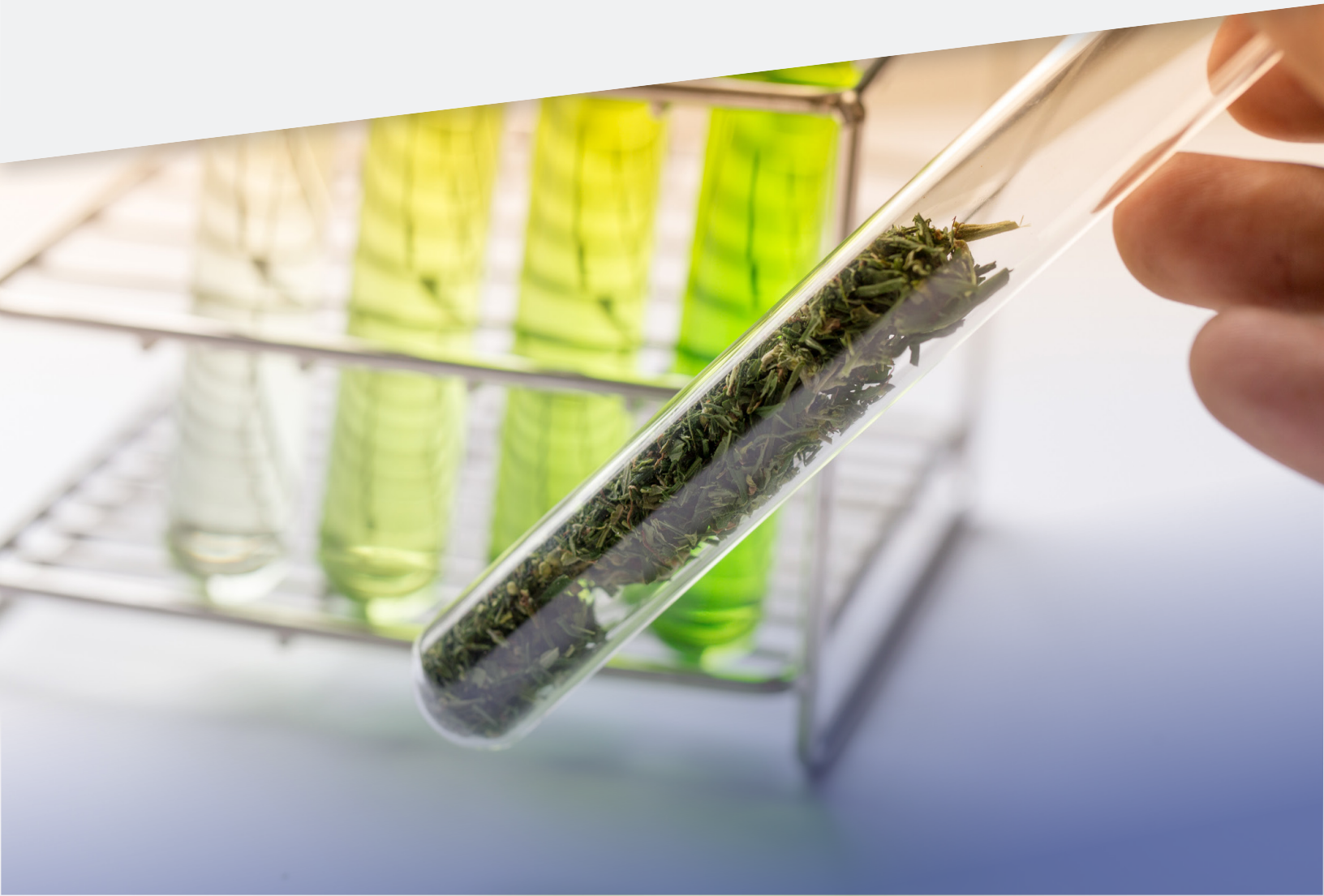
04/2020

WHITE PAPER

The Critical Role of Hemp-Derived Cannabinoids

Cannabinoids are an exciting area of research with far-reaching implications for human health. Because cannabinoid receptors are located throughout the body, they have been found to influence everything from appetite to the immune response.

