

The Benefits of Hemp-Derived Phytocannabinoids

WHITE PAPER ABSTRACT

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WHAT ARE PHYTOCANNABINOIDS?

Phytocannabinoids are plant-derived compounds capable of directly interacting with cannabinoid receptors in the body. Cannabinoids, derived from the Cannabis plant, have been utilized the most for therapeutic purposes. Over 100 cannabinoids exist in various Cannabis species, but clinical research has focused primarily on the psychotropic cannabinoid, tetrahydrocannabinol (THC), and its non-psychotropic antagonist, cannabidiol (CBD). Hemp (*Cannabis sativa L.*) is a tall, narrow plant rich in CBD, which is harvested from its flowers, seeds and/or stalk fibers. This species is relatively low in THC, containing less than 0.3%. (Contrast this with marijuana [*Cannabis indica*], which is short and densely populated with broad leaves that contain up to 30% THC and are virtually devoid of CBD.)

THE ENDOCANNABINOID SYSTEM

Both CBD and THC act upon the endocannabinoid system of the human body, which is a signaling system laced throughout the central nervous system and distributed among peripheral tissues, including the immune and reproductive systems, gastrointestinal tract, sympathetic ganglia, endocrine glands, arteries, lungs and heart.¹

The endocannabinoid system contains two subtypes of G-protein coupled cannabinoid receptors, CB1 and CB2, which are modulated by endocannabinoids. The primary endocannabinoids are arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG), derivatives of arachidonic acid.²

CB1 receptors are widely distributed throughout the brain, especially in the frontal cortex and the limbic system.³ Their agonists, including THC, exert psychotropic effects as activation of CB1 receptors leads to retrograde inhibition of the neuronal release of acetylcholine, dopamine, GABA, histamine, serotonin, glutamate, cholecystinin, D-aspartate, glycine, and noradrenaline.⁴ CB1 agonists also have antispastic, analgesic, antiemetic, neuroprotective, and anti-inflammatory actions, and are effective against certain psychiatric diseases.⁴

CB2 receptors are distributed throughout the brain, immune system, spleen, and leukocytes.³ Their agonists, such as CBD, modulate pain and inflammation, and are neuroprotective without producing negative side effects in the central nervous system.⁵ There are some overlapping pathways between the cannabinoid receptors. Activation of either or both types of receptors by endocannabinoids can result in neuromodulation that offers a “protective role” in many medical conditions.⁶ Research supports a role for modulation of the endocannabinoid system in managing a variety of issues, including emesis, pain, inflammation, multiple sclerosis, anorexia, epilepsy, glaucoma, schizophrenia, cardiovascular disorders, obesity, metabolic syndrome related diseases, Parkinson’s disease, Huntington’s disease, Alzheimer’s disease and Tourette’s syndrome.⁶

HEALTH BENEFITS OF PHYTOCANNABINOIDS

Pain Modulation

- Several CB2 agonists have reached clinical Phase II trials for pain management and numerous studies show their efficacy against chronic nonmalignant neuropathic pain.^{8,9}
- Joint pain is often rooted in central sensitization, characterized by significant spinal astrogliosis and increases in activity of metalloproteases MMP-2 and MMP-9 in the spinal cord. CB2 agonists exert analgesic effects in osteoarthritis models by attenuating the activity of these enzymes.¹⁰
- Analgesic actions of CB2 agonists may also be a result of their anti-inflammatory actions, reduction of basal NGF tone, induction of beta-endorphin release from keratinocytes, and direct action on nociceptors.¹¹

Cancer Support

- Cannabinoids are approved in many countries as an adjunctive analgesic in those with progressed cancer and malignant diseases where standard opioid treatment is ineffective. A systematic review of literature indicates cannabinoid therapy reduces pain intensity by >30% in those with malignant diseases.¹²
- Oral mucositis is a common outcome of the oxidative stress induced by chemotherapy and radiation. The antioxidant, anti-inflammatory and analgesic properties of cannabidiol (CBD) have been shown to protect the oral cavity from oral mucositis.¹³
- Cannabidiol acts on GPR12 receptors that are involved in cancer metastasis, and alters the viscoelasticity of metastatic cancer cells, providing a novel approach to preventing metastasis.¹⁴
- Anti-emetic effects of cannabidiol have been mediated by indirect activation of somatodendritic 5-HT_{1A} receptors, which reduces the release of 5-HT (serotonin) in the terminal forebrain. Nausea and vomiting are closely associated with the endocannabinoid system, giving more evidence for the use of cannabidiol as an anti-emetic in cancer patients undergoing chemotherapy.¹⁵

Systemic Inflammation

- Cannabinoids have shown therapeutic potential in a variety of chronic inflammatory conditions, including inflammatory bowel disease, arthritis, autoimmune disorders, multiple sclerosis, HIV-1 infection, stroke, and Alzheimer's disease.³
- CB2 agonists have been shown to inhibit chemokine-induced chemotaxis of various cell types, including neutrophils, lymphocytes, macrophages, monocytes and microglia. Migration of human monocytes is diminished in the presence of CB2 agonists.³
- In vitro studies showed CB2 agonists reduced TNF- α -induced activation of human coronary artery endothelial cells, but also reduced secretion of monocyte chemoattractant protein-1 (MCP-1) and attenuated monocyte transendothelial migration. Endothelium in the brain and other organs possesses CB2 receptors, allowing CB2 agonists to modulate inflammatory actions.³
- CB2 receptors are found in the enteric nervous system and colonic epithelium. The anti-inflammatory actions of CB2 agonists have shown both protective and healing effects on colitis and related inflammatory intestinal conditions.^{16,17}
- CBD has been shown to reduce joint inflammation, including cartilage degradation and bone erosion in several animal models and suppressed release of TNF- α from synovial cells.¹⁷
- CBD treatment reduces mitochondrial superoxide, inducible nitric oxide synthase (iNOS), nuclear factor kappa B (NF- κ B) activation, and transendothelial migration of monocytes, attenuating inflammation induced by hyperglycemia in diabetic mice.¹⁷

