

## Review Article

# Pharmacological Effects of Cannabinoids Extracted from Industrial hemp on Epilepsy

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### Abstract

Epilepsy is a disease caused by abnormal brain activity due to disturbed nerve cell activity. It is the fourth most common neurological disorder. Only about 7 out of 10 individuals with epilepsy are successfully treated using anti-epileptic drugs. In the pharmaceutical industry, there has been a growing demand for cannabinoids from *Cannabis sativa*, commonly known as marijuana, for therapeutic, clinical, and nutraceutical supplements. More recently, the legalization of marijuana for clinical research has allowed to further explore the efficacy in the treatment of several neurological disorders like epilepsy. Unlike opioids, cannabinoids are not

psychoactive, making it a potentially more favorable therapeutic drug. Most studies showing the efficacy of *Cannabis* as a treatment strategy point to the pain management associated with the binding of endocannabinoid G coupled protein receptors CB1 and CB2. Though there are cannabinoid therapeutic drugs like Epidiolex approved by the Food and Drug Administration (FDA), plant-based natural compounds are safer, and effective with no side effects.

**Keywords:** Cannabinoids, Epilepsy, Endocannabinoid system, CBD, *C. Sativa*

## 1. Introduction

Evidence of medicinal *Cannabis sativa* use dates back to BCE with ancient civilizations using it as therapy for a variety of diseases [1]. There is evidence of delta 9-tetrahydrocannabinol (delta 9-THC) in ashes dating back to 400 AD, providing evidence of medical cannabis use. The plant has more than 100 phytocannabinoids leading to its diverse medicinal and psychotropic uses that have been used for centuries. It was first used in the United States as a patent medicine in the late 19th and early 20th centuries.

The female *Cannabis sativa* (*C. sativa*) flower is of therapeutic interest, as it is high in cannabinoids and low (< 0.3%) in tetrahydrocannabinol (THC). Most nutritional supplements commercially available in the market focus on CBD, however there are other cannabinoids such as cannabigerol (CBG), cannabichromene (CBC), cannabitriol (CBT), cannabinol (CBN) that have shown promising clinical results in the preliminary studies [2]. Delta 9 THC contains the psychoactive property in which recreational marijuana users seek for the euphoric feeling, known as a “high” [3]. While CBD, CBG, CBC, CBN, and CBT does not have psychoactive properties, it is being studied for its potential in treating symptoms of neurological disorders such as epilepsy.

The FDA has also approved one *Cannabis*-derived drug, Epidiolex, which is a pharmaceutical-grade CBD [4]. The FDA has also approved three synthetic *Cannabis*-based products. Out of these three, Marinol and Syndros are pharmaceutical grade Dronabinol, which is an isomer and a synthetic version of THC. The third one is Cesamet, which is pharmaceutical grade nabilone that is similar in chemical structure to

THC [5]. It is used primarily to treat nausea and vomiting caused by chemotherapy treatments.

### 1.1 Endocannabinoid System

CBD exerts its effect via the endocannabinoid (eCB) system in addition to other mechanisms [6]. The eCB system consists of eCB ligands, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), lipids that activate CB1 and CB2 - such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and metabolic enzymes - including N-acyl-phosphatidylethanolamine (NAPE), NAPE-specific phospholipase D (NAPE-PLD), and fatty acid amide hydrolase (FAAH) among others [7-8]. The eCB system is often found to be altered in patients with neurological diseases or has experienced a traumatic brain injury, and the components of the system became therapeutic targets. The endocannabinoidome is the regulation system of the endocannabinoid system and often becomes the target of therapy for neurological diseases [8].

The secondary metabolites of the endocannabinoid system are AEA and 2-AG [7, 9]. AEA, known as the bliss molecule, which results in the feeling of well-being when it binds to presynaptic CB1 or CB2. The levels of AEA and 2-AG present are known as the endocannabinoid tone which is regulated by FAAH and monoacyl-glycerol lipase (MAGL) both of which metabolize these chemical analogs [7, 9]. Endocannabinoids inhibit the release of neurotransmitters by inhibiting the influx of intracellular calcium. Usually, endocannabinoids are produced after trauma; they can also be produced by large amounts of nerve cell depolarization. It is produced locally and has a brief activity as it is quickly degraded due to its short half-life [9].

