mature stalks and stems of the plant (no-GMO and pesticide free). The final daily quantity of CBD given to dogs through the supplement administration was about 2.4 mg (range from 2.04 to 2.56 mg) per 15 kg of body weight. Then, Casperome® (Indena, Italy) is a purified mixture of terpenes acids ( $\geq 25\%$ ) from the *Boswellia serrata* Roxb. resin. The extract was obtained using the Phytosome® technology [19] in order to improve the absorption. The final daily quantity of Casperome® given to dogs through the supplement was about 150 mg (range from 145 to 155 mg) per 15 kg of body weight. Finally, a lyophilized hygroscopic micro-encapsulated powder obtained from concentrated juice and pulp of fresh melons (cantaloupe melon, *Cucumis melo* L.) was added to the mixture. The daily quantity given to dogs through the supplement administration was about 10.08 mg (range from 9.81 to 10.22 mg) per 15 kg of body weight. A full list of ingredients is reported in **Table 1**. The dogs enrolled in the study were subject to a veterinary examination and an owner evaluation of their pain level at different time points during the period under observation: Baseline (T0), then after 15 (T1) and 30 (T2) days.

**Table 1** Ingredients included in the tested supplement. Quantity of each ingredient contained in in each tablet.

Ingredients	Quantity (mg) in a tablet of 1,2 gr
<i>Cucumis melo</i> L.	10.08
Hempseed oil ( <i>Cannabis sativa</i> )	35.64
Casperome®( <i>Boswellia serrata</i> Roxb.)	150
Cannabidiol (CBD assay nml 99.9%)	2.4
Technological additives (antioxidants, emulsifiers, stabilizing agents)	1001.88

## Veterinary and owner evaluation

A veterinary assessed each dog included in the study at baseline (T0), at 15 (T1) and 30 (T2) days. A clinical general examination and an orthopedic examination were performed at each visit. A radiological assessment was carried out before enrolling the dog in the study, no other radiographies were requested at T2 based on the very low probability to find significant changes in radiographic findings after 30 days of treatment. The veterinarian collected data on sex, age, breed, and body weight. In addition to the veterinary assessment, a validated questionnaire on chronic pain in dogs was used to evaluate the effect of the supplement on pain over time. The functional behavior-based owner questionnaire (Helsinki Chronic Pain Index - HCPI) was translated from English to Italian [20]. A total of 11 questions on the dog's mood, lameness, and willingness to move, play, and jump were present in each questionnaire. The answers vary from a score of 0 to 4, where scores of 0 and 1 indicate a normal movement and behavior, scores from 2 to 4 indicate a crescent pain status. Owners had to mark the answer that best described their dog between visits. The minimum index number is 0 (11 × 0) and the maximum index number is 44 (11 × 4). Based on the literature, a dog is considered "healthy" when the HCPI is between 0 and 11, being a score of 1 considered "normal". Dogs with chronic pain have a HCPI between 12-44. This index is commonly used to assess chronic pain in dogs and cats, and its use is very common to see the progress of pain [21,22].

A scale from 0 to 3 was used to score the ease of tablet administration (0=easy, 1=quite easy, 3=difficult), the palatability of the product (0=low, 2=medium, 3=high) and its effectiveness (0=low, 2=moderate, 3=high). The three scores were given at each visit by the owner, while the veterinarian independently scored the effectiveness of the product only.

## Statistical analysis

Mean value of dog age (years, yr), weight (Kilograms, Kg), and standard deviation (SD) were reported. Fraction of males and females were calculated. The mode of the scores given at each visit on the ease of administration of the tablets, the palatability of the product and its effectiveness was calculated. Results of HCPI questionnaires were graphically represented. Generalized Linear Mixed Model (GLMM) was applied to investigate the pain score reduction during the study period based on results of the HCPI.

The model formula:  $Score = Time + Case_{rnd}$

Score represented the HCPI; Time is T0, T1 and T2;  $Case_{rnd}$  is the animal random effect. The random effect was included in the model to account for individual variation. The Poisson distribution was set as the statistical distribution to perform the model. The analysis was performed using R software (2018) [23].

## Results

Eight dogs out of 10 completed the study. An autoimmune disorder was diagnosed to one dog after 21 days of

supplementation and the owner of the second dog decided to suspend the administration of the supplement.

Dogs' ages ranged from 5 to 14 years (mean  $10.4 \pm 3.1$  SD), with 2 dogs (20%) being females and 8 dogs (80%) being male. Breeds of dogs included in the study are listed here: Mixed Breed, German Shepherds, Labrador Retriever, Pointer, Border Collie, Italian Mastiff, Belgian Shepherd dog. They were all large size companion dogs weighting 20-50 kg (mean  $31.2 \pm 13.8$  SD kg), apart from one small size dog weighting 7.4 Kg.

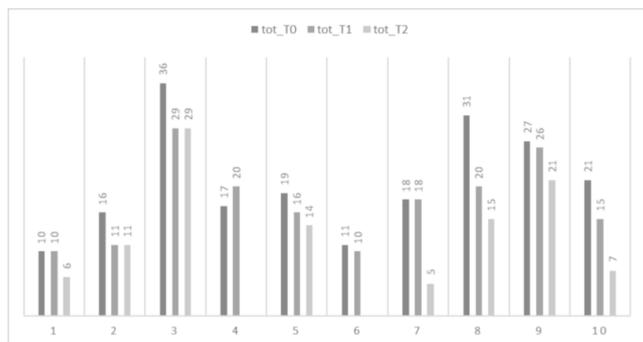
The supplement was well tolerated and no episodes of vomiting or diarrhea was reported. The mode of scores registered at T1 and T2 on the following three parameters is reported in **Table 2**: The ease of administration of the tablet, the palatability of the product and its effectiveness. The tablets were found to be ease to administer by the owner, none reported a score different from 0. The palatability of the product was found to be very good (mode=3) during the whole study period. A good agreement on the effectiveness of the product based on the owner and veterinary scores was highlighted. In five cases (50%) a score increase of 1 point from T1 to T2 was recorded, in the other 5 cases it remained unchanged.

