Anti-Aging Therapeutics
Volume XVII
2014 Conference Year

Editors
Dr. Ronald Klatz
and
Dr. Robert Goldman

An official educational work published by The American Academy of Anti-Aging Medicine (A4M)
1510 West Montana Street
Chicago, IL 60614 USA
TEL: (773) 528-6100 |
WEBSITES: www.worldhealth.net | www.a4m.com | www.a4minfo.net

Chapter 10

Nutritional & Medical Applications for Cannabidiol: Hemp Health Benefits without THC

Joseph Maroon, M.D., FACS[1];
Jeff Bost PAC[2]; Christina Mathyssek, Ph.D.[3]
1 Board-Certified Neurosurgeon, Senior Vice President-A4M, Heindl Scholar in Neuroscience-University of Pittsburgh School of Medicine, Team Neurosurgeon-Pittsburgh Steelers
2 Clinical Instructor-Neurological Surgery, Clinical Assistant Professor-University of Pittsburgh School of Medicine
3 Research Associate-University of Pittsburgh School of Medicine

ABSTRACT

Hemp and marijuana are two different varieties of *Cannabis sativa L.*, a flowering herb indigenous to many parts of the world. Marijuana is cultivated for its high levels of tetrahydrocannabinol (THC), which is concentrated mostly in the flowers and trichomes of the plant and has psychoactive properties. Traditionally, hemp has been cultivated for its fiber and food extracts and has almost undetectable levels of THC. Hemp has been grown and cultivated worldwide for thousands of years for industrial and medical purposes, making useful items like rope, clothing, sails, paper, and thousands of other products. Research into other uses for hemp has found comparatively high levels of cannabidiol (CBD), a non-psychoactive compound, which has shown significant human health benefits in numerous clinical trials.

In the 1970's CBD's anticonvulsive effects in humans were discovered. Later, other studies have shown anti-nausea, anti-anxiety, antioxidant, anti-inflammatory and analgesic effects as well as other disease specific benefits. An orally-administered liquid containing CBD has received orphan drug status in the US for use as a treatment for Dravet syndrome, a severe form of infant seizure disorder as well as a novel adjunct treatment for brain tumors. Hemp production in the US is heavily regulated and extremely limited due to federal regulations from the 1920's. Recent changes in both federal and state laws have allowed hemp oil extracts containing CBD to be imported in the US. Concentrated CBD obtained from hemp oil is now available and sold as both a medicinal and natural health supplement targeting a wide variety of human health conditions.

Plant-derived CBD is referred to as phytocannabinoid and possesses similar properties as animal-produced endocannabinoids. CBD is an aromatic hydrocarbon whose actions are mediated in part through interaction (antagonistic) with the existing cannabinoid receptors that make up the endocannabinoid system found in mammals. Mammalian tissues express at least two types of cannabinoid receptor CB1 and CB2. CB1 receptors are expressed predominantly at nerve terminals of both central and peripheral neurons where they mediate inhibition of transmitter release. CB2 receptors are found mainly on immune cells and other immune system mediators that modulate various cytokine and chemokines as part of the inflammatory response. CB2 receptors are specifically located on lymphocytes, macrophages, mast cells, natural killer cells, peripheral mononuclear cells and microglia.

This chapter will provide background information on CBD discovery and sources, including the differences between psychoactive THC and non-psychoactive CBD. The interactions of CBD and the human endocannabinoid system will be presented as they are related to numerous human health benefits based on existing clinical human trials. An overview of CBD commercial availability, current legal status of hemp and recent pharmaceutical applications for CBD will also be discussed.

INTRODUCTION

Any discussion on the topic of an alternative human health treatment beyond the scope of traditional medical doctrine must consider the words of the 14th century historian, politician and diplomat Niccolò Machiavelli who said:

> *"It must be considered that there is nothing more difficult to carry out, nor more doubtful of success, nor more dangerous to handle, than to initiate a new order of things. For the reformer has enemies in all those who profit by the old order, and only lukewarm defenders in all those who would profit by the new order, this lukewarmness arising partly from fear of their adversaries, who have the laws in their favor."*[1]

