

A Review of Research into the Health Benefits of Cannabidiol (CBD)

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ABSTRACT

Cannabidiol (CBD) has become popular in the United States. CBD has derived from hemp plants (*Cannabis sativa*) which is a low amount of THC within the extraction. Cannabidiol is being investigated as a treatment for a various amount of health issues. CBD is prescribed in its pure form as Epidiolex, which was FDA-approved in 2018 to treat rare forms of epilepsy. There are some reports that CBD may provide anti-anxiety effects by helping people have calming and relaxing feelings by adjusting the CBD. Another possible use of CBD is as an antipsychotic. Animal studies of catalepsy was performed on rats that tested to see if they would have the same effect on humans. There is less evidence of CBD as an antidepressant, research over the years has not been conducted as much as other possible health benefits. Over time CBD has been used by individuals to help improve their skin, but not alot of results have been presented to the public. This paper will address clinical trials that were completed for epilepsy, psychosis, anxiety, depression, pain/inflammation, and skin conditions. Research into these potential health benefits of CBD is summarized in this paper.

INTRODUCTION

A decade ago, the acronym CBD had little meaning to the average person, but in today's world of corner CBD stores and multiple consumer products containing CBD, most Americans are aware of this non-psychoactive cannabinoid extracted from hemp plants. CBD stands for cannabidiol and its sales are rapidly growing in the United States. In 2019 CBD products have gained a little over five billion dollars in sales just in the United States alone (1). Even in the Pittsburgh area, there are at least fifteen stores dedicated to the sale of CBD products (Figure 1). Clearly, as described by a cannabis company board member quoted by the *New York Times*, “[CBD’s] hot, everywhere and yet almost nobody understands it.” (2) People are curious and want to know more, which is why as of April 23, 2019, there were ten million google searches related to CBD (3). In 2018 Corroon and Phillips (4) recruited a convenience sample through social media of 2,409 participants who answered a survey about CBD use; ~62% of respondents noted that they had used CBD in order to treat a medical condition. Scientists want to know more, too, which is why there have been over 300 clinical studies registered with ClinicalTrials.gov of research involving cannabidiol and human subjects, as well as many more preclinical animal model studies (5). Therefore this paper will provide background information about CBD and summarize research studies of the effect of CBD on various health issues.

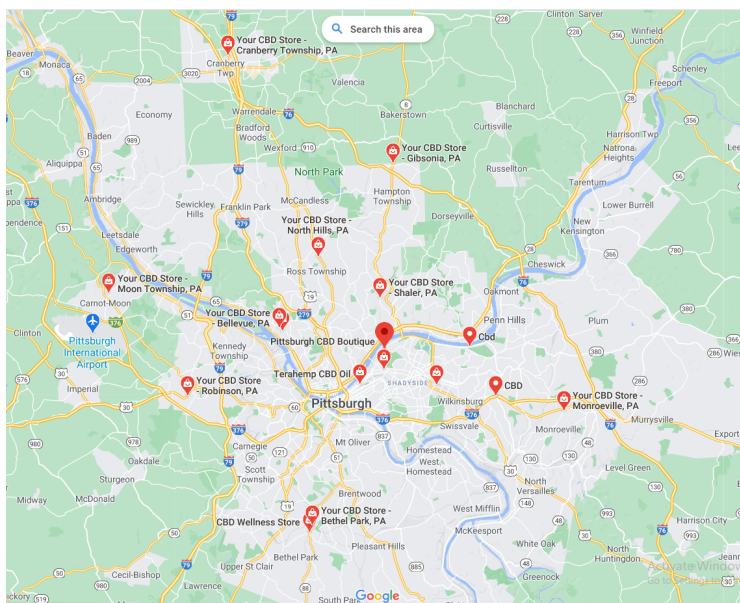


Figure 1: Google map search results for CBD stores in Pittsburgh, PA.

