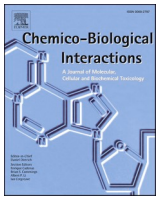
Chemico-Biological Interactions 394 (2024) 110988

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint



Review Article

# Decoding epilepsy treatment: A comparative evaluation contrasting cannabidiol pharmacokinetics in adult and paediatric populations

Mohamed Osman [a], Jamileh Khalil [a], Mostafa El-Bahri [a], Jamal Swalah Mcdahrou [a], Reem Fahda [a], Reymin Mustafa [a], Arthur Ooi [a], Marwa Attayee [a], Rachelle Catanzariti [a], Lisa Pont [a], Kylie Williams [a], Stewart Yeung [a,b], Kamal Dua [a,b,*], Gabriele De Rubis [a,b,**], Raimar Loebenberg [c,***]

[a] Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW 2007, Australia
[b] Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, Australia
[c] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2E1, Canada

ARTICLE INFO

*Keywords:*
Cannabis
Epilepsy
Paediatrics
Pharmacokinetics
Cannabidiol

ABSTRACT

Epilepsy is a neurological disorder characterized by overstimulation of neurotransmitters and uncontrolled seizures. Current medications for epilepsy result in adverse effects or insufficient seizure control, highlighting the necessity to develop alternative therapies. Cannabidiol (CBD), derived from cannabis plants, has been popularly explored as an alternative. CBD is shown to have *anti*-convulsivatng and muscle-relaxing properties, which have been used in patients with epilepsy with promising results. Current research explores varying dosages in either adult or paediatric patients, with little or no comparison between the two populations. In this review, we aim at consolidating this data and comparing the effect and pharmacokinetic properties of CBD across these two patient populations. When comparing the absorption, there was insufficient data to show differences between paediatric and adult patients. Similarly, limited information was available in comparing the distribution of CBD, but a higher volume of distribution was found in the paediatric population. From the metabolism perspective, the paediatric population had a greater success rate when treated with the drug compared to the adult population. In the elimination, there were no clear distinctions in the clearance rate between the two populations. The drug's half-life was highly variable in both populations, with paediatrics having a lower range than adults. In summary, the paediatric population had a more significant reduction in the severity of seizures compared to the adult population upon CBD treatment. The complexity in which CBD operates highlights the need for further studies of the compound to further understand why differences occur between these two populations.

## 1. Introduction

Epilepsy is a neurological disorder affecting around 0.7% of the world's population [1]. It is characterized by overstimulation of neurotransmitters which leads to prolonged predisposition to develop epileptic seizures of various types and intensity [2,3]. It is considered the third most important contributor to the worldwide burden of diseases for neurological disorders [4], and its management has an estimated yearly cost of 119.27 billion US dollars worldwide [5]. Epilepsy affects around 1 in 200 children [6]. Treatment mostly involves the use of different classes of anti-seizure drugs (ASDs) such as levetiracetam, lamotrigine, zonisamide and topiramate, often in conjunction with alternative therapeutic approaches such as neurostimulation and dietary therapies such as the ketogenic diet; however, the emergence of treatment resistance is common, limiting the efficacy of currently available treatment [3]. Furthermore, the prolonged use of ASDs leads to a wide range of adverse effects including obesity and cardiovascular diseases [7]. This underlines the necessity to develop novel treatment strategies for the management of epilepsy.

In this context, different extracts of the *Cannabis sativa* plant have

* Corresponding author. Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, 2007, Australia.
** Corresponding author. Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, 2007, Australia.
*** Corresponding author. Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2E1, Canada.
*E-mail addresses:* kamal.dua@uts.edu.au (K. Dua), gabriele.derubis@uts.edu.au (G. De Rubis), raimar@ualberta.ca (R. Loebenberg).

https://doi.org/10.1016/j.cbi.2024.110988
Received 25 January 2024; Received in revised form 19 March 2024; Accepted 2 April 2024

been used off-label to treat seizures for centuries [8]. The two main active ingredients of *Cannabis* extracts are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), with the latter considered being more effective and more suitable for clinical use due to the lack of psychotropic effects compared to THC [8]. Despite the pharmacokinetics of CBD and other cannabinoids have been extensively characterized [9] in adult populations, little is known about the pharmacokinetics of this molecule in paediatric populations. In the present review, we aim at providing a detailed comparison of the pharmacokinetics of CBD between these two patient cohorts.

The review will cover the rationale behind the use of CBD as an antiepilepsy agent, the role of the endocannabinoid system in synaptic regulation and neuroprotection, and a discussion of the current factors limiting the therapeutic use of CBD in epilepsy. Furthermore, the review will focus on providing a detailed comparison of the pharmacokinetics of CBD between adult and paediatric populations, analysing the available literature on the difference between these two populations in terms of absorption, distribution, metabolism, and elimination.

The literature reviewed shows that CBD therapy tends to be more effective in infants compared to adults, and this could be caused by an apparently higher volume of distribution of CBD in younger patients. However, this study highlights the current lack of more systematic clinical trials providing a direct, complete comparison between these two patient cohorts in terms of CBD pharmacokinetics. This underlines the necessity to conduct further studies aimed at providing a clearer understanding of the impact of age on the pharmacokinetics, and therapeutic efficacy, of CBD in the treatment of epilepsy.

## 2. Epilepsy and cannabidiol

### 2.1. Epilepsy

Epilepsy is defined by the hyperexcitable state that results from increased synaptic neurotransmitters and reduction in inhibitory neurotransmitters, which repolarise the cell, resulting in a resting state, an alteration in voltage-gated ion channels leading to hyperexcitable cells or an ion concentration influx in favour of depolarisation. The disease was initially thought to be developed throughout one's lifetime [10,11]. The research challenged that idea otherwise and introduced the concept of genetic predisposition that affects the removal of neurotransmitter-stimulating proteins, voltage-gated channel imbalance or ion imbalance that favours depolarisation states. The subsequent effect of these defects is uncontrolled seizures, muscular fits that affect airways, and frequent loss of focus and consciousness. Amongst all neurological diseases, epilepsy is the most common relative to the occurrence of genetic neurological disorders and is one of the most devastating diseases [12]. It is reported that thirty per cent of all epileptic cases have uncontrolled seizures, which can be linked to poor management and lifestyle. Epilepsy can not only alter but can change someone's life with its onset, especially when it is manifested at a young age, but it also has detrimental effects on a child's development [13,14]. In the present literature review, we provide an overview of the effects of cannabidiol in adults and children and how incorporating CBD pharmacological management techniques can help manage epileptic symptoms, reducing the developmental retardations that are present in children. These epileptic cases are known as developmental and epileptic encephalopathy (DEE) and are examples of early detected cases in children. The DEEs include a variety of epileptic syndromes with an incidence of 1 in 2000 births; these births are categorised with their high incidence of seizures and abnormal epileptiform, which severely impact their cognitive functions and overall behavioural reactions [15]. Children with DEE are expected to have a mortality rate of 24% within the first 20 years of diagnosis. The fortunate live with cognitive regression affecting their intelligence, behaviour, and motor functions. It was previously believed that these DEEs were acquired in a certain way. However, it was not until 2006 that the children showed a genetic similarity, leading to the belief that the incidence of DEE had a genetic component [11].