N-acylethanolamines and 2-acylglycerols share the same biosynthetic pathways and enzymes as AEA and 2-AG. They also target transient receptor potential cation channel V1 (TRPV1), peroxisome proliferator-activated nuclear receptor- $\alpha$  (PPAR $\alpha$ ), peroxisome proliferator-activated nuclear receptor  $\gamma$  (PPAR $\gamma$ ), T-type calcium ion channels, G-protein coupled receptor 18 (GPR18), G-protein coupled receptor 55 (GPR55), G-protein coupled receptor 110 (GPR110), and G-coupled protein receptor 119 (GPR119). The precursor to 2-AG is known to target the protein kinase C (PKC), GPR55, and lysophosphatidic acid receptors 1-3 (LPA1-3). The expanded endocannabinoid system also includes other long-chain fatty acid amides - including primary amides, lipoamino acids, and N-acyl-neurotransmitters. However, their targets are not fully known even though distinct biosynthetic pathways exist for lipoamino acids and N-acyl-neurotransmitters [8].

Enzymes of the endocannabinoid system have different substrate selectivity. Fatty acid amide hydrolase (FAAH) is known to break down long-chain N-acylethanolamines, N-acyl taurines, and N-acyl glycines. Fatty acid amide hydrolase 2 (FAAH2) however, prefers to break down oleoylethanolamide (OEA) and linoleoyl ethanolamide (LEA). N-acylethanolamine acid amidohydrolase (NAAA) reacts with and breaks down N-acylethanolamines. Monoacylglycerol lipase has substrate specificity for long-chain 2-acylglycerols, preferring its unsaturated form. 2-acylglycerols are also substrates for alpha and beta hydrolases 6 and 12. Cyclooxygenase 2 (COX 2) and lipoxygenases (LOX) are oxidizing enzymes of the arachidonate cascade. These enzymes recognize polyunsaturated fatty acid chains that contain endocannabinoid congeners. Metabolic

products derived from LOX or cytochrome P450 oxygenase (P450) have their specific receptors but can also activate CB1 and CB2 receptors [8].

CB1 and CB2 receptors of the endocannabinoid system are involved in many pathways and are an essential component in many biological processes - including but not limited to neuronal plasticity, pain, anxiety, neuroinflammation, immune function, metabolic regulation, and bone growth. The CB1 receptors are typically found in the brain and neuronal cells. CB2 cells are predominately found in tissue and immune cells leading to the pathways listed previously. These receptors also respond to plant-based ligands [7, 9]. This review highlights the current status of usage of Cannabinoids for the management and/or treatment of Epilepsy.

