

# A Review of the mechanisms and clinical effects of CBD for neurological conditions

## Abstract

Cannabinoids are compounds that have received much attention for their medicinal effects on the brain and nervous system. There has been intensive research into the therapeutic use of cannabinoids to treat anxiety, pain, epilepsy, addictions, and other neurological conditions. There is an increasing number of published papers on CBD mechanisms and clinical efficacy for neurological disorders.

**Keywords:** cannabinoids, CBD, cannabis, *cannabis sativa*, *cannabis indica*, endocannabinoid system hemp

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## Introduction

Cannabinoids are compounds that have received much attention for their medicinal effects on the brain and nervous system. There has been intensive research into the therapeutic use of cannabinoids to treat anxiety, pain, epilepsy, addictions, and other neurological conditions. This paper will examine the literature on the cellular mechanisms of cannabinoids, especially cannabidiol (CBD), and clinical benefits for brain and nervous system-related conditions in humans.

## Overview of CBD

*Cannabis sativa* (*C. sativa*), also known as Indian hemp, is a plant that is used as a source of marijuana, hemp, and CBD oils.<sup>1</sup> Marijuana and hemp are extracted from two different strains of the Cannabis family. Hemp is harvested from *Cannabis sativa* and marijuana from *Cannabis indica*. Cannabis contains over 400 chemical compounds and approximately 80 known biologically active chemical molecules.<sup>2</sup> The most well-researched compounds are the cannabinoids. About sixty cannabinoids have been identified, with the most psychoactive compound identified as tetrahydrocannabinol (THC), especially the isomer delta-9 ( $\Delta^9$ -THC).<sup>2</sup> Additional cannabinoids include CBD, which is the most extensively researched, and several others.

There are two main categories of cannabinoids, which include exogenous or endogenous. While this paper will focus on exogenous cannabinoids, it is important to recognize that the human body produces endogenous cannabinoids.<sup>3</sup> The two main endogenous cannabinoids (endocannabinoids) include anandamide and 2-arachidonoyl glycerol (2-AG). These cannabinoids function as transient neurotransmitters and are produced by postsynaptic nerve fibers.<sup>3</sup> The exogenous cannabinoids from cannabis are known as phytocannabinoids. *Cannabis indica* phytocannabinoids include THC, CBD, and others, while *Cannabis sativa* contains CBD and <0.3% THC.

There has been an emerging focus on full spectrum Cannabis sativa products. Researchers have found that there are more than 100 different cannabinoids and approximately 460 other known biologically active compounds.<sup>4</sup> For centuries human ailments have been treated with cannabis. Thus, the full therapeutic effects of Cannabis sativa may well go beyond what is currently used in isolate products. Human trials using the entire plant suggest the relevance of other compounds beyond isolated THC and CBD. For example, a review of full-

spectrum cannabis along with standardized concentrations of THC and CBD has shown to be effective for neuropathic pain, spasticity, and other symptoms associated with multiple sclerosis.<sup>4</sup> The same authors noted that previous research with isolated THC was not as effective.

## Safety profile

CBD has an excellent safety profile and very low toxicity in humans at a wide range of doses.<sup>5</sup> However, whether long-term CBD use during pregnancy is safe is unclear, and CBD should, therefore, be avoided because of potential teratogenic effects.<sup>6</sup> It has been demonstrated that CBD easily passes the blood-brain barrier.<sup>5</sup> CBD does, however, not cause the sensation of feeling "stoned".<sup>7</sup> The most commonly reported side effects of CBD are tiredness, diarrhea, and changes in appetite and weight.<sup>5</sup> There is potential for interaction with enzymes of the cytochrome P450 family, which can affect drug metabolism.<sup>5</sup> An additional safety assessment of a retail form of CBD involved a 2-year post-marketing and surveillance that included approximately five million product units sold.<sup>8</sup> Only 1,429 (0.03%) adverse events were reported, and no evidence of liver toxicity.<sup>8</sup> A report by the World Health Organization stated that CBD does not have concerns for abuse potential.<sup>9</sup> And lastly, a literature review showed that CBD doses up to 300 mg/day have been safely used up to six months, while doses of 1200 to 1500 mg/day were used in a study for up to four weeks.<sup>1</sup>