An example of DEEs is Dravet syndrome, a DEE that is manifested at a young age, typically from 3 months [16]. The epileptic tendencies include generalised tonic-clonic seizures with fevers, which develop into focal, myoclonic, absent, and non-convulsive seizures from age 5. 80% of all cases of Dravet syndrome have an outcome of intellectual disability [17]. The cause discovered for this disease is the pathogenic variant *SCN1A* gene, which encodes for the Alpha 1 subunits of the neuronal voltage-gated sodium channel [16].

A typical region known to be affected in the case of epilepsy is the hippocampus, which is located deep into the temporal lobe and consists of many layers of extensive neural pathways, many of which project electric impulses [11]. The neurotransmitters are the propagating factor released due to the reached action potential. The neurotransmitters then bind to the ligand-gated channels, releasing an influx of ions and creating a depolarisation state [11,18]. In the case of non-focal epileptic patients, the excitatory neurotransmitter glutamate binds to its corresponding ligand; because of the genetic abnormality, the neurotransmitter reuptake in the synaptic cleft is left uncleared, leading to a prolonged excitatory response in the neurons. This is the cause of epileptic seizures and overstimulation, as seen in Fig. 1.

While many of these conditions in the non-focal epileptic groups can be treated by antiepileptic drugs, many of these drugs have severe side effects, making patients and health professionals wonder if the medications' benefits outweigh their risks. Furthermore, most patients are children, which makes dosing these medications even more challenging [19]. In addition, conditions like Dravet syndrome have little to no response to common antiepileptic drugs, which piques the interest of different methods, such as environmental adaptations and exclusions from inducing triggers. A study by the Academy of Neurology gathered a sample space of 598 people with epilepsy over a 10-month study to identify the causes and triggers of epileptic seizures [20]. The study median was 32 years of age, and the total combined episodes were 1485 seizures, with 177 patients out of the 500 experiencing them. The primary triggers reported were stress-associated, often being linked to work-related events, reporting that 39% of the stress-induced episodes occurred in patients with full-time jobs, 20% with part-time jobs, 27% unemployed patients, and 28.6% in disabled patients [20]. Another reported contributing factor was medication adherence, with a 39.5% report of incidence related to missing medications. The rest of the triggers were linked to lack of sleep, which accounted for 18% of the episodes; menses had an effect with 12% of the total seizures related to them, and the rest were due to overexertion, diet and fever/infections with accounted for the last 26% [20].

### 2.2. Cannabidiol

Cannabidiol (CBD) is the decarboxylated form of the naturally occurring cannabidiolic acid which is present in *Cannabis* plants. The compound has a cyclohexene structure, containing a methyl group at position 1, a 2,6-dihydroxy-4-pentylphenyl group at position 3, and a prop-1-en-2-yl group at position 4. The chemical structure of CBD is shown in Fig. 2. CBD is an antimicrobial agent and a plant metabolite belonging to resorcinols, phytocannabinoids, and olefinic compounds [12].

Cannabidiol can be defined by its physicochemical properties. These properties include the melting point, boiling point, appearance, polarity, pKa, lipophilicity, partition coefficient, and pH in aqueous solution. Due to its low water solubility and high lipophilicity, CBD is classified as Class II according to the Biopharmaceutics Classification system for oral drugs [21,22]. CBD has a low water solubility of 12.6 mg/L and a logP of 6.3. CBD pertains to weak acid characteristics and presents a pKa of 9.1. CBD has a melting point of 67 °C and a varying boiling point of 187–190 °C [21,23,24]. Being CBD highly lipophilic, adipose tissue, brain, and other organs all experience fast distribution of CBD [2,25].

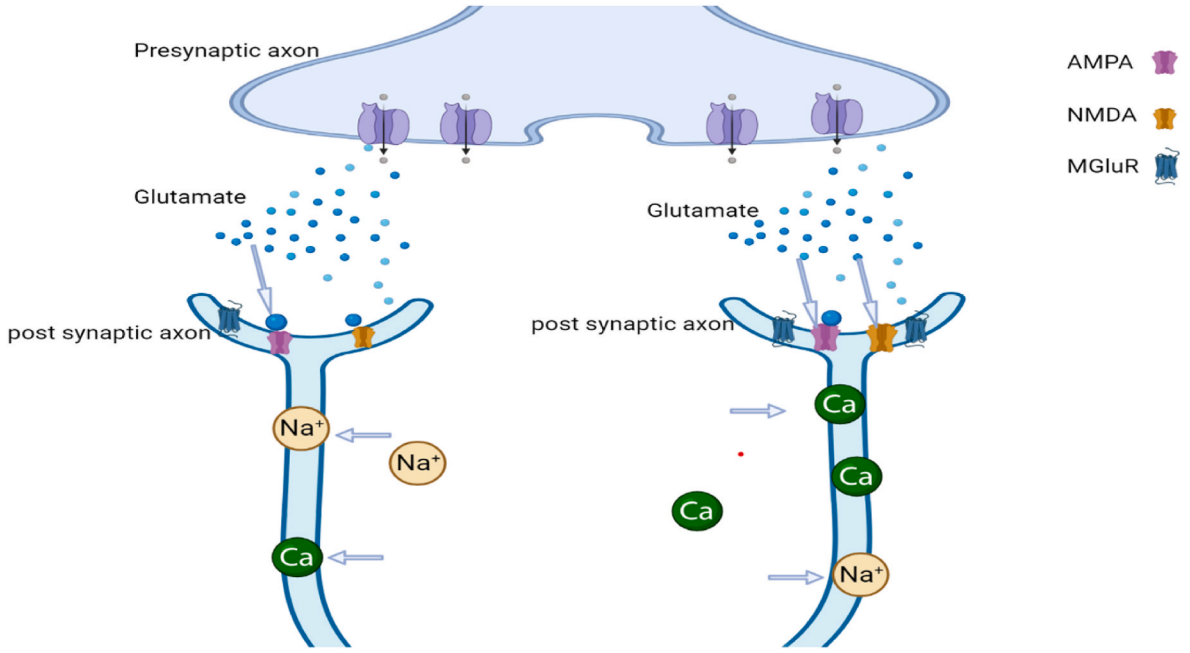



**Fig. 1.** Excitation of action potential in epileptic patients with glutamate mechanism of action. Glutamate acts on the receptors, producing neurotransmitters such as GABA and causing the excitation of cells via the rapid influx of sodium and calcium ions. The absence of the reuptake protein prevents and delays the repolarised state, leading to epileptic events such as seizures. Figure prepared with Microsoft Power Point.

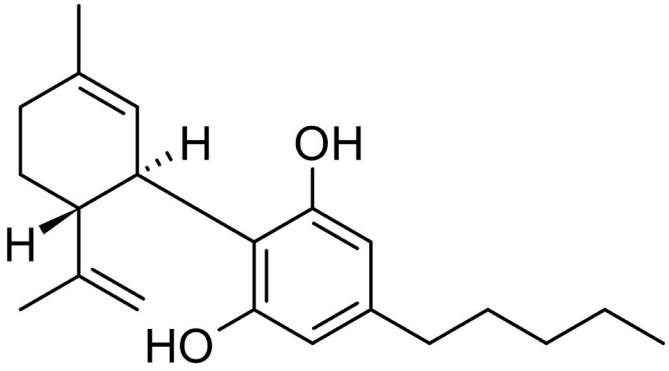



**Fig. 2.** Chemical structure of cannabidiol.

### *2.3. The role of the endocannabinoid system (ECS) in synaptic regulation and neuroprotection*

In the central nervous system (CNS), the endocannabinoid system (ECS) plays a momentous role in the regulation of excitatory and inhibitory synaptic transmission. Two G protein-coupled receptors, CB1 and CB2, alongside two endocannabinoid ligands, N-arachidonoylethanolamide and 2-arachinoylglycerol, constitute the ECS [26]. Several studies have shown the role of CB1 receptors in the CNS as potential therapeutic targets for treating epilepsy [26,27]. The CB1 receptor can be found as a heterodimer, hetero-oligomer, or a homodimer in conglomeration with other GPCRs. Aside from the primary binding site, the CB1 receptor also has a binding pocket responsible for allosteric modulation [28].

