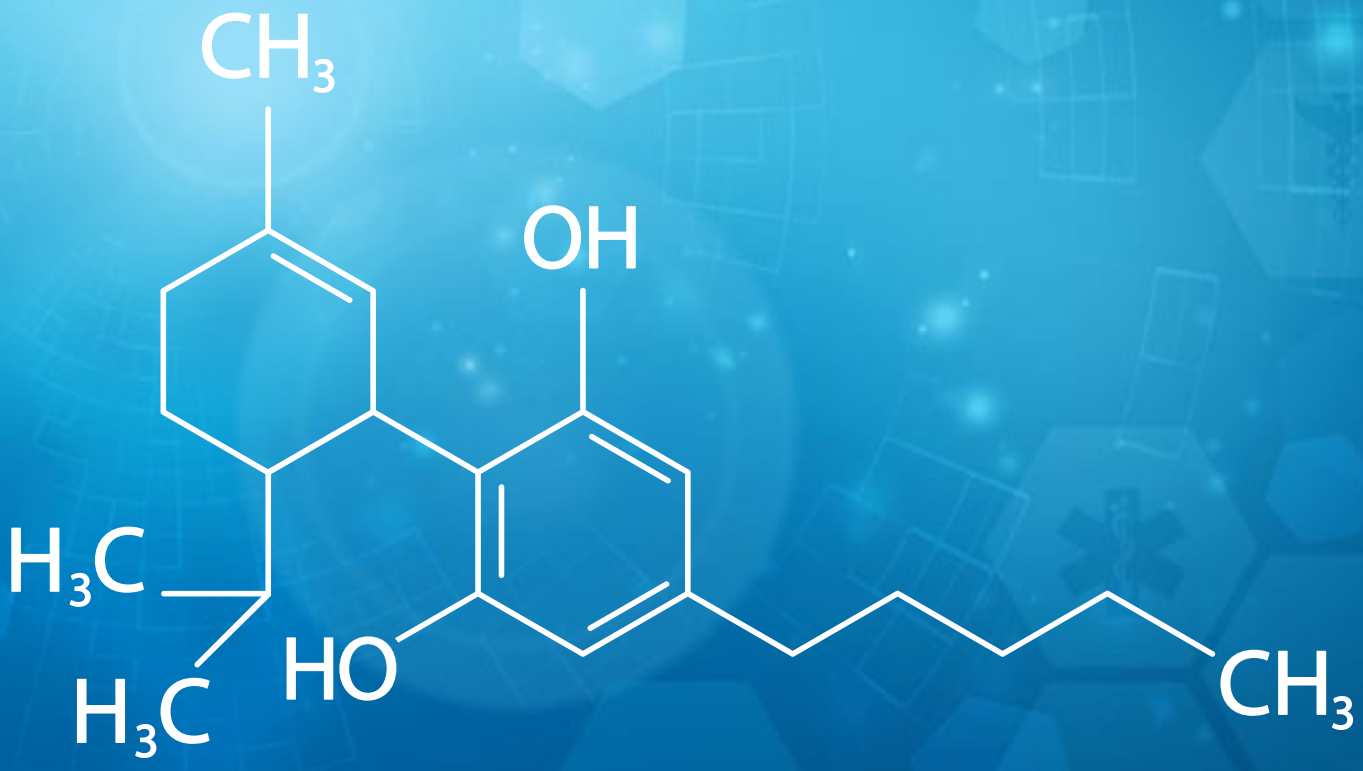
PATIENT'S GUIDE TO CBD

AMERICANS FOR SAFE ACCESS

2019



AmericansForSafeAccess

AmericansForSafeAccess.org

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ABOUT ASA

Americans for Safe Access (ASA) is the largest national member-based organization of patients, medical professionals, scientists, and concerned citizens promoting safe and legal access to cannabis for therapeutic uses and research.

Since 2002, ASA has worked tirelessly to expand knowledge, dispel myths, and change laws regarding medical cannabis. We have played a key role in ensuring access to safe, legal medical cannabis in more than 30 U.S. states and territories. As a 501(c)(3) nonprofit organization, we would not be able to serve as agents of change or perform the meticulous work necessary to produce publications of this caliber were it not for the generous support of our members and donors.

BECOME AN ASA MEMBER

Becoming a member of ASA means you are not just supporting the medical cannabis movement, you are becoming a part of it. For as little as $35 a year, you can ensure that ASA will be on the front lines of the fight to guarantee safe, legal, and affordable medical cannabis for patients in need. If you believe in and want to help sustain our critical work, join us online at www.safeaccessnow.org/membership or consider making a tax-deductible donation at www.safeaccessnow.org/donate.

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FOREWORD

It is a pleasure to introduce this practical guide for patients on cannabidiol (CBD). The topic is a complex one that requires discussion of myriad factors in various disciplines, including agriculture, medicine, pharmacology, and the law. Many differences of opinion compete for legitimacy in these realms, and the attendant rules that attach are in a constant state of flux. This publication serves admirably in clarifying the important factors that a patient or family should know when considering cannabidiol as a therapeutic modality.

A bit of background history is in order.[1, 2] Cannabidiol is the primary cannabinoid encountered in European hemp chemovars ("chemical varieties," Type III cannabis), but in low concentration. In ages past, in traditional hashish-growing areas such as Morocco, Lebanon, and Afghanistan, cannabidiol was present in equal measure with tetrahydrocannabinol (THC) (Type II cannabis). That situation has changed, however. After the positive identification of the chemical structures of cannabidiol in 1963[3] and tetrahydrocannabinol the following year,[4] THC became the subject of intense interest and research, with little attention devoted to CBD. Some even suggested that it was "inactive" merely because it lacked the intoxicating properties of THC. While a few stalwarts continued to investigate CBD, notably in Israel and Brazil,[5-8] THC garnered the vast majority of funding dollars and became the clear target of cannabis breeding. Much of this focus was a by-product of prohibition: just as bathtub gin and moonshine were preferred clandestine products for alcohol, increasing THC concentrations over time have presented a desired result in increasing the value of cannabis commodities with the greatest potency per unit of weight.[9, 10]

That situation began to change in 1998, however, as in that year GW Pharmaceuticals began its research and production of cannabis-based pharmaceuticals and included CBD in those efforts. A great deal of basic science investigation accompanied this work to demonstrate the anticonvulsant, analgesic, anti-inflammatory, anti-anxiety, and antipsychotic benefits of this most versatile substance (summarized[11-14]). Two prescription drugs containing CBD have resulted. Sativex® is a 1:1 preparation of the extracts of two cannabis chemovars, one rich in THC, the other rich in CBD, which is approved in 30 countries for treatment of spasticity in multiple sclerosis and for cancer pain and MS-associated pain in Canada. Epidiolex® is a 98% pure CBD preparation that was approved by the United States Food and Drug Administration in 2018 for treatment of severe epilepsy in Dravet and Lennox-Gastaut syndromes.[15, 16] In the interim, CBD became generally known to the public as a result of these investigations on the anticonvulsant effects of CBD. Selective breeding for cannabidiol content began in earnest in California and Colorado in the last 12 years, boosted greatly by the case of Charlotte Figi as publicized via a CNN documentary.[17] More recently, CBD has captured the public imagination and has become a drug of choice for many for their arthritis and dermatological conditions.

With this explosion of public exposure, there has been a corresponding profusion of confusion in relation to cannabidiol. Myths and misconceptions abound.[14] To emphasize the facts, rather than the falsehoods, the following points can be advanced:

- Cannabidiol is psychoactive by virtue of its anti-anxiety[18] and antipsychotic effects,[19, 20] but it contrasts with THC by lacking intoxicating features or drug abuse liability.[21]
- Cannabidiol in isolation is alerting.[22] Its frequent association in cannabis breeding with elevated myrcene concentrations creates a misconception that CBD is sedating.[23, 24]
- CBD is a functional neutral antagonist of the CB1 receptor by virtue of negative allosteric modulation[25] but totally lacks the adverse event (side effect) profile of inverse agonists such as rimonabant.[26]
- Cannabidiol can be converted to THC in the presence of strong acids[27] but this reaction does not occur in the human body.[28]
- Despite the FDA's approval of Epidiolex and its placement in Schedule V of the Controlled Substances Act, the passage of the 2018 Farm Bill, and the astounding profusion of CBD products touting that they are "legal in all 50 states," the fact remains that CBD is technically illegal on a federal level and remains in Schedule I as a forbidden drug according to FDA and DEA policy.[29] That situation will remain until or unless it is rescheduled or descheduled entirely by Congress, as has been recommended by the World Health Organization (WHO).

It is hoped that the information contained in this publication will be shared widely with patients and their families, enabling greater access to CBD, a therapeutic modality of unparalleled versatility and safety. It is similarly desirable that greater knowledge of CBD may be accompanied by reasonable regulation and safety standards for its commerce and distribution.

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INTRODUCTION

The Patient's Guide to CBD was created by Americans for Safe Access (ASA) for the benefit of patients, prospective patients, healthcare providers, consumers, and anyone interested in learning more about CBD. The goal of this guide is to be an informative and useful reference document that will be shared with others so that patients, doctors, and regulators can make informed decisions regarding CBD.

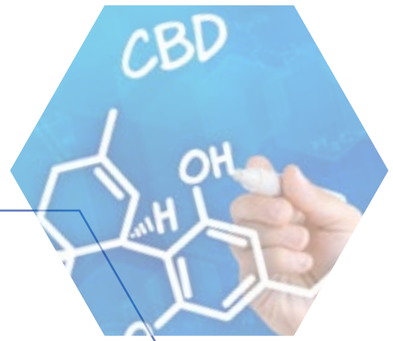
The information presented in this guide does not constitute medical or legal advice. Individuals should discuss the use of cannabis products (including those derived from hemp) with their physician(s) before using any products. Patients are encouraged to share this guide, and any relevant scientific research presented herein, with their doctors to facilitate that conversation.

Patients and consumers should also be aware of the legal and regulatory status of CBD products. As of May 2019, 47 U.S. states have passed some type of legislation permitting the use of cannabis or cannabinoids such as CBD; nevertheless, cannabis with THC in excess of 0.3% by dry weight is a Schedule I controlled substance under U.S. Federal law. Therefore, CBD-containing products that were produced from cannabis plants that exceed the federal threshold on THC may be legal at the state level, but are federally illegal. Additionally, even CBD products that are derived from plants containing not more than 0.3% THC by dry weight may violate laws such as the Food, Drug and Cosmetics Act and create further legal challenges for patients and consumers.

The passage of the Agriculture Improvement Act of 2018 (also known as the 2018 Farm Bill) will make industrial hemp (i.e., cannabis with no more than 0.3% THC by dry weight), including CBD-rich industrial hemp, an agricultural commodity in the United States, but the U.S. Department of Agriculture has yet to promulgate federal regulations or approve state regulations regarding the cultivation and processing of industrial hemp. Further, the U.S. Food & Drug Administration has yet to provide a pathway for the introduction of hemp-derived CBD products into the marketplace. Therefore, it is not yet federally legal to market hemp-derived CBD as a drug, dietary supplement, food product, or cosmetic. Patients and consumers are encouraged to stay up to date on these changing regulations to ensure that they, and their products, are in compliance with applicable laws.

Globally, the use of products containing CBD has risen dramatically as more and more people seek alternative ways to improve their health and their lives. The data has shown an increase in the sales of products containing CBD every year, and sales are expected to continue to rise in the coming years.

INDIVIDUALS SHOULD DISCUSS THE USE OF CANNABIS PRODUCTS (INCLUDING THOSE DERIVED FROM HEMP) WITH THEIR PHYSICIAN(S) BEFORE USING ANY PRODUCTS.



DEFINITIONS

- **Adjuvant** – enhancing the effectiveness of medical treatment
- **Agonist** – a substance that initiates a biological response when bound to a receptor.
- **Analgesic** – typically a drug used to relieve pain.
- **Antagonist** – a substance that interferes with or inhibits a receptor response.
- **Antioxidative** – a substance that inhibits oxidation, which can damage cells.
- **Antiproliferative** – inhibits cell growth, such as cancer and tumor cells.
- **Antipsoriatic** – typically a drug used to treat psoriasis.
- **Antipsychotic** – typically a drug used to treat psychoses.
- **Antispasmodic** – typically a drug used to relieve involuntary muscle spasms.
- **Anxiogenic** – a substance that causes anxiety.
- **Anxiolytic** – a substance, medication, or therapy used to treat anxiety.
- **Apoptosis** – the death of cells as part of an organism's normal growth and development.
- **Cannabinoid** – naturally occurring biologic compounds found inside the trichomes (glandular hairs) of the cannabis plant, including CBD(A), THC(A), CBG(A), and others.
- **Cannabis** – a member of the *Cannabaceae* family, it is a tall plant with a stiff upright stem, divided serrated leaves, and glandular hairs. It is used to produce hemp fiber, seeds and as a drug.
- **Chemotaxic** – analysis of the chemical constituents of a botanical variety.
- **Chemovar** – a chemotaxic variety of a plant family, it is determined by examining the chemical makeup of the plant including the cannabinoids and terpenes.
- **Cultivar** – a cultivated variety of a plant family, it is developed by various genetic breeding strategies.
- **Endocannabinoid** – cannabinoids that are produced naturally inside the body.
- **Endogenous** – naturally occurring inside the human body.
- **Exogenous** – occurring outside the human body.
- **Half-life** – the amount of time it takes for a substance to degrade by half.
- **Industrial Hemp** – as defined by U.S. law, a member of the Cannabaceae family with ≤0.3% THC by dry weight.
- ***In vitro*** – outside the living body and in an artificial environment
- ***In vivo*** – in the living body of a plant or animal
- **Kief** – the resinous trichomes of the cannabis plant that are often accumulated through dry sifting of the flowers.
- **Mechanism of Action** – the specific biochemical pathway by which a substance causes a biological response.
- **Phytocannabinoid** – cannabinoids that are produced by the Cannabis plant.
- **Terpene** – a chemical compound that contributes to the flavors and smells of the cannabis plant as well as other plants.
- **Trichome** – the glandular hairs of the cannabis plant that contain the majority of cannabinoids.

CANNABIS SATIVA L.

The primary source of naturally occurring cannabidiol (CBD) is the plant *Cannabis sativa L.* When these plants contain more than 0.3% tetrahydrocannabinol (THC) by weight, they are often referred to as marijuana plants. When THC does not exceed 0.3%, these plants are legally classified as industrial hemp and are referred to as such.

Cannabidiol (CBD) is one of at least 113 phytocannabinoids produced by *Cannabis sativa L.*[30] It is the most common cannabinoid in hemp plants, and the second most common cannabinoid, after THC, in some of the high-THC chemovars.[23] Cannabis plants are also capable of producing at least 120 different terpenes; these compounds give the plants their aroma and work together with cannabinoids to enhance cannabis' therapeutic effect.[30]

Cannabinoids and terpenes are formed in trichomes, which are small outgrowths similar to tiny hairs that form on the surface of cannabis flowers. The highest concentrations of CBD and other cannabinoids are found in the flowering tops of female cannabis plants. As these plants grow and develop, the cannabinoids they produce are primarily in acidic form. CBD is the neutral (i.e., non-acidic) homologue of cannabidiolic acid (CBDA); in order for CBDA to become CBD, it must be decarboxylated, which is what happens when CBDA is exposed to light or heat.[30]

"FOR DECADES, FEDERAL LAW DID NOT DIFFERENTIATE HEMP FROM OTHER CANNABIS PLANTS, ALL OF WHICH WERE EFFECTIVELY MADE ILLEGAL IN 1937 UNDER THE MARIHUANA TAX ACT AND FORMALLY MADE ILLEGAL IN 1970 UNDER THE CONTROLLED SUBSTANCES ACT – THE LATTER BANNED CANNABIS OF ANY KIND."

