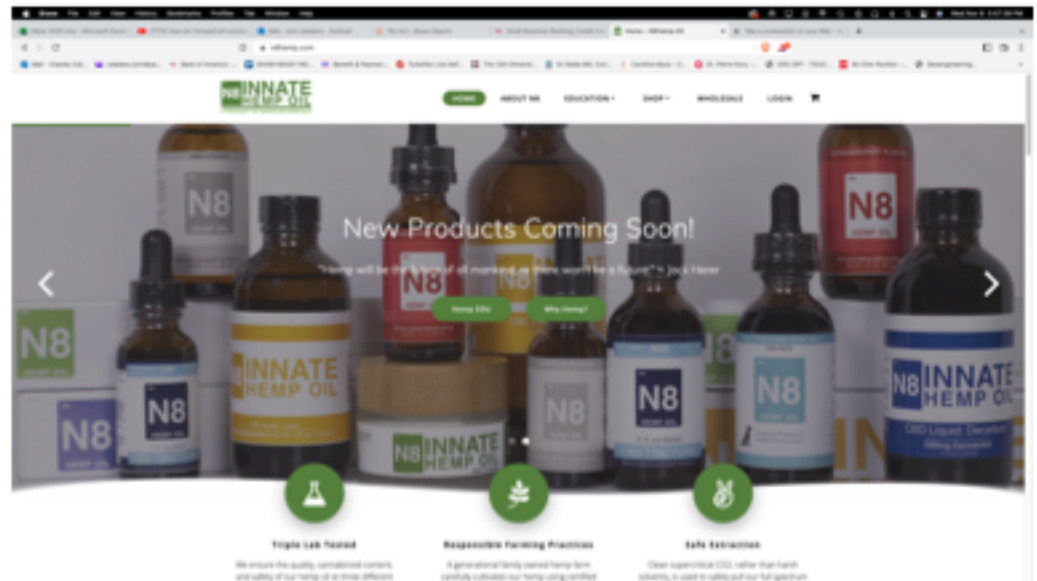


A BLUNT TRUTH

Information to fuel your health.....

There is a multi-billion dollar industry growing in the world. Hemp products are now mainstream and can be found in a variety of stores all over America. Medical marijuana has been approved in the majority of the U.S., and is approved for “recreational use” in many states as well. **The move towards complete legalization, we believe, is rooted in a**

SCIENTIFIC HEALTH DISCOVERY and more than just stoners wanting to get high.



Let's end the ambiguity on the effects of cannabis and be more definitive about the potential for this plant to create better health and a better living environment for our families and generations to come. The average American is still uncertain about cannabis safety and methods of use. Most medical schools do not teach the **endocannabinoid system (ECS)** as part of their standardized curriculum, and many health practitioners are uncertain or unable to communicate the true benefits of cannabis with confidence.

Throughout public school education (**Drug Abuse Resistance Education**), children are taught marijuana is a “gateway drug”, is ultimately detrimental, and should never be used for any reason.

First and foremost, cannabis is **NOT** the “evil weed” society has been conditioned to believe for several decades. We will discuss the stigma, racial propaganda, and other political and big business issues that influenced the prohibition of “**marijuana**” in the early 20th century, ultimately causing the cannabis plant to become completely ostracized as medicinal or therapeutic in the following generations.

Secondly, we must introduce the general public as well as health practitioners to an entire system in the body that is **INNATELY** designed to mediate the communication of ALL cells, tissues, and organs

in the body; this constant maintenance of balance and equilibrium of all the body's systems is called **homeostasis**.

When the body is given the proper alignment structurally, chemically, and psychologically, homeostasis is best achieved and creates maximal innate healing.

This **E-BOOK** is meant to be an introduction to the idea of cannabis as a **NUTRITIONAL SUPPLEMENT** and **Cannabidiol (CBD)** as an essential nutrient that needs to be **STANDARD** to the human diet, similar to supplementing with omega-3 fish oils, collagen, protein, etc.

It is strongly suggested to any individual interested in the topic to search the public research database archives for thousands of articles from the last 50 years that have detailed the intricacies of **ECS** in normal functioning, its effect and modulation in specific disease processes, and therapeutic benefits when supplementing with CBD and other **phytocannabinoids**.