This receptor has been found in the presynapse termini and axons of neurons of critical neurotransmitter systems such as GABA [28]. Additionally, CB1 receptors are found in the cortical, basal ganglia, cerebellum, and hippocampus region of the brain. The activation of the CB1 receptors activates potassium and calcium ion channels. In addition, the activation of CB1 receptors suppresses the release of essential neurotransmitters. For example, being CB1 receptors highly expressed in both neocortical and hippocampal regions in GABAergic neurons, their activation in the hippocampal region suppresses neurotransmission in the GABA system [28].

The CB2 receptor is found primarily in several immune cells and peripheral tissues, including B lymphocytes, microglia, natural killer cells, and macrophages [28]. Although the CB2 receptor shows a low level of expression in the CNS, it is highly expressed during epilepsy, making it a crucial target for neuroprotection. Moreover, CB1 and CB2 receptors show their expression in pericytes and astrocytes. Most CB1 and CB2 receptors inhibit the production of adenylyl cyclase and cAMP [26].

The ECS plays a significant function in brain excitability, predominantly via the activation of CB1 receptors. Furthermore, neuro-defence, reduction of inflammation, and oxidative stress are linked with the activation of CB2 receptors. Several studies have analysed the functions of CB2 agonists in halting neurodegenerative disorders [28].

### *2.4. CBD in epilepsy*

CBD is an active cannabinoid identified within the hemp and *Cannabis* plants. In some cases, it accounts for up to 40% of the cannabis extract. CBD has shown great potential as anticonvulsant, analgesic, muscle relaxant, anxiolytic, antipsychotic and even neuroprotective, anti-inflammatory and antioxidant activity. Research on CBD and its anticonvulsant effect on epilepsy in children and adults has recently emerged with promising results, which highlighted the possibility of using CBD in conjunction with other anticonvulsants. The most promising development area is represented by the use of CBD as an add-on agent in treating drug-resistant epilepsy in children and adults. CBD has shown potential to significantly improve the quality of life of both paediatric and adult patients, reducing the duration and occurrence of seizures experienced during epilepsy [29–31]. CBD is available globally in numerous forms, and it can be extracted and formulated into oral dosage forms of capsule pellets, solid tablets, oils (sublingual), and topical applicants such as ointments, gels, lotions, creams, powdered concentrates, and oral solutions [24,32]. Other dosage forms include the vaporisation of CBD through inhalation and its administration through transdermal patches [33,34].

When formulating CBD, the pharmacokinetic goal varies depending on the intended use. For example, in acute pain, a faster $T_{max}$ (time required to reach peak drug concentration) and higher $C_{max}$ (maximum drug concentrations in the body) are generally desired to help prevent and decrease the risk of overdose via premature self-repeated administration. There is no current known toxic dose of CBD; however, the highest tolerated dose applied in clinical studies is 1500 mg per day [35]. In treating chronic epilepsy conditions, the desired outcome is a larger area under the plasma time-concentration curve (AUC) for regular dosing schedules rather than a fast, sharp peak. Despite the available dosage forms, an ideal oral dosage form that provides consistent delivery and high bioavailability is unavailable and currently warranted [24].

Lennox-Gastaut syndrome is an uncommon epileptic encephalopathy caused by a multiple-type seizure disorder. It is characterised by a progressive decline in cerebral cognition and functioning [36]. Patients affected by this and other epileptic conditions have been enrolled in a wide variety of research that focused on various dosages of CBD. In treating drug-resistant epilepsy, Dravet syndrome, Lennox-Gaustaut syndrome and other epileptic conditions, the main dosage form of CBD used across multiple clinical research studies is oral, which is dosed depending on age, weight, and type of epileptic condition. Research undertaken by Szaflarski et al. dosed 607 patients with different anti-epileptic drugs, using a starting dose of CBD at 2–10 mg/kg/day, which escalated to 25–50 mg/kg/day for a median of 48 weeks [30]. Another study on cannabidiol in patients with treatment-resistant epilepsy by Devinsky et al. dosed patients with 25–50 mg/kg/day of CBD for 12 weeks [31]. A clinical trial undertaken by Thiele et al. used a highly purified CBD oral solution (Epidyolex 100 mg/mL), which was titrated from 2.5 to 20 mg/kg per day over two weeks depending on the patient tolerance to treatment [37].

Comparing these studies, it is evident that there is no fixed dosage regime for the application of CBD in epilepsy, being CBD still in the early stages of development and research, and researchers try to adjust dosages accordingly by taking into account treatment effectiveness for the treatment of chronic conditions, toxicity, adverse effects, and possible withdrawal outcomes that patients could experience at the provided dosages.

## 3. Factors limiting the therapeutic usage of CBD in epilepsy

The usage of CBD as a treatment for epilepsy has recently entered the medical industry. With the recent legalisation of growing cannabis for medicinal and scientific purposes in over 20 countries, new research and studies are emerging targeting numerous flaws and limitations of CBD. Despite the multiple therapeutic benefits of CBD in various diseases and conditions, there are a variety of limitations, potentially limiting the exploitation of CBD as a pharmaceutical treatment. Due to being an emerging treatment currently being tested in epilepsy and other neurological diseases and disorders, the reports of adverse effects and toxicity of cannabidiol at different dosages and dosage forms are continually increasing. Adverse effects include convulsions, somnolence, fatigue, lethargy, gait disturbance, *status epilepticus*, and sedation [31]. Unforeseen drug-drug interactions (DDI), adverse effects, and other limitations have led to numerous researchers testing the safety and efficacy of CBD in treating a wide variety of conditions and diseases.

DDI of CBD are still being studied. CBD is extensively metabolised by the cytochrome enzymes CYP3A4 and CYP2C19 in the liver [38]. CBD is shown to inhibit CYP2D6, CYP2C9, CYP2C19 and potentially inhibit members of the CYP3 family. This leads to pharmacological metabolic DDI with numerous drugs. Notable DDI are with warfarin sodium (increased serum levels of warfarin through inhibition of CYP2C9 metabolism, resulting in increased patient INR and bleeding), sildenafil (increased risk of myocardial infarction and adverse effects through CYP3A inhibition), and common antiepileptic drugs clobazam, topiramate, rufinamide, zonisamide, eslicarbazepine. The serum levels of these drugs were significantly changed as a result of DDI with CBD [39–41]. CBD has also shown DDI with tricyclic antidepressants such as desipramine and imipramine, where CBD increases the level of these drugs, and therefore their pharmacological effect, through the inhibition of CYP3A4 and CYP2C19 enzymes [38]. Furthermore, CBD interacts with opioid agonists causing additive central nervous system depression. The opioid agonists that interact with CBD include codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, opium, oxycodone, and tapentadol [42]. CBD has also been shown to interact with the following protease inhibitors: amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, and teleprevir. Combination with these drugs causes an increase in serum levels, bioavailability of CBD, and adverse effects [43,44]. The various metabolic DDI involving CBD are summarized in Table 1.