Although today's social and political climate surrounding medical marijuana and hemp extracts is evolving, there are few within the medical establishment that have embraced the routine use of these treatments for their patients. A major criticism for routine use by mainstream medicine has been the lack of large randomized controlled trials demonstrating disease or condition specific efficacy. This criticism is not without merit but over the last 8,000 years, since the earliest documented use by the Chinese, humans have used both marijuana and hemp for a wide variety of human conditions and obtained desired effects.[2]

The original uses for hemp were primarily as a fiber source and food in the form of a seed oil crop. Hemp is one of the oldest sources of textile fiber and widely cultivated in both ancient times and today. It was introduced to the US in the early colonial period and grown by many of the agrarian founding fathers, including George Washington at Mount Vernon. Later, the hemp produced in Kentucky, Missouri, and Illinois in the 1800's was used for sailcloth and ropes. The Federal Tax Act in 1938 that made the cultivation of cannabis illegal essentially ended hemp production in the US until very recently.[3]

Early medicinal uses of both hemp and marijuana include prescriptions for cannabis in Ancient Egypt for the treatment of glaucoma, inflammation, and menstrual pain. In Ayurvedic medicine cannabis extracts were believed to prolong life, improve judgment, lower fevers, induce sleep and cure dysentery. In the 1840's, British army surgeon Dr. William O'Shaughnessy, who had served in India, brought cannabis to Victorian England. Made as a liquid and bottled, it was commercially available and advertised to help a variety of ailments, including muscle spasms, menstrual cramps, rheumatism, rabies, epilepsy and to induce sleep. In the 1930s, prior to the ban of cannabis, American pharmaceutical companies Parke-Davis and Eli Lily sold standardized extracts of marijuana for use as an analgesic, an antispasmodic and sedative.[3]

Hemp is Not Marijuana

Despite hemp and marijuana originating from the same species of plant, *Cannabis sativa*, they are two separate subspecies that differ in several important ways. Hemp is cultivated for its fibrous content and tall stalks which are used as a plant source for hundreds of raw and finished products including ropes, fabrics, paper, plastics and construction materials. As a food source the hemp plant and seeds are used for oils, protein and fatty acids by both human and animals. Nutritional supplements and medicines make up a fraction of hemp's current applications. Cultivated commercial hempseed consists of approximately 44% edible oils, which contain about 80% essential fatty acids. Hempseed's amino acid profile is comparable to other sources of protein such as meat, milk, eggs and soy.[4]

Unlike marijuana, hemp is very low in THC and by law must contain <0.3% to be classified as hemp. Hemp naturally contains significantly more cannabidiol (up to 40%) more compared to marijuana. Marijuana is primarily grown to maximize the THC content (reportedly up to 40% in some hybridized plants).[4,5]

Modern Medical Marijuana

Sale and distribution of marijuana as a plant-based medicine remains illegal based on existing federal laws. There are now, however, 23 states that allow the sale of medical marijuana, mostly by prescription, for a variety of purported health benefits, including[5,6]:

- Intractable headaches;
- Cancer pain;
- Nerve pain;
- Muscle spasms/spasticity;
- Glaucoma;
- Nausea from cancer chemotherapy;
- Poor appetite and weight loss caused by chronic illness, such as HIV;
- Crohn's disease;
- PTSD;
- Intractable Seizures.

There are several FDA-approved prescription marijuana-like medications that contain synthetic THC. These include Marinol (dronabinol) prescribed for chemotherapy-induced nausea and Cesamet (nabilone), which is used as an anti-emetic and an analgesic for neuropathic pain.[3]

NUTRITIONAL AND MEDICAL APPLICATIONS FOR CANNABIDIOL

What is Cannabidiol?

Cannabinoids are a class of chemical compounds that act on specialized cellular receptors in both animals and humans. Cannabinoids originating from plants are called phytocannabinoid. The two most researched thus far are delta-9-tetrahydrocannabinol (THC), the psychoactive compound of cannabis and cannabidiol (CBD). There are currently 85 different cannabinoids isolated from the *cannabis sativa* species including hemp and marijuana. The hemp plant has significantly more CBD compared to marijuana, with CBD representing up to 40% of the total cannabinoids in this plant.[3]