## **2. Epilepsy**

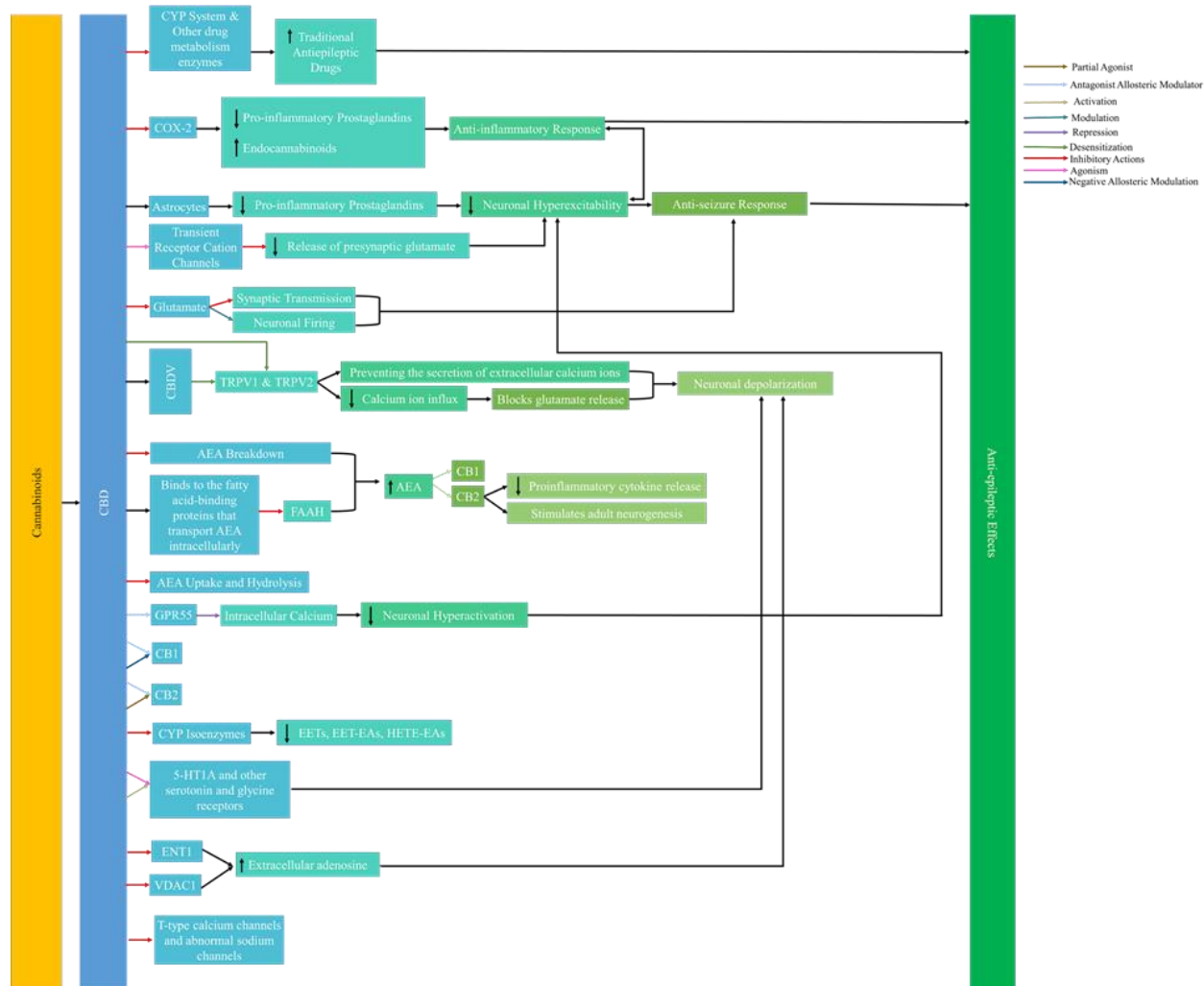
Around 50 million people globally, including an estimated 3.4 million people within the United States, have epilepsy [10-12]. Epilepsy is a chronic non-communicable neurological disorder characterized by seizures. It may occur because of neurological injuries, deficits, or brain abnormalities. However, most cases are thought to be caused by genetic factors that may play a role in the onset of epilepsy [13]. Seizures occur due to excessive electrical discharges in the neurons; this is known as neuronal hyperexcitability [10]. The resistance of approximately 1/3 of epileptic patients to traditional antiepileptic drugs is known as refractory epilepsy. Refractory epilepsy has been associated with worsened morbidity and mortality, and the issues can range from negative health consequences of uncontrolled seizures to decreased quality of life [14]. This leads to a medicinal demand for an

antiepileptic drug that has better efficacy and fewer adverse effects [13, 15].

### 2.1 Mechanisms of Action: Cannabinoids

Recent studies have linked epilepsy with neuro inflammation which is a pathophysiological mechanism that is directly related to the onset and severity of seizures. Studies have shown that

cannabinoids affect mediators of neuro inflammation including but not limited to the endocannabinoid system and ion channels [13]. Though research has recently expanded to other cannabinoids found in *C. sativa*, CBD is the most heavily studied for its antiepileptic effects [13, 16]. Figure 1 highlights the mechanism of action of cannabinoids in epilepsy.



**Figure 1:** The Mechanisms of Action of Cannabinoids in Epilepsy

There are many mechanisms of action by which cannabinoids can act in epilepsy. Figure 1 summarizes the mechanisms of action by cannabinoids in epilepsy that are currently understood [8, 13, 15, 17-27].

