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REVIEW article

Unveiling of cannabidiol in the treatment of rare childhood epilepsies: Dravet and Lennox Gastaut syndromes

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Abstract: In childhood, epilepsy is the most common globally widespread neurological problem, usually with serious consequences for this most critical period of development. Dravet and Lennox Gastaut syndromes are two forms of rare and severe treatment-resistant epilepsies that occur early in life. These resistant epilepsies recognised by continuous unrelenting seizures of many types including the occurrence of status epilepticus. In addition, it is associated with the development of behavioural, neurological, and cognitive deficits and the sequelae of increased risk of mortality rate. Historically, cannabis was found to possess several medical benefits including its use for epilepsy. In this review, information and data were extracted from 99 references using PubMed and Google Scholar (November, 2021). Data with clinical evidence on cannabidiol regarding its efficacy on Dravet syndrome and Lennox Gastaut syndrome, mechanism of action, safety, pharmacokinetic properties and interactions with anti-epileptic medications were all reviewed and discussed. Highly purified cannabidiol is a cannabis-derived compound that is suggested in recent research as an add-on therapy to the existing treatment of both resistant epileptic types; since it can reduce the duration, frequency and severity of seizure disorders. It is also characterised with multiple signalling transduction mechanisms, primarily via the inhibition of excitatory and potentiation of inhibitory pathways.

Introduction

Epilepsy is the most common neurological problem affecting over 60 million people around the world. In terms of incidence, the average GP will have between six and eight severely mentally handicapped patients in the practice, of whom between one and three will be children or adolescents with a seizure disorder. Epilepsy is categorized by recurrent seizures which are fleeting episodes of involuntary movements that may be partial (involving a part of the body) or a generalised (involving the entire body) [1]. Unfortunately, around one third of patients do not respond to any of the current antiepileptic drugs [2]. Epilepsy is a chronic non-communicable network disorder of the central nervous system; involving many complex underlying mechanisms and potential factors that influence the occurrence of this disease. It is driven by epigenetic dysregulation; elemental changes of cellular function which arise as a consequence of change in gene expression and its regulation [3]. Epilepsy is characterised by two or more seizure incidences [4], and excessive electrical

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discharges originating from cerebral neurons displaying as distinct behavioural and motor activity creating an alteration of consciousness [5]. Some seizure disorders cease or improve during puberty, some persist, some become worse and some change. Thus, the goal of this review is to highlight the use of the newly approved drug compound cannabidiol (CBD) for the treatment of childhood rare drug-resistant epilepsies. It will dive through the origins and nature of this compound, and the characteristics of these epileptic conditions and will demonstrate why CBD is beneficial to these conditions. By showing the pharmacological evidence collected from scientific literature supporting this area.

The aetiology of epilepsy: In general, epilepsy aetiologies are variable in different age groups and geographical areas. Epilepsies of childhood, adolescence and young adults are usually associated with congenital, developmental and genetic conditions. However, in elderly people; the most common causes are cerebrovascular diseases, central nervous system infections and tumours [6].

Selecting the appropriate therapy: Once the diagnosis of epilepsy in children is made, a seizure-preventing medication is prescribed. The selection of appropriate therapy therefore is based on a confirmed diagnosis, plus an accurate identification of the type of seizure disorder. Initial medication should consist of monotherapy, weighing possible side effects of anticonvulsant therapy against the expected benefits to the patient [7]. If the medication is unsuccessful, other management options arise; including surgery [8] (usually removal of tumour or malformed blood vessels), vagal nerve stimulation [9]. In addition, complementary therapy and a special diet that is known as the ketogenic diet in which high amounts of fat and low amounts of carbohydrates are consumed [10].