Hemp, unlike marijuana, is the major plant commercial source for CBD extracts. CBD is produced by the hemp plant in the form of a sticky resin produced in specialized glands located on young leaves, twigs and buds of the plant. The CBD-containing resin is a source of antioxidant, anti-inflammatory and numerous other protective molecules (that will be discussed) for the growth and reproductive functions of the plant.[7] Extracts obtained from hemp's resin are used to make concentrated CBD produced and sold as a legal non-psychoactive nutritional supplement.[8]

Actions of Cannabidiol

For thousands of years the consumption of plants containing both CBD and THC have been researched and used by humans for spiritual, health and psychoactive effects. Only since the 1940's, however, was CBD isolated and found to have significantly broader health applications and benefits compared to the psychoactive THC. Once isolated, it was discovered that there existed specific cannabinoid receptors on both animal and human cells. When bound to a cannabinoid receptor, CBD acts to regulate neurotransmitter release in both brain and body neurons. It was later discovered that our body also produces similar molecules that can bind to cannabinoid receptors; these are called endocannabinoids (Fig. 1).[3]

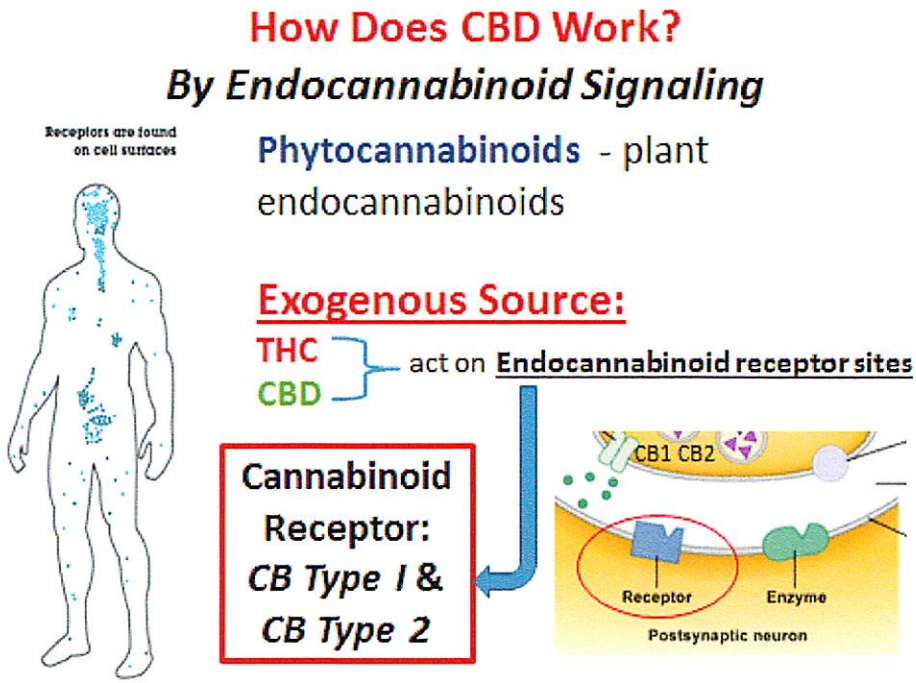

Figure 1. Cannabidiol exerts its effects upon the body by acting on endocannabinoid receptor sites

This system of neurotransmitter regulator molecules (ligands) and receptors is called the endocannabinoid system and functions throughout the body preforming a wide range of roles. The two major endocannabinoids are anandamide (AEA) and 2-acylglycerol (2-AG). The endocannabinoids are not stored in the interior of synaptic vesicles like other neurotransmitters but are "made on demand" when the proper physiological or pathological stimulation occurs.[9]

The endocannabinoid system works through two major receptors recently identified in the 1990's as CB1 and CB2. The CB1 cannabinoid receptor is widely found in the central nervous system as well as in the periphery, while CB2 is mainly expressed in immune cells. In the central nervous system, CB1 is predominantly expressed presynaptically, modulating the release of neurotransmitters, including g-aminobutyric acid (GABA), dopamine, noradrenaline, glutamate and serotonin. The phtyocannabinoids, THC and CBD, can also interact with the endocannabinoid receptors CB1 and CB2 resulting in wide range of physiologic and psychoactive responses. THC functions to a greater degree on the brain and central nervous system located CB1 receptors. Therefore, the psychoactive effects of THC are significantly stronger with THC than CBD that interacts to a greater degree on CB2 that is located on immune cells.[10,11] (See Tables 1 & 2)