Because of the growing collection of evidence for therapeutic benefits of cannabinoids, big pharmaceutical companies are actively pursuing opportunities to manufacture synthetic cannabinoids and patented molecules to use for CBD, THC, and other cannabinoid-like therapies. Their research is driving the public opinion towards confidence in **SYNTHETIC** versions of the natural cannabis plant.

Our mission is to educate YOU about the importance of NATURAL, PLANT-BASED phytocannabinoids to fuel your endocannabinoid system for overall health, wellness, and systemic benefits for chronic conditions and disease processes.

'Thank you for making your health a priority'

The History of Modern CANNABIS Culture

It's **CANNABIS SATIVA**, not "marijuana"

Let's set the record straight with an overview of cannabis terminology. "**Marijuana**" is a slang term used to describe the psychoactive cannabis buds that has been at the forefront of world consciousness since the creation of the term in the early 20th century. There are two major cannabinoids that have been identified and studied in depth, delta-9-tetrahydrocannabinol (**THC**) and cannabidiol (**CBD**).¹ THC is the main psychoactive constituent in the cannabis plant, while CBD is a non-psychoactive cannabinoid that researchers have discovered is an integral part of our body's ability to maintain balance and equilibrium. **The word "Hemp" is specific to the stems, stalks, and leaves of the plants (not the buds).** The flowering buds of "marijuana" have been engineered over the years to be highly concentrated with THC, and low amounts of CBD and other non-psychoactive cannabinoids, and are NOT ideal for extracting a non-psychoactive nutritional supplement. On the contrary, Industrial hemp is a version of the cannabis plant that contains an extremely high ratio of CBD and low trace amounts of THC, and is more fibrous, with long stalks, stems, and leaves, and barely has any of the dense buds that are generally thought of as "marijuana". It is also worth noting that there are several other plants such as liverwort, Helichrysum, kava root, echinacea, black pepper, and others that contain cannabinoid molecules that interact with the cannabis receptors in the body and are commonly utilized for supplemental and therapeutic benefits worldwide.^{2,3}

For patients, practitioners, and the average person wishing to avoid the undesirable effects of psychoactivity (getting "high"), we focus our attention on the **NON-PSYCHOACTIVE CBD** portion of the cannabis plant and deriving supplements, with low values of THC, and high concentrations of CBD and other plant-based cannabinoids and essential nutrients. Scientifically speaking, industrial hemp and "marijuana" fall under the umbrella of types of cannabis plants, specifically named Cannabis sativa.⁴

The American Medical Association had used Cannabis sativa extracts, lotions, tinctures, and other preparations of the plant as part of the US Pharmacopeia until 1937 when the passage of the Marihuana Tax Act effectively outlawed the production and consumption of cannabis in the US.

There are well documented accounts of how cannabis and hemp products were utilized prior to its illegalization. Chinese, Indian, and other Asian cultures have been using cannabis as a form of medicine and for its therapeutic benefits since 4000 BC. In American Colonial days, hemp was used as a method of paying taxes, commonly used in producing ropes and cloth, and oil extracted was used in lamps. **Thomas Jefferson is quoted saying "hemp is of first necessity to the wealth & protection of the country,"** illustrating the importance of hemp for the economy and for creating trade products⁵. He also transcribed drafts of the Declaration of Independence on hemp paper. Other famous colonials, Benjamin Franklin opened one of the first paper mills using hemp as raw material, and Betsy Ross stitched her first version of the American Flag with much stronger, hemp cloth.⁶

The term "Marijuana" did not exist prior to 1910. The word is deeply rooted in racial propaganda in the 20th century, formulated from popular Mexican names, Maria and Juana.⁷ Following the Mexican Revolution and the influx of legal Mexican immigrants into the United States, former director of the Federal Bureau of Narcotics, Harry Anslinger, took advantage of racial tensions, launching a campaign against hemp where he stated blasphemy such as "Reefer makes the darkies think they're as good as white men...the primary reason to outlaw marijuana is its effect on the degenerate races." He also stated that most users of marijuana were "negroes, hispanics, filipinos, and entertainers. Thier Satanic music, jazz, and swing result from marijuana use. This marijuana causes white women to seek sexual relations with Negroes, entertainers, and any others."⁸ Anslinger's big business associates, William Randolph Hearst, Andrew Mellon, and the Dupont family also had large investments in the timber and paper industries, and discounted the effectiveness of hemp paper as a legitimate raw material to make an effective substitute to paper. These types of racial and big business bias fueled movements against cannabis culminated into the passing of the Marihuana Tax Act of 1937 that placed a tax on hemp products and on the commercial sale of cannabis products. At the time, the American Medical Association was strongly opposed to the act and proposed that cannabis be added to the Harrison Narcotics Tax Act as a scheduled, controlled substance. However, in the end, the big business racial propaganda against cannabis continued on from 1930 and all therapeutic and industrial uses of hemp have ceased, until recently in the United States in 1996 when California passed Prop 215 Cannabis for medicinal use and in 2012 with recreational use of cannabis legalized in Colorado and Washington.