Antiepileptic drugs: The decision to treat seizures with antiepileptic drugs is a major event in a young person's life. It may be the final confirmation of the diagnosis of epilepsy, it may mean regular medication for long periods, and may have serious medical, psychological and social impacts. Antiepileptic drugs (AEDs) are considered the first line for treatment of epilepsy. They are introduced early on, in order to prevent seizures [11]. These medications interact with neurotransmitter receptors and ion channels thereby decreasing membrane excitability [12], either by inhibiting excitatory mechanisms or potentiation of inhibitory mechanisms. For instance, carbamazepine, felbamate and topiramate block the excitatory voltage-gated sodium channels [13]. However, voltage-gated calcium channels are blocked by ethosuximide and lamotrigine. However, the calcium channel $\alpha_{2\text{-}\delta}$ subunit is modulated by gabapentin and pregabalin [14]. In the mammalian brain, the main inhibitory and excitatory neurotransmitters mediating synaptic transmissions are amino acids gamma-aminobutyric acid (GABA) and glutamate, respectively [15]. It has been recognised that GABA can be potentiated by barbiturates, diazepam, felbamate, stiripentol, topiramate and valproate [16]. Whereas felbamate, lamotrigine and topiramate antagonise the excitatory glutamate receptors [17].

Epidemiology of epilepsy in childhood: Epidemiological studies provide information on the prevalence, incidence, causal factors and natural history of epilepsy in childhood, but rates vary depending on how epilepsy is defined, on the completeness of case-finding and on the populations studied. It is well recognized that the rate of epilepsy found in child population studies varies according to the definition used. The rates vary from 1.5-150 per 1,000 children. It is not possible to obtain information on the natural history of epilepsy or fits in children from cross-sectional studies. Some longitudinal studies, which follow children over some time, are required. However, it is difficult to tell whether the epidemiology of epilepsy is changing over time because of the different definitions and different populations studied. According to the published data, epilepsy is the most common neurological disease affecting about 1.0% of children, with the incidence of it being 5-7 cases per 10,000 children from birth to age fifteen [18]. Amongst several childhood epilepsies; Dravet syndrome (DS) and Lennox Gastaut syndrome (LGS) are forms of rare, worse and severe treatment-resistant epilepsies (TRE) that occur early in life. Each of these syndromes is classified as epileptic encephalopathy

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disorder; in which unrelenting and continual epileptic activity occurs. Thus, eliciting cognitive and behavioural defects that may develop over time into progressive cerebral dysfunction [19].

Dravet Syndrome: Dravet syndrome has previously been known as severe myoclonic epilepsy of infancy (SMEI) and was first described by Dravet in 1978 [20]. In all the cases of DS, seizures begin within the first year of life with an estimated prevalence of 0.5-1 per 20,000 newborns [21]. The onset is usually between 5-8 months of age accompanied by frequent febrile unilateral clonic convulsions and sometimes non-febrile seizures could be present. These early DS seizures are typically prolonged and correlated to fever or infection. After this stage, seizures of multiple types emerge (myoclonic, atypical absences and complex focal seizures) which habitually advance to status epilepticus (SE) and associated severe psychomotor deterioration. The persistent progression stops at about 10 years of age with a decline in seizure frequency although abiding neurologic sequelae [22]. Seizure stimulants besides fever, infectious illnesses [23] or vaccinations [21], also include elevated body temperature (maybe by hot bath water) and photic (light) or pattern stimulation [23]. Unfavourably, in most cases the prognosis of DS is poor; seizures become intractable and resistant to drugs. Further, cognitive and motor impairment pan out in all cases and the mortality rate is notably high [23].

Genetic predisposition in Dravet syndrome: Dravet syndrome is described as a genetic disease, due to a voltage-gated sodium channel alpha subunit 1 *SCN1A* gene mutation (haploinsufficiency) [24]. Mutations in this gene were found in 67% to 86% of patients from larger studies as described by Charlotte Dravet and colleagues [23]. However, the majority of mutations occur de novo and inherited cases are depicted [25]. As for genetics, a family history of epilepsy is also frequent in many cases. These mutations are found in other forms of epilepsy, non-epileptic disorders and febrile seizures [26]. The spectrum of *SCN1A* disorders extends from mild familial hemiplegic migraines to febrile seizures, generalised epilepsy with febrile seizures, intractable childhood epilepsy with generalised tonic-clonic seizures to DS being the most severe form [27].