The following literature underlines the critical limitations of cannabidiol in both paediatric and adult patients. A systematic review by Huestis et al., in 2019 found that CBD is not risk-free [46]. Evaluating articles gathered from a search on PubMed, EMBASE and CENTRAL, an adept understanding of CBD's toxicology, safety, complications, adverse reactions/events, and side effects was attained. The review found that testing CBD on animals and humans produced similar findings. The main areas of concern were how CBD could affect the development and mortality of the embryo-foetal, cause central nervous system inhibition and neurotoxicity, hepatocellular injuries, spermatogenesis reduction, hypotension, organ weight alterations, and alterations to the male reproductive system [46]. Similarly, long-term CBD safety and efficacy in children and adults with intractable epilepsies were challenged in a clinical study by Szaflarski et al., who found that 24% of patients withdrew from this study due to the failed efficacy of CBD whilst 88% experienced severe adverse effects. The main adverse effect reported was uncontrollable convulsions [30]. A clinical trial run by Devinsky et al. from 2016 to 2018 focused on CBD's efficacy in treating Dravet syndrome and Lennox-Gastaut syndrome. The treatment of these two genetic epileptic conditions was an open-label clinical trial of 214 patients aged 1–30 years who met the requirement of having either Dravet syndrome or Lennox-Gastaut syndrome. The patients also had to have treatment-resistant epilepsy [31]. Treatment consisted of 25–50 mg/kg/day of CBD for 12 weeks. One hundred sixty-two patients in this trial reported diverse adverse effects. The reported adverse effects were somnolence, fatigue, lethargy, gait disturbance, sedation, and convulsions. Thirty percent of these patients also reported severe adverse events [31]. The most reported severe adverse event was *status epilepticus*. Another drawback of using CBD in this study was the moderate to significant increase in transaminases. Seven percent of patients had slightly elevated liver function tests, and one patient was considered hepatotoxic, resulting in CBD withdrawal [31].

A 2020 trial by Wang et al. investigated the effects of disposition in oral cannabidiol-rich cannabis extracts on paediatric epileptic patients. Despite this study's helpful information, a few limitations are apparent. One significant drawback was the lack of authorised CBD cannabis extract products at the time of the study. This led to increased variability in the pharmacokinetic estimates because of the use of natural extracts used by the general population [29]. While this method had practical application, it also made it difficult to standardise items and dosages, limiting the thorough assessment of all pharmacokinetic characteristics [29]. The legal restrictions on cannabis product use on college campuses also made it challenging to establish standardisation. Even though the study examined patients who used CBD products with laboratory-verified content, potential drug interactions may have been hidden due to the low CBD dose and the small population size of 29 paediatric patients who also received concurrent anticonvulsants [29]. As CBD is metabolised by CYP enzymes, especially CYP3A4 and CYP2C19, medication interactions were a concern as CBD concentrations could be altered [29]. Significant interactions were observed between CBD and other medications, such as clobazam, rufinamide, and topiramate. This ultimately raised the concentration of clobazam and

**Table 1**
Drug-drug interactions of CBD occurring on metabolic enzymes.

| Enzyme | Affected Medication Examples | Effect of the interaction | References |
|---|---|---|---|
| **CYP2C8/9 substrates** | Montelukast, celecoxib, rosuvastatin, naproxen, valsartan, warfarin, buprenorphine | CBD Increases the side effects of drugs and inhibits/reduces function of the drugs. | [44,45] |
| **CYP3A4 inhibitors** | Protease inhibitors, loperamide, ketoconazole, amiodarone, verapamil, imatinib, cimetidine, nefazodone | Increases the bioavailability of CBD and increases the risk of adverse effects. | [44] |
| **CYP3A4 inducers** | Topiramate, rifampicin, enzalutamide, phenytoin, carbamazepine, pioglitazone | CBD bioavailability and effectiveness is decreased. | |
| **CYP3A4 substrates** | Opioids, antipsychotics, Calcium channel blockers, benzodiazepines, antidepressants, immunosuppressants | CBD increases the risk of experiencing drug-related side effects. | |
| **CYP2C19 inhibitors** | Fluoxetine, proton pump inhibitors, ketoconazole, clopidogrel, fluconazole, fluvoxamine | Increases the bioavailability of CBD and increases the risk of adverse effects. | |
| **CYP2C19 substrates** | Clopidogrel, propranolol, antidepressants, antiepileptics, warfarin, proton pump inhibitors | CBD Increases the side effects of drugs and chances for adverse events. | |
| **CYP2C19 inducers** | St. John's Wort, rifamprin, carbamazepine, phenobarbital, phenytoin | CBD bioavailability and effectiveness is decreased. | |

may have exacerbated the sedative effect [29]. The need to exercise caution while using CBD extracts with anticonvulsants must therefore be emphasised, according to Wang et al.'s study.

Another limitation was the possible interference with CBD metabolism when supplied with delta-9- tetrahydrocannabinol (THC). Even though some study participants received detectable THC doses, prior research has shown that CBD and THC have little effect on each other's metabolisms [47]. Due to the lack of initial CBD metabolite concentrations at the time of blood collection, the study could not correctly assess this. The study's analytical strategy, which used LC/MS/MS, allowed for the separation of 7-CBD-COOH from 6a- and 6β-hydroxyl CBD, setting it apart from other studies on CBD products with FDA approval [29]. This method did not, however, deal with the study's inability to gather crucial pharmacokinetic data, including AUC, apparent clearance, and terminal elimination half-life. The changes in dosing and participants further increased the uncertainty of these estimates. Additionally, because of the short follow-up period in the study, it was impossible to assess the bioavailability from intravenous dosage and other crucial pharmacokinetic parameters [29].

Similarities between these studies can be identified and compared. It was showcased that CBD is currently limited in its approach to treating medical conditions, with patients receiving varying dose regimens, no set therapeutic doses, numerous present and unseen drug-to-drug interactions and varying adverse events. In particular, the serious adverse effects experienced by patients with treatment-resistant and genetic epilepsy outweigh the benefits of the treatment and significantly highlight the importance of understanding the properties of CBD. Despite these limitations, numerous studies have been conducted and evaluated to delve into the parameters of CBD and how CBD is vital to the future of epilepsy treatment in paediatric and adult patients.

## 4. Comparison of the pharmacokinetics of CBD between adult and paediatric populations

Studies have found that younger patients have greater seizure improvement rates in comparison to older patients upon treatment with CBD. A study using a rating scale of seizure reduction, 0–49%, 50–75%, and 75–99%, found that patients younger than ten years at the onset of treatment had a more significant improvement rate of 78% compared to older patients at 48% [48]. A study compared the pharmacokinetic parameters of 45 drugs in children and adults and found that across the board, CBD had larger volumes of distribution in children. This is due to the aging process resulting in increased body fat, reduced lean body mass and total body water. Increased body fat increases the volume of distribution for highly lipophilic drugs, resulting in more significant elimination half-lives [49]. Cannabidiol is highly lipophilic and is rapidly distributed throughout the body in compartments such as the brain, adipose tissue, and other organs [50]. Lipophilic drugs have a greater volume of distribution in infants (12 months) at compared with older children (15 years old) [51]. This is because the distribution of drugs is dependent on body composition. Therefore, it has been found that CBD has a larger volume of distribution in children compared to older adults. This is due to increased levels of CBD distributed into peripheral tissues due to the low body mass, and this is in accordance with the fact that younger children have more significant seizure reduction compared to older patients.