Table 1. CB1-Mediated (Brain) Effects of THC

• **Psychoactive effects** • **Memory Impairment** • **Impaired coordination**	**Characteristics not beneficial as a Medication or Nutritional Supplement**
• **Reduced pain sensitivity** • **Suppress nausea** • **Increased appetite** • **Weight (fat) gain**	**Characteristics shown to have human health benefits for Chemotherapy related nausea Medication or Nutritional Supplement**

Table 2. CB2-Mediated Effects of CBD

CB2 Location	Immune cells: Monocytes, macrophages B-cells T-cells	Peripheral nerves	GI Track	Brain
Actions	Anti-inflammatory, Antioxidant, etc	Analgesic effects	Modulate intestinal inflammatory response Protect intestinal flora Decease hypermobility Reduce N/V	Antianxiety

Selective CB1 and CB2 Actions of THC and Cannabidiol

Because the endocannabinoid system is comprised of two different cellular receptors that have various concentrations throughout the body and THC and CBD bind selectively greater to one type of receptor than the other, the actions of THC and CBD vary significantly in animal and human models. The molecular pathways of endocannabinoid system activation for THC, CBD and most other cannabinoids demonstrates cellular hormesis, and a wide range of health benefits occur when CBD binds to the CB2 receptors throughout the body. In general these actions are most prominently related to activation of antioxidant and anti-inflammatory pathways of the immune system.[7] (See Figure 2.)

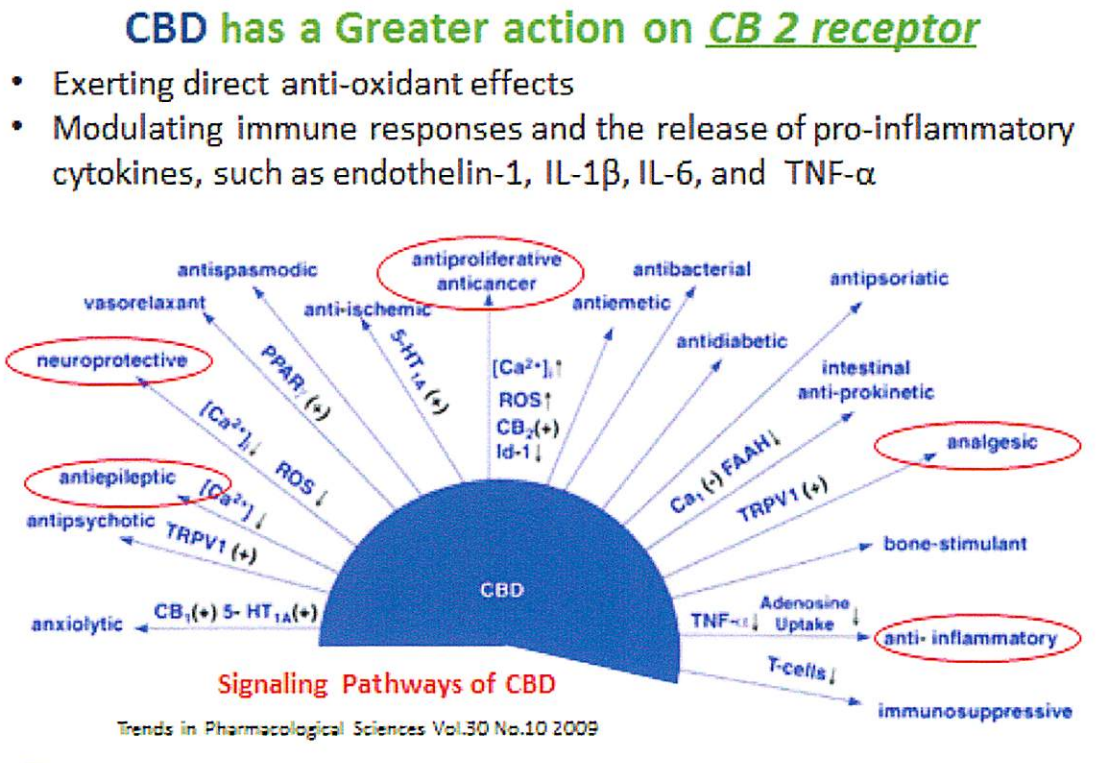

Figure 2. Signaling pathways of cannabidiol[3]