Lennox Gastaut syndrome: In parallel to DS, LGS primarily labelled as “Petit mal variant” by Lennox in 1966 [28] is likewise a childhood onset of severe rare epileptic encephalopathy contributing to intellectual and developmental disabilities. It has a prevalence rate of 01.0-10.0% of all childhood epilepsies [29] but is more predominant in males [30]. It is first diagnosed between the ages of three and eight years [31], though a few studies reported 10.0-16.0% of LGS cases have late onset (over eight years) [32, 33]. This condition characterised by multiple seizures, most commonly tonic-clonic seizures. Patients of LGS suffer through at least one episode of SE in their history usually following tonic, atonic and myoclonic seizures as well as immobilizing seizures known as “falls” or “epileptic drop attacks” [30]. Due to these drop attacks, patients with LGS are continuously prone to be injured, they have to physically protect themselves by using helmets and remain in wheelchairs [34]. This not only affects their health-related quality of life (HRQL) but also impacts their caregivers [35].

Causes of Lennox Gastaut syndrome: Lennox Gastaut cases can be either cryptogenic (de novo) or from aetiological causes such as cortical dysplasia, perinatal hypoxia, congenital infections, central nervous system infections such as encephalitis and meningitis [36].

Mortality rate of Dravet syndrome and Lennox Gastaut syndrome: Mortality rate in DS and LGS syndromes is higher than other rates found in the general population of epilepsy patients. In DS, for instance, the mortality rate ranges from 5 to 20% [37], most commonly due to sudden unexpected death in epilepsy (SUDEP) occurring during sleep. It has been marked with the highest SUDEP rate 9.32 per 1 000 persons yearly, higher than the latest 5.1 SUDEP rate per 1 000 persons yearly for adults with refractory epilepsy. Furthermore, the elevated mortality rate could be a result of SE and its subsequent complications [38]. On the other hand, LGS has a lower mortality rate ranging from 3.0 to 7.0% usually resulting from seizure accidents and injuries [36].

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Treatment of Dravet syndrome and Lennox Gastaut syndrome: Antiepileptic drugs provide little to no relief from seizures in the treatment of resistant epilepsies. In such syndromes, as complete seizure cessation is highly unachievable; the main aim of the treatment is to reduce and limit either seizure occurrence or frequency, control symptoms, and decrease co-morbidities and neurological sequelae [39]. In case of DS, the first line of treatment includes valproate and clobazam but are inadequate as therapeutic options when used on their own [40]. As a consequence, an alternative second line and adjunctive therapy should be used as topiramate [41] and stiripentol [42]. Similarly, the first line of treatment mainly used in LGS are valproate and clobazam [39] as well as lamotrigine [43]. Since LGS is also treatment resistant, add-on therapy is typically indicated and proven to be beneficial. Some adjunctive therapies used are topiramate, felbamate, rufinamide and fenfluramine [44, 45]. What makes the treatment in both syndromes peculiar? it is a fact that many of the generally well-known antiepileptic drugs are found to cause seizure exacerbation. Either those used in DS (carbamazepine, phenytoin, lamotrigine [46], oxcarbazepine [47], phenobarbital and others) [48] or in LGS (carbamazepine, phenytoin, vigabatrin) [30, 49] (**Table 1**). Last but not least, a novel drug known as cannabidiol has recently emerged as a new hope for the treatment of DS and LGS.

Table 1: Antiepileptic drugs in the treatment of Dravet and Lennox Gastaut syndromes

Treatment resistant epilepsy	First line	Second line Adjunctive	Causing seizure exacerbation	Novel drug
Dravet syndrome	Valproate Clobazam [40]	Stiripentol Topiramate [41, 42]	Phenytoin Carbamazepine Lamotrigine [46] Oxacarbazepine [47] Phenobarbital [48]	Cannabidiol
Lennox Gastaut syndrome	Valproate Clobazam [39] Lamotrigine [43]	Topiramate Felbamate Rufinamide Fenfluramine [44, 45]	Carbamazepine Phenytoin Vigabatrin [30, 49]	

Medical history and drug profile of Cannabis: Cannabis (*Cannabis sativa, Cannabis indica*, hashish, hemp and marijuana) is one of the oldest cultivated plants around the world. The word cannabis refers to all products derived from the plant *cannabis sativa*. Its medical use and multiple indications were first recorded in the world's oldest pharmacopeia of ancient China in 2,700 BC [50].