The effect of age on the efficacy of CBD in treating adult and paediatric epileptic patients was investigated. Various studies confirm the efficacy in the treatment of epileptic patients, yet the majority of the results indicate a much more effective success rate whilst treating the paediatric population [52]. Raucci et al. discussed the success rate of CBD treatment for epilepsy, which is indicated as a 50% reduction rate in seizures in approximately 30–40% of patients [53]. Fasinu et al. conducted treatment on 214 patients between the ages of 1–30. After 12 weeks of testing, 37% of the patients showed a reduction in seizures [54]. Based on the evidence analysed from various articles and research papers, it has been suspected that treating epilepsy using CBD has more successful results in paediatric patients [53].

### 4.1. Absorption

THC is the main active principle that is most studied in cannabis, and it currently represents the most popular cannabis formulations on the market, including smoking, oral THC, rectal THC and topical THC (creams, balms and patches). There is not much research on CBD or how individuals can use CBD. The most common route of administration of CBD consists in smoking and oral administration through capsules, edibles, and liquid forms. With the different consumption methods, differences arise within the duration and onset of action due to their pharmacokinetic profile [55].

While smoking is the preferred route of administration by many, medicinal cannabis for epilepsy is mainly administered through oral administration – capsules, oils, or edibles. The advantage of the oral route is the period of action compared to smoking/vaporising, which has a faster onset but shorter duration. Cannabinol (CBN), a compound that has newly surfaced as an assuring treatment for epilepsy, holds antiepileptic characteristics, which can be likely due to the indirect activation of the CB1 and CB2 receptors in the endocannabinoid system [56]. Furthermore, understanding how the bioavailability and absorption of CBN for treating epilepsy differ between paediatrics and adults will be critical for developing safe and effective dosage regimes across age groups.

Various fundamental pharmacokinetic indicators establish that oral CBN formulations absorb faster and have higher bioavailability in paediatric populations when compared to adults [24]. A study administering CBD in paediatric patients with refactored epilepsy found a higher mean $C_{max}$ of 9.1 ng/mL/mg/kg/d compared to 4.1 ng/mL/mg/kg/d in adults. In addition, the time to reach $C_{max}$ ($T_{max}$) was 3.2h (1.9 ± 6.2) in children, which was similarly found in the results for adults [57]. These findings indicate a more rapid absorption to a higher peak concentration

in children following oral ingestion.

Pharmacokinetic studies also reveal differences between different factors affecting absorption. However, insufficient studies indicated the effect of absorption with age ranges, and factors such as diet intake were observed to change the AUC of CBD exposure. In one study, the AUC for oral CBD in adults with refractory epilepsy when in a fed state resulted in a significant difference of AUC - 8374 (34.1) ng/h/mL - when compared to adults in a fasted state resulting with an AUC of 1987 (53.6) ng/h/mL [58]. In the study conducted by Wheless et al., the AUC of paediatric patients with epilepsy varied in comparison with studies of single-dose administration, being 473.5, 914.5 (126.3) AUC ng/h/mL to multiple dose administration over ten days, resulting in 2108, 2708 (66.1) AUC, ng/h/mL; giving an insight into total systemic exposure with prolonged use.

In summary, cannabinoid absorption varies amongst individuals, even within the same age range. Variability is influenced by factors such as product formulation and development. With many differences between children's and adults' pharmacokinetic profiles, insufficient studies show that absorption is reduced or increased in children compared to adults. Furthermore, current research suggests that other pharmacokinetic parameters like distribution may influence the efficacy and efficiency of cannabidiol and will be discussed and compared.

### 4.2. Distribution

The movement of the drug from the bloodstream to the intended site of action differs based on the drug's physicochemical properties and the distribution volume. Distribution aims to achieve the effective drug concentration required for the site of action [22]. Specifically, the volume of distribution is a pharmacokinetic parameter that describes the apparent amount of a drug within the body divided by the plasma drug concentration. The human body comprises several compartments represented by extracellular, intracellular, plasma, tissues, and organs. The volume of distribution attempts to evaluate the volume in each of these theoretical compartments [22]. A low volume of distribution signifies that the drug is primarily located within the bloodstream. The molecules that are generally huge, charged, protein-bound, and unable to diffuse. A high volume of distribution indicates that the drug is extensively distributed throughout the body's organs and tissues. Such molecules are generally smaller due to their distribution into extracellular fluid [22]. Cannabidiol is highly lipophilic and has a high volume of distribution, spreading rapidly into highly vascularised organs such as the lung, heart, brain, and liver. The rate of distribution of cannabidiol can also be affected by history of cannabis use, genetics, gender, body size and composition, disease state, diet, and microbiome composition [9]. A study investigating the pharmacokinetic properties of CBD in the treatment of epilepsy found that there was a large volume of distribution, ranging from 20,963L to 42,849L [57]. In addition, a study investigating the pharmacokinetics of cannabidiol in humans also determined a mean volume of distribution of 2520L [59]. There is limited information regarding cannabidiol distribution comparing adults and children. Following the distribution of the drug, other factors, such as metabolism, should be investigated to determine its true effect on the body.

### 4.3. Metabolism

In treating epileptic patients, cannabinoids are generally metabolised in the liver. A variety of enzyme inhibition is reliable for cannabinoid metabolism, more specifically, the CYP450 enzymes [60]. These are membrane-bound hemoproteins that specifically function in cellular metabolism homeostasis and metabolise xenobiotics within the human body. Various CYP enzymes metabolise CBD which include CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 [61]. CYP3A4 and CYP2C19 are the main enzymes that work in the metabolism of CBD in the human body. Therefore, they represent the main potential sites of metabolism drug-drug interactions involving CBD [29]. 7-hydroxy-CBD is the active metabolite of cannabidiol, and it is generated by the enzyme CYP2C19. Metabolic pathways follow hydroxylation, and oxidation at C-7 occurs within the pentyl and propenyl groups [62] As shown in Fig. 3, the CYP2C19 enzyme is responsible for producing a metabolite called 7-OH-CBD (7-hydroxy-CBD), which is pharmacologically active and will then subsequently alter into the inactive metabolite 7-COOH-CBD (7-carboxy-CBD).

As initially indicated, CBD is primarily metabolised in the liver; therefore, if there are any functional changes in the liver, this will impact CBD pharmacokinetics. Uridine diphosphate glucuronidase (UGT) enzymes UGT1A7, UGT1A9, and UGT2B7 are also involved in CBD metabolism. UGT1A9 and UGT2B7 then convert these metabolites into glucuronide conjugates [25].

It has been noted from many sources that there are various interactions between THC and CYP enzymes concerning drug-drug interactions. Evidence of increased metabolism of THC and CBD has been shown through the CYP3A4 inducers where the drugs stimulate the enzyme activity. However, an increase in the THC and CBD levels in the body slows down the metabolism of the enzymes CYP3A4 and CYP2C9 inhibitors, which affects the drugs that inhibit the activity of these enzymes. While THC and CBD have the potential for drug-drug interactions, current research on their inhibition or activation of necessary human CYP enzymes suggests a usually minimal clinical risk [63].