We have moved on from this racial and big business driven matrix. **There is an exponentially growing research database on the body's INNATE, endogenous cannabinoid system that signals the body to heal and maintain homeostasis.** There is conclusive research indicating that there is an entire system in the human body that is DESIGNED to create, utilize, and degrade cannabinoid molecules for practically every cell, tissue, and organ in the body.⁹

Anatomy and Physiology of the Endocannabinoid System

To maintain balance and equilibrium in all of the body's systems, the endocannabinoid system (ECS) has receptor sites on virtually every cell, tissue, and organ in the body. **Since its first discovery in 1964**, we have accumulated a tremendous database of research on the homeostatic role of the ECS. Today, scientists have identified 113 different cannabinoid molecules¹⁰, mostly focused on the effects of THC and CBD and their interactions with the two main types of **N8** cannabinoid receptors, CB1 and CB2 receptors in the ECS. CB1 receptors are found mostly in the central nervous system, whereas CB2 receptors are found in the cells and tissues of the immune system including the digestive system, spleen, pancreas, etc. The body is constantly maintaining cannabinoid balance by producing its main endogenous cannabinoids, 2-Arachidonylglycerol (2-AG) and anandamide, and are degraded by monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH), respectively. These cannabinoid interactions are essential in directing basic cell and systemic functions such as brain signaling, hormone regulation, mood and appetite, muscular contraction, energy production, waste removal, and signaling the immune response when there is disease or pathology present.

In the nervous system, endocannabinoids function similar to regular neurotransmitters, except the ECS works retrograde from normal neurotransmission. The endogenous cannabinoids, anandamide and 2-AG, are produced in the secondary neuron and are released back into the synaptic cleft to attach to CB1 receptors on the primary neuron. This retrograde neurophysiology is as an innately born mechanism in the body to regulate the release of other neurotransmitters such as dopamine, serotonin, glutamate, GABA, and others. Additionally, CB2 receptors of immune cells - astrocytes and microglial cells - maintain the immune health and integrity of the nerve cells, combatting neuroinflammation and can directly affect autoimmune inflammation¹¹.

The growing body of research on endocannabinoid system receptors and the influence of exogenous cannabinoids such as CBD, has uncovered an irrefutable role of the human endocannabinoid system in maximal immune function.

Studies have also shown CBD to help protect the blood brain barrier and blood vessel wall against damage from high glucose and diabetes.¹² Research has indicated CBD plays an essential role in modulating the immune system and turning on and off inflammatory factors. benefits autoimmune conditions in the United States, especially in digestive system dysfunctions such as leaky gut syndrome¹³ and inflammatory bowel diseases¹⁴; skin conditions such as dermatitis¹⁵ eczema¹⁶, and other chronic pain disorders¹⁷.

More evidence shows CBD can be a huge player in benefitting conditions such as seizure disorders in children, adolescents, and adults¹⁸, multiple sclerosis^{19,20}, Parkinson's disease^{21,22}, Alzheimer's^{23,24}, ALS²⁵, and conditions of the nervous system can be benefitted by the neuroprotective and antioxidant properties of CBD and other cannabinoids.²⁶ The dynamic and multi-faceted abilities of CBD to affect and modulate the CB1 and CB2 receptors are a huge target for basic nutritional supplementation and therapeutic benefit.

The most groundbreaking impact of CBD that has been conclusive across multiple studies is its ability to affect the growth, development, and metastasis^{27,28} of cancer cells. The body possesses an N8 mechanism called, apoptosis and autophagy, that identifies when it is producing cancerous cells and keep them from growing, developing, and spreading to other places in the body.