Then it was introduced in India, as an analgesic, anticonvulsant and tranquilizer amongst its many recognised uses around 1,000 years BC [51]. In 1,464 AD, the Arab historian Ibn Al-Badri reported that the caliph's chamberlain's epileptic son was given "hashish" as medication and that it had completely cured him but also caused him to be in a state of addiction [52]. Later on, the modern use of cannabis was common in the Western world in the years of the 1,800s, its therapeutic uses were introduced by Irish physician William O'Shaughnessy as he was one of the first scientists to publish papers on this topic [53]. In the same era, Queen Victoria had used cannabis to alleviate her menstrual symptoms. According to a cannabis history review by Crocq 2020, CBD was isolated from the plant for the first time in 1940 by an Illinois University team, however, its structure was elucidated in 1963 [54]. In the wake of the development of modern medicaments, cannabis' medical use notably declined and it was not until the second half of the 20th century that it intrigued interest in the scientific world [51].

A decade later, cannabis was perceived as dangerous in 1970 when it was placed amongst heroin, LSD (Lyser-

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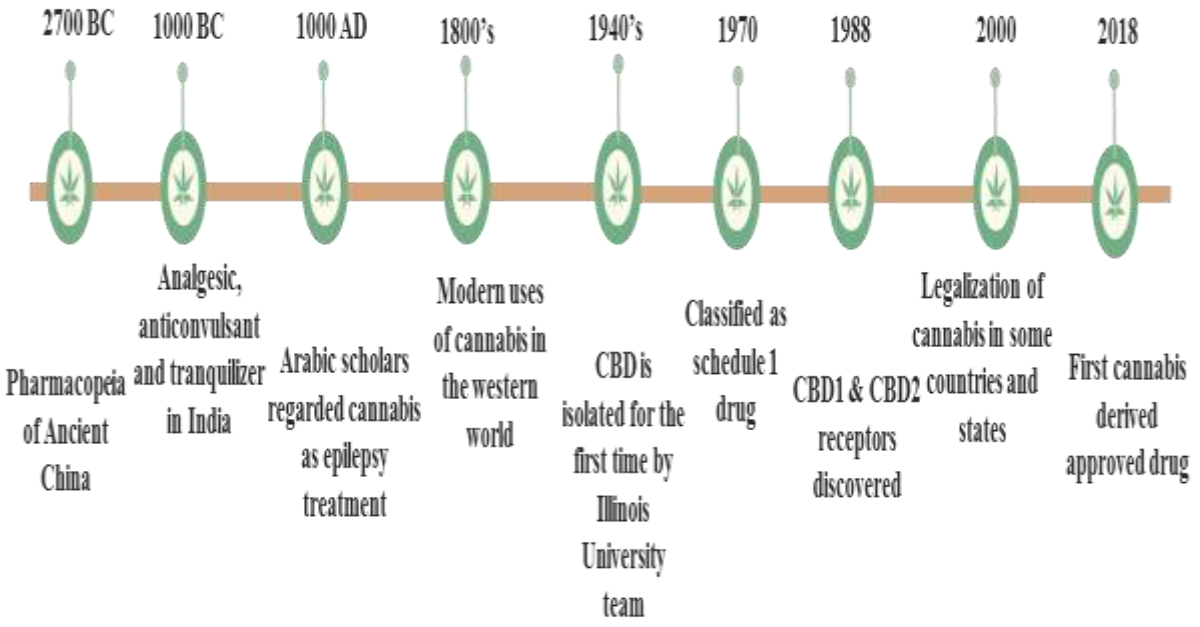
gic acid diethylamide) and MDMA (3, 4-Methylenedioxymethamphetamine) in the classification of schedule 1 drugs [54]. After cannabinoid receptors were discovered in the human body, the medical uses of CBD were further explored [54] which led to the legalisation of cannabis in some parts of the world in the 2000s [55]. This history of cannabis in medical use is summarized in **Figure 1**. In June 2018, a pharmaceutical drug (oral solution) known as Epidiolex® (GW Pharmaceuticals, Cambridge, UK) was approved by the Food and Drug Administration (US FDA) as the first and only drug consisting solely of highly purified cannabidiol (CBD) for the treatment of DS and LGS [56]. Lately, in September 2019, this drug gained marketing authorisation approval from the European Commission (EC) for patients with DS and LGS aged 2 years and more [57].