Cannabinoid research shows that cannabinoids target sodium, potassium, and calcium channels among others. The dysfunction of these ion channels including voltage or ion gated channels is what leads to epilepsy. Phytocannabinoids also interact with other diverse targets resulting in antiepileptic effects. It has been concluded throughout many years of studies that defects in ion channels at the axon hillock and their involved proteins are the primary reason for epilepsy [28]. CBD has been proven to treat pain, anxiety, stress, and depression. In addition to this, studies have shown that CBD acts as an antiepileptic agent with efficacy that rivals traditional therapeutic means while having only mild adverse effects on the patients [15]. New research shows multiple possible mechanisms of action for CBD. Specifically, CBD has been reported to be acting on at least 65 potential molecular targets in epileptic patients [17]. Its mechanism of action is proven to be independent of the CB1 receptor.

A study has also suggested that CB2 reduces postsynaptic neuronal hyper excitability [8]. This increases the availability to activate CB1 and CB2 receptors allowing for indirect regulation of the endocannabinoid system [18]. CBD is an antagonistic allosteric modulator of CB1, CB2, and G-protein coupled receptor 55 (GPR55) though it only binds weakly to CB1 and CB2 [16-17, 19, 21]. The activation of GPR55 increases intracellular calcium release which leads to neuronal hyper excitability. CBD's role as an antagonist to GPR55 leads to the repression of the intracellular calcium directly limiting and decreasing neuronal hyper activation [13].

A chronic epilepsy model showed that GPR55 mediated neurotransmission was potentiated in

excitatory neurons and reduced in inhibitory neurons. CBD antagonizes GPR55 at excitatory synapses which inhibits intracellular calcium release. This decreases the excitatory currents decreasing seizure activity. In the same study, CBD blocked GPR55 mediated increase in excitatory postsynaptic current frequency in excitatory neurons but did not do so in inhibitory neurons which showed that CBD's anticonvulsant effect was due to knocking out GPR55 [8,18,22]. The results also indicated that CBD has a fluid affinity for both allosteric and orthosteric sites at CB1 receptors and acted as an orthosteric ligand at CB2 receptors [16, 19, 23].

This leads to an indirect effect on CB1 and CB2 receptors through up regulation and down regulation of downstream eicosanoids resulting in an anti-seizure effect on the patient [13, 29]. CBD is thought to be able to target abnormal sodium channels and block T-type calcium channels both of which have excitatory functions [8, 17, 21]. It is also believed that the anticonvulsant effect of CBD could be related to its ability to inhibit voltage-gated ion channels [20, 30]. CBD blocks T-type calcium channels similar to traditional antiepileptic drugs. A study found that CBD's ability to regulate calcium and sodium ion influx into the neuron by binding to human T-type voltage-gated channels and by melastatin and vanilloid type transient receptor potential membrane receptors leads to neuronal depolarization leading to an antiepileptic effect [16].

Cannabidivarin (CBDV) also showed anticonvulsant effects with limited neurotoxicity. It is believed to exert these effects independent of the CB1 receptor mechanism [15-16]. Since recent research shows multiple pathways exist in regards to CBD's antiepileptic activity, a multimodal mechanism of

action could exist by which CBD exerts its anticonvulsant properties on epileptic patients. Research is also moving towards studying other phytocannabinoids found in *Cannabis sativa* as well as studying the whole plant extracts for efficacy in epileptic treatment.

## 2.2 Pediatric Epilepsy

Globally, the prevalence of epilepsy in children is 3.2-5.5 per 1,000 children in developed countries and

3.6-4.4 per 1,000 children in undeveloped countries. Additionally, studies have found that the incidence of epilepsy is the highest during the first year of epilepsy. About 470,000 children in the United States have epilepsy [11-12, 31]. For pediatric epilepsy, there can be different developmental and epileptic encephalopathies which have been summarized in Figure 2.



**Figure 2:** Developmental and Epileptic Encephalopathies.

Figure 2 summarizes different developmental and epileptic encephalopathies that can be present in pediatric epilepsy [10,15-16,32-37].

In children, epilepsy has many causes and mechanisms and has many different characterizations as shown in figure 3.



**Figure 3:** The Causes, Primary Characterization, and Mechanisms of Pediatric Epilepsy

There are many causes, primary characterization, and mechanics of pediatric epilepsy. Figure 3 summarizes all three in relation to pediatric epilepsy [10, 15-16].

In addition to the details discussed in the figure, children are particularly vulnerable to seizures due to the developing brain and neural network. They have a reduced seizure threshold which often leads to neuronal excitation. [16].