"The Critical Role of Hemp-Derived Cannabinoids," compiles burgeoning cannabinoid research and highlights a 2019 study entitled, "Effects of CBD Hemp Extract on Opioid Use in Chronic Pain Patients."



The Critical Role of Hemp-Derived Cannabinoids

Cannabinoids are an exciting area of research with far reaching implications to human health. They are defined as any chemical substances found in the *Cannabis sativa* plant that bind to the cannabinoid receptors in the central nervous system (CNS), and are used for medicinal and recreational effects. *Cannabis sativa* contains at least 480 known natural chemicals, 80-100 of which are cannabinoids. In addition to the cannabinoids found in the *Cannabis sativa* plant, there are naturally occurring cannabinoids in the human body called *endocannabinoids*.

How Cannabinoids Function

Despite records of the medicinal marijuana use dating back 4700 years, we didn't understand how it worked in the human body until 1964 when Yechiel Gaoni and Raphael Mechoulam isolated the main psychoactive component of the Cannabis plant - tetrahydrocannabinol (THC).[1] Thanks to these researchers discovering the first cannabinoid, THC, the door was thrown open for further study into how cannabinoids work in the human body.

Endocannabinoid System

Cannabinoid receptors are found throughout the body and are part of the endocannabinoid system (ECS). The ECS is defined as a biological system composed of endocannabinoids (endogenous lipid-based retrograde neurotransmitters) that bind to cannabinoid receptors (CBRs).

Cell membranes of the receptors respond to cannabinoids, sending nerve signals to alter various processes in the body. The two most relevant cannabinoid receptors are known as CB1 and CB2. Endocannabinoids are naturally occurring substances produced by the brain that bind with CB1. One example of an endocannabinoid is anandamide (N-arachidonylethanolamine). CB1 and CB2 receptors are expressed predominantly in the brain and immune system, respectively.[2]

CB1 and its splice variant CB1A are densely located in the cerebellum, hippocampus, neocortex, amygdala, and striatum. As such, a wide range of behavioral functions related to emotion, memory, sensory perception, hunger, and motor responsiveness is mediated by CB1 receptors. CB1 is the predominant cannabinoid receptor in the CNS. CB2, on the other hand, is found outside the CNS - in the spleen and hematopoietic cells - making CB2 a modulator of the immune system.

The most common form of cannabinoid receptors (CB1) are located in the brain and are involved in just about every reaction in the body, from the immune system, decision-making and behavior to the dampening of excitatory transmission.

12 Main Classes of Cannabinoids

Tetrahydrocannabinolic Acid (THCA)	Cannabichromene (CBC)
Tetrahydrocannabinol (THC)	Tetrahydrocannabivarin (THCV)
Cannabidiolic Acid (CBDA)	Cannabinodiol (CBDL)
Cannabidiol (CBD)	Cannabicyclol (CBL)
Cannabinol (CBN)	Cannabielsoin (CBE)
Cannabigerol (CBG)	Cannabitriol (CBT)

A dysfunction in the ECS can have far-reaching implications since it may be involved in regulating fertility, pregnancy, various components of the immune system, appetite, pain sensation, mood and memory.

Appetite
The ECS has been shown to play a major role in the regulation of hunger. Thanks to the high concentration of CB1 receptor ligands in the hypothalamus, anyone who has tried cannabis is familiar with the heightened cravings for food. Researchers are, therefore, interested in suppressing hypothalamic CB1s to reduce eating in those suffering from obesity. Cannabinoid receptors also regulate fat metabolism via the liver. As a result, inhibiting cannabinoid function is being studied as a novel anti-obesity solution.[3]

Memory
Conversely, the activation of cannabinoids is being studied for the role they play in the dissipation of bad memories in patients with PTSD; the mice, genetically modified so they do not have CB1 receptors, find it harder to forget traumatic events and have a fearful response.[4]