CBD BACKGROUND

Cannabidiol (CBD) is a chemical compound that is derived from *Cannabis sativa* plants. The IUPAC name for cannabidiol (CBD) is 2-[(1*R*,6*R*)-3-methyl-6-prop-1-en-2-yl]cyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol, which is shown in **Figure 2**. CBD is a large hydrocarbon with two alcohol groups, which makes CBD primarily nonpolar and is often found in oil form. Most people are familiar with *Cannabis sativa* as marijuana, a substance that gets you high, but that is not the case with CBD. “Marijuana” describes *Cannabis sativa* varieties that have high levels of THC, which is the psychoactive Δ -9-tetrahydrocannabinol substance that results in a “high” among users. “Hemp” is often the term used to describe *Cannabis sativa* plants that have low concentration of THC (<0.3%). In the 2018 Farm Bill, the U.S. Congress separated hemp from marijuana as a controlled substance, making it legal to grow hemp in large quantities (6). Hence, there was a boom in the production of hemp and the marketing of hemp-based products (7). Prior to the 2018 Farm Bill, pilot programs of hemp production had grown from zero in 2013 to over 90,000 acres in 2018. The year following the passage of the Farm Bill, the land dedicated to hemp production quadrupled(8).

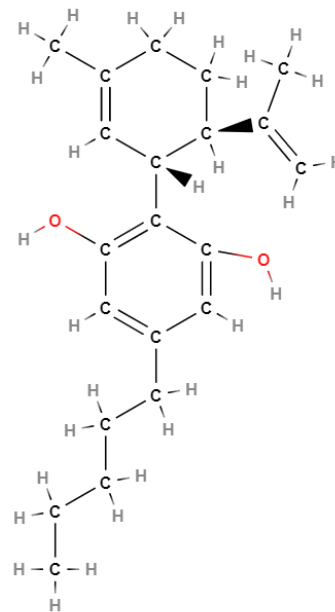


Figure 2. Structure of CBD ($C_{21}H_{30}O_2$)

Hemp plants are the source of both CBD and hemp seed oil, which are not synonymous terms although many consumers may confuse the two. CBD is not found in the seeds of hemp plants, but hemp seed oil may contain CBD due to cross contamination during processing. In fact, research has shown that many commercial hemp seed oils contain CBD, even if the label does not indicate its presence(9). Using HPLC scientists are able to extract CBD. Regulation of CBD by the Food and Drug Administration (FDA) is more complicated than its regulation of hemp because, as of June 2018, CBD is approved for pharmaceutical use as the anti-epileptic drug Epidiolex. As an active ingredient of a prescription medication, according to the FD&C Act, CBD cannot be sold as a dietary supplement unless formally exempted through an exception by the FDA. By the FDA needing approval by people selling CBD, it had left a gray area for people to see. Manufacturers have labeled their products “hemp” instead of stating that there is CBD in the product.

Although CBD is a hot commodity today, it took decades to capture the attention of clinical scientists for the treatment of various health issues. In fact, some might say it took millennia to make CBD a mainstream medication, because there are anecdotal reports dating to 2000 B.C. regarding the use

of *Cannabis sativa* to treat seizures(10).

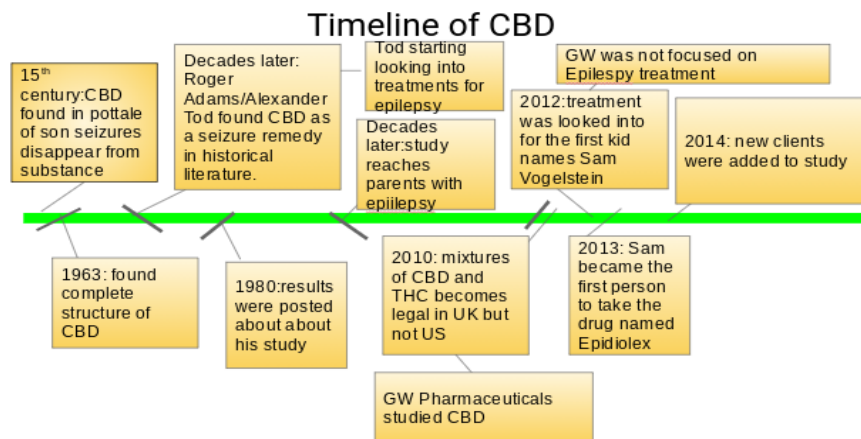


Figure 3. Timeline of Cannabis Sativa

Throughout Cannabis sativa timeline, CBD was first discovered to be used as a potential way to help people who suffer from seizures in the 15th century. It was not until the 1960s that the complete structure of CBD was found by Roger Adams and Alexander Todd who also found a remedy in historical literature. In the 1980s the study was finally posted to the public and was able to reach a family decades later with a son who has epilepsy in the US. At this time the CBD was not legal in the US, but instead was legal in the United Kingdom. CBD has now become a potential treatment for a variety of health issues.