## Endocannabinoid system

The endocannabinoid system (ECS) is an endogenous signaling system.<sup>5</sup> The ECS contains two primary G protein-coupled cannabinoid receptors known as CB1 and CB2.<sup>5</sup> These endocannabinoid receptors have distinctive distribution within the body and are located within the brain and throughout the central and peripheral nervous system.<sup>5</sup> Both receptors can co-locate in the same tissues at various concentrations<sup>5</sup> and have different ligands.<sup>3</sup> The CB1 receptors are found predominantly in the brain and spinal cord, and their location at the end of nerve endings function to reduce pain sensation.<sup>3</sup> CB1 receptors located in the amygdala affect memory and emotional processing, while those in the hypothalamus affect appetite regulation.<sup>3</sup> CB2 receptors are more common in the peripheral nervous system and immune cells and reduce inflammation.<sup>3</sup> The molecular

targets of CBD include cannabinoid and non-cannabinoid receptors, enzymes, transporters, and cellular uptake proteins.<sup>5</sup>

The class of endocannabinoid lipid mediators and related enzymes that regulate their tissue levels, receptors that mediate their action, proteins required for biosynthesis and function and inactivation, and the genes encoding the proteins are known as the “endocannabinoidome.”<sup>10</sup>

The ECS plays a vital role in cell homeostasis where endocannabinoids and local mediators are synthesized on demand to activate targets as part of an adaptive response.<sup>10</sup> Tissue endocannabinoid levels and their targets are modified in nearly all chronic disorders as an adaptive response for homeostasis or as a maladaptive mechanism that contributes to the disease process.<sup>10</sup> The manipulation or influencing of endocannabinoid levels has shown to be of benefit in animal diseases.<sup>10</sup> As a result, there is a great deal of interest and research in the use of pharmaceuticals or phytocannabinoids (such as CBD) in the treatment of human diseases.

### CBD Mechanisms

Cannabinoids interact with cannabinoid receptors, yet many authors state that CBD has a low affinity for cannabinoid receptors.<sup>11</sup> However, CBD acts as an inverse agonist at CB1 and CB2 receptors.<sup>12</sup> CBD has more interaction with serotonin receptors, opioid receptors, non-endocannabinoid G protein-coupled receptors, and other targets such as ion channels and enzymes.<sup>11</sup> CBD has exhibits neuroprotective properties in neurodegenerative diseases, including Amyotrophic Lateral Sclerosis, epileptic seizures Parkinson’s, Huntington’s, and Alzheimer’s diseases.<sup>11</sup> In addition, CBD has anti-inflammatory properties via modulation of pro-inflammatory cytokines and regulation of cell cycle and immune cell functions. Another anti-inflammatory mechanism of CBD is binding to, and desensitization of, Transient Receptor Potential Vanilloid Type 1 (TRPV1), which detects and regulates body temperature<sup>11</sup> Also, CBD demonstrates potent antioxidant activity by modulating inducible nitric oxide synthase and nitrotyrosine in addition to reducing reactive oxygen species.<sup>11</sup>

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### Epilepsy and CBD

CBD was used in several studies to treat epilepsy. The literature and clinical trials studying the effects of CBD combined with common anti-epileptic drugs (AEDs) for severe treatment-resistant epilepsy were recently reviewed.<sup>11</sup> Most of the clinical trials involved pediatric genetically-based epilepsy.<sup>11</sup> In general, trials combining CBD with common AEDs reported good safety and efficacy.<sup>11</sup> Although the exact anti-epileptic mechanisms of CBD are not known, it seems

to normalize intracellular calcium. It should be noted that several of the trials used the FDA-approved CBD oral solution known as Epidiolex®. The FDA has approved Epidiolex® for the treatment of seizures associated with the rare forms of epilepsy known as Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) and for seizures associated with tuberous sclerosis complex (TSC) in patients one year of age and older.<sup>13</sup> Also, the CBD doses used to treat childhood epilepsy in the published trials are much higher than what is currently used in over-the-counter CBD formulations.