Metabolic Functioning
The ECS has also been shown to support metabolic functions, such as energy storage, nutrient transport and modulating insulin sensitivity and, therefore, playing a role in obesity, diabetes and artherosclerosis.[5]

Stress Adaptation
With repeated exposure to stress, the ECS has been shown to modulate the hypothalamic-pituitary-adrenal axis (HPA axis). Studies have shown synthesis of anandamide during times of stress, and, as expected, a hypersecretion of corticosterone was found to decrease anandamide found along the axis.[6]

Immune Response
Activation of the cannabinoid receptors influenced the activation of GTPases in macrophages, neutrophils, and bone marrow cells, and help regulate IgM levels.[7]

Fertility
It has been shown that the developing fetus is receptive to anadamide secreted in the uterus and that this signaling is critical to implantation. In humans, the risk of miscarriage increases if anandamide levels are too high or low.[8]

Sleep
In an animal study, slow-wave and REM sleep have been shown to increase with the administration of cannabinoids. Increasing the endocannabinoid signaling within the central nervous system decreases wakefulness and promotes sleep induction.[9]

Effects of CBD Hemp Extract on Opioid Use in Chronic Pain Patients
In one study with chronic pain patients, full hemp extract cannabidiol (CBD) was used to determine impact on opioid use and quality of life indicators. The National Academies of Science, Engineering, and Medicine has stated that there is extensive evidence of cannabinoids efficacy in pain relief with good tolerability, and that CBD has been specifically been investigated for its potential to reduce the addiction risk and physiological dependence features of opioid use while subsequently managing pain.[10]

Preclinical models demonstrate CBD's ability to decrease relapse risk by reducing opioid seeking behavior,[11] and early human trials confirm CBD's potential in reducing opioid withdrawal symptoms.[12] A recent survey study concluded that 44% of hemp CBD users reported it helped reduce the use of their opioid pain medication.[12]

Specifically, CBD was found to reduce the craving, anxiety and psychological manifestations significantly in drug-abstinent individuals with previous opioid dependency.[13,14] Emerging literature supports evidence for CBD in pain relief and opioid reduction, but no studies to date had evaluated the effects of readily available hemp CBD in chronic pain and opioid use in a single cohort. This study was "aim[ed] at investigating the impact of hemp CBD use on opioid use in chronic pain, disability, physical and psychosocial symptoms, sleep, and motivation to taper opioids."

Participants were educated on safe CBD use, and ultimately elected whether or not to use CBD and self-titrated their dose of CBD. Of the 97 participants who completed the study, 94 chose to use the CBD soft gels. Almost all participants (91) used two soft gels (~30 mg) daily. One participant supplemented his free bottle of CBD soft gels and consumed four soft gels (~60 mg) daily. Two participants reported using only one soft gel (~15 mg) daily.

This study concluded that using CBD for chronic pain in patients using opioids has a significant effect on reducing opioid intake, reducing pain and improving quality of life (QoL). Over half of the participants who added CBD hemp extract reduced or eliminated opioids over the course of 8 weeks, and almost all CBD users reported improvements in QoL (figure 1).[15]