Medical Therapeutics of Cannabidiol

The scientific reporting of medical applications for CBD has historically been limited to case reports and small case studies. Recently several larger, randomized controlled studies have been published in animal and humans showing strong evidence that several conditions, including intractable childhood epilepsy and certain cancers, might benefit from future clinical use of CBD.[12-14] In 2009 a group of Italian and Israeli researchers review of both animal and human studies done to date on both THC and CBD concluded that cannabinoids such as CBD, that don't have psychoactive properties, are "therapeutically promising" for inflammation, diabetes, cancer, affective and neurodegenerative diseases, including the treatment of epilepsy and obesity. Interestingly they noted the effects of CBD follow a bell-shaped dose-response curve suggesting a loss of effectiveness with the highest-doses.[3]

From a more focused review from Canada in 2012 researchers specifically targeted randomized and crossover studies that administered CBD to healthy human controls and clinical patients to assess therapeutic results (see Figure 3). These results of CBD given orally demonstrated that high-dose CBD (300 to 600mg) decreases anxiety and increases mental sedation in healthy individuals and may offer treatment for social anxiety disorder, insomnia and epilepsy. This review also reported two studies in which an analgesic effect of CBD was noted among mixed neurogenic pain due to MS and in cancer pain patients. Interestingly, these results were achieved using low-dose CBD of 2.5 mg. Finally this review also noted that CBD alone has antiepileptic properties by blocking low-voltage-activated (T-type) Ca2 channels, increasing the activity of inhibitory glycine receptors and modulating NMDA receptors in the brain.[14]

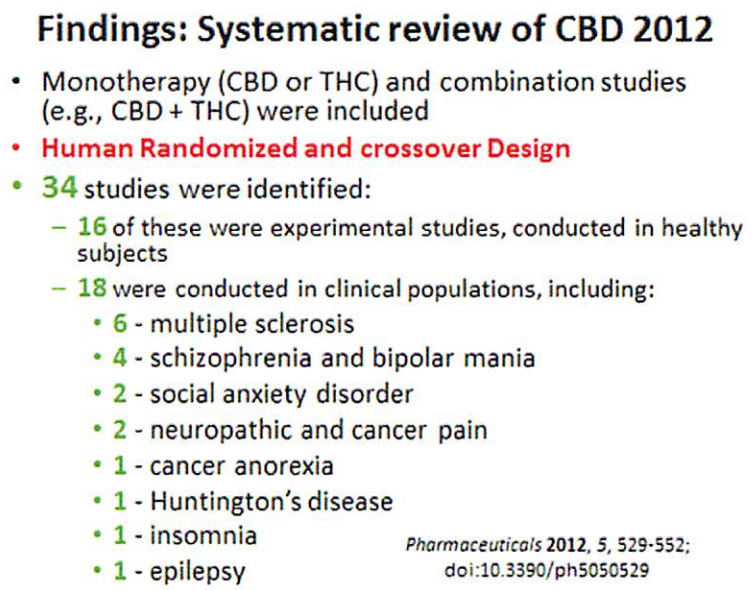

Figure 3. Findings of a review of randomized and crossover studies of CBD administered to healthy human controls and clinical patients[14]

Summary: Actions of CBD

CBD has been studied and found in both in vivo and in vitro studies to exert anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic and anti-epileptic actions that may offer significant human health benefits.

Anti-inflammatory[15]

- CBD – analgesic and anti-inflammatory effect mediated by dual COX and LOX inhibition;
- Anti-inflammatory effect is several hundred times more potent than aspirin when measured in standard animal tests and isolated cell assays;
- CBD, like THC, also stimulates the release of prostaglandin E2 (anti-inflammatory) from synovial cells and, like THC, inhibits leukotriene B4 synthesis in human WBCs;
- Topical CBD Cream shown to reduce acne by reducing sebum overproduction, unwanted sebocyte proliferation and inflammation.[16]

Analgesic Effects[17,18]

- Modulates immune response – anti-inflammatory and reduces WBC-mediated cytokine action;
- Blocks peripheral nerve fibers – used for multiple sclerosis spasticity and associated neuropathic pain;
- CBD, unlike morphine, effective at relieving chemotherapy-induced neuropathic pain with no psycho-active effects.[19]

Anti-nausea, Anti-emetic & Gastrointestinal Benefits[11,20-22]

- Direct action on gut smooth muscle;
- Inhibits acetylcholine induced contractions in the isolated mouse ileum;
- Effective to suppress nausea and vomiting;
- Anti-proliferative actions in human colorectal carcinoma;
- Prevents oxidative stress intestinal epithelial cells.