Studies have documented CBD exhibits pro-apoptotic and anti-proliferative actions in different types of tumors and may exert anti-migratory, anti-invasive, anti-metastatic, and anti-angiogenic properties.

Recent research has demonstrated CBD benefits in endometrial cancers^{30,31}, stopping the growth and metastasis of human breast cancers^{32,33}, pancreatic cancer³⁴, prostate cancer³⁵, leukemia³⁶, neuroblastoma³⁷, gliomas^{38,39}, and a variety of other cancer cells^{40,41}. **The evidence for CBD and cannabinoid-like molecules in cancer treatment seems irrefutable** and will continue to grow as pharmaceutical companies and other CBD manufacturers further studies on phytocannabinoids and synthetic cannabinoids.

Clinical Implications

Why Plant-based instead of Synthetic Cannabinoids?

A recent, groundbreaking study done by researchers in Israel presents evidence that a plant-based hemp may have more therapeutic benefits than a single-molecule CBD extract.⁴² At **N8 Hemp**, we strongly recommend using CBD and other cannabinoids that come from a PLANT SOURCE. The N8 Hemp supplements are derived from industrial hemp from hand-selected farms in Northern Europe that contain high CBD content, low trace-amounts of THC, and other vital nutrients including omega 3 & 6 essential fatty acids, and over a dozen vitamins and minerals, like iron, calcium, magnesium, vitamins A, B, C, and E, and beta-Carotene, often missing from the average diet. The combination of all of the naturally occurring components of the cannabis plant produces an "Entourage Effect"^{43,44,45,46}.

It is important to note that synthetically produced CBD drugs are lacking in the naturally occurring components of the cannabis plant besides CBD, trace amounts of THC, other cannabinoids, bioflavonoids, terpenes, and other plant constituents. Synthetic cannabinoids also pose the risk of serious adverse side effects, in comparison to hemp oils with non-psychoactive plant-based cannabinoid that have benign side effects.^{47,48,49}

TO BE CLEAR, we do not state that cannabis or CBD cures or treats any disease, condition, or disorder. The supplementation of cannabinoids into one's diet can produce excellent effects in homeostasis and will bring the body's systems back to equilibrium and proper function. Because of its innately designed structure and function, there are countless conditions, diseases, and disorders that researchers have focused on targeting therapeutically.

Studies indicate that doses of 700 mg per day for 6 weeks did not show any toxicity in humans, suggesting that CBD can be utilized for prolonged periods, and sheds light onto a therapeutic serving size recommendation for clinicians and practitioners to use for patients.⁵⁰

A comprehensive review of the current literature published in 2017⁵¹ from multiple groups describes conclusive evidence for therapeutic benefits of CBD and cannabinoids for nausea/vomiting, chronic pain syndromes, and **neuroinflammation** in multiple sclerosis. The same review also indicates the following conditions that CBD and cannabinoids can be beneficial for:

CANCER,

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING,

ANOREXIA AND WEIGHT LOSS,

IRRITABLE BOWEL SYNDROME,

EPILEPSY.

EPILEPSY,
SPASTICITY ASSOCIATED WITH MULTIPLE SCLEROSIS OR SPINAL CORD INJURY, TOURETTE SYNDROME,
AMYOTROPHIC LATERAL SCLEROSIS,
HUNTINGTON'S DISEASE,
PARKINSON'S DISEASE,
DYSTONIA,
DEMENTIA,
GLAUCOMA,
TRAUMATIC BRAIN INJURY/INTRACRANIAL HEMORRHAGE,
ADDICTION,
ANXIETY,
DEPRESSION,
SLEEP DISORDERS,
POSTTRAUMATIC STRESS DISORDER,
SCHIZOPHRENIA AND OTHER PSYCHOSES.

Studies have highlighted the importance of CBD in directing stress hormones and affects neuronal signaling in the brain, producing anti-psychotic⁵², antidepressant-like⁵³, anti-panic^{54,55}, anti-anxiety effects.^{56,57,58}

Researchers have observed the **neuroprotective** ⁵⁹ property of CBD and have demonstrated indisputable implications in multiple sclerosis^{60,61,62} and suggest strong evidence of therapeutic benefits for a myriad of other neurological conditions⁶³.