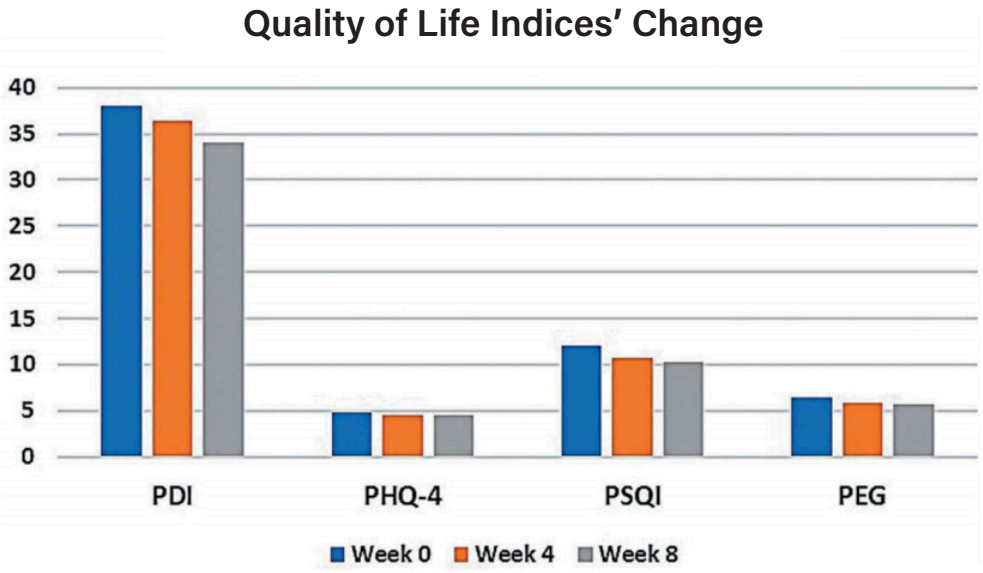


Figure 1. Quality of Life Indices' Change.

References:

1. Y Gaoni, R Mechoulam. Isolation, structure, and partial synthesis of an active constituent of hasish. Journal of American Chemical Society, 1964.
2. Pertwee RG (January 2008). "The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin". British Journal of Pharmacology. 153 (2): 199–215.
3. Ravinet Trillou C, Arnone M, Delgorge C, Gonalons N, Keane P, Maffrand JP, Soubrie P. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced mice. Am J Physiol Regul Integra Comp Physiol. 2003 Feb;284(2):R345-53.
4. Ken Mackie. Understanding the Cannabinoid Psychoactivity with Mouse Genetic Models. PLoS Biol. 2007 Oct; 5(10).
5. Bellocchio L, Cervino C, Pasquali R, Pagotto U (June 2008). The endocannabinoid system and energy metabolism. *Journal of Neuroendocrinology*. 20(6):850-7.
6. Hill MN, McLaughlin RJ, Bingham B, Shrestha L, Lee TT, Gray JM, Hillard CJ, Gorzalka BB, Viau V (May 2010). Endogenous cannabinoid signaling is essential for stress adaptation. *Proceedings of the National Academy of Sciences*. 107(20):9406-11.
7. Basu S, Ray A, Dittel BN. Cannabinoid rexeptor 2 is critical for the homing and retention of marginal zone B lineage cells and for efficient T-independent immune responses. The Journal of Immunology. December 2011.187(11):5720-32.
8. Maccarrone M, Valensise H, Bari M, Lazzarin N, Romanini C, Finazzi-Agrò A. Relation between decreased anandamide hydrolase concentrations in human lymphocytes and miscarriage. 2000. Lancet. 355(9212):1326-9.
9. Murillo-Rodríguez E, Sánchez-Alavez M, Navarro L, Martínez-González D, Drucker-Colín R, Prospéro-García O. "Anandamide modulates sleep and memory in rats". *Brain Research*. November 1998. 812 (1–2): 270–4.
10. Khan SP, Pickens TA, Berlau DJ. Perspectives on cannabis as a substitute for opiod analgesics. Pain Manag. 2019 Jan 25;9(2):191-203.
11. Ren Y, Whittard J, Higuera-Matas A, et al. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. J Neurosci. 2009 Nov 25;29(47):14764-14769.
12. Moeller-Bertram T, Schilling J, Hughes C, et al. (360) can CBD reduce the use of pain medication? Lessons from a survey in a pain clinic environment. J Pain. 2019 Apr 1;20(4):S64.
13. Hurd YL, Yoon M, Manini AF, et al. Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. Neurotherapeutics. 2015 Oct 1;12(4):807-815.
14. Hurt YL, Spriggs S, Alishayev J, et al. Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial. Am J Psychiatry. 2019 May 21.
15. Capano A, Weaver R, Burkman E. Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. Postgraduate Medicine. 2019 DOI: 10.1080/00325481.2019.1685298.