Cytochrome P450 enzymes play a crucial role in the initial stage of metabolising drugs, and reactions are facilitated by the UDP glycosyltransferases [64]. Tetrahydrocannabinol, also known as THC, follows through the step of phase 1 hepatic metabolism through the enzymes CYP2C9 and CYP3A4. As this occurs, THC oxidises from 11-OH-THC to 11-COOH-THC [65]. Phase 1 metabolism of CBD changes the original compound into various metabolites that have increased water solubility, making them easier to remove from the body through urine or bile [66]. These metabolites are generally less potent in terms of their pharmacological activity when compared to CBD. Following phase 1 metabolism, the metabolites can proceed to phase 2 metabolism, where they might engage in conjugation reactions, like glucuronidation, to further boost their water solubility before being excreted.

It has been noted that around 60% of prescription medications such as clarithromycin, itraconazole and ritonavir are also metabolised in the CYP3A4 enzyme. This metabolic pathway shared by various drugs can

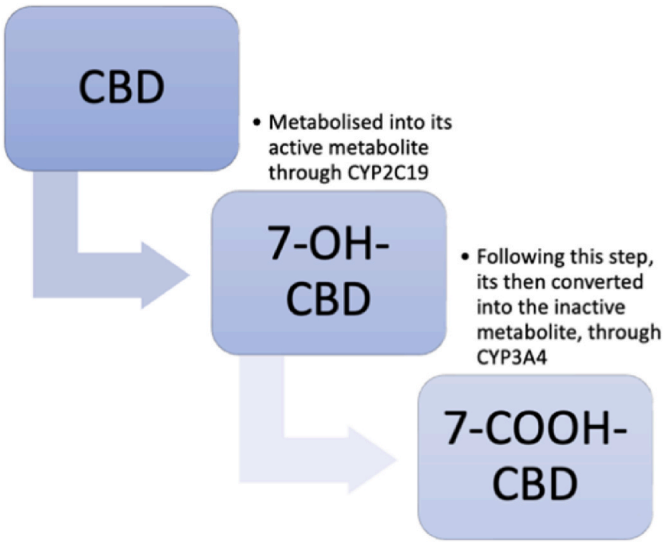



**Fig. 3.** *The principal metabolic pathway of CBD. This figure illustrates the metabolism relation between the active metabolites through the illustrated enzyme and then converted into the inactive metabolite into the other enzyme.* Figure prepared with Microsoft Power Point.

increase levels of CBD if taken together. Combining these prescription drugs with the enzyme CYP3A4 causes delayed CBD breakdown, which can result in greater, therapeutically potent CBD levels for an extended amount of time. Based on various studies, CBD has been determined to inhibit THC's effects and diminish THC's effect on the brain regarding anxiety, memory, and body temperature regulation [38].

### 4.4. Elimination

Cannabidiol is mainly excreted in the stools (>65%) and, to a minor extent, in the urine (~20%) [67]. Approximately 80–90% of the drug is excreted within five days as hydroxylated and carboxylated metabolites [68]. It has been identified that eighteen acidic metabolites of cannabis are present in urine, and most of these metabolites form a conjugate with glucuronic acid, which increases its water solubility. Delta-9-THC is one of the present metabolites and is known to be highly soluble in lipids, which results in tubular re-absorption, therefore leading to low renal excretion of the unchanged drug. Estimates of the elimination half-life and clearance of CBD vary between different studies, as shown in Table 2.

The papers presented show varying results completed with a significant outlier included. Zeine & Teasdale's study shows that the clearance is much higher than the other studies. An issue with some studies is that clearance is sometimes given in L/h or L/kg/h. Although adults and children's studies slightly differed, the main clearance ranges were between 12 and 15L/kg/h. Gherzis' study is an outlier in the research presented. However, it does show that there is still no clear evidence of clearance rates of CBD, as there are many other factors that affect cannabidiol clearance that need to be further investigated. This shows us that age may not be a contributing factor in determining the clearance of CBD. As seen in Tables 2 and it is evident that both adults and children exhibit a large variety regarding half-life. Literature reports range from 8 to 312 h in adults. This is when a frequent user of cannabis is taken into consideration. The study shows that this medication would not be preferred as a long-term treatment because of its increase in half-life parameters after prolonged use. This will keep cannabidiol within the body for extended periods, which could lead to other significant side effects and toxicity [72]. Within paediatrics, we see that half-life ranges from 1 to 33.5 h. Within both age groups, we see a significant range of half-life. This might show that there are other factors affecting the half-life of cannabidiol.

An important limitation of the studies analysed in this section is that none of these studies provides a direct comparison of the pharmacokinetics of CBD in the two patient cohorts considered. Furthermore, the fact that the type of cannabis extract and route of administration employed differed between different studies further complicates the interpretation of the data from these studies. This highlights the necessity to conduct further experimentations to better characterize the pharmacokinetics of CBD across adult and paediatric patients.

## 5. Conclusion and future directions

As a successful anxiolytic, antipsychotic, analgesic, muscle relaxant, and even with neuroprotective, anti-inflammatory, and antioxidant action in both children and adults, CBD has demonstrated promising benefits in terms of its therapeutics and pharmacokinetics. In paediatric and adult populations, CBD has considerably increased the quality of life and decreased the frequency and length of seizures experienced by people with epilepsy. The present work aimed at providing a thorough analysis of the available literature on comparing the effect of CBD in epilepsy among different age groups, specifically focusing on adults and paediatric patients.

The results of the pharmacokinetic studies showed insufficient information and research to demonstrate how age affects absorption. However, it was found that younger individuals display a larger seizure reduction when compared to older patients, likely reflecting a greater rate of CBD distribution. It was also showcased that the therapeutic use of CBD in epilepsy has a higher success rate in paediatric patients in reference to its metabolism. However, age did not affect the clearance of cannabidiol majorly, suggesting that there might be other factors affecting the half-life of cannabidiols through excretion.

Dosing variability across the studies was expected and dependent on the study's aim. With differing severity in epilepsy across individuals, a one-size-fits-all approach may not be ideal, and treating epilepsy with cannabidiol may require specific individual-tailored treatment. Given the currently limited amount of data available, further research is required to understand the cannabidiol compound and its pharmacokinetics. In this context, the field would enormously benefit from a clinical study which involves a direct, standardized comparison of the differences in pharmacokinetics and therapeutic effects of CBD between adult and paediatric populations.

## Data sources

The data and information used to produce this literature review has been sourced from the databases, including PubMed, Medline, Ovid, Scopus, JSTOR, Science Direct, Google Scholar, SpringerLink, ProQuest and Frontiers.