A 2013 review of studies suggests that cannabinoid modulation should be considered for a broad range of diseases, including neurodegenerative, cardiovascular, and inflammatory disorders; obesity/metabolic syndrome; cachexia; chemotherapy-induced nausea and vomiting; tissue injury and pain, amongst others.⁶⁴

Scientists have discovered that symptoms of headaches, chronic pain and fatigue, and autoimmune conditions could be due to an underlying **endocannabinoid deficiencies**, such as in migraines, fibromyalgia, irritable bowel syndrome, and a growing list of other medical conditions.⁶⁵

This nutrient-based deficiency is a key factor that practitioners, patients, and common people ought to be supplementing with hemp CBD and other phytocannabinoids to prevent the onset of signs and symptoms.

The most clear contraindication to using PLANT-BASED cannabinoids would be a sensitivity or allergy to cannabis/hemp, however systematic reviews have documented the side effects of cannabidiol (CBD) are generally benign.^{66,67}

We encourage **EVERYONE** to search the public research forums for the thousands of articles supporting the therapeutic benefits of cannabis. Search "phytocannabinoids", "CBD", and any of the conditions we have previously mentioned and beyond.

Cannabinoids for Health & Wellness

As part of our mission to educate people about the endocannabinoid system and its essential role in maintaining the body's (N8) INNATE healing and wellness processes, we strive to provide the BEST quality hemp oil supplements on the market.

-

Again, CBD from hemp is considered a DIETARY SUPPLEMENT and is legal in all 50 states. Our hemp oil comes from imported industrial hemp, and contains less than 0.3% THC by weight and in compliance with the Federal Controlled Substances Act. All of our hemp crops are grown without chemical fertilizers, herbicides, and pesticides.

We test our hemp oil multiple times from harvest to shipping to ensure accuracy in potency information and to check for contaminants like pesticides, herbicides, heavy metals, and mold, as well as to discern adequate cannabinoid content. Our distributors use a supercritical CO2 method when extracting our hemp oil, instead of harsh solvents like butane and propane. CO2 is a much healthier choice than other potential solvents and is "generally regarded as safe" (GRAS) by the FDA.⁶⁸

Besides CBD, our hemp oil contains various other phytocannabinoids, essential for roles in neurotransmission, immune function, mitochondrial functioning, and in virtually every other system in the body.

Each person's human **endocannabinoid system** will react to different concentrations of CBD differently, and each person has a different optimal serving size. If you have questions about what an optimal serving size might be for you, schedule a consultation with one of our doctors to see which of our products would best help your body.

Our hemp oil supplements come in a variety of different concentrations and potencies. In order to determine if CBD hemp oil is right for you, we strongly recommend consuming the product to completion. Our mission is to create consciousness that cannabinoid consumption ought to be a routine part of daily nutrition.

Reference Notes:

