WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Evaluating the Efficacy of Cannabinoids in Epilepsy: A Critical Examination of Hard Evidence

Charisse Jean Pepito[1], Princess Charlotte Cheryl Plaza[1], Margaret Gayle Rallos[1], Nicole Andrea Ranoco[1], Rosie Rosal[1], Frances Senarillos[1], Kent Niel Taclob[1], Jacqueline Abiso-Padilla[2]

[1,2]San Pedro College, Davao City, Philippines
DOI: https://doi.org/10.55248/gengpi.4.1223.123550

A B S T R A C T

Epilepsy, a prevalent neurological disorder, affects one-third of individuals with seizures resistant to standard antiepileptic drugs. *Cannabis sativa*, a plant that is reportedly used for seizure treatment, contains non-psychoactive cannabidiol (CBD) and psychoactive Δ9-tetrahydrocannabinol (THC). Although anecdotal accounts point to favorable results, there are insufficient reliable human data. This research examines the pharmacological basis of *cannabis sativa*, its anti-seizure benefits, centered around the effects of THC and CBD. This also covers the safety profile of cannabis, answering issues with safe usage and negative effects. Methodologically, clinical trials and systematic reviews from databases were examined. Since an imbalance in neural impulses causes epilepsy, treating it can be difficult. Due to the drawbacks of traditional antiepileptic medications, there is interest in complementary therapies like cannabis-based medicine. Epilepsy results from an imbalance in neuronal impulses, making its treatment challenging. Conventional antiepileptic drugs have limitations, leading to interest in alternative treatments, including cannabis-based therapies. CBD interacts with adenosine, TRPV1 receptors, and GPR55 receptors, potentially reducing seizures. Clinical evidence supports CBD's efficacy in managing seizures, especially in Dravet syndrome and Lennox-Gastaut syndrome. THC, the psychoactive component, has analgesic effects. The review underscores the importance of thorough studies to establish cannabinoids, particularly CBD, as safe and effective options for epilepsy treatment, acknowledging their potential to revolutionize seizure control and improve patients' quality of life.

Keywords: Epilepsy, Cannabinoid, Cannabis, THC, CBD, Cannabidiol, Δ9-tetrahydrocannabinol

1. Introduction

Epilepsy is recognized as a prevalent non-communicable neurological disease. It has been observed that standard antiepileptic drugs fail to control seizures in approximately one-third of individuals with epilepsy[1]. New pharmacological treatments have been the main focus of clinical studies for medically refractory epilepsy, yet many people with medication-resistant epilepsy continue to experience uncontrollable seizures.[2]. There have been significant claims of using cannabis products to treat epilepsy and other medical disorders over the years. While anecdotal reports have suggested positive outcomes, a lack of robust human data supports their efficacy[3].

The historical use of the cannabis plant, *Cannabis sativa*, for seizure treatment dates back to ancient times[2]. The two main cannabinoids obtained from cannabis are the non-psychoactive cannabidiol (CBD) and the psychoactive Δ9-tetrahydrocannabinol (THC)[4]. CBD, considered safer and more effective in seizure management, is preferred due to its reduced adverse psychotropic effects. Current studies have increased to investigate the pharmacological future use of different cannabis compounds as AEDs, or anti-epileptic drugs, including double-blinded, placebo-controlled trials[5]. The main chemical components of cannabis have been found and synthesized throughout the past fifty years. Both Δ9-THC and CBD components have demonstrated the ability to prevent seizures and lower death in tolerable and low-toxic animal models[3,4]. Despite their structural similarity, these cannabinoids in pharmacology and mechanisms for exerting anticonvulsant effects focus on their potential anticonvulsant and neuroprotective properties. Although the precise mechanisms of how cannabinoids interact with the brain to diminish seizures are not fully understood, research suggests that CBD may regulate neuronal excitability and inflammation[3-5].

This review investigates the pharmacological basis of cannabinoid anti-seizure properties, focusing on its non-psychoactive components. Furthermore, the intention is to critically analyze the increasing amount of data demonstrating the efficacy of cannabinoid compounds in addressing various seizure types and epilepsy syndromes.

2. Methods

This review compares the safety and effectiveness of cannabinoids as a management for epilepsy problems using systematic reviews and clinical trials from the databases MEDLINE (PubMed), ResearchGate, and Google Scholar. The researchers evaluated article titles and abstracts using search engines

to determine if they met the inclusion requirements for this review. The thorough approach of the investigation is to highlight the possible benefits of using alternative cannabinoid therapies for epilepsy.

3. Mechanisms of Epilepsy

Epilepsy, a prevalent chronic condition, involves recurrent and unexpected seizures due to an imbalance between the electrical impulses that stimulate and inhibit neurons[5]. This imbalance may result from altered energy metabolism, disrupted ion balance, or changes in receptor function and neurotransmitter activity[6].