**2.2.1 Cannabinoids**

Multiple animal models of generalized and focal-onset epilepsy have demonstrated and confirmed the anticonvulsant properties of CBD and showed that when administered with other anticonvulsants, its effects become stronger. It is believed that the anticonvulsant effect is not from its metabolites, but from CBD itself based on the correlation of the effect and the concentration of CBD in the brain [15-16].

A review from 2018 detailed that 20mg/kg per day of Epidiolex was more effective than the placebo and 48.5% of the patients experienced a 50% reduction in seizures. The Quality of Life in Childhood Epilepsy scores also improved by 55.8%. Adverse effects in patients were only reported 2.2% of the time and were deemed infrequent [16, 38]. Another review from 2018 analyzed data from four studies of Epidiolex clinical trials in children with treatment-resistant Lennox-Gastaut and Dravet syndromes. The pooled average difference in seizure frequency between the placebo and the treatment group was 19.9% in favor of the treatment group with 37.2% of the treatment group and 21.2% of the placebo group

experiencing a 50% reduction in seizure frequency. A study showed that CBD was consistent in reducing major motor seizures by 50% and total seizures by 44% with the most common adverse effects being somnolence and diarrhea [39]. Based on this study, CBD may be an effective long-term treatment option for children and adults with Lennox-Gastaut syndrome or Dravet Syndrome.

Studies examining artisanal and CBD-enriched *cannabis* herbal extract (CHE) oil in epilepsy also showed efficacy in reducing seizures and improving quality of life. However, clinical studies in children have shown certain antiepileptic drugs to be more effective than *cannabis* products such as stiripentol in Dravet syndrome and rufinamide in Lennox-Gastaut syndrome. A meta-analysis also reported that a larger percentage of children taking CHE with lower daily CBD doses had a reduction in seizure frequency when compared to Epidiolex [16, 40]. Evidence suggests that CBD is effective in lowering the seizure burden in children with Dravet and Lennox-Gastaut syndromes [41].

Studies have reported the side effects of cannabis use to treat epilepsy in children to be 51%, but these effects were considered mild. The secondary effects included sleepiness, fatigue, and gastrointestinal symptoms. The potentially serious effects reported were elevations of liver enzymes, worsening of seizures, and blood dyscrasias. The elevation of liver enzymes was particularly seen in children who took valproic acid simultaneously with CBD. These effects were reported higher in patients taking Epidiolex than those taking CHE. Studies need to be done on weighing the developmental effects of cannabinoids against the neurodevelopmental harm caused by uncontrolled seizures [16]. Studies done on

the side effects of CBD in epilepsy treatment have been inconclusive as they showed either no effect, improved, mild side effects, and some more serious adverse side effects. However, the side effect of CBD on the comorbidities of epilepsy is minimal. It is believed that CBD may have antipsychotic and anxiolytic properties, but the cannabinoid's role in drug metabolism requires careful monitoring of patients for drug-drug interactions to prevent side effects [42].