**Table 2** The mode scores registered at T1 and T2 by owners on the ease of administration, palatability, and effectiveness and by the veterinarian on the effectiveness of the administered tablets.

	Owner		Veterinarian	
	T1	T2	T1	T2
Ease of administration	0	0		
Palatability	3	3		
Effectiveness	0	3	1	3

The questionnaires on chronic pain in dogs were completed by all the owners at each visit and the results are graphically represented in **Figure 1**. Only two questionnaires were not completed at T2 because the dogs suspended the treatment. Our results on HCPI highlighted that only two dogs (20%) had a baseline score of 10 and 11 respectively, these scores correspond to the upper limit for defining a dog as "healthy" based on the literature. The indexes we calculated for the other cases were included in the range of 16-36. The GLMM performed on HCPI data (**Table 3**) highlights a reduction of score at both T1 and T2 compared to the baseline (T0). At T2 the index is significantly ( $p < 0.01$ ) lower than the baseline (T0).

We didn't notice any difference in the effect of age, weight, breed or sex on the pain score (data not shown). The study was not designed with this purpose and the sample size was not sufficient to perform further statistical analysis.



**Figure 1** The Helsinki chronic pain index (HCPI) at T0 (tot\_T0), T1 (tot\_T1) and T2 (tot\_T2) in 10 cases. On the top of each bar the HCPI is reported.

**Table 3** Results of the GLMM applied to investigate the pain score reduction during the study period (T1, T2). T0 is the reference time.

Variable	Effect (95% CI)
Intercept	2.97 (2.67, 3.27) **
<b>Time (Ref T0)</b>	
Time T1	-0.16 (-0.39, 0.06)
Time T2	-0.47 (-0.74, -0.21)**
**p<0.01	

## Discussion

The management of OA is a well-known challenge for clinicians in both Veterinary and Human Medicine. The main goal of clinicians is the reduction of pain and the improvement of the general conditions of their patients. In the past years there was an increase interest in the use of alternative approaches to the disease. For example, the use of diet supplements to reduce pain and inflammation in veterinary settings is starting to be considered as a good alternative to traditional drugs, primarily to avoid more and more common side effects mostly associated with a long-term use. Several literature reviews report the need of *in vitro* and *in vivo* studies on the speed of absorption, bioavailability, dosage regimen, biomarkers, safety, and long-term use of natural ingredients included in diet supplements [20]. Beside this, in our pilot study the administration of a new diet supplement was devoid of negative effects. No alteration of the normal animal conditions was reported by the veterinarian, confirming the safety and tolerability of the product used in our animals. In terms of effectiveness of the new supplement, there is a good agreement between the mode scores of veterinarians and owners, in most cases at T2 there is an increase in score of 1 point. An overall positive opinion of veterinarians and owners on the new supplement was already highlighted after 15 days from the beginning of the treatment. To straighten this subjective outcome, the results of our statistical model confirmed that a significant reduction in pain was observed after 30 days of

treatment. Despite in the scientific literature is shown that a greater effect of diet supplements should be seen after at least 8 weeks of treatment [24], in our case a satisfactory improvement of animal conditions was registered well before this time window. However, our statistical analysis approach took into consideration variations within individual. Finally, based on our observations lengthening of the treatment duration could lead to an even better result of the product. Using diet supplements and specifically, multicomponent formulations seem to be more effective than an ingredient used alone [25]. More and more often, the preparation of new diet supplements provides the use of combination of ingredients easily available in nature and able to synergically work to amplify their anti-inflammatory, chondroprotective and analgesic effects [25-29]. The strength of our new supplement is its formulation based on several components confirmed in literature to have anti-inflammatory and anti-oxidant effects. At our knowledge no studies reported the synergic effects of Cannabidiol (CBD)-rich fraction, *B. serrata* Roxb. and *Cucumis melo* L. extract in veterinary medicine. Data on the usefulness of these components in single formulations has already been demonstrated to be effective in the treatment of OA and other inflammatory conditions and oxidative stress in animals [17,28,30].

Being OA a chronic condition, its treatment could last for the whole animal life, thus the owner needs to be also reassured for the ease of administration and for the good palatability of a product. Interestingly, the scores summarized in **Table 2**, show that the tablets given to the animals in our study were found to be ease to administer; none reported a score different from 0. The palatability of the product was found to be very good in all cases. These results are encouraging for owners always worried about administering new products to their pets every day and for a long period of time.

## Conclusion

Our study shows beneficial effects of a new dietary supplement on the pain management and mobility in dogs with OA. The combination of natural ingredients seems to work well in this formulation being the overall effect of the treatment very satisfying. In addition to the tolerability and safety of our product, its good palatability and its ease of administration have to be considered relevant points for the success of a long lasting treatment in animals with a chronic pain like OA. A new study is currently underway for the purpose of reinforcing these preliminary results.

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## Conflict of Interest

One of the authors is employee of the Candioli Pharma S.r.l. (Italy). Two of the authors are scientific consultants for the

Candioli Pharma S.r.l (Italy). Candioli Pharma S.r.l is a company that may be affected by the research reported.

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