Anxiolytic[13,23]

- Animal models and healthy human volunteers, demonstrate anxiolytic-like effects of CBD;
- CBD reduces anxiety in clinical patients with social anxiety disorder;
- Countered THC-induced anxiety effects.

Anti-epileptic[14,24-26]

- Human studies have been equivocal:
  - In a double-blind study Cunha et al (1980) evaluated CBD for intractable epilepsy in 16 grand-mal patients. Each patient received 200 to 300 mg daily of CBD or placebo along with antiepileptic drugs continued up to 4-months. In the treatment group 7 of 8 responded with fewer seizures. In the placebo group 1 of 8 responded with fewer seizures[14,27,28];
  - In a human study of intractable epilepsy with 12 subjects, Ames et al (1986) were unable to duplicate these results and participants showed no response to CBD[14,27,29];
  - In 2012, in a review of 3 studies that exclusively used CBD for intractable seizures, Hill et al found that two of the three demonstrated significant anti-seizure effects[14,27,30,31];
- In 2014 Insys Therapeutics (USA) was granted orphan drug designation for its pharmaceutical CBD for the treatment of glioblastoma multiforme (GBM) and two rare forms of epilepsy, Lennox-Gastaut Syndrome and Dravet Syndrome. GW Pharmaceuticals has also been given the same designation for a CBD drug for Dravet Syndrome in children.

Neuroprotective[10,32]

- In experimental models activation of CB2 receptors (the receptors primarily associated with CBD) CBD has delayed progression of neurodegenerative events, in particular, those related to the toxic influence of microglial cells (excessive immune response) on neuronal homeostasis[33];
- CBD has been shown to reduce glutamate toxicity of the brain[34];
- CBD can reduce oxidative damage from glutamate via antioxidant effects[35,36];

- Neuroprotective benefits of CBD are reported to be greater than those of vitamin C and vitamin E.

Anti-cancer[37]

- Cannabinoids including CBD offer potential applications as antitumor drugs, based on the ability to limit inflammation, cell proliferation, and cell survival;
- In particular, emerging evidence suggests that agonists of cannabinoid receptors expressed by tumor cells may offer a novel strategy to treat cancer;
- GW Pharmaceuticals (UK) has preclinical data and has been approved for a human trial for GBM using submaximal doses of THC and CBD along with temozolomide (TMZ). This pharmaceutical THC and CBD has produced a strong antitumoral action in both TMZ-sensitive and TMZ-resistant tumors, and will be therapeutically exploited for the management of GBM.[38]

Dosing and Safety

To date studies investigating the therapeutic benefits of CBD for humans have ranged widely based on condition-specific dosing, subject age and purity of the CBD being used. Therefore, the appropriate dose recommendations have yet to be established. Thus far, most studies have consistently reported little to no side effects or interactions making CBD appear to be very safe for human use. One side effect that is consistently noted has been sedation and therefore driving or using machinery should be avoided if taking CBD.

One of the most comprehensive safety studies on CBD was published by Bergamaschi et al in 2011.[39] This study noted the following:

- Studies have consistently shown that CBD is non-toxic:
  - Does not induce adverse changes on food intake, does not induce catalepsy, does not affect physiological parameters (heart rate, blood pressure and body temperature);
  - Does not adversely affect gastrointestinal transit nor alter psychomotor or psychological functions;
  - Chronic use and high doses up to 1,500 mg/day of CBD_are reportedly well tolerated in humans.
- Rarely, studies have shown that CBD has some mild metabolic effects at very high doses, including:
  - Inhibition of hepatic drug metabolism, alterations of in vitro cell viability, decreased fertilization capacity;
  - Decreased activities of p-glycoprotein and other drug transporters.