- 1 FERNANDO RODRIGUEZ de FONSECA, IGNACIO DEL ARCO et al. THE ENDOCANNABINOID SYSTEM: PHYSIOLOGY AND PHARMACOLOGY, Alcohol and Alcoholism, Volume 40, Issue 1, 1 January 2005, Pages 2–14, <https://doi.org/10.1093/alcalc/agh110>
- 2 Curr Top Med Chem. 2008;8(3):173-86.CB receptor ligands from plants.
- 3 Russo, Ethan B. Beyond Cannabis: Plants and the Endocannabinoid System. Trends in Pharmacological Sciences , Volume 37 , Issue 7 , 594 - 605
- 4 Russo, Ethan B. Beyond Cannabis: Plants and the Endocannabinoid System. Trends in Pharmacological Sciences , Volume 37 , Issue 7 , 594 - 605
- 5 <http://rotunda.upress.virginia.edu/founders/TSJN.html>
- 6 <https://www.veteransflagdepot.com/american-flag-history>
- 7 http://www.sino-platonic.org/complete/spp153_marijuana.pdf
- 8 Common Sense for Drug Policy 2006.
- 9 Oláh, A., Szekanecz, Z., & Biró, T. (2017). Targeting Cannabinoid Signaling in the Immune System: "High"-ly Exciting Questions, Possibilities, and Challenges. *Frontiers in Immunology*, 8, 1487. <http://doi.org/10.3389/fimmu.2017.01487>
- 10 Evolution of the Cannabinoid and Terpene Content during the Growth of Cannabis sativa Plants from Different Chemotypes Oier Aizpuna-Olaizola et al. *Usobiaga Journal of Natural Products* 2016 79 (2), 324-331 DOI: 10.1021/acs.jnatprod.5b00949
- 11 Kozela, E., Juknat, A., & Vogel, Z. (2017). Modulation of Astrocyte Activity by Cannabidiol, a Nonpsychoactive Cannabinoid. *International Journal of Molecular Sciences*, 18(8), 1669. <http://doi.org/10.3390/ijms18081669>
- 12 Rajesh, M. et al (2007). Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption. *American Journal of Physiology. Heart and Circulatory Physiology*, 293(1), H610-H619. <http://doi.org/10.1152/ajpheart.00236.2007>
- 13 Eur J Gastroenterol Hepatol. 2017 Feb;29(2):135-143. doi: 10.1097/MEG.0000000000000779.Role of cannabis in digestive disorders.
- 14 J Endocrinol Invest. 2006;29(3 Suppl):47-57.Endocannabinoids and the gastrointestinal tract.
- 15 Nam G et al. Selective Cannabinoid Receptor-1 Agonists Regulate Mast Cell Activation in an Oxazolone- induced Atopic Dermatitis Model. *Ann Dermatol*. 2016 Feb;28(1):22-9. doi: 10.5021/ad.2016.28.1.22.
- 16 Mounessa, Jessica S. et al. The role of cannabinoids in dermatology *Journal of the American Academy of Dermatology* , Volume 77 , Issue 1 , 188 - 190
- 17 Adv Pharmacol. 2017;80:437-475. doi: 10.1016/bs.apha.2017.05.003. Epub 2017 Jun 20. Cannabinoids and Pain: Sites and Mechanisms of Action.
- 18 Epilepsy Behav. 2017 May;70(Pt B):341-348. doi: 10.1016/j.yebeh.2016.11.012. Cannabinoids in treatment- resistant epilepsy: A review.
- 19 J Neuroinflammation. 2018 Mar 1;15(1):64. doi: 10.1186/s12974-018-1103-y. Hypoxia mimetic activity of VCE- 004.8, a cannabidiol quinone derivative: implications for multiple sclerosis therapy.
- 20 skedjian M, Bereza B, Gordon A, Piwko C, Einarson T R. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Current Medical Research and Opinion* 2007; 23(1): 17-24. [PubMed]
- 21 Neurotherapeutics. 2018 Jan 19. doi: 10.1007/s13311-018-0603-x. Cannabinoid CB1 and CB2 Receptors, and Monoacylglycerol Lipase Gene Expression Alterations in the Basal Ganglia of Patients with Parkinson's Disease.
