

# EUFORIS SCIENTIFIC SUBSTANTIATION

## Hemp extract

There are many clinical studies underway regarding the use of cannabis or CBD to treat different disorders: cancer, anxiety, epilepsy, etc. that can be checked at the U.S. National Library of Medicine<sup>1</sup>.

At a veterinary level, three professionals in the USA that have been working with cannabis extracts for treating cats and dogs stand out: Gary Richter, Robert Silver and Caroline Coile. We can read about their clinical experiences and recommendations on the therapeutic use of cannabis on different publications<sup>2-4</sup>. Although in the USA the legal situation of cannabis is complex, the therapeutic efficacy of this plant has allowed to find a way to enable its safe administration to pets.

It is therefore undeniable that cannabinoids have fully entered the research field because of their novel and safe mechanism of action. They are also providing an answer to disorders that can currently only be tackled partially or symptomatically, and that is why the clinical expectations and interest are even greater.

Delta (9)-tetrahydrocannabinol binds cannabinoid (CB (1) and CB (2)) receptors, which are activated by endogenous compounds (endocannabinoids) and are involved in a wide range of physiopathological processes (e.g. modulation of neurotransmitter release, regulation of pain perception, and of cardiovascular, gastrointestinal and liver functions). The well-known psychotropic effects of Delta (9)-tetrahydrocannabinol, which are mediated by activation of brain CB (1) receptors, have greatly limited its clinical use. However, the plant Cannabis contains many cannabinoids with weak or no psychoactivity that, therapeutically, might be more promising than Delta (9)-tetrahydrocannabinol. Here, we provide an overview of the recent pharmacological advances, novel mechanisms of action, and potential therapeutic applications of such non-psychotropic plant-derived cannabinoids. Special emphasis is given to cannabidiol, the possible applications of which have recently emerged in inflammation, diabetes, cancer, affective and neurodegenerative diseases, and to Delta (9)-tetrahydrocannabivarin, a novel CB (1) antagonist which exerts potentially useful actions in the treatment of epilepsy and obesity<sup>5</sup>. Cannabidiol has extended proof on its powerful anti-inflammatory, analgesic, anxiolytic, antioxidant and neuroprotective properties<sup>6-8</sup>.

The ECS has been shown to be involved in the development of canine OA in a very recent study in which endogenous molecules that regulate the ECS activity were measured<sup>9</sup>. Surprisingly, it was seen that the levels of two of them (2-AG and oleoylethanolamide) were higher in the patients with OA in comparison with healthy dogs, this suggesting, for the first time, a direct involvement of the ECS in the development of this joint disease in dogs. The authors of the article point out that the CBR agonists, such as phytocannabinoids from Cannabis sativa, can become an innovative treatment for canine OA<sup>9</sup>. In fact, therapies with different (synthetic or plant) cannabinoids have been already developed for human patients with OA or rheumatoid arthritis (RA)<sup>10</sup>. Moreover, in year 2000, researchers from the Kennedy Institute of Rheumatology in London showed that CBD has an anti-arthritic ability in mice<sup>11</sup>.

Cannabinoids have proved their analgesic effects through different mechanisms<sup>12</sup>. One of them is related to the neurotransmission of glutamate. The activation of the glutamate receptor in the postsynaptic neuron induces the synthesis of 2-AG, that releases and activates CBR1 in the presynaptic neurons. This blocks the calcium inflow and stops the release of

neurotransmitters. Cannabinoids exert a negative feedback mechanism (retrograde signaling), that can act directly, by activating the CBR1, or indirectly, by modifying the activity of the enzymes that synthesize or break down cannabinoids (FAAH or MGL, for example). Probably, the antinociceptive effect may be mediated by the inhibition of the release of glutamate in the areas related to pain.