Hudak, J. (2018, December 14). *The Farm Bill, hemp legalization and the status of CBD: An explainer*. Retrieved from The Brookings Institution: https://www.brookings.edu/blog/fixgov/2018/12/14/the-farm-bill-hemp-and-cbd-explainer/

Given that CBD is derived from cannabis, which is listed under Schedule I of the Controlled Substances Act (CSA), CBD products have not been widely available for purchase until fairly recently. "For decades, federal law did not differentiate hemp from other cannabis plants, all of which were effectively made illegal in 1937 under the Marihuana Tax Act and formally made illegal in 1970 under the Controlled Substances Act – the latter banned cannabis of any kind."[30] Nevertheless, over the past several years, some producers have offered CBD products purported to be made from the mature stalks of cannabis plants, which are excluded from the definition of marijuana in the CSA.[32] Such claims should be met with skepticism: "Cannabidiol expression is typically limited to flowering buds and not stalk fiber, or sterilized seeds; this is true of all cannabis varieties."[33] Additionally, this strategy is of dubious legal value given that any resin extracted from the stalk remains a Schedule I substance – "an exception to the exemption."[33] Other producers took advantage of the industrial hemp pilot programs authorized under the Agricultural Act of 2014 (also known as the 2014 Farm Bill) to sell CBD products under the guise of market research.

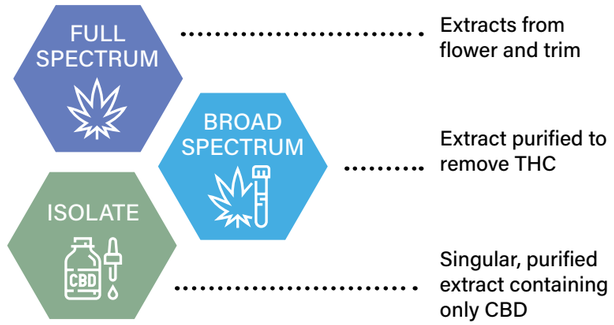
Cannabis with more than 0.3% THC remains illegal under U.S. Federal law, but the passage of the Agriculture Improvement Act of 2018 (also known as the 2018 Farm Bill) means that we are on the brink of explosive growth in the hemp CBD industry. The 2018 Farm Bill removed industrial hemp from the Controlled Substances Act and provided the legislative framework for the creation of a shared state-federal regulatory regime through

which the U.S. Department of Agriculture (USDA) and/or states with USDA-approved regulatory plans may license hemp cultivators.[30] While the cultivation of hemp will still be subject to very stringent guidelines and controls, the hemp CBD industry is expected to be worth billions of dollars within the next few years.[34]

While the 2018 Farm Bill will make legal hemp-derived CBD widely available to consumers once the regulatory regime is in place and the first set of crops has been harvested and processed, hemp-derived CBD of dubious legality can be purchased online and is finding its way into an increasing number of retail stores. Additionally, medical cannabis patients in some jurisdictions with active dispensaries can procure CBD products derived from cannabis plants with THC levels in excess of 0.3%. In fact, dispensaries often carry an assortment of products with a range of THC:CBD ratios and terpene profiles, which allows patients to experiment and find the cannabinoid ratios and terpene profiles that work best for them.

AVAILABLE FORMS FOR USE

Before delving too deeply into the various forms available for use, it is important to first address three terms that consumers may come across when shopping for CBD products: full spectrum, broad spectrum, and isolate. Full-spectrum products contain the full array of cannabinoids and terpenes present within the cannabis flower, including THC; this applies to CBD products derived from hemp as well as THC-rich cannabis since even hemp plants may have up to 0.3% THC. Broad-spectrum products are created or processed in such a manner as to ensure that the final product does not contain THC. CBD isolate is CBD in its molecular form, and it is often marketed as being 99+% pure. Unless otherwise noted on the packaging, products made with CBD isolate do not contain any other cannabinoids or terpenes. The type of product becomes important when considering the "entourage effect" – the therapeutic potential created by the interaction among cannabinoids and terpenes within the body – and any restrictions or concerns the consumer may have with regard to the consumption of THC.



It is also important to consider the means by which cannabinoids can be administered. Vaporizing or smoking CBD-rich products will result in quick onset because the cannabinoid(s) are absorbed through the lungs into the bloodstream and the therapeutic effects generally last for several hours. Putting CBD-rich products under the tongue or against the tissues of the cheek for absorption results in slower onset than inhalation, but the therapeutic effects may persist for longer. Ingesting CBD products will result in the slowest onset because the CBD must first pass through the stomach, be absorbed in the intestine, and be metabolized by the liver before becoming bioavailable, but the therapeutic effects can last the longest. CBD-containing products also can be formulated for topical application, which provides a pathway for local rather than systemic absorption of CBD. Topical products are rubbed into the skin at the desired site (e.g., where there is pain or inflammation).

As previously mentioned, CBD and other cannabinoids are primarily produced within the flowering tops of female cannabis plants. The most basic form of consumable CBD is found in the raw flower. The process of vaporizing or smoking cannabis flowers converts the CBDA present in the floral material into CBD. Alternatively, one could use an oven or a specialized device to decarboxylate the cannabis flowers, at which point the floral material primarily would contain CBD rather than CBDA. Decarboxylated flowers can be used to create CBD-rich infusions or tinctures that can be ingested, taken orally, or used topically.

Kief

The trichomes that contain cannabinoids and terpenes can be separated from the rest of the plant through a variety of means. For example, sifting cannabis through fine mesh screens can yield a collection of trichomes that is often referred to as "kief". While this term has historically been used to describe trichomes from plants with psychoactive levels of THC, the emergence of high-CBD cultivars of cannabis means that one could separate CBD-rich kief from cannabis flowers. As with raw flower, high-CBD kief would have to be vaporized, smoked, or otherwise decarboxylated to convert the CBDA within it to CBD. While it is a more concentrated form of cannabis, kief can be used in the same ways raw flower can be used. Additionally, with the application of gentle heat and pressure, CBD-rich kief can be formed into dry-sift CBD hash.

Bubble Hash

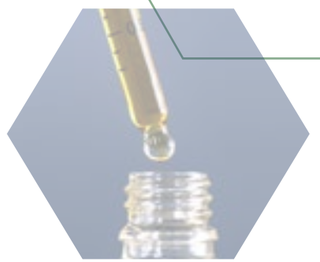
Ice water can also be used to separate trichomes from plant material, since the cold temperature makes the trichomes more rigid and prone to breakage. Agitating raw flowers in ice water and capturing the trichomes in a series of mesh screens of decreasing size is the process by which bubble hash is made. When CBD-rich flower is used as the input material, CBD bubble hash is the end product.

Infused Products and Tinctures

Infused products such as food and beverages, topicals, and tinctures are among the most accessible forms of CBD products. They allow for easy and consistent dosing, which is particularly helpful for people who don't have significant prior experience with the administration of cannabis. Full-spectrum CBD infusions may be created by heating decarboxylated CBD-rich flowers in oil (such as hemp seed oil, olive oil, coconut oil, or a medium-chain triglyceride (MCT) oil) or butter. Since cannabinoids are fat-soluble, the active compounds are pulled into the oil or butter. Once the infusion process is complete, the spent floral material is strained out of the fat and discarded. Infused butter may be consumed as is or used to prepare CBD-infused food and beverages; infused oils may be used in these ways and also applied topically.

CBD tinctures generally are created using either ethanol or vegetable glycerin as a solvent. Ethanol is a powerful solvent that can dissolve both polar and nonpolar substances. Glycerin is a weaker solvent than ethanol, but it is a good option for those who do not want an alcohol-based product. The process by which full-spectrum glycerin-based tinctures are made is very similar to the process by which infusions are made; the key difference is that glycerin is used in lieu of an oil. Full-spectrum ethanol-based tinctures are made by soaking CBD-rich flowers in ethanol. Gentle heat may be used to speed extraction time. Once the extraction process is complete, the floral material is strained out of the tincture.

CBD tinctures and infused oils can be directly absorbed under the tongue or through the tissue of the cheek. Alternatively, these products can be added to beverages or food products prior to consumption, which will cause the CBD to be digested and metabolized through the liver instead of being absorbed directly into the bloodstream.



Concentrates

Manufacturers can produce cannabis concentrates – products with higher concentrations of CBD and/or other cannabinoids – through a variety of means. Squeezing CBD-rich cannabis flowers, CBD kief, or CBD hash between heated plates at high pressure will separate the resin from the plant material, thereby producing CBD rosin. This process does not make use of solvents, so there is no need for significant processing or concern regarding residual solvents with rosin.

Manufacturers also can produce concentrates by using specialized equipment with solvents like carbon dioxide (CO_2) or butane, among others, to strip cannabinoids from floral material. During CO_2 extraction, by carefully controlling the temperature and pressure at which the CO_2 passes through the plant matter, producers can precisely control which components are extracted. Individual components can be extracted and blended back together according to the producer's specifications. When butane, propane, or a blend of hydrocarbons is used, the resulting concentrate will contain the full spectrum of cannabinoids and terpenes within the plant material. While concentrate production processes may also strip less-desirable components from the plant material (e.g., plant wax), additional post-extraction processing can further refine the end product. CBD products created through these manufacturing processes are essentially CBD hash oil, but the specific name will vary based on the final form of the product. Variations include CBD honey oil, CBD shatter, CBD wax, CBD crumble, etc. Regardless of the form, these products can be vaporized, smoked, or decarboxylated and ingested.

CBD hash oil can be put through additional processing to further concentrate CBD content. For example, manufacturers can use heat and vacuum power to extract and separately concentrate various components (e.g., cannabinoids and terpenes) from within the oil in a process called fractional distillation. The highly concentrated product resulting from this process is called CBD distillate. Terpenes may be blended in with the distillate according to the manufacturer's specifications. Distillate can be vaporized or smoked, and since it is already decarboxylated, it also can be ingested, taken orally, or used topically without further activation.

Many manufacturers offer CBD cartridges that can be attached to batteries, which heat the oil within the cartridge to the point of vaporization. These cartridges may be a convenient and discreet means to administer CBD, but consumers must be cautious concerning the safety of the products they purchase. Due to its viscous nature, concentrated CBD oil that is intended for use in a cartridge may need to be mixed with a thinning agent to allow the cartridge to function as intended. Cartridges that contain CO_2 oil or CBD distillate with cannabis-derived terpenes as the sole thinning agent are generally regarded as relatively safe. Some producers, however, thin their products with propylene glycol (PG), polyethylene glycol 400 (PEG 400), or other such additives. These products have been generally recognized as safe by the FDA for ingestion, but there is evidence they produce noxious compounds when they are heated past a certain temperature.[35] For the safety of the consumer, it is best to avoid such products and any other CBD products that do not have documented laboratory testing results. See, "Packaging, Labeling, and Handling - What to Know" on page XX for more information.

INDICATED USES

Research into the types of conditions and symptoms that cannabidiol may be used to treat is increasing, but there is a need for further research in order to continue to elucidate not only additional medicinal properties of CBD, but the ratios of cannabinoid to terpene content that are best suited for treatment. Many are familiar with CBD's anticonvulsant properties and its use as a treatment for seizure disorders, but CBD has also been indicated for use as an antispasmodic, analgesic, antipsoriatic, anxiolytic, and antipsychotic because of its neuroprotective and immunosuppressive properties. Figure 1 highlights some of the cannabinoids, their medicinal properties, and a theoretical mechanism of action for their indicated uses

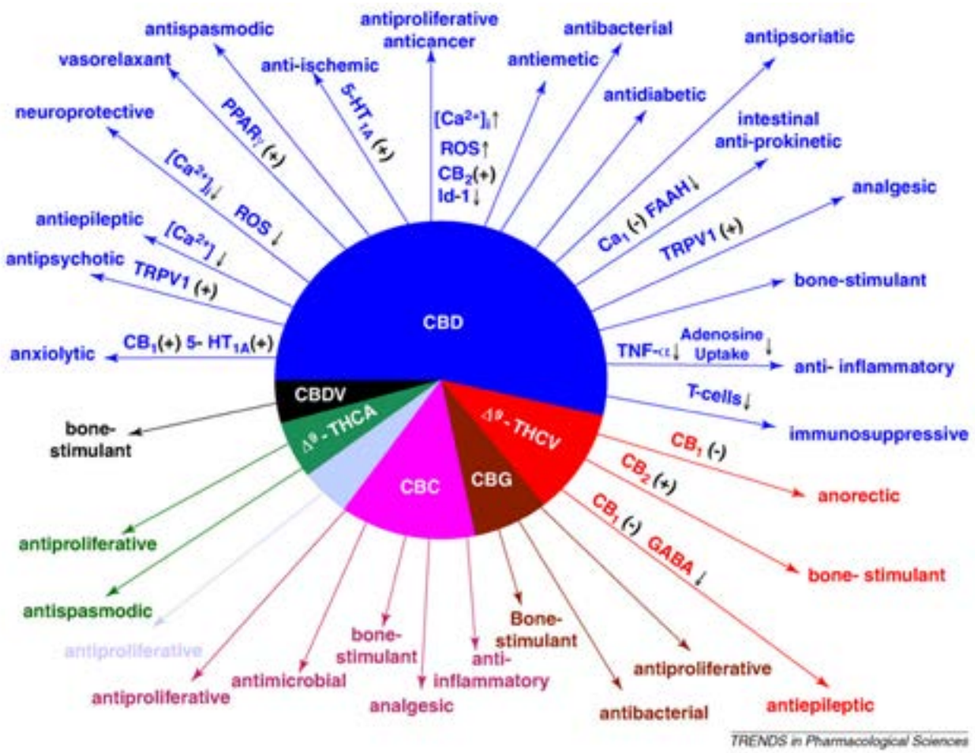


Figure 1: Indicated Uses of Various Cannabinoids[36]

Epilepsy and Seizure Disorders

Anecdotal stories abound about the successful use of CBD to treat seizure disorders, but what is happening inside the body to create this outcome? CBD has been studied since the 1970s as an anti-seizure and anti-epileptic compound.[37] Different mechanisms of action have been studied, but the exact mechanism has yet to be defined.

Epidiolex was approved by the Food and Drug Administration (FDA) in 2018 for the treatment of Dravet Syndrome and Lennox-Gastaut Syndrome. Both are rare diseases that manifest in early childhood with the onset of seizures and can cause significant neurodevelopmental problems. While this drug's exact mechanism of action is unknown, it is believed that it may act by modulating endogenous systems such as neuronal inhibition, intracellular calcium, and adenosine modulation.[38]

CBD COULD FORM THE BASIS FOR TARGETED CANCER TREATMENTS THAT COULD REDUCE THE SIDE EFFECTS MANY PATIENTS EXPERIENCE WHEN UNDERGOING CHEMOTHERAPY AND RADIATION THERAPY.