### Anxiety and CBD

In a review of several pre-clinical and clinical studies on the use of CBD for the treatment of anxiety, evidence was found for a possible role of CBD in the treatment of anxiety disorders.<sup>14</sup> The clinical research of CBD in humans is limited but includes beneficial studies for healthy volunteers, those with Seasonal Affective Disorder, and those with anxiety disorders and Post-Traumatic Stress Disorder. Further research is required to determine the effects on Generalized Anxiety Disorder and other anxiety disorders, as well as differences in gender. Also, neuroimaging studies involving healthy volunteers given a single oral dose of CBD (400 mg) compared to placebo was shown to decrease subjective anxiety in those receiving the procedure.<sup>15</sup> Also, single-photon emission computed tomography images showed increased activity in the limbic and paralimbic brain areas after taking CBD.<sup>15</sup> In addition, an outpatient study at a psychiatric clinic involving patients with primary concerns of anxiety and sleep complaints evaluated the potential benefit of CBD.<sup>16</sup> Most patients with anxiety were given 25 mg of oral CBD in the morning after breakfast. If insomnia complaints predominated, they were given the CBD after dinner. Researchers found that anxiety scores decreased rapidly and sustained during the 3-month study. CBD treatment was not very effective for insomnia as sleep scores improved in the first month in 66.7% of patients but were not sustained during the study period.

### Opioid withdrawal and CBD

CBD also has appeal in the treatment of opioid use disorder. There is evidence in animal models that CBD reduces the rewarding properties of opioid drugs and withdrawal symptoms and reduces heroin-seeking behavior. More importantly, a human pilot study demonstrated CBD (400 mg or 800 mg) reduced subjective cue-induced craving as well as reduced anxiety.<sup>12</sup> Unlike THC, CBD appears to decrease sensitivity to drugs of abuse, and decrease reward and drug-seeking anxiety.<sup>12</sup> While more research is needed, CBD offers promise for treating people dependent on opioids.

### Pain and CBD

There has been much interest in the use of CBD to treat pain, especially chronic pain. A review on CBD for chronic pain found that CBD has therapeutic potential as it provides analgesia in certain conditions and improves the quality of life.<sup>6</sup> However, the results of studies since the early 2000s have been quite mixed in terms of quality and effectiveness. The research included pain relief for patients with intractable pain due to multiple sclerosis, spinal cord injury, brachial plexus injury, and limb amputation; chronic pain associated with kidney transplantation; fibromyalgia; and improved quality of life and quality of sleep in chronic pain patients. However, it should be noted that most clinical studies evaluating intractable chronic pain with CBD often used a 1:1 combination of CBD:THC. The precise pain-reducing mechanisms are not clear, but research suggests the selective

activation of  $\alpha_1$ - and  $\alpha_2$ -glycine receptors, interaction with  $\alpha_3$ -glycine receptors, and interactions with spinal cord 5-HT(1A) receptors.<sup>6</sup>

## Conclusion

In conclusion, there is great interest in the molecular mechanisms of CBD on the brain and nervous system. A number of studies have been published on the phytocannabinoid CBD and its molecular mechanisms. However, further research is required to consolidate these mechanisms as well as interactions of CBD within the endocannabinoid system. The safety data for CBD is excellent, while the dosing used in studies varies greatly. The use of CBD for human neurological conditions is limited. However, there is research that supports the use of CBD for conditions such as epilepsy, anxiety, opioid use disorder, and chronic pain. There is a need for randomized controlled trials to evaluate CBD for neurological conditions that CBD is purported to benefit. Additional research is needed to further elucidate the benefit of full spectrum compared to isolate CBD products.

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## Conflicts of interest

The author declares there is no conflict of interest.

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