The variety of methods in which the normal nervous system regulates this equilibrium makes the existence of several systems unsurprising. On the other hand, since seizures are usually a result of a malfunctioning neurological system, it is more challenging to comprehend seizures in the brain of an epileptic[7,8]. Sudden epileptic activity can result from increased excitatory signals, decreased inhibitory signals, or a combination. Studies employing medications to increase inhibition or decrease excitation have demonstrated an imbalance between these signals, which results in seizures in healthy brain tissue. Toxic exposures, such as stimulating receptors by domoic acid or suppressing inhibitory receptors by theophylline, cause this imbalance. This imbalance can cause recurrent seizures that are difficult to treat medically, even in otherwise healthy people[9,10].

Burst activity can be prevented from spreading by inhibitory neurons creating a zone of inhibition and disregarding hyperpolarization. A variety of methods facilitates adequate activation of nearby neurons[10]. Presynaptic terminals accumulate calcium ions as a result of repetitive discharges;2) extracellular K+ rises, which tends to blunt the magnitude of hyperpolarizing outward K+ currents, depolarizing nearby neurons; and 3) depolarization triggers the activation of the NMDA subtype of the excitatory amino acid receptor, leading to an influx of Ca++ and enhanced neuronal activity[6,7].

Extending on the imbalance between excitatory and inhibitory conductances is crucial for understanding this illness. In those with this syndrome, continuous activity rather than sudden exposure is what typically causes seizures. Unlike acute seizures, those in chronic epilepsy are typically infrequent, approximately one percent of the total brain activity, with the exception of severe encephalopathies associated with epilepsy. Furthermore, the timing of these seizures is unpredictable, emphasizing the need for a comprehensive understanding of the underlying imbalance[10,11]. The fact that the etiology of epilepsy usually does not support this kind of imbalance hampers the implementation of a hypothesis of imbalanced inhibition and excitation. Sometimes, mutations that cause inhibitory conductances to lose function are found due to causative changes in the genetic etiology of hereditary epilepsies[12]. Nonetheless, several excitatory conductances also have mutations that cause a loss of function[13]. The bulk of causative mutations result in the loss of gene function without directly changing the ratio of excitation to inhibition[13,14].

3.1 Epilepsy and Its Conventional Treatment

3.1.1 Types of Seizures

It is crucial to identify the seizure type to tailor the diagnostic approach to a specific cause, select the correct treatment plan, conduct thorough research involving clinical and EEG phenotypes, and provide important prognosis information[15]. Various seizure types show characteristic behavioral alterations and electrophysiological abnormalities usually discernible in scalp electroencephalogram (EEG) recordings[16]. A single seizure does not always indicate epilepsy; rather, a seizure is a transient disruption of brain function[17]. About 10% of adult individuals will, at any moment in their lives, suffer a seizure, with durations ranging from a few seconds to a few minutes. A seizure follows a discernible pattern with a clear beginning, middle, and end. Patients and medical personnel may not immediately notice certain signs or symptoms. These signs include convulsions (uncontrolled shaking), loss of consciousness, blank staring, limb-jerking motions, or lip-smacking, right away[17,18].

3.1.1.A. Partial (Focal) Seizures

A specific body region is often the only one affected, at least initially, by partial seizures, which are limited to distinct parts of the cerebral cortex. On the other hand, diffuse brain areas are where generalized seizures are observed[18].

A) **Simple partial,** although they don't seem to impact consciousness directly, simple partial seizures can cause motor, sensory, autonomic, or mental symptoms. Vision, balance, autonomic function, hearing, smell, and physical sensations like paresthesias or tingling may all change and suggest the existence of these seizures[15].

B) **Complex partial,** there is a localized seizure activity that causes a temporary impairment of consciousness. A generalized seizure, which is typically characterized by tonic-clonic movements, can result from partial seizures that intensify to affect both cerebral hemispheres[19,20].

3.1.1.B. Primarily (Generalized) Seizures

Both cerebral hemispheres can cause generalized seizures. The hallmark of absence seizures, also known as petit mal, is abrupt, fleeting unconsciousness combined with maintaining a posture. Usually, the seizure lasts a few seconds; postictal disorientation does not occur, and consciousness returns as quickly as lost[16].

A) Atypical Absence Seizures Clinically and electrophysiologically, atypical absence seizures differ from regular seizures in several aspects. For instance, the beginning and end of the loss of consciousness are often less sudden and last longer[16,19].

B) **Simple Absence Seizures,** are a type of seizure where a person briefly loses awareness or consciousness. During these seizures, the brain shows an abnormal electrical activity that affects the whole brain. If additional signs are present, it is classified as a complicated absence seizure[19,20].

C) **Atonic Seizures** are brief, one to two-second loss of postural muscular tone. Although consciousness is momentarily compromised, postictal confusion is typically absent [19-21].

D) **Myoclonus seizures** are quick, intense muscular contractions that can affect one or both sides of the body[16].

3.3 Synthetic Treatments

The prescribing physician or healthcare provider must carefully select the appropriate antiepileptic drugs (AEDs) or combination of medications to manage seizures effectively with satisfactory side effects[22,23]. It is recognized that around half of patients can achieve full control of seizures, while an additional 25% may see notable improvement[23]. Given the family history, type of seizure, and severity of abnormalities in the brain, those with epilepsy who receive a new diagnosis are more likely to succeed[23,24].