EPILEPSY

As previously noted, CBD has been approved by the FDA to treat rare forms of epilepsy since June 2018. Epilepsy is a neurological disorder that often causes seizures, which is a burst of electricity that happens between the brain cells that causes involuntary muscle movement within the body, and can also cause death (11) According to the World Health Organization, epilepsy affects roughly 50 million people worldwide; the Centers for Disease Control reports 3.4 million people in the United States have epilepsy. There are multiple forms of epilepsy and some are more successfully treated with current medications than others. For those difficult cases of epilepsy, such as Dravet syndrome, pure CBD (99%) can be prescribed as the pharmaceutical Epidiolex.

Multiple clinical trials using purified CBD have demonstrated cannabidiol's effectiveness in reducing the frequency of seizures for participants with epilepsy. Silvestro, et al. reviewed clinical trials identified on www.clinicaltrials.gov. They summarized fourteen studies in which CBD was used in conjunction with other approved therapies. Not THC in a medical marijuana, but instead CBD can that can be purchased over the counter in CBD stores.

Even if the cbd can help the body and improve the seizures. A clinical trial took place in 2015 for three months with 137 children and adults with different types of epilepsy. Each person was treated using CBD Epidiolex and were given 200-300mg oral. The patients were evaluated through blood and urine samples. The patients were showing side effects such as, tiredness, diarrhea, loss of appetite, etc (12). But the study did show that the CBD was able to be tolerated. A larger study was conducted in September of 2016, and was made up of 167 people ranging from ages one to thirty but, mainly children. The study took place for a year where each participant was given 25mg of CBD. The CBD was able to help reduce the amount of seizures the patients had. In this study there was no control group which made it hard to understand where the side effects were coming from. Also since there was not a control group the trial could not have a complete conclusion if the CBD was the reason for the side effects within the help participants (13).

PSYCHOSIS

In addition to epilepsy, CBD has been studied for other brain-based issues like schizophrenia and bipolar disorder. Since 1982, CBD's antipsychotic properties have been studied in mice, rats and human subjects. Zuardi, et al. reviewed six rodent model studies and eighteen studies with humans related to CBD as an antipsychotic. One of the animal studies that showed positive results was by Moreira and Guimarães, in which they compared CBD to clozapine and haloperidol(14). This study used catalepsy and ketamine hyperlocomotion as the specific models of psychosis. Catalepsy is a condition where the limbs remain in whatever position they were placed in(15). Ketamine hyperlocomotion is often used in mice and rats to slow them down. CBD treatment was comparable to haloperidol.

The first study looked into that was done on humans was referenced by Zuardi in 2006, which took three patients that had a form of schizophrenia. The trial gave the people up to 1280mg of cbd which had no improvement to their condition and did not have any side effects on them. The second trial referenced Leweke and had 42 patients with schizophrenia or schizophreniform disorder. The participants received 800mg of cbd and had less of an effect with CBD than the first trial that was completed with Leweke as the reference(15).

ANXIETY

Anxiety is one of the most common forms of mental health disorders. It affects 18 percent of the population in the United States. There are different forms of anxiety such as panic disorder, social anxiety, and posttraumatic stress disorder. Cannabidiol has been used in certain situations to help relax the person's nerves. CBD works to create an increase of serotonin in the brain, which is a biological function that can moderate the brain and give a person a change in their mood, learning, and memory. A study was

completed by Raquel Linge, who found out SSRI (selective serotonin reuptake inhibitors) does not work as fast as CBD does to calm the brain down. Both animal and human studies in clinical trials have been completed to find out the effects that CBD has on anxiety.

One animal study researched the effects that CBD has compared to SSRI. The evidence shows that by using CBD it can affect the brain to the point where suicidal thoughts and behavior come about while the person is being affected by their anxiety. An animal study was completed with male rats. The study was started with taking away water for the mice for 24 hours, then three minutes of non-harming where they gave the mice food for three minutes. After that occurred the rats were given an injection of 10mg of CBD 30 minutes before the trial started. The study was completed again with depriving the animals of water than giving them three minutes of food. And it was clear that the CBD was ineffective on the animals.