Neuroinflammation

- CB2 agonists offer neuroprotection by suppressing microglia activation via inhibiting the release of neurotoxic factors and by decreasing neuronal cell damage in cells or tissue.³
- Cannabinoids can also offer neuroprotection via their immunomodulatory properties, which include 1) induction of apoptosis, 2) suppression of cell proliferation, 3) inhibition of pro-inflammatory cytokine/chemokine production and increase in anti-inflammatory cytokines, and 4) induction of regulatory T cells.³
- Neuroinflammatory conditions, including MS, amyotrophic lateral sclerosis (ALS), Down syndrome, Alzheimer's disease, and stroke show upregulation of CB2 receptors in affected tissues, to enhance the opportunity for modulating inflammation and immunity.^{3,18-20}
- CB2 agonists have been shown to reduce iNOS production and prevent neuronal injury during neuroinflammation.³
- In studies using primary human brain microvascular endothelial cells and human monocytes, CB2 agonists diminished adhesion of leukocytes to activated endothelium and down-regulated adhesion molecules. Blood brain barrier injury and increased permeability were prevented.³
- Anti-psychotic effects of CBD have been noted, as it attenuated the behavioral and glial changes observed in an animal model of schizophrenia based on NMDA receptor hypofunction.⁷

Epilepsy

- Oral cannabidiol is a well-researched, effective, long-term therapy for treatment-resistant epilepsies, reducing monthly convulsions and the number of total seizures by an average of 50%.²¹
- CBD-enriched cannabis reduced seizure frequency in adolescents (aged 1 to 20 years) with refractory epilepsy up to 50%.²²
- CBD-enriched cannabis improved sleep, alertness and mood by 53%, 71%, and 63%, respectively, in adolescents with infantile spasms (IS) and Lennox-Gastaut syndrome (LGS), two forms of refractory epilepsy.²³

Parkinson's Disease

- Several clinical studies have shown cannabidiol as an effective treatment modality for reducing psychotic symptoms, improving dystonic symptoms, diminishing events related to REM sleep behavior disorder, and improving quality of life in movement disorders such as Parkinson's disease.²⁴
- Animal models suggest CBD may exert its greatest benefit as a preventative for numerous movement disorders, due to its neuroprotective and antioxidant properties, as well as its actions on 5-HT_{1A}, CB₁, CB₂, and/or PPAR_γ receptors.²⁴

Schizophrenia

- Antipsychotic effects of cannabidiol are evident in both animal and human models by facilitating endocannabinoid signaling and CB₁ antagonism. Randomized controlled trials on patients with schizophrenia show CBD, as an adjunct therapy, reduces psychotic symptoms, and improves cognitive performance and overall functioning.^{25,26}

Anxiety

- CBD can be an acute anxiolytic in individuals with generalized social anxiety disorder by modifying cerebral blood flow and as a 5-HT_{1A} receptor agonist.²⁶
- Animal models show CBD clearly possesses an anxiolytic effect that may be useful as therapy in social anxiety disorder, post-traumatic stress disorders, panic disorders, and obsessive compulsive disorder.²⁷
- A single CBD dose significantly reduced anxiety-related measures such as cognitive impairment and discomfort and anxiety, while increasing alertness and altering resting activity in limbic and paralimbic brain areas in test subjects during a public speaking test, a standard method for simulating panic disorders.²⁸

Post-Traumatic Stress Disorder

- CBD improves several symptoms associated with post-traumatic stress disorder (PTSD) including reducing acute heart rate and blood pressure, delays (24 hour) anxiogenic effects of stress by activating the by 5-HT_{1A} receptor, reducing arousal and avoidance, and enhancing the extinction and blocking the reconsolidation of persistent fear memories.²⁹
- Cannabinoids may also improve sleep quality, reduce frequency of nightmares, and lessen hyperarousal in those with PTSD.³⁰

Depression

- CBD modulation of the 5-HT_{1A} receptor and reduction of autonomic indices of stress, such as heart rate and blood pressure, have been shown to reduce symptoms of depression.³¹⁻³³
- CBD may stimulate hippocampal neurogenesis and modulate levels of hippocampal anandamide (an endogenous cannabinoid) with subsequent CB₁ activation, resulting in antidepressant-like effects.^{31,33}

Drug/Nicotine Withdrawal

- Through modulation of the endocannabinoid, serotonergic and glutamatergic systems, CBD may reduce the withdrawal symptoms experienced during therapy for cannabis/tobacco dependence.²⁶
- Preclinical studies suggest CBD may be an effective intervention for opioid, cocaine, and psychostimulant addiction, owing to its actions on various neurotransmission systems involved in addiction and due to its protective effect against stress vulnerability and neurotoxicity.³⁴

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