- 22 Cannabinoids in Parkinson's Disease. Cabral, G.A., Rogers, T.J. & Lichtman, A.H. *J Neuroimmune Pharmacol* (2015) 10: 193. <https://doi.org/10.1007/s11481-015-9615-z>
- 23 Watt, G., & Karl, T. (2017). In vivo Evidence for Therapeutic Properties of Cannabidiol (CBD) for Alzheimer's Disease. *Frontiers in Pharmacology*, 8, 20. <http://doi.org/10.3389/fphar.2017.00020>
- 24 Behav Pharmacol. 2017 Apr;28(2 and 3-Spec Issue):142-160. doi: 10.1097/FBP.0000000000000247.The therapeutic potential of the phytocannabinoid cannabidiol for Alzheimer's disease.
- 25 Carter et al. 2010. Cannabis and amyotrophic lateral sclerosis: hypothetical and practical applications, and a call for clinical trials. *American Journal of Hospice & Palliative Medicine* 27: 347–356. doi: 10.1177/1049909110369531
- 26 <https://www.google.com/patents/US6630507> Cannabinoids as antioxidants and neuroprotectants
- 27 cAllister, S. D. et al (2011). Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. *Breast Cancer Research and Treatment*, 129(1), 37–47. <http://doi.org/10.1007/s10549-010-1177-4>
- 28 Mol Cancer Ther. 2007 Nov;6(11):2921-7. Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells.
- 29 Massi, P., Solinas, M., Cincina, V., & Parolaro, D. (2013). Cannabidiol as potential anticancer drug. *British Journal of Clinical Pharmacology*, 75(2), 303–312. <http://doi.org/10.1111/j.1365-2125.2012.04298.x>
- 30 McAllister, S.D., Soroceanu, L. & Desprez, P.Y. Cannabinoid-induced cell death in endometrial cancer cells: involvement of TRPV1 receptors in apoptosis. *J Neuroimmune Pharmacol* (2015) 10: 255. <https://doi.org/10.1007/s11481-015-9608-y>
- 31 J Physiol Biochem. 2018 Feb 13. doi: 10.1007/s13105-018-0611-7. [Epub ahead of print]Cannabinoid-induced cell death in endometrial cancer cells: involvement of TRPV1 receptors in apoptosis.
- 32 Pharmacol Exp Ther. 2006 Sep;318(3):1375-87. Epub 2006 May 25. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma.
- 33 Mol Cancer Ther. 2011 Jul;10(7):1161-72. doi: 10.1158/1535-7163.MCT-10-1100. Epub 2011 May 12. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy.
- 34 Cannabinoids inhibit energetic metabolism and induce AMPK-dependent autophagy in pancreatic cancer cells. *Cell Death & Disease*, 4(6), e664–. <http://doi.org/10.1038/cddis.2013.151>
- 35 De Petrocellis, L., Ligresti, A., Schiano Moriello, A., Iappelli, M., Verde, R., Stott, C. G., ... Di Marzo, V. (2013) on-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms. *British Journal of Pharmacology*, 168(1), 79–102. <http://doi.org/10.1111/j.1476-5381.2012.02027.x>
- 36 Scott, K.A., Dalgleish, A.G., & Liu, W.M. (2017). Anticancer effects of phytocannabinoids used with chemotherapy in leukaemia cells can be improved by altering the sequence of their administration. *International Journal of Oncology*, 51, 369-377. <https://doi.org/10.3892/ijo.2017.4022>
- 37 Fisher T, Galan H, Schibu G, BriChen S, Smoun B, Morha L, Topp A (2016). In vitro and in vivo efficacy of non-psychoactive