CBD has been administered to teens as a treatment for social anxiety in a clinical trial from DATE. One of the main anxieties that teenagers face is social anxiety. Social Anxiety disorder also known as SAD is where a person is fighting with themselves to get over the fear of being judged in performing situations and connecting with others (16). SAD is shown to affect 3 to 13 percent of teens in the United States and affects more females than males. A clinical trial was completed in Japan with teens suffering from diagnosed SAD (ages 18 to 19 on 26 males and 11 females). During the six months before the trial started, eligible participants were interviewed and they tracked their rate of stress to establish that these participants were suffering from social anxiety. The participants were then prescribed to take a daily dose of hemp oil that contained 500 mg of CBD. Over the span of the next six months the study subjects would come in every four weeks to be interviewed once they were on the CBD. They also tracked their stress during this time using the same study as pre-CBD. The results showed that CBD allowed the people to have more brain activity and was not so focused on the fact that they were being interviewed. (transition sentence)

A large clinical case trial was conducted in 2019 on adults with anxiety and their sleep. The trial was completed only for once a month for documentation of 103 adults. The participants were given 25 mg of CBD in a capsule form. The study proved that the CBD actually did calm the people's brains down therefore most people used CBD after the trial was over (17).

DEPRESSION

(18)When it comes to anxiety and depression they are often grouped together. Depression is a mood disorder that often has symptoms of sadness and loss of interest in life. Sometime depression can even cause suicidal thoughts. CBD is often used with depression like how it is used with anxiety. The CBD is used to regulate the serotonin in the body. Not that many studies have been done to conclude that

CBD is the best drug to use as an antidepressant. A study was completed in 2019 on rats that showed that there were antidepressant effects of the CBD on the rats. The study used two strains of mice that are often used to mimic depression. In the mice test it was only a single dose where they injected CBD into the mice, but because it was only a single dose more studies and clinical trials should be conducted. The study had positive results with the rats showing that CBD can help with depression stimulated in animals. Scientists believe that the CBD has various effects on the body to help with Anti-depressants.(19)

PAIN/INFLAMMATION

Studies have shown that CBD may be able to be used as an anti-inflammatory drug to help reduce the swelling. Anti-inflammatory is a treatment that can help swelling or inflammation such as a drug that affects the center of the nervous system. A study was completed in 2019 that consisted of 19 participants. The trial allowed patients to have one dose of CBD to help control mild to moderate musculoskeletal pain. The participant was given a green tea tablet containing 5mg of CBD. to conduct the information of how the person feels they participants had to give a 1-10 idea of how much pain they were in. The study was completed and knowing that the number that the patients gave was indeed lower than when it started(20). A study completed by Raku ect. To show if CBD can be used as an anti-inflammatory for rheumatic diseases. Over 72 hours patients were monitored over to see how much pain they were in. Then in the last 24 hours they were given cannabis sativa in a smoking form to help with their skin. The study found that it did help the reduction of swelling in the patients and did help with the pain(21).

SKIN CONDITIONS

Different studies have been conducted to determine if CBD can help your skin in different situations. A study was conducted to determine if CBD can help reduce different factors in your skin like wrinkles, body heat, but also help with melanin. Some studies were completed to observe how CBD would affect the skin. One of the studies used topical CBD lotions on 20 patients, and had to be used twice a day, once at night and then again in the morning, The participants had a photoshoot at the beginning of and at the end of the trial to conduct the difference in their faces(22). They also were given a questionnaire at the beginning to find out different products that they used and how their skin reacted to different things. It was shown that using this certain ointment helps improve the people's skin, and with no allergic breakouts on the patients, but that is not certain for everyone. A different study was conducted by a team of dermatologists to determine if CBD and THC can help people with skin disorders with positive results(23). The trial was done on three patients and proved that there was a reduction in facial pains and toleration to different drugs and ointments applied to the skin.

CONCLUSION

In conclusion, CBD has shown significant benefits in the treatment of epilepsy and is being actively tested as a potential treatment for other ailments. Trials that were completed that involved epilepsy, anxiety, inflammation, and also skin conditions had positive results showing that CBD can work for the different trials that people have been put in. Some trials had issues of completions such as studies on depression and antipsychotics, the researchers' reviews, most of the time for the trials have not been completed all the way through, or not enough research has been conducted.

CBD research is a new field, many more studies are necessary to understand the effects of CBD and how it can be helpful in treating a variety of health issues. For instance, several studies included in this review were limited to single doses of CBD, limited on participants, and also studies had limitations on the milligrams of CBD that were given to the patients, and lastly the time of the trials. To improve trials in the future scientists should gather more data to improve the chances of having a better outcome for the study, and allow enough time to complete the study and trials before documenting to the public.

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