The findings led the authors to conclude: *"Based on recent advances in cannabinoid administration in humans, CBD shown to be safe in humans and animals but additional in vivo studies, as well as randomized, double-blind placebo controlled clinical studies are still needed."*

CONCLUDING REMARKS

The final determination for approved medicinal and psychoactive use of marijuana and THC will continue to evolve. Currently, this process is still undergoing intense legal and scientific review, and this may take decades longer to complete. Hemp-based dietary supplements, however, do not contain high levels of THC, and are currently legally sold and used throughout the US. Hemp's active cannabinoid is CBD, a non-psychoactive molecule that has profound actions on our intrinsic endocannabinoid system, which has been shown to be generally safe in low-to-moderate dose ranges. It is by this action on this system, found mostly on neuronal and immune system cells, that CBD has been shown through both animal and human study to have a wide range of health benefits. These include:

- Anti-inflammation;
- Antioxidant;
- Analgesic;
- Anti-seizure;

- Apoptotic;
- Immune-inflammatory suppression;
- Deceased cytokine and chemokine;
- Reduces gut hypermobility, peripheral nerve pain and neural excitability;
- Safe without serious toxic effects;
- Still limited data on dosing;
- Still limited number of human studies.

The current state of CBD research is still in its early phases and large randomized studies will still be needed before mainstream acceptance occurs. Early adopters, however, are reporting human health benefits that will demand further investigation and confirmation over time. We believe at this time that hemp-based CBD is a novel supplement that with further study could indeed have a profound effect on improving human health.

REFERENCES

1. Niccolò Machiavelli quote. http://www.gurteen.com/gurteen/gurteen.nsf/id/X0003D096/ Accessed February 19, 2015.
2. Mack, A, Joy J. Marijuana as Medicine: Beyond the Controversy. The Institute of Medicine. http://ytdj.org/Drugs/Cannabis/Marijuana%20as%20Medicine%20-%20The%20Science%20Beyond%20the%20Controversy%20%282001%29.pdf Published 2001. Accessed February 18, 2015.
3. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci.* 2009;30:515-527.
4. Leizer C, Ribnicky D, Poulev A, Dushenkov S, Raskin I. The Composition of Hemp Seed Oil and Its Potential as an Important Source of Nutrition. *J Nutraceut Function Med Foods.* 2000;2:35-53.
5. Annas,GJ. Medical Marijuana, Physicians, and State Law. *N Engl J Med.* 2014;371:983-985.
6. Pertwee RG. Cannabidiol as a potential medicine. Cannabinoids as Therapeutics. *Milestones in Drug Therapy MDT.* 2005;47-65.
7. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci U S A.* 1998;95:8268-8273.
8. Small E, Marcus D. Hemp: A New Crop with New Uses for North America. In: J Janick ,A Whipkey, eds. *Trends in new crops and new uses.* Alexandria, VA: ASHS Press;2002.
9. Pacher P, Kunos G. Modulating the endocannabinoid system in human health and disease--successes and failures. *FEBS J.* 2013;280:1918-1943.
10. Fernández-Ruiz J, Pazos MR, García-Arencibia M, Sagredo O, Ramos JA. Role of CB2 receptors in neuroprotective effects of cannabinoids. *Mol Cell Endocrinol.* 2008;286:S91-96.
11. Capasso R, Izzo AA. Gastrointestinal regulation of food intake: general aspects and focus on anandamide and oleoylethanolamide. *J Neuroendocrinol.* 2008;20 (Suppl 1):39-46.
12. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav.* 2013;29:574–577.
13. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr.* 2008;30:271-280.
14. Zhornitsky S, Potvin S. Cannabidiol in Humans – The Quest for Therapeutic Targets. *Pharmaceuticals.* 2012;5:529-552.
15. Mecha M, Feliú A, Iñigo PM, Mestre L, Carrillo-Salinas FJ, Guaza C. Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors. *Neurobiol Dis.* 2013;59:141-150.
16. Oláh A, Tóth BI, Borbíró I, Sugawara K, Szöllősi AG, Czifra G, et al. Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. J Clin Invest. 2014;124:3713-3724.
17. Russo EB. Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag.* 2008;4: 245–259.
18. Piomelli D, Giuffrida A, Calignano A, De Fonseca FR: The endocannabinoid system as a target for therapeutic drugs. *Trends Pharmacol Sci.* 2000;21:218-224.
19. Grotenhermen F. Cannabinoids in cancer pain. Cannabinoids 2010;5:1-3.
20. Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. *Pharmacol Ther.* 2010;126:21-38.