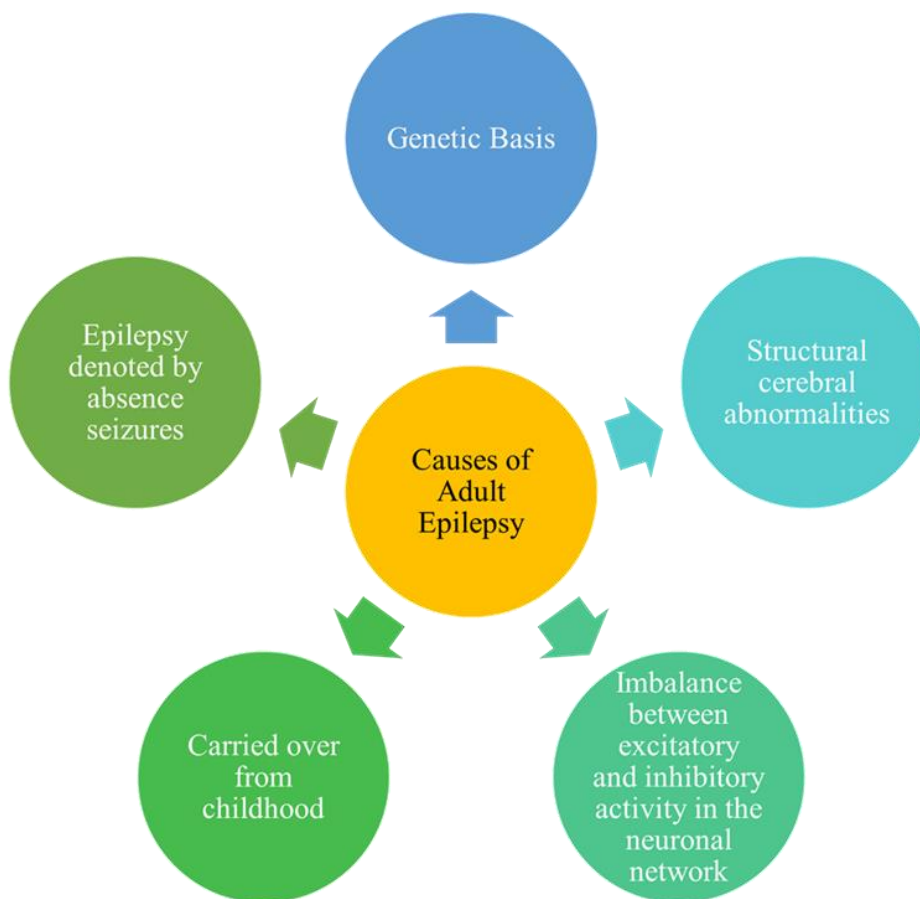
Observational studies describing Epidiolex and CBD oils with or without THC and limited data on vaporization or smoking of dried cannabis flower buds have reported *cannabis* to be successful in seizure reduction in sometimes as many as 71% of children. The dosage, formulations, and patient populations were known to vary in these studies [43]. Future research is needed in support of cannabis products as treatments for pediatric epilepsy as well as to define the appropriate dose, frequency, route, and form [44]. However, FDA has approved a pharmaceutical-grade CBD, Epidiolex, for Dravet Syndrome and Lennox-Gastaut Syndrome for anyone older than 2 years old [13,16,45].

### 2.3 Adult Epilepsy

Globally, the prevalence of epilepsy is 4-10 per 1000 people. More diagnoses of epilepsy occur in low and middle-income countries because of the increased presence of endemic conditions; about 80% of people with epilepsy live in low and middle-income countries. Approximately 3 million adults in the United States have epilepsy [11-12, 46]. About 1/3 of epilepsy patients have refractory epilepsy [10, 13, 15]. It is also reported that about 1/3 of newly diagnosed patients will not achieve seizure freedom [47]. There are many different reasons for the



occurrence or onset of adult epilepsy as shown in figure 4.



**Figure 4:** The Causes of Adult Epilepsy

There are many causes as to why adult epilepsy occurs. Figure 4 summarizes these potential causes of adult epilepsy [10, 15, 48].

The pathophysiology of what causes epileptic seizures is not completely known, but it is believed that seizures are primarily caused by abnormal activity in cortical neurons and glial cells and axons in the white matter [48].

### 2.3.1 Cannabinoids

Most of these studies involved purified CBD products mainly Epidiolex. Additionally, only a few studies involved both CBD and THC. Twenty-three studies reported seizure freedom using *cannabis*

treatment, but another 3 studies reported that no child achieved seizure freedom in their study. Overall, among children with Dravet syndrome who received CBD treatment in one 14 week randomized controlled trial (RCT), 5% became seizure-free in comparison to none in the placebo group while this number was 8% in non-randomized studies (NRS). Fourteen studies looked at seizure frequency. Overall, these studies found that the total monthly seizures were reduced by CBD when compared to the placebo in the RCTs and NRS. Six studies also

assessed the impact on the quality of life of the children, but no studies have considered the impact on caregivers. Three 14-week RCTs with children with Dravet or Lennox-Gastaut Syndrome reported no statistically significant effect, but data from NRS suggest an improvement relative to before the treatment but this is said with very low certainty. Fourteen studies also reported changes in sleep. In children with Dravet or Lennox-Gastaut syndrome in three-week RCTs, there was no statistically significant difference reported, but improved sleep was reported in six NRS. Status epilepticus was reported in 11 studies. While in RCTs there was no statistically significant difference, in NRS, 7% of children receiving *cannabis* treatment-experienced status epilepticus. Out of 1713 children who received *cannabis* treatment in 10 studies, 26 deaths occurred which includes 7 from unexpected death in epilepsy? However, most of these deaths were reported to be unrelated. Gastrointestinal adverse effects were reported among children receiving treatment with the risk of diarrhea being higher for those who received CBD [49].