Figure 1: Timeline of medical cannabis



CBD: Cannabidiol, CBD1 and CBD2: Cannabinoid receptors 1 and 2, LSD; Lysergic acid diethylamide, MDMA: 3,4-methylenedioxy-methamphetamine.

Cannabidiol

So far, more than 540 natural compounds of diverse chemical classes have been discovered to contribute to the peculiar pharmacological characteristics of the cannabis plant [57]. Of the compounds 113 identified cannabinoids [59]. Cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) are the most prevalently studied. These two compounds are found in variable concentrations depending on the genus of the cannabis plant [60]. The major psychoactive cannabinoid THC, is proven to hold anti-inflammatory, anti-emetic, appetite-stimulant and analgesic properties [61]. On the contrary, CBD or "2-[(6R)-6-Isopropenyl 3-methyl-2-cyclohexen-1-yl]-5-pentyl-1,3-benzene-diol" as in, **Table 2**, is a completely non-psychoactive agent [62] that has demonstrated remarkable medical benefit in epilepsy [63], anxiety [64], cancer, diabetes, as well as neuroprotection and reduction of tobacco dependence [58]. CBD is found in multiple approved medical formulations for example Epidiolex® [65] and Sativex® [66] (**Table 3**).

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ISSN: 2958-3101 print

Table 2: Chemical name, structure and molecular formula of cannabidiol [62]

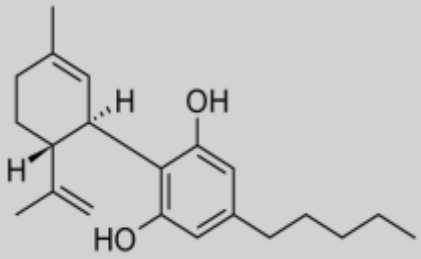
Chemical name	Structure	Molecular formula
Cannabidiol (CBD) 2-[(6R)-6-Isopropenyl3-methyl-2-cyclohexen-1-yl]-5-pentyl-1,3-benzene-diol		$C_{21}H_{30}O_2$

Table 3: FDA-approved drugs containing cannabidiol [65, 66]

Drug	Active ingredient	Dosage form	Indication
Epidiolex®	Cannabidiol	Oral solution	Lennox Gastaut syndrome, Dravet syndrome, Tuberous sclerosis complex
Sativex® (nabiximols)	delta-9-tetrahydr-ocannabinol, cannabidiol	Oromucosal spray	Multiple sclerosis

Pre-clinical trials: By 2018, many trials were carried out, investigating the effects of CBD on seizure models. It is found to be effective in acute seizures for rodents, following intraperitoneal administration [67]. In another study, CBD also prevented the tonic convulsions that are induced by convulsant drugs or electrical currents. Moreover, differential effects were simultaneously examined and findings suggested that CBD does in fact inhibit the seizure spread in the central nervous system through GABA but not glycine mechanisms [68]. In pre-clinical *in-vivo* studies of the DS model, cannabidiol was tested on *SCN1A+/−* mice; because this well-defined phenocopy of human DS. They present thermally induced, spontaneous seizures besides autism-like traits (autistic-like social deficits). After treatment with CBD (100 mg/kg), a reduction in the spontaneous seizure rate by 70.0% was noted. It significantly reduced the frequency, duration, and severity of seizures (spontaneous and febrile), and improved the social interaction behaviours of DS mice. In fact, DS mice are hyperactive compared to the wild type. In an open-field test for locomotor activity, treating DS mice with 100 mg/kg CBD considerably reduced their distance travelled [68]. Upon chronic administration of CBD in a recent animal study of DS, premature mortality was reduced. Furthermore, it was observed that the social behaviour, as well as the memory function of mice, had improved [24].