A report drafted by the National Academies of Sciences Engineering Medicine affirms that there are substantial or conclusive evidences that show the efficacy of cannabis in the treatment of chronic pain in adults<sup>13</sup>, highlighting, once more, the great potential of cannabis for treating pain. Likewise, there are a pair of examples that serve, once more, as a great indication of this analgesic effect:

1. The improvement of pain was the most noted effect in the pets that were administered a cannabis-containing product<sup>14</sup>.
2. In those countries where medicinal cannabis has been legalized, the use of opioids has dropped dramatically<sup>15</sup>.

A reason that causes frequent visits to the veterinarian is itching, because it bothers both the pet and the owner. In these disorders there is a clear immune, nervous and inflammatory problem for which cannabis extract offers a therapeutic window. Along these lines, a study discovered an overexpression of CBR1 and CBR2 in epithelia of dogs with atopic dermatitis<sup>16</sup>. In addition, the immunomodulating ability of phytocannabinoids<sup>17</sup> can also help to control the skin disorders not only for reducing the annoying symptoms, but also to regulate the hyperactivity of the immune cells implied in their physiopathology.

Epilepsy is one of the most common chronic neurologic disorders in dogs, and it is characterized by an imbalance in the neuronal excitability that causes recurrent convulsions<sup>18</sup>. It is deemed that this disease cannot be controlled in 25% of the dogs that suffer it<sup>19</sup>, showing the urgent need for finding alternative treatments with less side effects. There is a great deal of research with regard to the use of cannabinoids against epilepsy in humans<sup>20</sup>, including five Chinese studies<sup>1</sup>. Although the use of phytocannabinoids for canine and feline epilepsy has not been thoroughly studied, the great number of veterinary clinical experiences, coupled with the good results as anticonvulsants in human patients, suggest that phytocannabinoids can be an excellent therapeutic support tool for these disorders.

Cannabinoids have proven their ability in modulating the activity of microglia in several in vitro and in vivo models<sup>21</sup>. In an Alzheimer's disease model in mice, the administration CBD reduced the expression of several proinflammatory cytokines released from microglia (such as iNOS and IL-1 $\beta$ )<sup>22</sup>, that caused an improvement in cognitive function<sup>23</sup>. Likewise, in animals with memory loss, CBD helps to improve it<sup>24</sup>.

Last but not least, it is not surprising that phytocannabinoids, particularly cannabidiol, have an anxiolytic effect, because they can regulate the activity of the ECS at the central nervous system level and thus modulate the processes related to anxiety<sup>25</sup>. In pets, a report revealed that almost 50% of the owners noticed an obvious improvement of anxiety in their dogs when they administered them a product containing cannabis<sup>26</sup>.

## **Fish oil and omega-3 fatty acids**

Omega-3 fatty acids have an antioxidant and anti-inflammatory ability, and therefore they are very useful in cases of joint problems in dogs. A study conducted in 2010 showed that the supplementation with omega-3 fatty acids improved the walking ability in dogs with osteoarthritis (OA) in one or more joints<sup>27</sup>. Along the same lines, dogs with OA showed a decrease in lameness and an increase in the weight bearing ability when they were provided an

omega-3 rich diet<sup>28</sup>. Bearing these results in mind, it is not a surprise that the supplementation with omega-3 fatty acids allows to reduce the amount of anti-inflammatory medications (carprofen) needed by dogs with OA<sup>29</sup>.

Bearing in mind the key role of omega-3 fatty acids on brain performance, it is not surprising that the supplementation with omega-3 fatty acids has shown important benefits in the improvement of cognitive dysfunction. For instance, the supplementation with docosahexaenoic acid (DHA) from seaweed improved the cognitive performance parameters in an in vivo study of canine ageing in Beagles<sup>30</sup>. Likewise, omega-3 fatty acids also have a positive impact in the neuronal development of puppies. By fortifying the diet of pregnant bitches, the DHA levels are increased in the pups, and this turns into an improvement in the electroretinogram responses<sup>31</sup>.

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