Although there is one medication on the market approved for the treatment of these specific disorders, more research is needed into improving the efficacy and creating new medications that are targeted specifically to additional seizure disorders and different seizure types.

Anxiety and Sleep

A preliminary sleep study involving healthy human volunteers suggests that CBD acts as an anxiolytic.[12] This preliminary finding has also been replicated in animal models.[39] In a larger case study of human individuals with anxiety and sleep complaints, 79.2% (57 out of 72) of patients had decreased anxiety scores and 66.7% (48 out of 72) of patients had improved sleep in the first month, fluctuating in subsequent months.[40]

In a simulated public speaking task, involving healthy humans, CBD was shown to reverse the anxiogenic effects of Δ^9-THC and reduce anxiety.[18] There are also preclinical studies that indicate that CBD may also be used as an adjuvant in exposure-based psychotherapies for anxiety disorders.[41]

Inflammation and Immune Responses

The body's immune system is designed to protect it from disease, but disruptions in functionality can lead to a number of different conditions, including rheumatoid arthritis, lupus, celiac disease, and psoriatic arthritis. In well-established models of neuropathic and inflammatory pain and acute and chronic inflammation, CBD has been shown to be an effective treatment option.[42] It demonstrates an immunosuppressive effect[43] and has been shown to inhibit the formation of keratinocytes that are typical of psoriatic arthritis.[44]

Cancer

Cancer is caused by gene mutations and can be formed in any part of the body. Many cannabinoids, including CBD, Δ^9-THC, CBC, and CBG have been shown to have various anti-cancer characteristics, including anti-proliferative and pro-apoptotic properties. The effects of CBD on numerous cancer cell lines have been studied, both *in vivo* and *in vitro*:

- Breast carcinoma
- Prostate carcinoma
- Colorectal carcinoma
- Gastric adenocarcinoma
- Skin cancer
- Pancreatic cancer
- Lung cancer
- Bone cancer

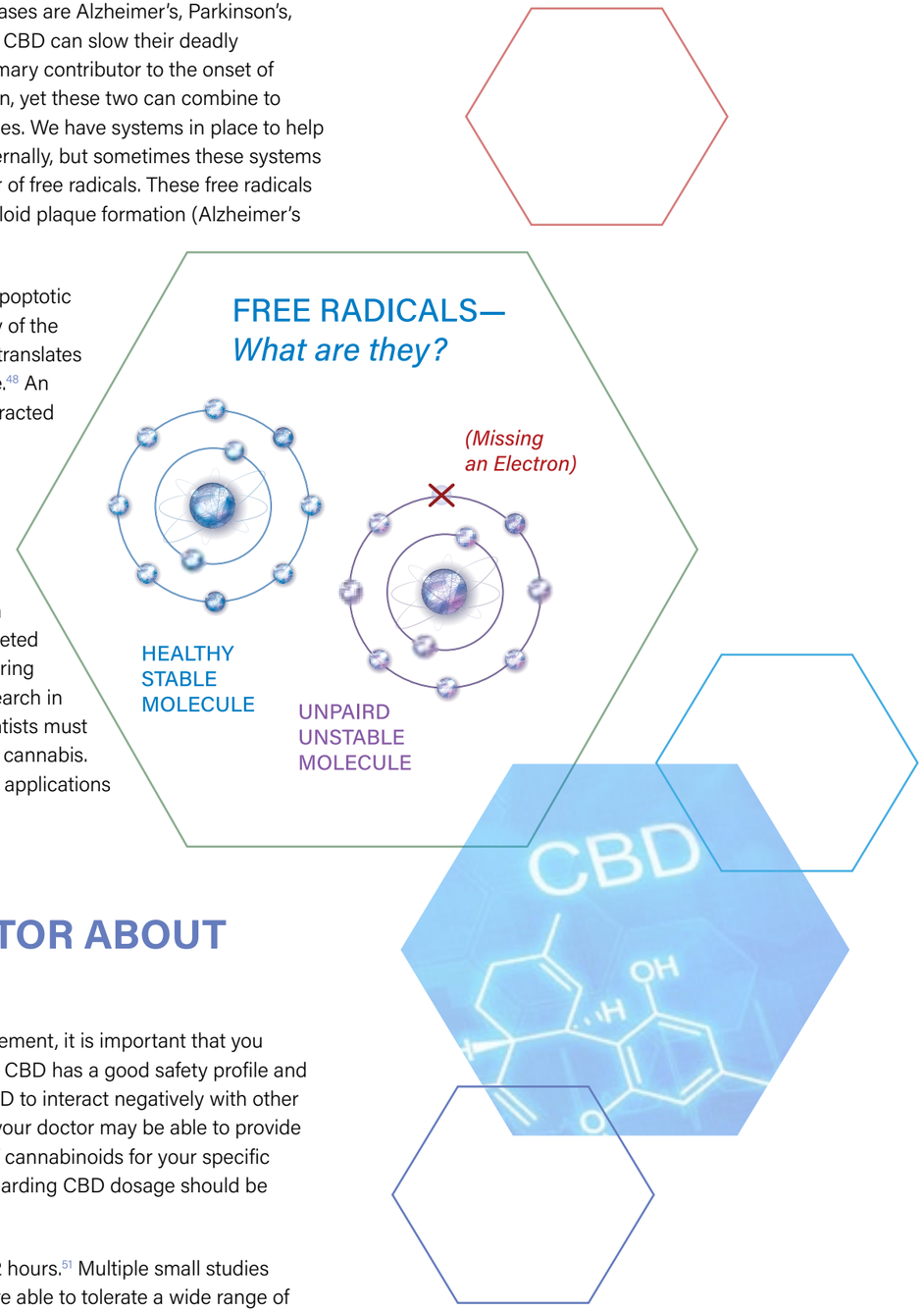
The positive outcomes of these studies indicate that in the future, CBD could form the basis for targeted cancer treatments that could reduce the side effects many patients experience when undergoing chemotherapy and radiation therapy. A number of researchers have also begun to explore additional cancer cell lines to see if CBD treatment may also be effective in treating lesser known cancers that may have fewer traditional treatment options.[45]

Neuroprotection and Neurodegenerative Diseases

Three of the most debilitating neurodegenerative diseases are Alzheimer's, Parkinson's, and Huntington's, and each has been studied to see if CBD can slow their deadly progression. It is believed that oxidative stress is a primary contributor to the onset of these diseases. Our bodies need both food and oxygen, yet these two can combine to create what are known as free radicals inside our bodies. We have systems in place to help reduce these free radicals and maintain a balance internally, but sometimes these systems break down, which leads to an increase in the number of free radicals. These free radicals cause oxidative stress, which can in turn result in amyloid plaque formation (Alzheimer's and Parkinson's)[46] or gene mutations (Huntington's).[47]

CBD exerts neuroprotective, anti-oxidative, and anti-apoptotic effects[42]. It has been shown to inhibit the neurotoxicity of the beta amyloid peptide in mouse models *in vivo*, which translates to a slowing of the progression of Alzheimer's Disease.[48] An additional investigation showed that CBD also counteracted a decrease in copper-zinc enzyme, which can lead to additional signs of oxidative stress.[49]

When it comes to the diseases for which CBD might be a viable treatment, those listed above are only the tip of the iceberg. More research is needed to elucidate the specific mechanisms of action of CBD in the body, which could enable the development of targeted solutions and personalized medicine for patients suffering from a myriad of issues. In order to conduct more research in the United States as to how best to treat people, scientists must have greater access to cannabinoids and whole-plant cannabis. At the end of this guide, we will review current clinical applications and consider future research needs.



TALKING TO YOUR DOCTOR ABOUT CANNABINOIDS

As with any medication, medical food, or herbal supplement, it is important that you speak with your doctor before consuming CBD. While CBD has a good safety profile and is generally well tolerated, there is the potential for CBD to interact negatively with other medications and for other side effects.[50] Additionally, your doctor may be able to provide helpful information and guidance regarding the use of cannabinoids for your specific health conditions. Any guidance your doctor gives regarding CBD dosage should be followed carefully.

CBD is metabolized in the liver with a half-life of 18-32 hours.[51] Multiple small studies of the safety of CBD in adults have shown that they are able to tolerate a wide range of doses.[52] There is currently little data on the types of drug-drug interactions that may occur between CBD and other pharmaceutical drugs, but CBD is an inhibitor of cytochrome P450 enzymes,[53] which is how many pharmaceutical drugs are metabolized. Patients should talk to their doctors about whether any of the medications they're taking are metabolized by the cytochrome P450 system before taking CBD.

Patients and consumers should be forthright when having these discussions. There is nothing wrong or illegal about discussing medical cannabis or cannabinoids with a doctor. The First Amendment protects doctors' ability to discuss these topics with their patients. Doctors are accustomed to patients bringing ideas to them about treatment options and preferences, and cannabis therapeutics should be no different. As some doctors are better versed in cannabis and cannabinoid therapeutics than others, it may be helpful to provide documentation showing how CBD or medical cannabis could be beneficial for one's specific condition(s), including the information presented here in this guide.

FINDING THE RIGHT DOSE

The type of product you use will impact dosing requirements. Products made with purified CBD (e.g., CBD isolate and CBD distillate) seem to have a narrower therapeutic window than full-spectrum products. This is because purified CBD exhibits a bell-shaped dose-response curve when administered; as one team of researchers noted, "Healing was only observed when CBD was given within a very limited dose range, whereas no beneficial effect was achieved at either lower or higher doses."[54] Full-spectrum products, on the other hand, tend to show a direct correlation between dose and response, with increased doses resulting in increased responses until a medicinal plateau is reached.[54] This may be a result of the entourage effect.[54] Once a medicinal plateau has been reached, increasing the dose will not markedly change the response one way or another.

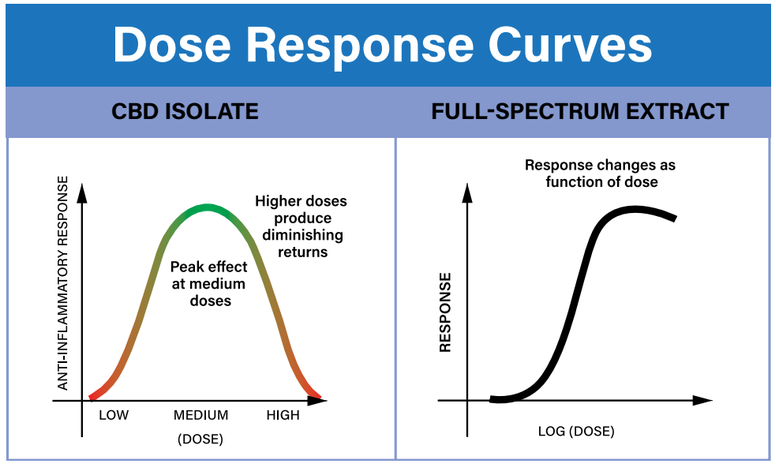


Figure 2: The dose-response relationships of CBD isolate and full-spectrum extract.

In practical terms, the information above means that individuals taking products made with purified forms of CBD must be more precise and deliberate when finding the right dosage because not only will they find too little CBD ineffective, they will also find too much CBD ineffective. Patients who are able to take a full-spectrum product may be able to start with a higher dosage and titrate more rapidly as they do not risk overshooting the therapeutic target. Nevertheless, individuals using a full-spectrum product should attempt to find the smallest dose that provides maximum therapeutic effect in order to minimize potential for side effects and unnecessary expenditures.

Given the variation in the types and forms of CBD products and individual responses to CBD and other constituents of cannabis, it is beyond the scope of this document to provide concrete dosing information. Patients must go through a process of trial and error to find the correct dose for the condition(s) being treated, and the correct dose may change over time due to age, tolerance, body fat percentage, genetics, metabolism, and other factors.

A journal can be a valuable tool for patients and consumers who are trying to establish an optimal treatment regime with CBD. A log of your use can provide insight into the effects of different products, doses, and methods of ingestion and aid in reaching a determination as to what works best. Capturing the following information within a journal may prove helpful:

- Date/Time: Record every time you consume CBD or a CBD-containing product with the current date and time of day.
- Amount: Record the amount of CBD consumed (milligram estimate or other consistent measure).
- Cultivar (Strain): If using high-CBD flower or a broad- or full-spectrum CBD concentrate, record the name of the cannabis variety (cultivar) used. If you don't know the name, write a detailed description of the product. If you used CBD isolate, note that here.
- Form consumed: Record whether you used dried flower, a concentrate, a tincture, a spray, an edible product or drink, or a topical product.
- Cannabinoid and terpene content: Record the cannabinoid (e.g., THC, CBD, CBN) and terpene (e.g., myrcene, linalool, pinene) content of the product used. If you have this information available to you, write down percentages of each cannabinoid and terpene. If you're using edibles, a description of preparation may be helpful.

- Mode: Write down how you consumed your medication (S=smoke, V=vapor, E=eat/digest, T=tincture or spray, TO=topical).
- Therapeutic effects: List any positive effects that you experience (physical, mental, social, behavioral, etc.).
- Negative side effects: Record any negative effects.
- Timing: How quickly did you experience the first therapeutic effect(s)? When did you feel the peak of relief? When did it start to noticeably dissipate? How long until effects were gone?
- What prompted your CBD use: List the specific factors that told you it was time for medicine, as well as the general symptoms or conditions being treated (e.g., pain, nausea, anxiety, etc.).
- How did you feel (mindset): Record your mood and feelings before and after you used CBD.

Each person is different, therefore capturing at least a week's worth of information and then assessing the data can help them identify the dosing regimen that will be most effective, which they can then take to their doctors to discuss. Some conditions may require repeated administrations over time before efficacy can be observed. To facilitate the journaling process, Americans for Safe Access has partnered with the developers of the Releaf app, which patients and consumers can use to track their medical cannabis or CBD consumption. Those who are interested in anonymously sharing their data for research purposes can join ASA's Releaf group by opening the app, navigating to more > my groups, tapping the + icon, and entering the code: *safeaccess*.

To join the ASA Releaf group: https://releaf.at/safeaccess

Join Americans for Safe Access on Releaf app.

You've been invited to anonymously share your session data with the group's owner to help give them insight into what's working, and what isn't, for patients like you.

To join the group:

1. Launch the Releaf app
2. Go to "more > my groups"
3. Tap the + icon
4. Enter the code below

safeaccess

WHAT TO KNOW ABOUT PACKAGING, LABELING, AND HANDLING

Due to a current lack of adequate governmental regulation with regard to hemp-derived CBD products, consumers purchasing CBD products from a source other than a medical cannabis dispensary must be wary of unscrupulous actors and poor production processes. It should also be noted that not all medical cannabis dispensaries are the same. Product safety testing is not required by all states, and patients should be aware of the testing that is done on the products they are consuming.

Unless the producer has appropriate certifications from an independent oversight body (e.g., ASA's Patient Focused Certification), it may be difficult for consumers to ascertain whether the products they wish to purchase are well made and accurately labeled. A 2017 analysis of 84 products from 31 companies found that 43% contained more CBD than was indicated on the label and that 26% contained less CBD than was indicated on the label; additionally, THC was found in 18 out of the 84 samples even though none of the labels indicated that the products contained THC.[55]

Consumers must pay close attention to how products are packaged, labeled, and stored to ensure product safety and efficacy. Light, heat, and oxygen affect, and can degrade, cannabinoids and terpenes. Excessive moisture in a product can promote spoilage and fungal growth. Generally, cannabis floral material and products derived therefrom should be packaged in a manner that minimizes exposure to these factors and should be stored in a climate-controlled setting to avoid elevated temperatures. To protect the contents within, containers should be rigid, airtight, and made out of a non-absorptive material (e.g., glass, stainless steel) that is appropriate for the type of product in question.