Clinical trials: Following the pre-clinical studies, many clinical trials were performed for the efficacy of CBD on patients with DS and LGS. There are different studies conducted including randomized double-blind clinical trials, multinational randomized double-blind clinical trials, double-blind placebo-controlled randomized clinical trials, retrospective clinical studies and open label extension studies. All of these trials were similar in the outcome and main findings, as the administration of CBD resulted in a decrease in overall seizures, ranging from 43.0% to 57.0% reduction. Generally, most patients who used cannabidiol experienced an improvement in their seizure symptoms and frequencies and some even became seizure-free (about 05.0% in a trial). These clinical trials are summarised in **Table 4** [70, 71-74].

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Table 4: Clinical trial of cannabidiol for Dravet and Lennox Gastaut syndromes

Syndrome	Type of study	Key points	References
Dravet syndrome	Randomized double-blind clinical trial	Convulsive seizure frequency compared with baseline was reduced by 48.7% in the 10 mg/kg/d cannabidiol group and 45.7% in the 20 mg/kg/d cannabidiol group	Miller et al. [70]
	Multinational, randomized, double-blind trial	Treatment with cannabidiol BD (20 mg/kg): - About 43% of patients had at least a 50% reduction in convulsive-seizure frequency - 5% of patients became seizure-free	Devinsky et al. [71]
	Retrospective clinical study	Administration of CBD showed more than 50% reduction of seizure frequency in 30%	Koo et al. [72]
Lennox Gastaut syndrome	Double-blind, placebo-controlled, randomized clinical trial	Addition of CBD at a dose of 10 mg or 20 mg/kg per day to a conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures by 37.2% and 41.9%, respectively)	Devinsky et al. [73]
	Open-label extension (OLE) study	An interim analysis reported: - Median reduction in monthly total seizure frequency ranged from 48% to 57% - 88% of patients/caregivers reported an improvement in the patient's overall condition	Thiele et al. [74]
	Retrospective clinical study	Cannabidiol administration showed an overall reduction of seizure frequency in the Lennox Gastaut group was 52.9%	Koo et al. [72]

Proposed mechanisms of action of CBD: Although the exact mechanism of cannabidiol has not yet been fully understood, CBD is known as a "multi-target drug" [75], since it interacts with several endocannabinoids and non-endocannabinoid signalling systems, having multimodal mechanisms of actions (**Figure 2**). For instance, CBD can work as a partial agonist on dopamine-D_2 [76] and serotonin $5HT_{1A}$ receptors [77]. Whereas, it is an agonist of transient receptor potential (TRP) cation channels, specifically activating and acting as an agonist on TRP vanilloid receptor-1 channel (TRPV1), as well as transient receptor potential vanilloid 2 (TRPV2) and the ankyrin-1 transient receptor potential channel (TRPA1) resulting in decreased calcium levels and intrinsic neuronal excitability [78, 79]. The most well-known mechanism of CBD is the activation of the endocannabinoid system through the modulation of G protein coupled cannabinoid receptors CB1 and CB2 [80]. CBD inhibits fatty acid amide hydrolase (FAAH) which results in the raising of anandamide levels due to the blockage of the re-uptake and breakdown of anandamide; a lipid mediator that acts as an endogenous ligand of the CB receptors [81]. Consequently, stimulation of cannabinoid receptors suppresses the presynaptic release of multiple neurotransmitters such as GABA, glutamate, acetylcholine, serotonin and noradrenaline [82]. CBD also inhibits the reuptake of adenosine, therefore, increasing adenosine extracellular levels and activating adenosine receptors [83]. Specifically, activates pre-synaptic A1 receptors, thus the reduction of glutamate release from excitatory terminals [84]. In recent studies, CBD has been indicated to influence and regulate gene expression through the activation of the nuclear peroxisome proliferator-activated receptor gamma (PPARγ). Parallel, the neuro-protection that CBD provides is attributed to the activation of adenosine receptors [83], PPARγ and 5-HT1A receptors [85]. Another putative novel orphan G protein