## CRediT authorship contribution statement

**Mohamed Osman:** Writing – review & editing, Writing – original

**Table 2**
Pharmacokinetic studies of CBD.

| Population | Dose | Formulation | Half-life (h) | Clearance (L/kg/h) | Reference |
|---|---|---|---|---|---|
| Adults | – | Inhaled CBD | 18–32 | 57.6–93.6 | [60] |
| 18 adults | 7g daily | Inhaled CBD | Infrequent user: 31.2<br>Frequent User: 120-312 | Men: 14.9 ± 3.7<br>Women: 11.8 ± 3<br>Naïve users: 36<br>Regular users: 60 | [69] |
| 8 Adults | 200 mg | Oral solution (Epidyolex®) | 8.58 | 422L/h | [58] |
| 10 young patients ranging from ages 2-23 | 25 mg | Galenic preparation (decoction) based on Cannabis Sativa inflorescence (FM2) | 1.0 | 7.25 | [70] |
| 5 infants, 9 children, and 6 adolescents | 5 mg/kg<br>10 mg/kg<br>20 mg/kg<br>40 mg/kg<br>20 mg/kg daily for 6 days | Oral solution (INSYS Manufacturing LLC) | 31.3<br>31.3<br>33.5<br>21.6<br>21.6 | –<br>12.1<br>15.3<br>13.2<br>– | [71] |

draft, Visualization, Investigation, Conceptualization. **Jamileh Khalil:** Visualization, Investigation, Conceptualization, Writing – review & editing, Writing – original draft. **Mostafa El-Bahri:** Writing – review & editing, Conceptualization, Investigation, Writing – original draft. **Jamal Swalah Mcdahrou:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Reem Fahda:** Writing – review & editing, Writing – original draft, Conceptualization, Investigation. **Reymin Mustafa:** Writing – original draft, Investigation, Writing – review & editing. **Arthur Ooi:** Writing – review & editing, Conceptualization, Investigation, Writing – original draft. **Marwa Attayee:** Writing – review & editing, Conceptualization, Investigation, Writing – original draft. **Rachelle Catanzariti:** Supervision, Conceptualization, Project administration. **Lisa Pont:** Conceptualization, Project administration, Supervision. **Kylie Williams:** Conceptualization, Project administration, Supervision. **Stewart Yeung:** Project administration, Supervision, Conceptualization. **Kamal Dua:** Project administration, Supervision, Conceptualization. **Gabriele De Rubis:** Project administration, Supervision, Writing – review & editing, Conceptualization. **Raimar Loebenberg:** Conceptualization, Project administration, Supervision, Writing – review & editing.

## Declaration of competing interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that there are no conflicts of interest.

## Data availability

No data was used for the research described in the article.

## References

[1] K.M. Fiest, et al., Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies, Neurology 88 (3) (2017) 296–303.
[2] O. Devinsky, et al., Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders, Epilepsia 55 (6) (2014) 791–802.
[3] O. Devinsky, et al., Epilepsy, Nat Rev Dis Primers 4 (2018) 18024.
[4] W.A. Hauser, E. Beghi, First seizure definitions and worldwide incidence and mortality, Epilepsia 49 (Suppl 1) (2008) 8–12.
[5] C. Begley, et al., The global cost of epilepsy: a systematic review and extrapolation, Epilepsia 63 (4) (2022) 892–903.
[6] S. Matricardi, et al., The latest advances in the pharmacological management of focal epilepsies in children: a narrative review, Expert Rev. Neurother. (2024).
[7] O. Devinsky, et al., Recognizing and preventing epilepsy-related mortality: a call for action, Neurology 86 (8) (2016) 779–786.
[8] S. Zaheer, et al., Epilepsy and cannabis: a literature review, Cureus 10 (9) (2018) e3278.
[9] C.J. Lucas, P. Galettis, J. Schneider, The pharmacokinetics and the pharmacodynamics of cannabinoids, Br. J. Clin. Pharmacol. 84 (11) (2018) 2477–2482.
[10] H.E. Scharfman, The neurobiology of epilepsy, Curr. Neurol. Neurosci. Rep. 7 (4) (2007) 348–354.
[11] E.B. Bromfield, J.E. Cavazos, J.I. Sirven, An introduction to epilepsy, in: E. B. Bromfield, J.E. Cavazos, J.I. Sirven (Eds.), An Introduction to Epilepsy, American Epilepsy Society Copyright © 2006, American Epilepsy Society, West Hartford (CT), 2006.
[12] H. Li, et al., Inclusion complexes of cannabidiol with β-cyclodextrin and its derivative: physicochemical properties, water solubility, and antioxidant activity, J. Mol. Liq. 334 (2021) 116070.
[13] C.E. Stafstrom, L. Carmant, Seizures and epilepsy: an overview for neuroscientists, Cold Spring Harb Perspect Med 5 (6) (2015).
[14] E.M. Ross, et al., Epilepsy in childhood: findings from the national child development study, Br. Med. J. 280 (6209) (1980) 207.
[15] T.L. Ware, et al., Epidemiology and etiology of infantile developmental and epileptic encephalopathies in Tasmania, Epilepsia Open 4 (3) (2019) 504–510.
[16] S. Ali, I.E. Scheffer, L.G. Sadleir, Efficacy of cannabinoids in paediatric epilepsy, Dev. Med. Child Neurol. 61 (1) (2019) 13–18.
[17] C. Gao, et al., Epilepsy in Dravet syndrome—current and future therapeutic opportunities, J. Clin. Med. 12 (7) (2023) 2532.
[18] M. Barker-Haliski, H.S. White, Glutamatergic mechanisms associated with seizures and epilepsy, Cold Spring Harb Perspect Med 5 (8) (2015) a022863.
[19] A. Anwar, et al., Dravet syndrome: an overview, Cureus 11 (6) (2019) e5006.
[20] A. Ge, et al., Seizure triggers in epilepsy patients: a national perspective (S37.002), Neurology 88 (16 Supplement) (2017). S37.002.
[21] L. Grifoni, et al., Promising nanocarriers to enhance solubility and bioavailability of cannabidiol for a plethora of therapeutic opportunities, Molecules 27 (18) (2022) 6070.
[22] S. Grogan, C.V. Preuss, Definition/Introduction, 2023.
[23] K.M. Nelson, et al., The essential medicinal chemistry of cannabidiol (CBD), J. Med. Chem. 63 (21) (2020) 12137–12155.
[24] B. Stella, et al., Cannabinoid formulations and delivery systems: current and future options to treat pain, Drugs 81 (13) (2021) 1513–1557.
[25] I. Ujváry, L. Hanuš, Human metabolites of cannabidiol: a review on their formation, biological activity, and relevance in therapy, Cannabis and Cannabinoid Research 1 (1) (2016) 90–101.
[26] X. Ji, Y. Zeng, J. Wu, The CB2 receptor as a novel therapeutic target for epilepsy treatment, Int. J. Mol. Sci. 22 (16) (2021) 8961.
[27] J. Tchekalarova, et al., *Pharmacological characterization of the cannabinoid receptor 2 agonist, β-caryophyllene on seizure models in mice.* Seizure, European Journal of Epilepsy 57 (2018) 22–26.
[28] F. Shahbazi, et al., Cannabinoids and cannabinoid receptors: the story so far, iScience 23 (7) (2020).
[29] G.S. Wang, et al., Disposition of oral cannabidiol-rich cannabis extracts in children with epilepsy, Clin. Pharmacokinet. 59 (8) (2020) 1005–1012.
[30] J.P. Szaflarski, et al., Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: expanded access program results, Epilepsia 59 (8) (2018) 1540–1548.
[31] O. Devinsky, et al., Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial, Lancet Neurol. 15 (3) (2016) 270–278.
[32] C.J.A. Morgan, et al., Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings, Addict. Behav. 38 (9) (2013) 2433–2436.
[33] L. Yu, et al., A reliable quantitative method for determining CBD content and release from transdermal patches in Franz cells, Phytochem. Anal. 33 (8) (2022) 1257–1265.
[34] C. Larsen, J. Shahinas, Dosage, efficacy and safety of cannabidiol administration in adults: a systematic review of human trials, J. Clin. Med. Res. 12 (3) (2020) 129–141.
[35] I. Kerstin, G. Franjo, An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies, Cannabis and Cannabinoid Research 2 (1) (2017) 139–154.
[36] M.U. Jahngir, M.Q. Ahmad, M. Jahangir, Lennox-gastaut syndrome: in a nutshell, Cureus 10 (8) (2018) e3134.
[37] E. Thiele, et al., Cannabidiol in patients with Lennox-Gastaut syndrome: interim analysis of an open-label extension study, Epilepsia 60 (3) (2019) 419–428.
[38] P. Balachandran, M. Elsohly, K.P. Hill, Cannabidiol interactions with medications, illicit substances, and alcohol: a comprehensive review, J. Gen. Intern. Med. 36 (7) (2021) 2074–2084.
[39] T.E. Gaston, et al., Interactions between cannabidiol and commonly used antiepileptic drugs, Epilepsia 58 (9) (2017) 1586–1592.
[40] G.W. Brown, et al., 9-tetrahydrocannabinol dose increase leads to warfarin drug interaction and elevated INR, J. Am. Pharmaceut. Assoc. 61 (1) (2021) e57–e60.
[41] A.L. McLeod, C.J. McKenna, D.B. Northridge, Myocardial infarction following the combined recreational use of viagra® and cannabis, Clin. Cardiol. 25 (3) (2002) 133–134.
[42] J. Desroches, P. Beaulieu, Opioids and cannabinoids interactions: involvement in pain management, Curr. Drug Targets 11 (4) (2010) 462–473.
[43] G.M. Keating, Delta-9-Tetrahydrocannabinol/Cannabidiol oromucosal spray (Sativex®): a review in multiple sclerosis-related spasticity, Drugs 77 (5) (2017) 563–574.
[44] J.D. Brown, A.G. Winterstein, Potential adverse drug events and drug–drug interactions with medical and consumer cannabidiol (CBD) use, J. Clin. Med. 8 (7) (2019) 989.
[45] R.T. Smith, S.A. Gruber, Contemplating cannabis? The complex relationship between cannabinoids and hepatic metabolism resulting in the potential for drug-drug interactions, Front. Psychiatr. (2023) 13.
[46] A.M. Huestis, et al., Cannabidiol adverse effects and toxicity, Curr. Neuropharmacol. 17 (10) (2019) 974–989.
[47] H.R. Ross, I. Napier, M. Connor, Inhibition of recombinant human T-type calcium channels by $\delta^9$-tetrahydrocannabinol and cannabidiol *, J. Biol. Chem. 283 (23) (2008) 16124–16134.
[48] M. Hausman-Kedem, S. Menascu, U. Kramer, Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents – An observational, longitudinal study, Brain Dev. 40 (7) (2018) 544–551.
[49] A.A. Mangoni, S.H.D. Jackson, Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications, Br. J. Clin. Pharmacol. 57 (1) (2004) 6–14.
[50] S. Chayasirisobhon, Mechanisms of action and pharmacokinetics of cannabis, Perm. J. 25 (1) (2021) 1–3.
[51] H.K. Batchelor, J.F. Marriott, Paediatric pharmacokinetics: key considerations, Br. J. Clin. Pharmacol. 79 (3) (2015) 395–404.
[52] S. Silvestro, et al., Use of cannabidiol in the treatment of epilepsy: efficacy and security in clinical trials, Molecules 24 (8) (2019) 1459.
[53] U. Raucci, et al., Cannabidiol treatment for refractory epilepsies in pediatrics, Front. Pharmacol. 11 (2020).
[54] P.S. Fasinu, et al., *Current Status and Prospects for cannabidiol Preparations as new therapeutic agents.* Pharmacotherapy, The Journal of Human Pharmacology and Drug Therapy 36 (7) (2016) 781–796.
[55] K. O'Brien, P. Blair, Routes of administration, pharmacokinetics and safety of medicinal cannabis, in: K. O'Brien, P. Blair (Eds.), Medicinal Cannabis and CBD in Mental Healthcare, Springer International Publishing, Cham, 2021, pp. 513–557.