21. Naftali T, Mechulam R, Bar Lev L, Konikoff FM. Cannabis for Inflammatory Bowel Disease. *Dig Dis.* 2014;32:468-474.
22. Parker LA, Kwiatkowska M, Burton P, Mechoulam R. Effect of cannabinoids on lithium-induced vomiting in the Suncus murinus (house musk shrew). *Psychopharmacology.* 2004;171:156-161. *Pharmacology & Therapeutics.* 2010;126:21-38.
23. Schier AR, Ribeiro NP, Silva AC, Hallak JE, Crippa JA, Nardi AE, Zuardi AW. Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug. *Rev Bras Psiquiatr.* 2012;34:S104-110.
24. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, et al. Cannabidiol: Pharmacology and potential therapeformuutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia.* 2014;55:791–802.
25. Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, Stephens GJ. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J Pharmacol Exp Ther. 2010;332:569-577.
26. Trembly B, Sherman M. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. Marijuana '90 International Conference on Cannabis and Cannabinoids. Kolympari, Crete, July 8-11, 1990.
27. Whalley BJ. Cannabis in the Management and Treatment of Seizures and Epilepsy: A Scientific Review American Herbal Pharmacopoeia. http://www.herbal-ahp.org/documents/press_releases/AHP%20Therapeutic%20Compendium-Cannabis%20Epilepsy%20and%20Seizures%20Scientific%20Review.pdf Published March 12, 2014. Accessed February 18, 2015.
28. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel G, Gagliardi R, Sanvito EL, Lander N, Mechoulam R. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology.* 1980;21:175-185.
29. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. *S Afr Med J.* 1986;69:14.
30. Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, Stephens GJ. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther.* 2010;332:569-577.
31. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacol Ther.* 2012;133:79-97.
32. Shohami E, Cohen-Yeshurun A, Magid L, Algali M, Mechoulam R. Endocannabinoids and traumatic brain injury. *Br J Pharmacol.* 2011;163:1402-1410.
33. Brites D, Vaz AR. Microglia centered pathogenesis in ALS: insights in cell interconnectivity. *Front Cell Neurosci.* 2014;8:117.
34. Panikashvili D, Simeonidou C, Ben-Shabat S, HanusÏ L, Breuer A, Mechoulam R, Shohami E. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. *Nature.* 2001;413:527-531.
35. Lafuente H, Alvarez FJ, Pazos MR, Alvarez A, Rey-Santano MC, Mielgo V, Murgia-Esteve X, Hilario E, Martinez-Orgado J. Cannabidiol reduces brain damage and improves functional recovery after acute hypoxia-ischemia in newborn pigs. *Pediatr Res.* 2011;70:272-277.
36. Hampson AJ, Grimwald M, Axelrod J, Wink D. Cannabidiol and (2)D9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc. Natl. Acad. Sci. USA.* 1998;95:8268-8273.
37. Sarfaraz S, Adhami VM, Syed DN, Afaq F, Mukhtar H. Cannabinoids for Cancer Treatment: Progress and Promise. *Cancer Res.* 2008;68:339-342.
38. Torres S, Lorente M, Rodríguez-Fornés F, Hernández-Tiedra S, Salazar M, García-Taboada E, Barcia J, Guzmán M, Velasco G. A combined preclinical therapy of cannabinoids and temozolomide against glioma. Mol Cancer Ther. 2011;10:90-103.
39. Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf. 2011;6:237-249.

ABOUT THE AUTHORS

Primary author Joseph Maroon, M.D., FACS, is a Board-Certified Neurosurgeon and Heindl Scholar in Neuroscience, University of Pittsburgh School of Medicine. A sports medicine and nutrition expert, he is also Team Neurosurgeon for the Pittsburgh Steelers. Dr. Maroon also serves as Senior Vice President of the A4M, and is author of The Longevity Factor.