It is important that consumers closely read product labels, which should include all of the following:

- Name and place of business of the manufacturer or distributor;
- Identity of the product;
- Cannabinoid content;
- Net quantity of contents in terms of weight, numerical count, or other appropriate measure;
- A batch, lot, or control number;
- Production date or expiration date (products susceptible to spoilage must bear a "use by" date and/or a "freeze by" date);
- Instructions for use;
- Dosing guidance;
- Appropriate warnings for use, including any individuals for whom the product is contraindicated, as appropriate; and
- Instructions for appropriate storage.

Edible products should be labeled with content and nutrition information, including:

- Ingredients, including cannabis ingredients;
- Cannabinoid content;
- Total calories and fat calories (when greater than 5 calories per serving);
- Total fat, saturated fat, and trans fat (when greater than 0.5 g per serving);
- Cholesterol (when greater than 2 mg per serving);
- Sodium (when greater than 5 mg per serving);
- Total carbohydrates (when greater than 1 g per serving);
- Dietary fiber (when greater than 1 g per serving);
- Sugars (when greater than 1 g per serving);
- Protein (when greater than 1 g per serving); and
- Vitamin A, vitamin C, calcium, and iron (when present at greater than 2% of the recommended daily intake).

CONSUMERS SHOULD NOT PURCHASE CANNABIS-DERIVED PRODUCTS FROM COMPANIES THAT CANNOT OR WILL NOT PROVIDE PRODUCT- AND BATCH-SPECIFIC "CoAs".

Note that the FDA has sent warning letters to companies that overstate the health effects and benefits of CBD products. Even if there is research indicating that CBD may be efficacious for a given condition, be wary of products that contain labeling statements that over promise or make outrageous claims like "this will cure cancer."

Generally, reputable producers will provide Certificates of Analysis (CoAs) from independent and properly certified testing laboratories for all of their products. CoAs show the amount and concentration of major cannabinoids and terpenes present in the tested sample, as well testing data regarding the lack or presence of microbial and fungal contaminants, levels of heavy metals, and measures of pesticide and solvent residues (if applicable).

Some producers provide CoAs proactively (e.g., provide a link on the product's webpage); others make them available upon request. *Consumers should not purchase cannabis-derived products from companies that cannot or will not provide product- and batch-specific CoAs.*

SAMPLE CERTIFICATE OF ANALYSIS

(Descriptions found on page 28-29)

CannaSafe

CannaSafe - LA
7027 Hayvenhurst Avenue
Van Nuys, CA 91406

(818) 922-2416
http://www.csalabs.com
Lic# C8-18-0000037-TEMP

1

R&D Testing

1 of 4

2

KOI Healing Balm 500mg

3

Sample ID: 1902CSALA0704.2613
Strain: Koi Healing Balm 500mg
Matrix: Other
Type: Other
Sample Size: 1 units; Batch: 0 units

Produced: N/A
Collected: 02/04/2019
Received: 02/04/2019
Completed: 02/06/2019
Batch#: 9032KHB500

4

Client
Koi CBD
Lic. #
14631 Best Ave
Norwalk, CA 90650

Summary

Pass

5

514.35 mg/unit Total Cannabinoids	**Pass** Pesticides	**Pass** Residual Solvents
Pass Microbials	**Pass** Mycotoxins	**Pass** Heavy Metals

Cannabinoids

Complete

6

Testing method: HPLC-SOP 101

Analyte	LOD	LOQ	Mass	Mass
	mg/unit	mg/unit	mg/unit	mg/g
THCa	0.01008	0.0450	ND	ND
Δ9-THC	0.01904	0.0450	ND	ND
Δ8-THC	0.01895	0.0450	ND	ND
THCV	0.01764	0.0450	ND	ND
CBDa	0.00914	0.0450	ND	ND
CBD	0.01679	0.0450	514.35	11.43
CBDV	0.00450	0.0450	ND	ND
CBN	0.00729	0.0450	ND	ND
CBGa	0.00882	0.0450	ND	ND
CBG	0.01679	0.0450	ND	ND
CBC	0.00644	0.0450	ND	ND
Total			**514.35**	**11.43**

ND
Total THC

514.35 mg/unit
Total CBD

Terpenes

Complete

7

Testing method: HSGCMS-SOP 201

Analyte	LOD	LOQ	Mass	Mass
	%	%	%	mg/g
Eucalyptol	0.00017	0.0013	0.61	6.13
Linalool	0.00015	0.0013	0.11	1.09
δ-Limonene	0.00016	0.0013	0.09	0.87
α-Pinene	0.00015	0.0013	0.09	0.86
β-Pinene	0.00034	0.0013	0.04	0.44
β-Myrcene	0.00012	0.0013	0.03	0.27
β-Caryophyllene	0.00017	0.0013	0.02	0.23
Camphene	0.00072	0.0013	0.02	0.20
δ-3-Carene	0.00040	0.0013	0.02	0.16
Ocimene	0.00013	0.0013	0.01	0.09
α-Terpinene	0.00012	0.0013	0.00	0.05
Terpinolene	0.00016	0.0013	0.00	0.03
Geraniol	0.00013	0.0013	0.00	0.02
α-Bisabolol	0.00015	0.0013	ND	ND
α-Humulene	0.00057	0.0013	ND	ND
Caryophyllene Oxide	0.00017	0.0013	ND	ND
cis-Nerolidol	0.00009	0.0013	ND	ND
γ-Terpinene	0.00012	0.0013	ND	ND
Guaiol	0.00018	0.0013	NR	NR
Isopulegol	0.00011	0.0013	<LOQ	<LOQ
p-Cymene	0.00010	0.0013	ND	ND
trans-Nerolidol	0.00058	0.0013	<LOQ	<LOQ
Total			**1.04**	**10.42**

8 9 10

NT Moisture SOP-103	**NT** Water Activity SOP-102	**Pass** Foreign Matter SOP-001

Date Tested: 02/06/2019
Total THC = THCa * 0.877 + d9-THC
Total CBD = CBDa * 0.877 + CBD
LOQ = Limit of Quantitation; LOD = Limit of Detection; NR = Not Reported; NT = Not Tested; ND = Not Detected. The reported result is based on a sample weight with the applicable moisture content for that sample;

ISO / IEC 17025:2017 ACCREDITED LABORATORY
Accreditation No. 73653

11

Mallory Speakman
Laboratory Director - LA
02/06/2019

12

Anya Engen
Quality Manager
02/06/2019

The values reported pertain only to the product tested. R&D sample only. Tested as-is/received from client. Unless otherwise stated all quality control samples performed within specifications established by the Laboratory. Sample tested per CALIFORNIA CODE OF REGULATIONS, TITLE 16, DIVISION 42. BUREAU OF CANNABIS CONTROL.

Figure 3: Page 1/4 of a Sample Certificate of Analysis[56]

CannaSafe

CannaSafe - LA
7027 Hayvenhurst Avenue
Van Nuys, CA 91406

(818) 922-2416
http://www.csalabs.com
Lic# C8-18-0000037-TEMP

R&D Testing

2 of 4

KOI Healing Balm 500mg

Sample ID: 1902CSALA0704.2613
Strain: Koi Healing Balm 500mg
Matrix: Other
Type: Other
Sample Size: 1 units; Batch: 0 units

Produced: N/A
Collected: 02/04/2019
Received: 02/04/2019
Completed: 02/06/2019
Batch#: 9032KHB500

Client
Koi CBD
Lic. #
14631 Best Ave
Norwalk, CA 90650

13

Pesticides

Pass

Test Method: LCMS & GCMS-SOP 301

Analyte	LOD	LOQ	Limit	Mass	Status	Analyte	LOD	LOQ	Limit	Mass	Status
	µg/g	µg/g	µg/g	µg/g			µg/g	µg/g	µg/g	µg/g	
Abamectin	0.0048	0.1	0.3000	ND	Pass	Fludioxonil	0.0005	0.1	30.0000	ND	Pass
Acephate	0.0090	0.1	5.0000	ND	Pass	Hexythiazox	0.0070	0.1	2.0000	ND	Pass
Acequinocyl	0.0050	0.1	4.0000	ND	Pass	Imazalil	0.0040	0.1	0.0040	ND	Pass
Acetamiprid	0.0040	0.1	5.0000	ND	Pass	Imidacloprid	0.0009	0.1	3.0000	ND	Pass
Aldicarb	0.0040	0.1	0.0040	ND	Pass	Kresoxim Methyl	0.0027	0.1	1.0000	ND	Pass
Azoxystrobin	0.0060	0.1	40.0000	ND	Pass	Malathion	0.0006	0.1	5.0000	ND	Pass
Bifenazate	0.0040	0.1	5.0000	ND	Pass	Metalaxyl	0.0008	0.1	15.0000	ND	Pass
Bifenthrin	0.0080	0.1	0.5000	ND	Pass	Methiocarb	0.0060	0.1	0.0060	ND	Pass
Boscalid	0.0007	0.1	10.0000	ND	Pass	Methomyl	0.0008	0.1	0.1000	ND	Pass
Captan	0.0007	0.1	5.0000	ND	Pass	Methyl Parathion	0.0070	0.1	0.0070	ND	Pass
Carbaryl	0.0006	0.1	0.5000	ND	Pass	Mevinphos	0.0030	0.1	0.0030	ND	Pass
Carbofuran	0.0050	0.1	0.0050	ND	Pass	Myclobutanil	0.0036	0.1	9.0000	ND	Pass
Chlorantraniliprole	0.0005	0.1	40.0000	ND	Pass	Naled	0.0036	0.1	0.5000	ND	Pass
Chlordane	0.0319	0.1	0.0319	ND	Pass	Oxamyl	0.0030	0.1	0.2000	ND	Pass
Chlorfenapyr	0.0100	0.1	0.0100	ND	Pass	Paclobutrazol	0.0130	0.1	0.0130	ND	Pass
Chlorpyrifos	0.0050	0.1	0.0050	ND	Pass	Pentachloronitrobenzene	0.0020	0.1	0.2000	ND	Pass
Clofentezine	0.0006	0.1	0.5000	ND	Pass	Permethrin	0.0006	0.1	20.0000	ND	Pass
Coumaphos	0.0090	0.1	0.0090	ND	Pass	Phosmet	0.0070	0.1	0.2000	ND	Pass
Cyfluthrin	0.0008	0.1	1.0000	ND	Pass	Piperonyl Butoxide	0.0013	0.1	8.0000	ND	Pass
Cypermethrin	0.0130	0.1	1.0000	ND	Pass	Prallethrin	0.0070	0.1	0.4000	ND	Pass
Daminozide	0.0210	0.1	0.0210	ND	Pass	Propiconazole	0.0080	0.1	20.0000	ND	Pass
DDVP	0.0040	0.1	0.0040	ND	Pass	Propoxur	0.0040	0.1	0.0040	ND	Pass
Diazinon	0.0006	0.1	0.2000	ND	Pass	Pyrethrins	0.0030	0.1	1.0000	ND	Pass
Dimethoate	0.0030	0.1	0.0030	ND	Pass	Pyridaben	0.0005	0.1	3.0000	ND	Pass
Dimethomorph	0.0007	0.1	20.0000	ND	Pass	Spinetoram	0.0005	0.1	3.0000	ND	Pass
Ethoprophos	0.0040	0.1	0.0040	ND	Pass	Spinosad	0.0050	0.1	3.0000	ND	Pass
Etofenprox	0.0050	0.1	0.0050	ND	Pass	Spiromesifen	0.0008	0.1	12.0000	ND	Pass
Etoxazole	0.0098	0.1	1.5000	ND	Pass	Spirotetramat	0.0090	0.1	13.0000	ND	Pass
Fenhexamid	0.0009	0.1	10.0000	ND	Pass	Spiroxamine	0.0060	0.1	0.0060	ND	Pass
Fenoxycarb	0.0070	0.1	0.0070	ND	Pass	Tebuconazole	0.0024	0.1	2.0000	ND	Pass
Fenpyroximate	0.0008	0.1	2.0000	ND	Pass	Thiacloprid	0.0070	0.1	0.0070	ND	Pass
Fipronil	0.0170	0.1	0.0170	ND	Pass	Thiamethoxam	0.0040	0.1	4.5000	ND	Pass
Flonicamid	0.0008	0.1	2.0000	ND	Pass	Trifloxystrobin	0.0007	0.1	30.0000	ND	Pass

Date Tested: 02/06/2019
LOQ = Limit of Quantitation; LOD = Limit of Detection; NT = Not Tested; ND = Not Detected.

ISO / IEC 17025:2017 ACCREDITED LABORATORY
Accreditation No. 73653

Mallory Speakman
Laboratory Director - LA
02/06/2019

Anya Engen
Quality Manager
02/06/2019

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Figure 4: Page 2/4 of a Sample Certificate of Analysis

CannaSafe

CannaSafe - LA
7027 Hayvenhurst Avenue
Van Nuys, CA 91406

(818) 922-2416
http://www.csalabs.com
Lic# C8-18-0000037-TEMP

R&D Testing

KOI Healing Balm 500mg

Sample ID: 1902CSALA0704.2613
Strain: Koi Healing Balm 500mg
Matrix: Other
Type: Other
Sample Size: 1 units; Batch: 0 units

Produced: N/A
Collected: 02/04/2019
Received: 02/04/2019
Completed: 02/06/2019
Batch#: 9032KHB500

Client
Koi CBD
Lic. #
14631 Best Ave
Norwalk, CA 90650

14 Residual Solvents

Pass

Testing method: HSGCMS-SOP 202

Analyte	LOD	LOQ	Limit	Mass	Status
	µg/g	µg/g	µg/g	µg/g	
1,2-Dichloro-Ethane	0.3	3	1	ND	Pass
Acetone	1.4	14	5000	ND	Pass
Acetonitrile	0.3	2	410	ND	Pass
Benzene	0.1	1	1	ND	Pass
Butane	2.5	25	5000	ND	Pass
Chloroform	0.4	4	1	ND	Pass
Ethanol	1.4	14	5000	ND	Pass
Ethyl-Acetate	1.4	14	5000	ND	Pass
Ethyl-Ether	1.4	14	5000	ND	Pass
Ethylene Oxide	0.3	3	1	ND	Pass
Heptane	1.4	14	5000	ND	Pass
Isopropanol	1.4	14	5000	ND	Pass
Methanol	1.8	18	3000	ND	Pass
Methylene-Chloride	0.4	4	1	ND	Pass
n-Hexane	1.7	17	290	ND	Pass
Pentane	1.4	14	5000	ND	Pass
Propane	1.0	10	5000	ND	Pass
Toluene	5.3	53	890	ND	Pass
Trichloroethene	0.5	5	1	ND	Pass
Xylenes	13.0	130	2170	ND	Pass

Date Tested: 02/06/2019
LOQ = Limit of Quantitation; LOD = Limit of Detection; NT = Not Tested; ND = Not Detected.