[56] S. Chayasirisobhon, Cannabis and neuropsychiatric disorders: an updated review, Acta Neurol. Taiwan 28 (2) (2019) 27–39.
[57] A. Morano, et al., Cannabinoids in the treatment of epilepsy: current status and future prospects, Neuropsychiatric Dis. Treat. 16 (2020) 381–396.
[58] L. Taylor, et al., A phase 1, open-label, parallel-group, single-dose trial of the pharmacokinetics and safety of cannabidiol (CBD) in subjects with mild to severe hepatic impairment, J. Clin. Pharmacol. 59 (8) (2019) 1110–1119.
[59] S.A. Millar, et al., A systematic review on the pharmacokinetics of cannabidiol in humans, Front. Pharmacol. 9 (2018).
[60] M. Pattabhiramaiah, S. Mallikarjunaiah, Medical cannabis in the treatment of epilepsy, in: R.R. Zeine, B.W. Teasdale (Eds.), Medical Cannabis and the Effects of Cannabinoids on Fighting Cancer, Multiple Sclerosis, Epilepsy, Parkinson's, and Other Neurodegenerative Diseases, IGI Global, Hershey, PA, USA, 2023, pp. 103–118.
[61] P. Schaiquevich, et al., Clinical pharmacology of cannabidiol in refractory epilepsy, Farm. Hosp. 44 (5) (2020) 222–229.
[62] E. Perucca, Cannabinoids in the treatment of epilepsy: hard evidence at last? J Epilepsy Res 7 (2) (2017) 61–76.
[63] D. Amaral Silva, et al., Phytocannabinoid drug-drug interactions and their clinical implications, Pharmacol. Therapeut. 215 (2020) 107621.
[64] A. Zöllner, et al., Production of human phase 1 and 2 metabolites by whole-cell biotransformation with recombinant microbes, Bioanalysis 2 (7) (2010) 1277–1290.
[65] M. Babayeva, Z.G. Loewy, Cannabis pharmacogenomics: a path to personalized medicine, Curr. Issues Mol. Biol. 45 (4) (2023) 3479–3514.
[66] S. Phang-Lyn, V.A. Llerena, Biochemistry, Biotransformation, 2019.
[67] E.L. Karschner, et al., Implications of plasma Delta9-tetrahydrocannabinol, 11-hydroxy-THC, and 11-nor-9-carboxy-THC concentrations in chronic cannabis smokers, J. Anal. Toxicol. 33 (8) (2009) 469–477.
[68] J.P. Goullé, E. Saussereau, C. Lacroix, [Delta-9-tetrahydrocannabinol pharmacokinetics], Ann. Pharm. Fr. 66 (4) (2008) 232–244.
[69] P. Sharma, P. Murthy, M.M. Bharath, Chemistry, metabolism, and toxicology of cannabis: clinical implications, Iran. J. Psychiatry 7 (4) (2012) 149–156.
[70] M. Gherzi, et al., Safety and pharmacokinetics of medical cannabis preparation in a monocentric series of young patients with drug resistant epilepsy, Compl. Ther. Med. 51 (2020).
[71] J.W. Wheless, et al., Pharmacokinetics and tolerability of multiple doses of pharmaceutical-grade synthetic cannabidiol in pediatric patients with treatment-resistant epilepsy, CNS Drugs 33 (6) (2019) 593–604.
[72] J. Gingrich, et al., Review of the oral toxicity of cannabidiol (CBD), Food Chem. Toxicol. 176 (2023) 113799.