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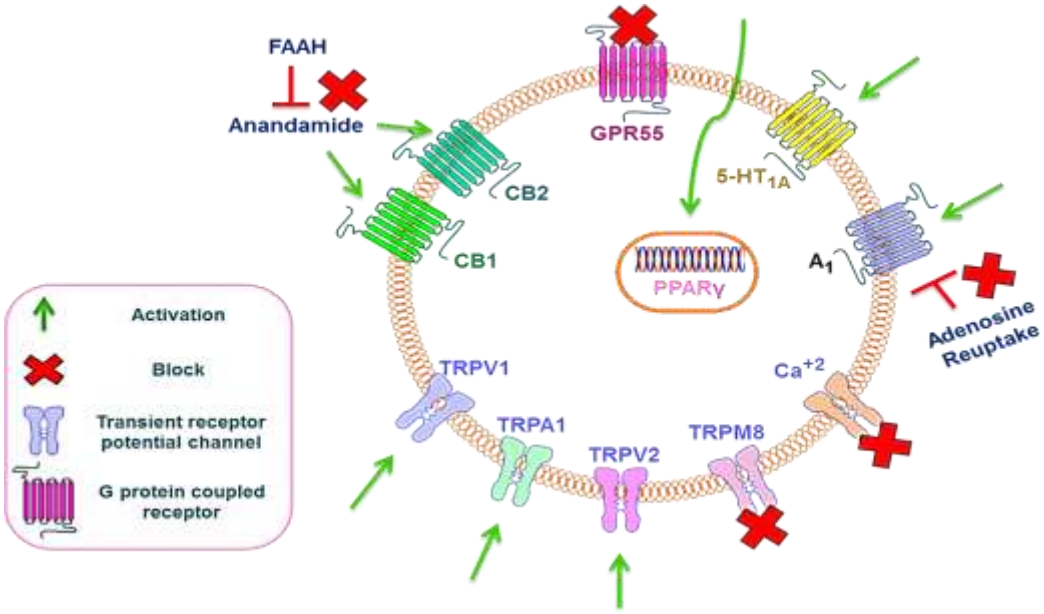
coupled receptor 55 (GPR55) was identified as a new promising target for cannabidiol. It is localised in axon terminals and by which presynaptic calcium ions are elevated thereby facilitating glutamate release. Therefore, CBD acts as an antagonist to GPR55 receptor, causing a reduction in glutamate exocytosis, as a deduction lowering neuronal excitation [84, 86]. Additional mechanisms that could explain the role of cannabidiol in epilepsy are the inhibitory effects of voltage dependent sodium channels [87] and the allosteric modulation of (δ) delta-opioid receptors [88]. These mechanisms altogether reduce neuro-excitability and vesicular release; in turn decreasing excitatory neurotransmission leading to a decline in seizure activity.

Figure 2: Multimodal signalling mechanism of actions of cannabidiol



A_1: Adenosine receptor, CB1: cannabinoid receptor 1, CB2: cannabinoid receptor 2, FAAH: fatty acid amide hydrolase, GPR55: G protein coupled receptor 55, 5-HT_{1A}: 5-hydroxytryptamine 1 subtype A receptor, PPARγ: peroxisome proliferator-activated receptor gamma, TRPA1: transient receptor potential ankyrin 1, TRPM8: Transient receptor potential cation channel subfamily M (melastatin), TRPV1: transient receptor potential vanilloid receptor 1 channel, TRPV2: transient receptor potential vanilloid receptor 2 channel.