ISO / IEC 17025:2017 ACCREDITED LABORATORY
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Mallory Speakman
Laboratory Director - LA
02/06/2019

Anya Engen
Quality Manager
02/06/2019

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Figure 5: Page 3/4 of a Sample Certificate of Analysis

CannaSafe

CannaSafe - LA
7027 Hayvenhurst Avenue
Van Nuys, CA 91406

(818) 922-2416
http://www.csalabs.com
Lic# C8-18-0000037-TEMP

R&D Testing

KOI Healing Balm 500mg

Sample ID: 1902CSALA0704.2613
Strain: Koi Healing Balm 500mg
Matrix: Other
Type: Other
Sample Size: 1 units; Batch: 0 units

Produced: N/A
Collected: 02/04/2019
Received: 02/04/2019
Completed: 02/06/2019
Batch#: 9032KHB500

Client
Koi CBD
Lic. #
14631 Best Ave
Norwalk, CA 90650

15 Microbials

Pass

Test method: PCR-SOP 401

Analyte	Result	Status
Aspergillus flavus	Not Detected	Pass
Aspergillus fumigatus	Not Detected	Pass
Aspergillus niger	Not Detected	Pass
Aspergillus terreus	Not Detected	Pass
Shiga toxin-producing E. Coli	Not Detected	Pass
Salmonella	Not Detected	Pass

Date Tested: 02/06/2019
LOQ = Limit of Quantitation; LOD = Limit of Detection; NT = Not Tested; ND = Not Detected.

16 Mycotoxins

Pass

Test method: LCMS-SOP 301

Analyte	LOD	LOQ	Limit	Units	Status
	µg/kg	µg/kg	µg/kg	µg/kg	
B1	0.001	0.005		ND	Tested
B2	0.007	0.022		ND	Tested
G1	0.007	0.022		ND	Tested
G2	0.006	0.021		ND	Tested
Total Aflatoxins			20	ND	Pass
Ochratoxin A	0.013	0.045	20	ND	Pass

Date Tested: 02/06/2019
LOQ = Limit of Quantitation; LOD = Limit of Detection; NT = Not Tested; ND = Not Detected.;

17 Heavy Metals

Pass

Testing method: ICPMS-SOP 501

Analyte	LOD	LOQ	Limit	Units	Status
	µg/g	µg/g	µg/g	µg/g	
Arsenic	0.001	0.01	1.5	0.018	Pass
Cadmium	0.001	0.01	0.5	ND	Pass
Lead	0.001	0.01	0.5	0.084	Pass
Mercury	0.001	0.01	3.0	ND	Pass

Date Tested: 02/06/2019
LOQ = Limit of Quantitation; LOD = Limit of Detection; NT = Not Tested; ND = Not Detected.

ISO / IEC 17025:2017 ACCREDITED LABORATORY
Accreditation No. 73653

Mallory Speakman
Laboratory Director - LA
02/06/2019

Anya Engen
Quality Manager
02/06/2019

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Figure 6: Page 4/4 of a Sample Certificate of Analysis

The Sample Certificates of Analysis (pages 24-27) were provided by CannaSafe, a Patient Focused Certification (PFC) and ISO/IEC 17025 accredited laboratory located in Van Nuys, CA, and is reprinted here with permission from their client KOI. Below are some things to take note of that are present:

1. The name, address, contact information, and the license # (where applicable) of the testing facility.
   a. Cannabis testing laboratories are required to be licensed by most states, and in some states, hemp cultivators may send their products for testing to licensed cannabis testing facilities.
2. The name of the product and any other identifiers printed on the label (e.g., the amount of CBD in the bottle, in this case 500mg).
   a. What is printed on the report should match the label with regard to product name, dosage, lot number, batch number, and any other identifiers listed.
3. Sample identification number
   a. This number is used by the laboratory to track the sample. This may include any state-required tracking information, a unique identifier developed by the laboratory, or both.
4. The date the product was submitted for testing and the date testing was completed.
   a. This is important to know to ensure that newly cultivated and manufactured products are being tested and that testing is done in a timely manner upon receipt of the sample.
5. Testing Summary
   a. This summary table shows all the tests that the sample was subjected to and what the outcomes of those tests were. This section is not required on a CoA but is nice to have so that consumers know immediately what standards the product has been tested to and what their outcome was without reading the entire report.
6. Cannabinoid Content
   a. This is also known as the potency of the product. This is where to find information on what cannabinoids have been detected and in what quantity. This is especially important for people to know so that they can determine the exact dose that they are taking in the event it needs to be adjusted. It is also important to know if the consumer does not want a specific cannabinoid, such as THC, in their product.
   b. For flower products, dosage is typically presented in a percent by weight, e.g., 15% CBD.
   c. For non-flower products, such as edibles or topicals, dosage information is typically presented in mg/g or mg/mL. Patients may then use this information to determine how much is in a dose that they are taking.
   d. This CoA also lists the LOD and LOQ. LOD is the Limit of Detection, which is the smallest amount that the instrument can accurately identify. LOQ is the Limit of Quantification, which is the smallest amount that the instrument can accurately quantify.
7. Terpene Content
   a. Terpenes impart flavors and scents to cannabis and contribute to the entourage effect.

8. Moisture Content
   a. This is a measurement of the amount of water in a product and is determined by drying the sample. This is typically only done on flower samples.
   b. In the case of this product, NT stands for Not Tested. This product is a lip balm and not subject to moisture content analysis.
9. Water Activity
   a. This is a measurement of the amount of free water in a product. This is traditionally a test performed on food products to determine its potential for microbial growth, but can be performed on other product types as well such as flowers and concentrates.
10. Foreign Matter
    a. This is a test that looks at the amount and type of extraneous material found in cannabis flower and products.
11. Accreditations
    a. This laboratory has chosen to place any accreditations and certifications it has received here.
    b. Accreditations and certifications show that the laboratory has undergone review of its quality and operating systems by third-party reviewers to ensure compliance with their respective standards.
12. Signature Marks
    a. All tests should be reviewed by the laboratory prior to release. This test report has been reviewed and approved by the Laboratory Director and the Quality Manager.
13. Pesticides
    a. This is a test to determine the presence, and quantity, of pesticides. Pesticides are regulated by the Environmental Protection Agency (EPA), and none have been approved for use specifically on cannabis and hemp. Some states have approved certain products or classes or products for use in the cultivation of cannabis and hemp, and some require testing for a range of allowed and prohibited pesticides.
14. Residual Solvents
    a. Cannabinoids and terpenes are extracted using a number of different methods, some of which may include potentially harmful or toxic solvents such as butane or isopropyl alcohol. This test determines and quantifies the presence of any of those solvents.
15. Microbials
    a. Microbiological contamination is a test for microbial species such as *E. Coli* and *Salmonella*. These contaminants can be quite harmful to people and pets who are exposed to them, particularly those with compromised immune systems.
16. Mycotoxins
    a. Mycotoxins consist of four aflatoxins (O_1, O_2, G_1, G_2) and Ochratoxin A. Ochratoxin A is a known carcinogen and can be dangerous. Aflatoxins are toxic and may cause immunotoxicity, teratogenicity, and hepatotoxicity.[57]
17. Heavy Metals
    a. The four heavy metals typically tested for are lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As). Acute heavy metals poisoning can lead to feeling confused or numb, feeling sick and throwing up, or passing out. Chronic heavy metals poisoning can cause headaches, achy joints and muscles, and constipation.[58]

THE SUPPLY CHAIN

CBD and CBD-containing products that are sold through cannabis dispensaries are subject to the same regulations as any other cannabis-derived product at each step of the supply chain. Regulations begin at the application stage – where criteria are set for who can own, operate, and work in cannabis businesses – and end with purchasing criteria at the retail point. From seed to consumption, regulations include track and trace functions, security requirements, product safety protocols, staff training, adverse event reporting, and recall procedures. State agencies create these regulations and conduct inspections or work with third-party accreditors to ensure compliance, monitor adverse event reporting, and implement product recalls if necessary. Mandated laboratory testing means that medical cannabis patients and consumers in states that allow the adult use of cannabis are able to obtain safe, reliable, consistent products to treat their medical needs. Refer to the State Medical Cannabis Program Regulations and Oversight infographic on pages 32 and 33 for more details.

MANDATED LABORATORY TESTING MEANS THAT MEDICAL CANNABIS PATIENTS AND CONSUMERS IN STATES THAT ALLOW THE ADULT USE OF CANNABIS ARE ABLE TO OBTAIN SAFE, RELIABLE, CONSISTENT PRODUCTS TO TREAT THEIR MEDICAL NEEDS.

The U.S. Department of Agriculture has yet to promulgate federal regulations or approve state regulations relating to the cultivation and processing of industrial hemp, and the U.S. Food and Drug Administration has not yet provided a clear path forward for the introduction of CBD and CBD-containing products into the marketplace. To ensure efficacy and consumer safety, a strong regulatory regime around hemp-derived CBD products would feature many of the same characteristics depicted in the infographic, such as inspections, mandatory testing, appropriate training for staff across the industry, recall protocols, and so on. Americans for Safe Access will provide input on standards and best practices to ensure that federal agencies develop a comprehensive regulatory regime that protects consumer safety and the environment.

STATE MEDICAL CANNABIS PROGRAM REGULATIONS AND OVERSIGHT

Figure 7 [59]

REGULATIONS

MORE THAN 310 MILLION AMERICANS LIVE IN STATES WITH MEDICAL CANNABIS LAWS. THESE PROGRAMS ARE INFLUENCED BY LOCAL, STATE, AND FEDERAL REGULATIONS. AFTER A LAW IS ENACTED, STATE AGENCIES CREATE A SERIES OF REGULATIONS THAT GOVERN EVERYONE PARTICIPATING IN THE PROGRAM AND ALL PRODUCTS PRODUCED.

MEDICAL MARIJUANA REGULATORY AGENCY

State agencies or groups of several agencies (such as the Departments of Health, Agriculture, Consumer Affairs, etc.) are tasked with creating and monitoring regulations through all phases of the production line, issuing licenses for businesses, and coordinating patient enrollment. These agencies also conduct inspections or work with third-party accreditors to ensure compliance, monitor adverse event reporting, and implement product recalls if necessary.

- DEPARTMENT OF COMMERCE
- DEPARTMENT OF HEALTH
- DEPARTMENT OF AGRICULTURE

INSPECTIONS

Medical cannabis businesses must pass inspections to maintain licenses to operate. These inspections may be conducted by the state medical cannabis regulatory agency, accredited third-party agencies, law enforcement, OSHA, municipal safety inspectors, etc.

SUPPLY CHAIN

REGULATIONS BEGIN AT THE APPLICATION STAGE, WHERE CRITERIA ARE SET FOR WHO CAN OWN, OPERATE, AND WORK IN MEDICAL CANNABIS BUSINESSES, AND END WITH PURCHASING CRITERIA AT THE RETAIL POINT. FROM SEED TO CONSUMPTION, REGULATIONS INCLUDE TRACK AND TRACE FUNCTIONS, SECURITY REQUIREMENTS, PRODUCT SAFETY PROTOCOLS, STAFF TRAINING, AND ADVERSE EVENT REPORTING AND RECALL PROCEDURES. MEDICAL CANNABIS BUSINESSES ARE SUBJECT TO INSPECTIONS. REGULATORS NOW HAVE RESOURCES, SUCH AS THE AMERICAN HERBAL PHARMACOPOEIA CANNABIS MONOGRAPH AND THE AMERICAN HERBAL PRODUCTS ASSOCIATION RECOMMENDATIONS FOR REGULATORS, TO INFORM THE CREATION OF ROBUST PRODUCT SAFETY PROTOCOLS. ALL COMPANIES MUST DEMONSTRATE ABILITY TO TRACK ADVERSE EVENTS AND INITIATE A RECALL.

TESTING LAB FACILITY

All staff have proper training. Companies must adhere to Good Laboratory Practices and be accredited by an International Laboratory Accreditation Cooperation (ILAC) signatory for ISO 17025 accreditation and related certifications. Testing laboratories must offer potency testing for a variety of cannabinoids and screen for pesticides and contaminants. Specifications for these tests are set by the American Herbal Pharmacopoeia Cannabis Monograph. Strong regulatory regimes require laboratories to retain samples in order to assist in product recalls and public health inquires.

OWNERS AND STAFF

Regulations include legal conduct for owners and staff and often require unique IDs issued by the state. All staff and management are required to have legal compliance and product safety protocol adherence training.

MEDICAL PROFESSIONALS

Regulators create guidelines for medical professionals to enroll their patients into the program, including forms and number of visits required. Some require medical professionals to take specific training courses and have built-in audits.

CULTIVATION FACILITY

All staff have required legal compliance and product safety protocol adherence training. Companies must adhere to Good Agricultural Practices. Facilities may only use certain approved pesticides.

MANUFACTURING FACILITY

All staff have required legal compliance and product safety protocol adherence training. Companies must adhere to Good Manufacturing Practices. Products are packaged to prevent accidental ingestion by children.

DISPENSING/RETAIL FACILITY

Staff are trained to provide guidance to patients in making cannabis product selections. Regulations require the retail store to maintain certain hours and limit the scope of advertising to fit within community standards. Security cameras and increased foot traffic help deter crime. Under state laws, dispensaries can only serve verified patients and caregivers.

PATIENTS AND THEIR CAREGIVERS

Regulators create enrollment and renewal procedures for patients that usually include the issuance of an ID. Rules for patients also govern how much medicine a patient can possess, places where patients can legally use their medicine, and the transportation of cannabis.

MEDICAL CANNABIS PRODUCTS

Products are labeled in accordance with state guidelines to display cannabinoid profile and other useful information, including the expiration date if the item is perishable.

PRODUCT SAFETY

Each batch of raw plant material and cannabis-derived product must be quality assurance tested in order to ensure the integrity, purity, and proper labeling of medical cannabis products.

TRANSPORTATION

Regulations extend to transportation of cannabis products throughout the supply chain. Regulations require drivers to be registered with the state and require paperwork at pickup and drop-off locations, including weighing the product. Regulations also include special instructions for dealing with waste.

RECALL

When a product containing contaminants, molds, or mildew – or an improperly labeled product – enters the supply chain, regulatory agencies trigger a product recall to prevent patient consumption. This includes alerting the manufactures, retail outlets, and the public. Recalled products are destroyed.

QUALIFICATION

ONCE THE AUTHORIZING STATUTE HAS BEEN ADOPTED, REGULATORS SET THE REQUIREMENTS FOR PATIENT AND MEDICAL PROVIDER PARTICIPATION IN THE MEDICAL CANNABIS PROGRAMS, CREATE RELEVANT GUIDELINES AND FORMS, AND SET RULES REGARDING TRANSPORTATION AND USE.

AmericansForSafeAccess.org

CHEMICAL STRUCTURE AND ACTIVITY

While more than 100 different cannabinoids have been identified to date, few are being as widely studied as cannabidiol.