- 37 Fisher, T., Golan, H., Schøy, G., PriChen, S., Smoum, R., Moshé, I., ... Toren, A. (2016). In vitro and in vivo efficacy of non-psychoactive cannabidiol in neuroblastoma. *Current Oncology*, 23(Suppl 2), S15–S22. <http://doi.org/10.3747/co.23.2893>
- 38 Vaccani, A., Massi, P., Colombo, A., Rubino, T., & Parolaro, D. (2005). Cannabidiol inhibits human glioma cell migration through a cannabinoid receptor-independent mechanism. *British Journal of Pharmacology*, 144(8), 1032–1036. <http://doi.org/10.1038/sj.bjp.0706134>
- 39 *J Pharmacol Exp Ther*. 2004 Mar;308(3):838-45. Epub 2003 Nov 14. Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines.
- 40 The Antitumor Activity of Plant-Derived Non-Psychoactive Cannabinoids Dando, I., Donadelli, M., Costanzo, C., Dalla Pozza, E., D'Alessandro, A., Zolla, L., & Palmieri, M. (2013).
- 41 Guindon, J., & Hohmann, A. G. (2011). The endocannabinoid system and cancer: therapeutic implication. *British Journal of Pharmacology*, 163(7), 1447–1463. <http://doi.org/10.1111/j.1476-5381.2011.01327.x>
- 42 Gallily, R., Yekhtin, Z. and Hanuš, L. (2015) Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol. *Pharmacology & Pharmacy*, 6, 75-85. doi: 10.4236/pp.2015.62010.
- 43 *Eur J Pharmacol*. 1998 Jul 17;353(1):23-31. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity.
- 44 *Pharmacol Res*. 2016 Aug;110:173-180. doi: 10.1016/j.phrs.2016.04.015. Epub 2016 Apr 23. Where's my entourage? The curious case of 2-oleoylglycerol, 2-linolenoylglycerol, and 2-palmitoylglycerol.
- 45 Russo, E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology*, 163(7), 1344–1364. <http://doi.org/10.1111/j.1476-5381.2011.01238.x>;
- 46 Di Marzo, V. & Piscitelli, F. *Neurotherapeutics* (2015) 12: 692. The Endocannabinoid System and its Modulation by Phytocannabinoids <http://doi.org/10.1007/s13311-015-0374-6>
- 47 Characteristics of Synthetic Cannabinoid and Cannabis Users Admitted to a Psychiatric Hospital: A Comparative Study *J Clin Psychiatry* 2016;77(8):e989–e995 10.4088/JCP.15m09938
- 48 Tait R et al (2015). A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clinical Toxicology*, 54:1, 1-13, DOI: 10.3109/15563650.2015.1110590
- 49 Anahita Bassir, et al. Psychiatric comorbidity associated with synthetic cannabinoid use compared to cannabis. *Journal of Psychopharmacology* July 26, 2016 <https://doi.org/10.1177/0269881116658990>
- 50 Massi, P., Solinas, M., Cinquina, V., & Parolaro, D. (2013). Cannabidiol as potential anticancer drug. *British Journal of Clinical Pharmacology*, 75(2), 303–312. <http://doi.org/10.1111/j.1365-2125.2012.04298.x>
- 51 National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington (DC): National Academies Press (US); 2017 Jan 12. 4. Therapeutic Effects of Cannabis and Cannabinoids.
- 52 *Schizophr Res*. 2015 Mar;162(1-3):153-61. doi: 10.1016/j.schres.2015.01.033. Epub 2015 Feb 7. A systematic review of the antipsychotic properties of cannabidiol in humans.
- 53 *CNS Neurol Disord Drug Targets*. 2014;13(6):953-60. Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of *Cannabis sativa*.
- 54 Soares, V. P., & Campos, A. C. (2017). Evidences for the Anti-panic Actions of Cannabidiol. *Current Neuropharmacology*, 15(2), 291–299. <http://doi.org/10.2174/1570159X14666160509123955>
- 55 *Psychopharmacology (Berl)*. 2013 Mar;226(1):13-24. doi: 10.1007/s00213-012-2878-7. Epub 2012 Sep 25. Involvement of serotonin-mediated neurotransmission in the dorsal periaqueductal gray matter on cannabidiol chronic effects in panic-like responses in rats.
- 56 Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report *Journal of Psychopharmacology* September 9, 2010 <https://doi.org/10.1177/0269881110379283>
- 57 *Braz J Med Biol Res*. 2006 Apr;39(4):421-9. Epub 2006 Apr 3. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug.
- 58 *Schizophr Res*. 2015 May;164(1-3):155-63. doi: 10.1016/j.schres.2015.01.015. Epub 2015 Feb 10. Decreased glial activity could be involved in the antipsychotic-like effect of cannabidiol.
- 59 *J Neurosci*. 2009 Apr 8;29(14):4564-70. doi: 10.1523/JNEUROSCI.0786-09.2009. Selective CB2 receptor agonism protects central neurons from remote axotomy-induced apoptosis through the PI3K/Akt pathway.
- 60 *J Neurosci*. 2007 Feb 28;27(9):2396-402. Cannabinoid CB1 and CB2 receptors and fatty acid amide hydrolase are specific markers of plaque cell subtypes in human multiple sclerosis.
- 61 Loria F, et al. An endocannabinoid tone limits excitotoxicity in vitro and in a model of multiple sclerosis. *Neurobiol Dis*. 2010;37:166–76. [PubMed]
- 62 Mestre L et al. A cannabinoid agonist interferes with the progression of a chronic model of multiple sclerosis by downregulating adhesion molecules. *Mol Cell Neurosci*. 2009;40:258–66. [PubMed]
- 63 *Recent Pat CNS Drug Discov*. 2016;10(2):157-177. Phytocannabinoids and Cannabimimetic Drugs: Recent Patents in Central Nervous System Disorders.
- 64 Pacher, P., & Kunos, G. (2013). Modulating the endocannabinoid system in human health and disease: successes and failures. *The FEBS Journal*, 280(9), 1918–1943. <http://doi.org/10.1111/febs.12260>
- 65 *Neuro Endocrinol Lett*. 2014;35(3):198-201. Clinical endocannabinoid deficiency (CECD) revisited: can his concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?
- 66 ffland, K., & Grotenhermen, F. (2017). An Update on Safety and Side Effects of Cannabidiol: A Review of clinical Data and Relevant Animal Studies. *Cannabis and Cannabinoid Research*, 2(1), 139–154. <http://doi.org/10.1089/can.2016.0034>
- 67 *Curr Drug Saf*. 2011 Sep 1;6(4):237-49. Safety and side effects of cannabidiol, a Cannabis sativa constituent.
- 68 FDA GRAS Guidelines <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=184>