Recent clinical studies show that CBD reduces seizure frequency in patients with refractory epilepsies. One of these studies even found that CBD is an effective form of treatment for patients with Lennox-Gastaut syndrome who experience drop seizures [50-51]. Short term analysis deems CBD as a safe drug for humans as it has no psychoactive properties, no changes in clinical and laboratory examination, and has no effect on the electroencephalogram (EEG) and electrocardiogram (ECG). CBD also has a long half-life if given intravenously or orally. If administered intravenously, the half-life is 30 hours while given orally, the half-life is 23 hours. This long half-life is helpful in patient-compliance. A

study by Devinsky showed that CBD had antiepileptic effects with a few adverse effects that were mild to moderate in severity. Another study showed a 43.9% reduction in drop seizures in the treatment group that was treated with CBD while only seeing a 21.8% reduction in patients in the placebo group. The most serious treatment-related adverse effect was the elevation of liver enzymes, but this effect diminished on its own with the continuation of the treatment [15].

Observational studies describing Epidiolex and CBD oils with or without THC and limited data on vaporization or smoking of dried *cannabis* flower buds have reported *cannabis* to be successful in seizure reduction in sometimes as many as 89.5% of adults. The dosage, formulations, and patient populations were known to vary in these studies [43]. These studies show that CBD can be an effective form of treatment for epilepsy and severe side effects have not been reported. However, more research is needed in specifically studying the effects of CBD, and in determining the treatment mechanism itself.

### 3. Conclusions

*Cannabis* shows promising applications in the treatment of epilepsy. Specifically, CBD is preferred over THC as it is non-psychoactive, and it has multiple targets. These various mechanisms of action, as well as its non-psychoactive characteristic, make this molecule preferred over THC. Epilepsy studies have found CBD to be effective in treating epilepsy, as it lacks psychoactive properties, and has an anti-inflammatory effect, as well the ability to limit seizures. The endocannabinoid system is not yet fully understood and requires further research to comprehend the extent to which cannabis can be used for the treatment of epilepsy.

## Abbreviations

2-AG: 2-arachidonoylglycerol  
 AEA: anandamide  
 CB1: cannabinoid receptor 1  
 CB2: cannabinoid receptor 2  
 CBC: cannabichromene  
 CBD: cannabidiol  
 CBDV: cannabidivarin  
 CBG: cannabigerol  
 CBN: cannabinol  
 CBT: cannabitriol  
 CHE: *cannabis* herbal extract  
 COX 2: Cyclooxygenase 2  
 eCB: endocannabinoid  
 ECG: electrocardiogram  
 EEG: electroencephalogram  
 FAAH: fatty acid amide hydrolase  
 FAAH2: fatty acid amide hydrolase 2  
 FDA: Food and Drug Administration  
 GPR110: G-protein coupled receptor 110  
 GPR119: G-protein coupled receptor 119  
 GPR18: G-protein coupled receptor 18  
 GPR55: G-protein coupled receptor 55  
 LEA: linoleoyl ethanolamide  
 LOX: lipoxygenases  
 LPA1-3: lysophosphatidic acid receptors 1-3  
 MAGL: monoacyl-glycerol lipase  
 NAAA: N-acylethanolamine acid amidohydrolase  
 NAPE: N-acyl-phosphatidylethanolamine  
 NAPE-PLD: NAPE-specific phospholipase D  
 NRS: non-randomized studies  
 OEA: oleoylethanolamide  
 P450: cytochrome P450 oxygenase  
 PPAR $\alpha$ : peroxisome proliferator-activated nuclear receptor- $\alpha$   
 PPAR $\gamma$ : peroxisome proliferator-activated nuclear receptor  $\gamma$

RCT: randomized controlled trials

THC: tetrahydrocannabinol

TRPV1: transient receptor potential cation channel V1

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this review.

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