Pharmacokinetic aspects of cannabidiol: Epidiolex®, as mentioned, is the first approved medication purely containing CBD. It is an oral solution with a concentration of 100 mg/ml. The absorption of CBD following an oral administration is slow and irregular. CBD has pharmacological effects with an onset time of 30 to 60 minutes, which most likely would be attributed to the lipophilic nature of the drug and its low water solubility (12.6 mg per L) [84, 89]. The bioavailability of CBD lasts for about eight hours, reaching a peak after 2-4 hours. An advantage of CBD as medication is that even though it has a half-life of 1.4-10.9 hours, the half-life extends to 2-5 days with repeated oral administration [89]. CBD is extensively and rapidly distributed in most vital organs including the lungs, liver, heart, brain and the hypo-vascularized tissues [90]. Its concentration in the plasma and brain elevates in a dose dependent manner, mainly following high fat meals due to its lipophilicity [89]. The metabolism of CBD in humans takes place entirely in the liver-by-liver cytochrome enzymes (CYP2C19 and CYP3A4). About 75.0% of CBD is removed by hepatic metabolism before reaching systemic circulation. It is reported to be excreted unchanged in the faeces [90].

Medical cannabidiol drug interactions, adverse effects and safety: The most important interactions that may occur with CBD are with other antiepileptic drugs, especially ones that concomitantly interact with liver enzymes. As stated above, CBD undergoes metabolism through cytochrome enzymes present in the liver. This is also the case for other AEDs such as phenobarbital, phenytoin and stiripentol; as well as drugs either

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inducing or inhibiting CYP2C19 metabolism as oxcarbazepine, felbamate and topiramate [91]. In conditions like DS and LGS, multiple drugs are commonly used. Therefore, checking of liver function tests (LFTs) and serum concentrations of AEDs must be done continuously. In open label safety study, the pharmacokinetic interactions of AEDs were determined. In patients taking valproate with CBD simultaneously, the LFT results were found to be abnormal and significantly high. However, serum levels were remarkably changed for drugs when used with escalated doses of CBD such as that seen in decreased clobazam, while increased rufinamide and topiramate levels [92]. Hence, dosage adjustments should be made accordingly with each patient individually depending upon which medications and dosages are taken.

Cannabidiol has an overall good safety profile. Generally well tolerated, especially when it is compared with other AEDs that have more distressing side effects [93]. The most common adverse events noted in patients taking the drug CBD/Epidiolex® included gastrointestinal discomfort and disturbances such as diarrhoea, nausea and vomiting [94]. This may be a result of the irregular and low solubilisation of CBD in the gastrointestinal tract as it is hydrophilic environment [89]. Also, loss of weight is an untoward effect caused by CBD [95]; although it not being a serious side effect, it is important to some degree, especially for children in the stages of growth. Somnolence, sedation and fatigue were other side effects that resulted in patients of DS and LGS taking CBD/Epidiolex® [94]. Furthermore, somnolence and elevations in serum aminotransferases were precipitated by concomitant AED therapy such as clobazam [96] and valproate [97]. Nevertheless, many of these mentioned side effects are not considered serious and can be avoided by giving individual dosage adjustments.

Conclusion: Overall, not only does CBD reduce seizures by 50.0%, but it is also reported that patients taking it noticed an improvement in their health-related quality of life (HRQL). This was emphasized by caregivers through the Caregiver Global Impression of Change scoring, a drastic and significant improvement was noted in the overall condition of the children who took CBD/Epidiolex® for treatment of DS [98]. It is important that AEDs are assessed on their efficiency in the reduction of seizures, reduction of seizure frequencies, reaching seizure-free days and improving the HRQL of patients. Hence, CBD represents a good choice of medication for DS and LGS. However, CBD is a novel drug for epilepsy, so it is still not legal worldwide, which limits its use. Due to it being a cannabis-based medication, there is a stigma surrounding it. This maks its medical use controversial socially and religiously; thus hindering the hopeful outcomes of the medication that could be seen otherwise. Another downside to the available CBD /Epidiolex® is its cost [98] which makes it highly inaccessible for most patients. Ultimately, there is a huge excitement regarding the future prospects of CBD.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Author contributions: Both authors substantially contributed to the conception, compilation of data, checking and approving the final version of the manuscript.
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