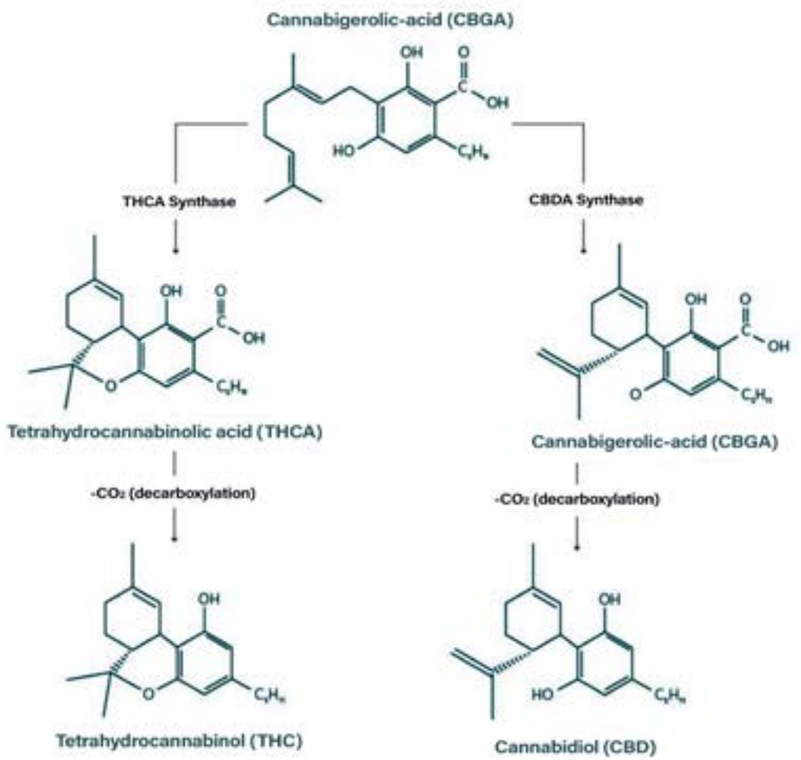


Figure 8: Chemical Pathway to CBD Formation.[60]

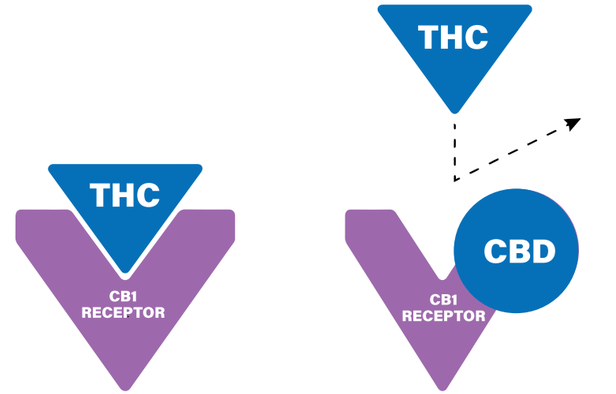
CBD is formed in the trichomes of the cannabis plant through a unique chemical pathway. Other cannabinoids are formed through similar pathways and with similar synthases. The primary structural difference between CBD and Δ^9- tetrahydrocannabinol (THC), another well known cannabinoid, is that where THC has a ring formation on the bottom, CBD has a hydroxyl (-OH) group. The slight change in structure between these two molecules is what causes such different outcomes in biological responses.

Each neutral cannabinoid begins in the plant in its acidic form and must be decarboxylated to achieve the neutral form. Decarboxylation is the process of removing the carboxylic acid (-COOH) side chain, which is typically done by the application of heat or through light exposure. This is why it is recommended that products be stored in opaque containers, ideally in a cool, dry location. Neutral cannabinoids are considered to be the "active" form as they cause more biological responses, however the acidic cannabinoids have also shown biological activity.

UNDERSTANDING THE ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) is an endogenous system that acts on many bodily functions, including those relating to the immune system and homeostasis. The ECS consists of endocannabinoids, cannabinoid receptors, and enzymes responsible for the synthesis and degradation of endocannabinoids. The most common endocannabinoids are anandamide (AEA) and 2-arachidonoyl glycerol (2-AG).

There are two cannabinoid receptors, CB_1 and CB_2. CB_1 receptors are located primarily in the central nervous system, and CB_2 receptors are primarily immunomodulatory and found in the periphery. Both THC and CBD compete to bind to the CB_1 receptor. THC is known as a potential partial agonist[61] and orthosteric binder, which means that it can cause a strong stimulation of the receptor which leads to feelings of euphoria and other psychotropic effects. CBD is a negative allosteric modulator[25] of the CB_1 receptor, which means that it alters the shape of the receptor and reduces the binding ability of THC.[62] By changing the shape of the CB_1 receptor, CBD impacts how THC and endogenous cannabinoids affect the body.



THC is a potent agonist against of CB1

CBD is a negative allosteric of CB1

Figure 9: THC and CBD binding at the CB1 receptor.[60]

When cannabinoids and other compounds bind to these receptors, they act as either agonists or antagonists. Agonists produce a biological response, such as feelings of euphoria, hunger, or thirst. Antagonists block the response of the agonist, and in some cases, may cause the opposite action of an agonist. Some compounds can bind to another spot on the receptor and change its shape; these are called allosteric modulators.

The first cannabinoid receptor was discovered in 1990 and the second in 1993; these were called CB_1 and CB_2, respectively. They are members of a family of receptors called G-Protein Coupled Receptors (GPCR).[63] Since their discovery, it has been found that cannabinoid receptors are dispersed throughout the body and are involved in many different bodily functions.

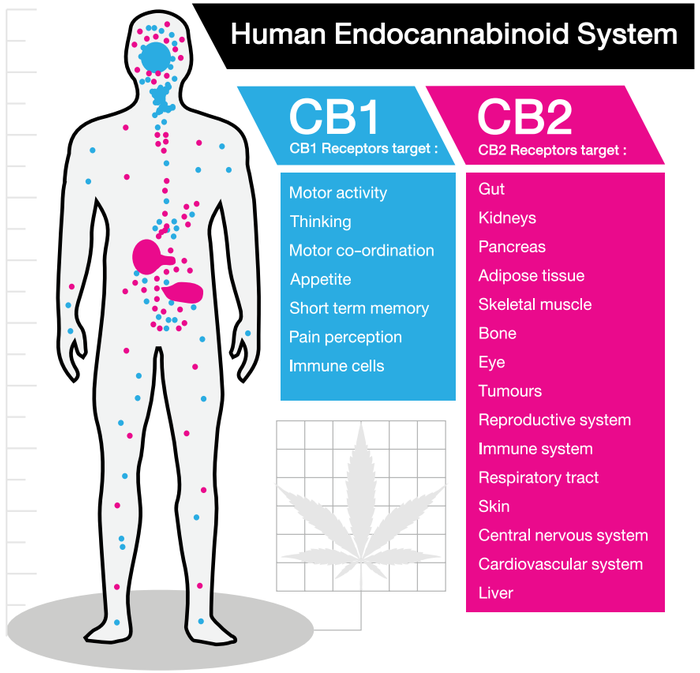


Figure 10: The Endocannabinoid System

Some of the aspects of one's physiological state and the physiological processes controlled by the endocannabinoid system include:

- Motion sickness (CB_1)[64]
- Body weight (CB_1/CB_2)[65]
- Appetite stimulation/suppression(CB_1)[66]
- Insulin secretion (CB_1)[67]
- Neurodevelopmental signaling (CB_1)[68]
- Inflammation (CB_2)[69]
- Vasodilation (CB_1)[70]
- Heart rate (CB_2)[70]

It was previously thought that CB_1 receptors were only present in the cells of the central nervous system and that CB_2 receptors were only present in the peripheral nervous system, but a number of studies have since documented the presence of CB_1 receptors in non-central nervous systems and CB_2 receptors in the brain.[71] The presence of these receptors throughout the body creates a wide array of potential therapeutic targets.

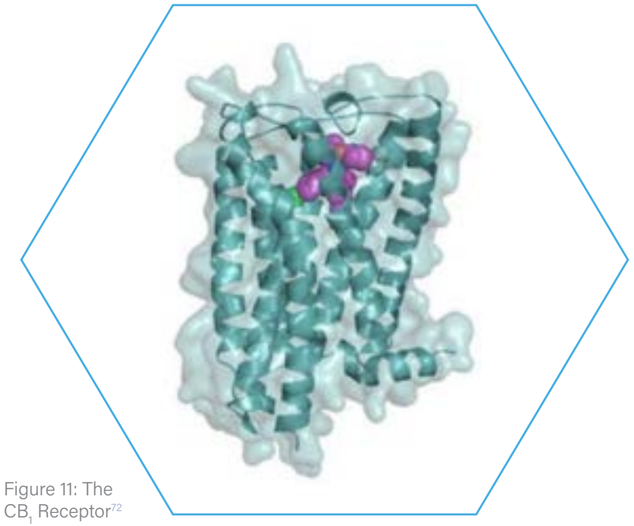


Figure 11: The CB_1 Receptor[72]

The CB_1 receptor shown in Figure 5 is represented by the blue ribbons, while the purple portion represents a compound that is bound inside the binding pocket. Some compounds may block the binding pocket, inhibiting activity, and some may bind to another spot, causing the binding pocket to change shape and altering the signalling cascade. A compound entering the receptor will attach inside the binding pocket with a specific affinity, cause the receptor to change shape, prevent anything else from entering the pocket, and thus begin a signalling cascade and biological response. The location in the body of the receptor will determine the specific signalling cascade that is initiated and the type of biological response achieved.

Scientists have studied many different GPCR's in the quest to elucidate the structure of the CB_2 receptor,[73] which is shown in Figure 6. The structure is very similar to that of the CB_1 receptor, but the slight differences are what cause the different array of responses in the human body.

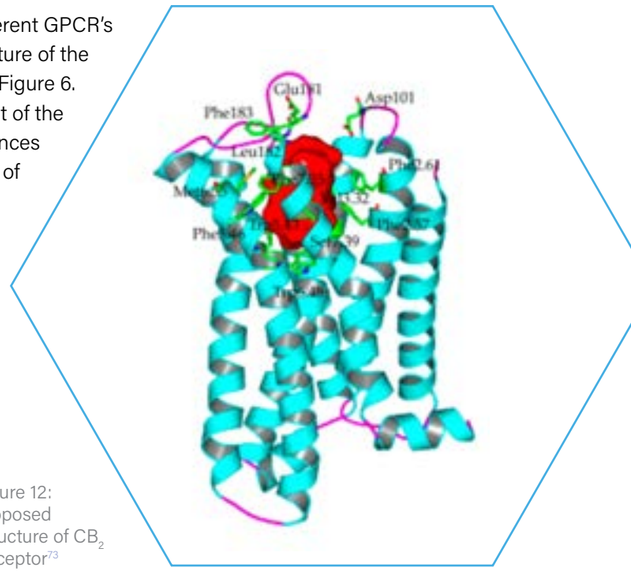
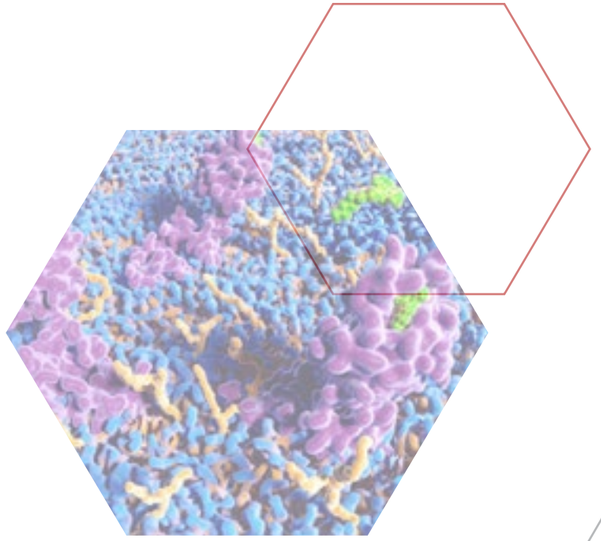


Figure 12: Proposed Structure of CB_2 Receptor[73]

There are currently four pharmaceutical drugs approved for use (three of which are available in the U.S.*) that specifically target CB_1 and CB_2 receptors:

- *Marinol[74] (synthetic THC)
- *Nabilone[75] (analog of THC)
- Sativex[76] (naturally derived THC:CBD)
- *Epidiolex[77] (naturally derived CBD)

A fifth drug, Rimonabant, was removed from the market because of negative side effects. Rimonabant was indicated for use in the treatment of obesity and acts as a CB_1 receptor antagonist/inverse agonist.[78]



CANNABINOIDS, TERPENES, AND THE ENDOCANNABINOID SYSTEM

Phytocannabinoids, endocannabinoids, synthetic cannabinoids, and terpenes all bind to receptors in the endocannabinoid system (ECS) or act in some way on the ECS. Some of these have a stronger binding affinity, thereby causing a more heightened biological response, while others have a low binding affinity, thereby causing a more subtle biological response. Some even block the receptor altogether, stopping any response or causing a different response. All of them compete to bind to or block the receptor.

THC, anandamide, and 2-AG are capable of binding to both the CB_1 and CB_2 receptors and act as partial agonists. This means that they can cause both weak and strong reactions in the body.[63] CBD is an allosteric modulator which means that it changes the shape of the receptor to block the binding pocket and alter the physiological response. CBD may also bind to CB_1 and CB_2 receptors. By being able to both alter the shape of the cannabinoid receptors and bind to the receptors, CBD has an increased number of biological responses that may be achieved, which is why it is implicated in the treatment of so many different maladies.

FULL-SPECTRUM MEDICINE AND THE ENTOURAGE EFFECT

Professors Raphael Mechoulam and Shimon Ben-Shabat first presented the hypothesis of the "entourage effect" in 1998, when they noticed that molecules with structures similar to AEA and 2-AG increased the endocannabinoids' activity. They further hypothesized that this may be the reason why botanical medicines are often more efficacious than singular compound drugs.[79]

There are several studies that highlight the case for the entourage effect:

- A randomized controlled trial of patients with intractable pain showed that a whole plant extract containing both THC and CBD had better results than synthetic THC.[80]
- Animal studies showed that a full-spectrum extract of cannabis, rich in CBD and low in THC produced, a linear dose-response curve as opposed to the standard bell-curved response of purified CBD when used as an analgesic.[54]
- A study of breast cancer cell lines done in tissue cultures showed better results in treating the tumor with an extract that contained CBG and THCA rather than a singular THC extract.[81]

A recent meta-analysis of studies done on patients with Dravet and Lennox-Gastaut syndromes indicated that patients were able to achieve similar reductions in seizure activity and seizure type when using a lower-dose whole-plant CBD formulation vs. a purified CBD extract.[82]

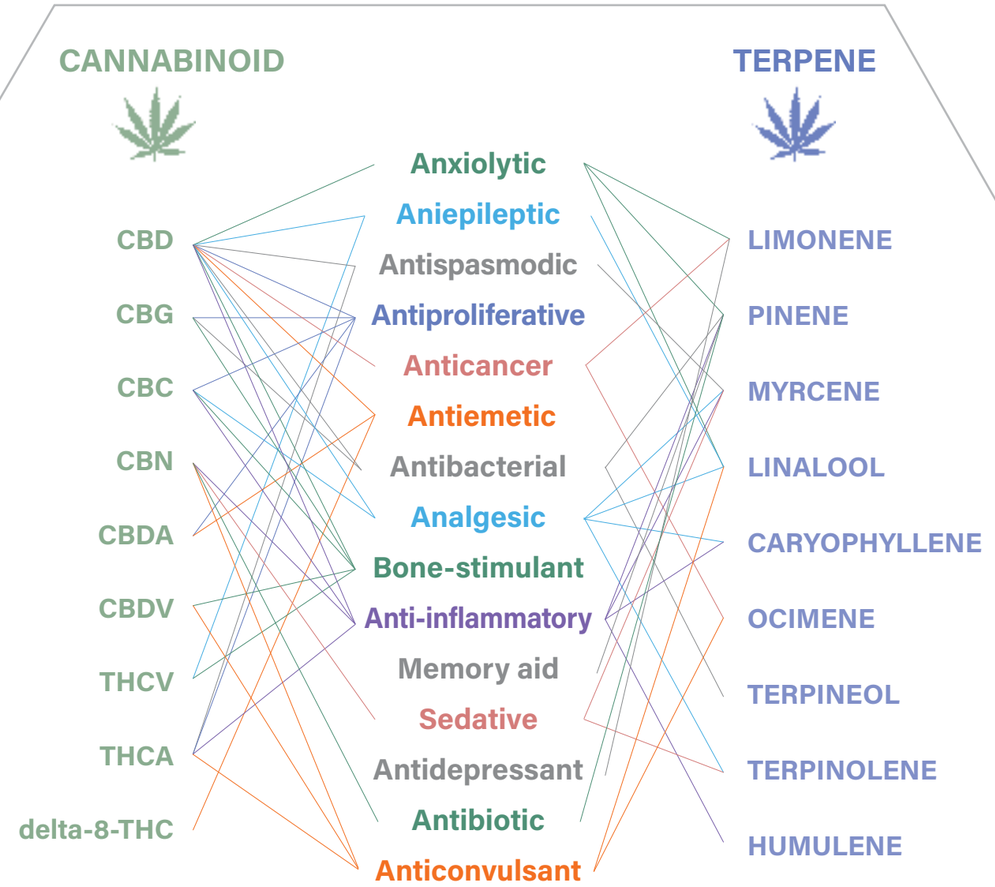


Table 1: Summary of Cannabinoid and Terpene Activity

Table 1 features a number of conditions that cannabinoids have been indicated as a treatment for as well as the terpenes that are indicated in treating the same condition. In order to effectively study the various cannabinoid and terpene combinations, there must be a systematic approach to cultivation to ensure the same content from harvest to harvest. This will help to ensure that the whole-plant products that are used in research and clinical trials can be more effectively studied.

CERTIFICATIONS AND THE NEED FOR STANDARDS

Americans for Safe Access (ASA) worked closely with the American Herbal Products Association (AHPA) and the American Herbal Pharmacopoeia (AHP) to create the Cannabis Inflorescence Monograph, a set of standards that forms the basis for ASA's Patient Focused Certification (PFC) program. These standards are necessary to ensure that testing laboratories and cultivation, manufacturing, and dispensing operations are operating according to best practices, which in turn assures that the products produced and sold by certified operations are accurately labeled, stored and distributed in a manner that protects and preserves the contents, and are safe for the end user (i.e., are not contaminated with microbes, mold, pesticide residue, etc.). The standards that ASA helped to create also form the basis for ASA's Recommendations for Regulators, a resource for state regulators to ensure that best practices are followed by businesses that work in cannabis cultivation, manufacturing, packaging, labeling, dispensing, and laboratory analytics.

PFC audits are based on AHPA guidelines and the AHP Cannabis Inflorescence Monograph along with relevant state laws and regulations. Therefore, companies that receive Patient Focused Certification are known to be in compliance with the standards ASA worked with AHP and AHPA to create as well as state and local laws and regulations. PFC also offers standardized training to ensure industry compliance with applicable standards.

Additionally, ASA and the International Cannabis and Cannabinoids Institute, a center of excellence ASA co-founded, have partnered with the American Society for Testing and Materials (ASTM International), a global standard-setting body, to create standards to be used worldwide. Cultivation standards are being prioritized; these will be followed by standards relating to cosmetics, food supplements, extracts, and medicinal and laboratory-related standards.

ASA also has partnered with A2LA, an independent, nonprofit accrediting organization, to offer dual ISO/IEC 17025 and PFC certification for testing laboratories where ISO/IEC 17025 is the international standard for testing and calibration laboratories. The International Organization for Standards (ISO) is an independent international nongovernmental organization composed of 164 national standards bodies. ISO and PFC certifications reflect the quality and competence of an organization and serve as a means of assuring patients, consumers, and regulators of the certified bodies' adherence to applicable standards.

CURRENT RESEARCH

As awareness of CBD's therapeutic potential has spread, the pace of research into the cannabinoid has accelerated. In addition to validating the preclinical and anecdotal evidence of CBD's therapeutic value, this research may reveal new applications for CBD and provide clarity around dosing for different conditions.

As of May 7, 2019, www.clinicaltrials.gov lists 187 clinical trials examining cannabidiol as an intervention for a variety of conditions. Of those 187 clinical trials, 40 are actively recruiting patients. Some of the conditions and diseases currently being studied are:

- **Substance use disorder/cocaine dependence disorder** (Centre de recherche du Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada)
- **Psoriatic arthritis** (Department of Rheumatology, Aalborg University Hospital, North Aalborg, Denmark)
- **PTSD** (VA San Diego Healthcare System, San Diego, California, United States)
- **Chronic pain** (University of Utah, Salt Lake City, Utah, United States)
- **Parkinson's disease** (University of Colorado Hospital, Aurora, Colorado, United States)
- **Autism Spectrum Disorder** (NYU Langone Health, New York, New York, United States)
- **Drug-resistant epilepsy** (University Hospital Campus, London Health Sciences Centre, London, Ontario, Canada; University Health Network - Toronto Western Hospital, Toronto, Ontario, Canada)
- **Epilepsy** (Unidade de Pesquisa Clínica HCRP-USP, Ribeirao Preto, Sao Paulo, Brazil)
- **Anxiety** (McLean Hospital Brain Imaging Center, Belmont, Massachusetts, United States)
- **Amyotrophic Lateral Sclerosis (ALS)** (Gold Coast Hospital and Health Service, Gold Coast, Queensland, Australia)
- **Bipolar disorder** (Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande Do Sul, Brazil)
- **Prader-Willi Syndrome** (University of Arizona, Tucson, Arizona, United States; Rady Children's Hospital, UC San Diego, San Diego, California, United States; University of Iowa, Iowa City, Iowa, United States; Johns Hopkins University, Baltimore, Maryland, United States; The University of Oklahoma Health Sciences Center, Tulsa, Oklahoma, United States; Institute for Research and Innovation | MultiCare Health System, Tacoma, Washington, United States)

Of the 87 active clinical trials (including those actively recruiting and those that are not actively recruiting) there are 36 different diseases or conditions being studied.

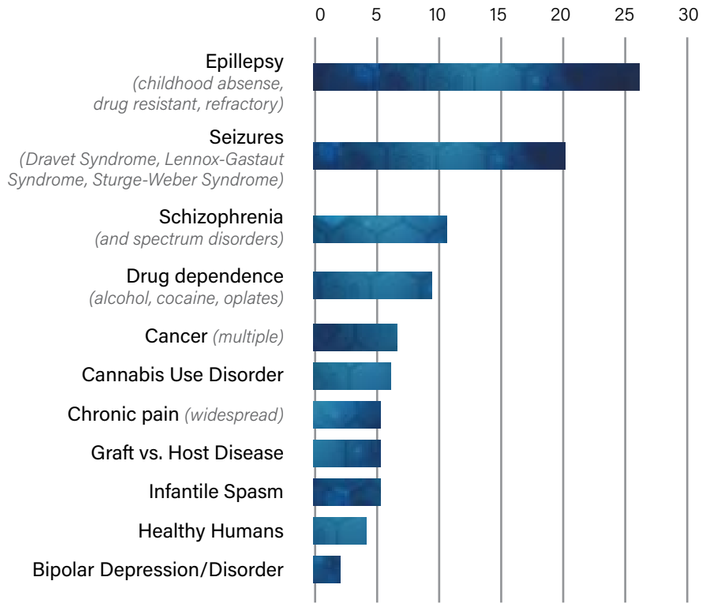


Figure 13: The medical conditions for which CBD is most commonly studied and the number of ongoing studies for each condition as of May 2019[83]

Currently, epilepsy is being studied in 26 clinical trials and another 20 clinical trials are studying specific seizure disorders such as Dravet Syndrome, Lennox-Gastaut Syndrome, and Sturge-Weber Syndrome. Additional conditions being examined include schizophrenia, drug dependence, and chronic pain. Each of these studies is in one of the various four phases of clinical trials, which any drug must go through before being approved as a medicine by the FDA.

In May 2019, the FDA gave fast-track designation to Zygel, a synthetic transdermal CBD product in the last stages of a clinical trial. Zygel is intended for the treatment of Fragile X syndrome.[84]

CBD ON A GLOBAL SCALE

References have been made in this guide to the scheduling status of cannabis and CBD under U.S. law, but it is important to note that scheduling decisions are also made at the international level. The World Health Organization (WHO) Expert Committee on Drug Dependence (ECDD), a body of independent experts in the fields of drugs and medicine, reviews scientific literature and data about substances to determine their therapeutic applications and potential for dependence and abuse; based on the established criteria and protocols, the ECDD may recommend the scheduling, rescheduling, de-scheduling, or continued surveillance of a given substance.[85] The United Nations (UN) Commission on Narcotic Drugs (CND) can vote on the ECDD's recommendations to initiate, modify, or end international controls on a substance under international law.

'Preparations containing predominantly cannabidiol and not more than 0.2 percent of delta-9-tetrahydrocannabinol are not under international control.'

WHO ECCD's recommended change to the 1961 Single Convention on Narcotic Drugs.

The ECDD released a pre-review report on CBD at its 39th meeting in November 2017. The committee concluded that CBD does not exhibit effects indicative of abuse or dependence potential and confirmed that CBD has therapeutic applications; the committee further declared that "CBD is generally well tolerated with a good safety profile."[86] With regard to international scheduling, the ECDD noted that cannabidiol itself is not listed in the schedules of the 1961, 1971, or 1988 UN drug control conventions, but that CBD produced as an extract of cannabis would fall under Schedule I of the 1961 Convention.[86]

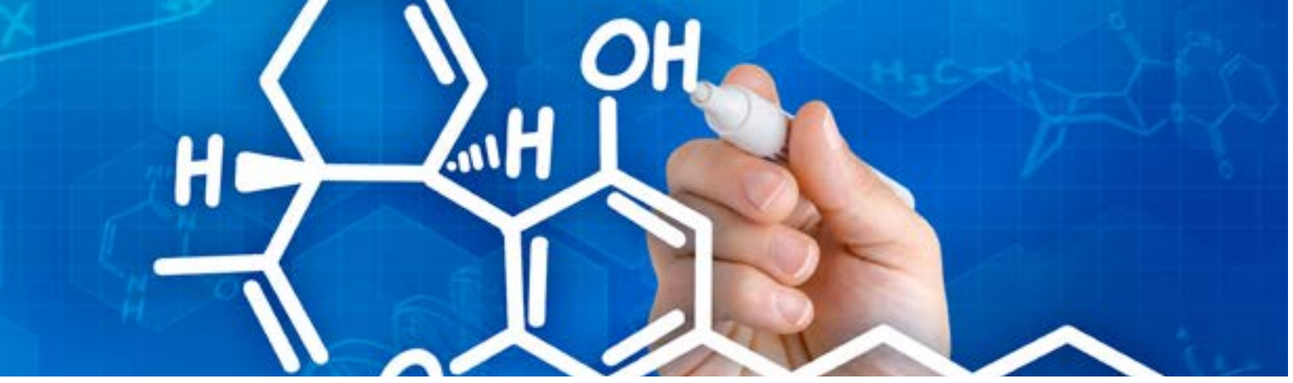
The 40th meeting of the ECDD in June 2018 was a specially convened session at which the committee carried out a critical review of CBD as well as pre-reviews of cannabis (plant and resin), extracts and tinctures of cannabis, delta-9-tetrahydrocannabinol (THC), and isomers of THC.[87] In its final report after the critical review of CBD, the committee "recommended that preparations considered to be pure CBD should not be scheduled."[88]

The ECDD carried out critical reviews of cannabis (plant and resin), extracts and tinctures of cannabis, delta-9-tetrahydrocannabinol (THC), and isomers of THC at its 41st meeting in November 2018. The committee recognized the therapeutic applications of cannabis and recommended that it be retained in Schedule I but removed from Schedule IV of the 1961 Single Convention on Narcotic Drugs; substances listed in both Schedules "are particularly liable to abuse and to produce ill-effects and have little or no therapeutic use."[89] The ECDD determined that "cannabis and cannabis resin should be scheduled at a level of control that will prevent harm caused by cannabis use and at the same time will not act as a barrier to access and to research and development of cannabis-related preparation [sic] for medical use."[89]

The committee also reaffirmed its earlier determination that CBD should not be scheduled and, noting that cannabidiol preparations may contain trace amounts of THC, "recommended that a footnote be added to Schedule I of the 1961 Single Convention on Narcotic Drugs to read: 'Preparations containing predominantly cannabidiol and not more than 0.2 percent of delta-9-tetrahydrocannabinol are not under international control.'"[89]

The UN Commission on Narcotic Drugs is empowered to decide by consensus not to vote on recommendations set forth by the ECDD.[90] However, it is expected that the CND will vote on the ECDD's recommendations when it convenes in March 2020. Given that the determinations were made by a panel of experts after a critical review of the scientific evidence, it is likely that a majority of the 53 countries that make up the commission will vote in favor of the recommended changes, which is all that is necessary in order to alter the scheduling of substances controlled by the 1961 Single Convention.[90] At the international level, a decision to explicitly de-schedule CBD preparations containing up to 0.2% THC and to remove the cannabis plant and cannabis resin from Schedule IV could take effect almost immediately: "Decisions taken concerning the scope of control of substances of the schedules of the 1961 Convention become effective with respect to each Party on the date of its receipt of such communication."[90]

Such changes would be important, although the full implications are not yet clear. States party to the 1961 Single Convention on Narcotic Drugs are obligated to update their domestic laws to reflect changes in scheduling at the international level. However, in the United States, it's not clear that the removal of cannabis and cannabis resin from Schedule IV of the Single Convention would trigger the rescheduling of those substances out of Schedule I of the Controlled Substances Act. Encouragingly, there are signs in Congress of growing bipartisan support for the reform of cannabis-related laws.[91]



On the other hand, the Controlled Substances Act almost certainly would be amended to de-schedule CBD preparations with no more than trace amounts of THC (including CBD isolate). It remains to be seen whether and how U.S. legislators or administration officials might reconcile the WHO's recommendation that uncontrolled CBD preparations contain up to 0.2% THC with U.S. law classifying cannabis with no more than 0.3% THC as industrial hemp – for example, whether industrial hemp might be redefined in U.S. law to reduce the THC content to no more than 0.2% by dry weight. The explicit de-scheduling of CBD should, however, facilitate the production of, trade in, and distribution of CBD and CBD-containing products, which would be to the benefit of consumers and CBD-related businesses alike.

CONCLUSION

While this guide reflects the current state of science, regulation, and laws regarding CBD, we know that much relating to CBD remains to be seen as developments play out in the fields of international and domestic law, agriculture, scientific research, pharmaceutical discovery, and medicine. The purpose of this guide was to better inform the reader on how the endocannabinoid system is intricately linked to several physiological processes that are critical to our health and wellbeing and to break down where CBD comes from, what it does, how it interacts with the endocannabinoid system to influence our health, how to ensure that CBD products are safe, and how to use them properly.

For decades, the U.S. federal government seemed indifferent, or even hostile, to new research into, and discoveries about cannabis and cannabinoids. Years of advocacy work has made a difference in the lives of medical cannabis patients and the people who care about them. Over the course of our history, ASA has educated countless patients, healthcare providers, legislators, policy makers, and members of the public on the science of medical cannabis. Now, there is bipartisan support in Congress for meaningful reforms around cannabis. The American people are calling for a different approach. This is is an evolving industry that can change at the speed of light and consumers have an important role to play in determining how it unfolds and in demanding safe access to their medicine.

REFERENCES

1. Russo, E.B., *History of cannabis and its preparations in saga, science, and sobriquet.*Chem Biodivers, 2007. 4(8): p. 1614-48.
2. Russo, E.B., *The pharmacological history of Cannabis.*, in *Handbook of Cannabinoids.*, R. Pertwee, Editor. 2014, Oxford University Press: Oxford, United Kingdom. p. 23-43.
3. Mechoulam, R. and Y. Shvo, *Hashish-I. The structure of cannabidiol.*Tetrahedron, 1963. 19: p. 2073-2078.
4. Gaoni, Y. and R. Mechoulam, *Isolation, structure and partial synthesis of an active constituent of hashish.*J Am Chem Soc, 1964. 86: p. 1646-1647.
5. Carlini, E.A. and J.M. Cunha, *Hypnotic and antiepileptic effects of cannabidiol.*J Clin Pharmacol, 1981. 21(8-9 Suppl): p. 417S-427S.
6. Cunha, J.M., et al., *Chronic administration of cannabidiol to healthy volunteers and epileptic patients.*Pharmacology, 1980. 21(3): p. 175-85.
7. Karniol, I.G. and E.A. Carlini, *Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol.* Psychopharmacologia, 1973. 33(1): p. 53-70.
8. Mechoulam, R. and E.A. Carlini, *Toward drugs derived from cannabis.*Naturwissenschaften, 1978. 65(4): p. 174-9.
9. Potter, D.J., P. Clark, and M.B. Brown, *Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology.*J Forensic Sci, 2008. 53(1): p. 90-4.
10. Chandra, S., et al., *New trends in cannabis potency in USA and Europe during the last decade (2008-2017).*Eur Arch Psychiatry Clin Neurosci, 2019.
11. Russo, E. and G.W. Guy, *A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol.*Med Hypotheses, 2006. 66(2): p. 234-46.
12. Mechoulam, R., et al., *Cannabidiol - recent advances.*Chem Biodivers, 2007. 4(8): p. 1678-1692.
13. Thomas, A., et al., *Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro.*Br J Pharmacol, 2007. 150(5): p. 613-23.
14. Russo, E.B., *Cannabidiol Claims and Misconceptions.*Trends Pharmacol Sci, 2017. 38(3): p. 198-201.
15. Devinsky, O., et al., *Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome.*N Engl J Med, 2017. 376(21): p. 2011-2020.
16. Thiele, E.A., et al., *Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial.*Lancet, 2018. 391(10125): p. 1085-1096.
17. Maa, E. and P. Figi, *The case for medical marijuana in epilepsy.* Epilepsia, 2014. 55(6): p. 783-6.
18. Bergamaschi, M.M., et al., *Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients.* Neuropsychopharmacology, 2011. 36(6): p. 1219-26.
19. Leweke, F.M., et al. *Cannabidiol as an antipsychotic: a double-blind, controlled clinical trial on cannabidiol vs. amisulpride in acute schizophrenia.*in *Symposium on the Cannabinoids.* 2005. Clearwater, FL: International Cannabinoid Research Society.
20. McGuire, P., et al., *Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial.*Am J Psychiatry, 2018. 175(3): p. 225-231.
21. Babalonis, S., et al., *Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers.*Drug Alcohol Depend, 2017. 172: p. 9-13.
22. Nicholson, A.N., et al., *Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults.*J Clin Psychopharmacol, 2004. 24(3): p. 305-313.
23. Russo, E.B., *Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects.*Br J Pharmacol, 2011. 163(7): p. 1344-64.
24. Lewis, M.A., E.B. Russo, and K.M. Smith, *Pharmacological Foundations of Cannabis Chemovars.*Planta Med, 2018. 84(4): p. 225-233.
25. Laprairie, R.B., et al., *Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor.*Br J Pharmacol, 2015. 172(20): p. 4790-805.
26. McPartland, J.M., et al., *Are cannabidiol and Delta(9) -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review.*Br J Pharmacol, 2015. 172(3): p. 737-53.
27. Adams, R., et al., *Conversion of cannabidiol to a product with marihuana activity. A type reaction for synthesis of analogous substances. Conversion of cannabidiol to cannabinol.* Journal of the American Chemical Society, 1940. 62(8): p. 2245-2246.
28. Grotenhermen, F., E.B. Russo, and A.W. Zuardi, *Even high doses of oral cannabidiol do not cause THC-like effects in humans.*Cannabis and Cannabinoid Research, 2017. 2.1: p. 1-4.
29. Mead, A.P., *International control of cannabis.*, in *Handbook of Cannabis*, R.G. Pertwee, Editor. 2014, Oxford University Press: Oxford, UK. p. 44-64.

30. Aizpurua-Olaizola, et al. (2016, February 2). Evolution of the Cannabinoid and Terpene Content during the Growth of Cannabis sativa Plants from Different Chemotypes. *Journal of Natural Products*, *79*(2), 324-331.
31. Hudak, J. (2018, December 14). *The Farm Bill, hemp legalization and the status of CBD: An explainer*. Retrieved from The Brookings Institution: https://www.brookings.edu/blog/fixgov/2018/12/14/the-farm-bill-hemp-and-cbd-explainer/
32. Drug Enforcement Agency. (2018, May 22). *DEA Internal Directive Regarding the Presence of Cannabinoids in Products and Materials Made from the Cannabis Plant*. Retrieved from Diversion Control Division: https://www.deadiversion.usdoj.gov/schedules/marijuana/dea_internal_directive_cannabinoids_05222018.html
33. Mead, A. (2017, May). The Legal Status of Cannabis (Marijuana) and Cannabidiol (CBD) Under U.S. Law. *Epilepsy & Behavior, 70*(Part B), 288-291.
34. Romero, D. (2018, December 16). *Hemp industry expected to blossom under new Farm Bill*. Retrieved from NBC News: https://www.nbcnews.com/news/us-news/hemp-industry-expected-blossom-under-new-farm-bill-n947791
35. Troutt, W. D., & DiDonato, M. D. (2017, November). Carbonyl Compounds Produced by Vaporizing Cannabis Oil Thinning Agents. *The Journal of Alternative and Complementary Medicine, 23*(11).
36. Izzo, A.A. et al. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. (2009) Trends in Pharmacological Sciences 30(10) 515-527.
37. Ghosh P and Bhattacharya SK. (1978) Anticonvulsant action of cannabis in the rat: role of brain monoamines. *Psychopharmacology,* 59(3), 293–297.
38. GW Pharmaceuticals statement, retrieved March 14, 2019. https://www.gwpharm.com/healthcare-professionals/research/mechanism-action
39. Zuardi, A.W. (2008) Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Rev. Bras. Psiquiatr. 30, 271– 280.
40. Shannon, S., et al. Cannabidiol in Anxiety and Sleep: A Larger Case Series. Perm J 2019;23:18-041.
41. Bitencourt, R.M. et al. (2008) Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. Eur. Neuropsychopharmacol. 18, 849–859.
42. Costa, B. et al. (2007) The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. Eur. J. Pharmacol. 556, 75–83.
43. Jan, T.R. et al. (2007) Suppressive effects of cannabidiol on antigen-specific antibody production and functional activity of splenocytes in ovalbumin-sensitized BALB/c mice. Int. Immunopharmacol. 7, 773–780.
44. Wilkinson, J.D. and Williamson, E.M. (2007) Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. J. Dermatol. Sci. 45, 87–92.
45. Chakravarti, B., et al. (2014) Cannabinoids as therapeutic agents in cancer: current status and future implications. Oncotarget 5(15):5852-5872.
46. Cheignon, C. et al. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biology (2018) 14, 450-464.
47. Kumar, A. and Ratan, R.R. Oxidative stress and Huntington's Disease: the good, the bad and the ugly. J Huntingtons Dis. (2016) 5(3), 217–237.
48. Esposito, G. et al. (2006) The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells. J. Mol. Med. 84, 253–258.
49. Garcia-Arencibia, M. et al. (2007) Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. Brain Res. 1134, 162–170.
50. World Health Organization Expert Committee on Drug Dependence. Cannabidiol (CBD) Critical Review Report. May 2018. Retrieved on April 2, 2019. Available from https://www.who.int/medicines/access/controlled-substances/WHOCBDReportMay2018-2.pdf?ua=1
51. Devinsky, O. et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. (2014) Epilepsia 55(6) 791-802.
52. Bergamaschi MM, Queiroz RHC, Zuardi AW, et al. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Current drug safety. 2011; 6:237–249.
53. Harvey, D.J. Absorption, distribution, and biotransformation of the cannabinoids Marihuana and medicine. Springer; 1999. p. 91-103.
54. Gallily, R., Yekhtin, Z. and Hanuš, L.O. (2015) Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol. Pharmacology & Pharmacy, 6, 75-85.
55. Bonn-Miller, M.O. et al. Labeling Accuracy of Cannabidiol Extracts Sold Online. JAMA. 318(17):1708-1709. November 7, 2017.
56. Reprinted with permission from CannaSafe April 5, 2019.
57. Kumar P, et al (2017) Aflatoxins: A Global Concern for Food Safety, Human Health and Their Management. Front. Microbiol. 7:2170.
58. https://www.webmd.com/a-to-z-guides/what-is-heavy-metal-poisoning#1 retrieved April 16, 2019.
59. "Medical Cannabis in America: The Medical Cannabis Briefing Book - 116th Congress." Americans for Safe Access, 2019, 28-29.

60. https://www.analyticalcannabis.com/articles/cbd-vs-thc-what-are-the-main-differences-297486
61. Howlett, A.C. et al. (2011) Endocannabinoid tone versus constitutive activity of cannabinoid receptors. *Br J Pharmacol,* 163(7), 1329-1343.
62. Ignatowska-Jankowska, B.M. et al. (2015) A cannabinoid CB1 receptor-positive allosteric modulator reduces neuropathic pain in the mouse with no psychoactive effects. *Neuropsychopharmacology,* 40(13), 2948-2959.
63. Pertwee, R.G. et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid Receptors and Their Ligands: Beyond CB_1 and CB_2. *Pharmacological Reviews* 62(4) 2010 588-631.
64. Choukèr A, Kaufmann I, Kreth S, Hauer D, Feuerecker M, et al. (2010) Motion Sickness, Stress and the Endocannabinoid System. PLoS ONE 5(5): e10752.
65. Sipe JC, Scott TM, Murray S, Harismendy O, Simon GM, et al. (2010) Biomarkers of Endocannabinoid System Activation in Severe Obesity. PLoS ONE 5(1):e8792.
66. Kunos, G., et al. Endocannabinoids and the Control of Energy Homeostasis. J. Biol. Chem. 283(48):33021-33025.
67. Horvath B., et al. The endocannabinoid system and plant-derived cannabinoids in diabetes and diabetic complications. The American journal of pathology. 2012; 180:432–42.
68. Skaper, S.D.; Marzo, V.D. Endocannabinoids in nervous system health and disease: the big picture in a nutshell. Phil. Trans. R. Soc. B (2012) 367, 3193–3200.
69. Klein, T.W. Cannabinoid-Based Drugs as Anti-Inflammatory Therapeutics. Nature (2005) 4, 400-411.
70. Pacher, P., et al. Modulation of the Endocannabinoid System in Cardiovascular Disease: Therapeutic Potential and Limitations. Hypertension. 2008 October; 52(4): 601–607.
71. Gong, J. P., et al. (2006). Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. Brain Res. 1071, 10–23.
72. Shao, Z., et al. High-resolution crystal structure of the human CB1 cannabinoid receptor. *Nature*, 2016.
73. Feng, Z., et al. Modeling, Molecular Dynamics Simulation, and Mutation Validation for Structure of Cannabinoid Receptor 2 Based on Known Crystal Structures of GPCRs. J. Chem. Inf. Model. (2014) 54, 2483–2499.
74. Pertwee, R.G. Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. Phil. Trans. R. Soc. B (2012) 367, 3353–3363.
75. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf retrieved April 10, 2019.
76. https://www.medicines.org.uk/emc/product/602 retrieved April 10, 2019. Not approved for use in the US.
77. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf retrieved April 10, 2019.
78. Sam, A.H., Salem, V., and Ghatei, M.A. (2011). Rimonabant: From RIO to Ban. *J Obes.* 432607
79. Russo, EB. (2019) The Case for the Entourage Effect and Conventional Breeding of Clinical Cannabis: No "Strain", No Gain. *Front. Plant Sci*. 9:1969.
80. Johnson, J. R., et al (2010). Multicenter, double-blind, randomized, placebo- controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J. Pain Symptom Manage. 39, 167–179.
81. Blasco-Benito, S., et al. (2018). Appraising the "entourage effect": antitumor action of a pure cannabinoid versus a botanical drug preparation in preclinical models of breast cancer. *Biochem. Pharmacol.* 157, 285–293.
82. Pamplona, F. A., da Silva, L. R., and Coan, A. C. (2018). Potential clinical benefits of CBD-rich *Cannabis* extracts over purified CBD in treatment-resistant epilepsy: observational data meta-analysis. *Front. Neurol.* 9:759.
83. All data from www.clinicaltrials.gov January 1, 2019 through May 9, 2019.
84. Wood, Sam. "Synthetic CBD from Main Line biotech gets fast track status from FDA." *The Philadelphia Inquirer*. May 6, 2019. Available from https://www.philly.com/business/zynerba-zygel-fda-fast-track-cbd-synthetic-cannabidiol-20190506.html. Accessed on May 24, 2019.
85. "WHO Expert Committee on Drug Dependence." World Health Organization. Available from www.who.int/medicines/access/controlled-substances/ecdd/en/. Accessed on April 24, 2019.
86. "Cannabidiol (CBD) Pre-Review Report: Agenda Item 5.2." Geneva: World Health Organization, 2017.
87. "Fortieth meeting of the Expert Committee on Drug Dependence." World Health Organization. Available from www.who.int/medicines/access/controlled-substances/ecdd_40_meeting/en/. Accessed on April 24, 2019.
88. "WHO Expert Committee on Drug Dependence: Fortieth report (WHO Technical Report Series, No. 1013)." Geneva: World Health Organization, 2018, 17.
89. "Annex I- Extract from the Report of the 41st Expert Committee on Drug Dependence: Cannabis and cannabis-related substances." World Health Organization. Available from www.who.int/medicines/access/controlled-substances/Annex_1_41_ECDD_recommendations_cannabis_22Jan19.pdf. Accessed on April 24, 2019.
90. "Scheduling Procedures," United Nations Office on Drugs and Crime. Available from www.unodc.org/unodc/en/commissions/CND/Mandate_Functions/Mandate-and-Functions_Scheduling.html. Accessed on April 25, 2019.
91. Shutt, Jennifer. "Congress Is Finally Going to Pot." *Roll Call*. March 6, 2019. Available from www.rollcall.com/news/congress/marijuana-gains-traction-both-parties. Accessed on April 25, 2019.

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