The decision to begin antiepileptic drug (AED) treatment is influenced by a number of factors, including the risk of recurring seizures, the impact of ongoing seizures, and the advantages and disadvantages of the medicine in preventing additional occurrences[25,27]. The table below shows the kind or type of seizures determines the corresponding approved synthetic AED [7].

Primary Generalized Tonic-Clonic Seizures	**Partial Seizures**	**Absence Seizures**	**Atypical Absence Myoclonic and Atonic Seizures**
First-line agents			
Valproic acid Lamotrigine Topiramate	Carbamazepine Phenytoin Oxcarbazepine Valproic Acid	Valproic Acid Ethosuximide	Valproic acid Lamotrigine Topiramate
Alternative agents			
Zonisamide Phenytoin Carbamazepine Oxcarbazepine Phenobarbital Primidone Felbamate	Levetiracetam Topiramate Tiagabine Zonisamide Gabapentin Phenobarbital Primidone Felbamate Eslicarbazepine Vigabatrin Lacosamide Pregabalin Rufinamide	Lamotrigine Clonazepam	Clonazepam Felbamate

Table 1. Antiepileptic Drugs Approved for the Treatment of Seizures. Adopted from Goldenberg, M. M. (2010)[7]

3.4 Alternative Treatments

Medication, nutritional therapy, and surgical procedures are available for treating epilepsy. Antiepileptic medications (AEDs) can cause long-term problems, including weight gain, skin rashes, and cognitive decline. They can also promote inhibitory processes or reduce excitatory processes[7]. Unfortunately, a sizable portion of people with severe epilepsy do not react well to anti-seizure medications[27]. Roughly one million Americans, or 40% of the epileptic population, still have seizures despite receiving appropriate medication treatment[28].

The majority of Antiepileptic drugs (AEDs) cannot prevent or reverse the underlying pathological processes of epilepsy. This has prompted a never-ending search for novel treatments with increased effectiveness and fewer adverse effects[29].

Furthermore, between 30 and 40 percent of patients usually experience pharmacoresistant or uncontrollable seizures[30]. Often, traditional healers become the initial point of contact in the pursuit of therapy due to their association with the natural form of treatment[31]. The expensive and scarce

nature of traditional AEDs in underdeveloped nations also fuels this tendency[32]. Some medicinal plants have shown promise as cutting-edge, secure therapy alternatives[33,34].

The problem of drug-resistant epilepsy is notable, prompting consideration of alternative treatments, including cannabis-based therapies. Δ9-tetrahydrocannabinol (THC) was frequently the focus of early investigations on cannabinoids effect on seizure management. Nevertheless, THC has few uses because of its psychotropic properties. The focus of recent studies has switched to non-psychoactive substances like cannabidiol (CBD)35].CBD's interaction with certain receptors, ion channels, and neurotransmitter transporters may contribute to its anti-seizure properties[36].

AED researchers express significant apprehension that the currently employed models restrict identifying innovative drugs that operate through familiar physiological mechanisms[37]. This limitation poses challenges in uncovering new therapies with distinct targets, particularly compounds effective against drug-resistant seizures. Various potential targets for epilepsy treatment have been proposed[32].

4. Pharmacokinetics and Mechanism of Action of Cannabinoids

4.1 Cannabidiol

CBD, a natural anticonvulsant, has been discovered to interact with three molecular targets: adenosine transport, TRPV1 receptors, and GPR55 receptors [38]. The effects of endogenous GPR55 agonist LPI are inhibited by CBD's GPR55 antagonistic action[39]. Generating Ca2+ flux in neuronal cell bodies and presynaptic hippocampal CA3-CA1 terminals inhibits pro-excitatory effects[40,41]. CBD also inhibits adenosine transport, which helps regulate calcium levels and reduces the likelihood of seizures [38].

CBD may work by acting on TRP channels, specifically TRPV1, which regulate calcium levels, potentially reducing the likelihood of seizures.The affinity of CBD for TRPV1 and its role as an agonist were identified by Bisogno et al. Additionally, it was also discovered evidence of CBD-induced fast desensitization[42,43]. TRPV1 may play a role in CBD's anticonvulsive action as it has been linked to the onset and progression of several forms of epilepsy[44,45].It has been shown that CBD activates and desensitizes TRPV1 receptors at low dosages in recombinant systems and initiates in vitro experimental models of epileptiform activity[46].

Adenosine, a natural anticonvulsant, can help stop seizures in the brain by stimulating A1 and A2A receptors. While some researchers suggest that activating A2A receptors has an anti-inflammatory effect, no conclusive evidence links neuroinflammation regulation to seizures[47,48]. Due to its special capacity to regulate neuronal excitability on several levels, adenosine homeostasis disruption can impact network excitability.The effects of particular pharmacological therapies and maladaptive changes in adenosine metabolism observed in epilepsy provide two different kinds of evidence that adenosine is involved in seizures[49]. Maladaptive alterations in adenosine metabolism, such as elevated levels of the astroglial enzyme adenosine kinase (ADK), are the main cause of epilepsy[50].

Additionally, CBD may impact the release of TNFα, a substance relevant to epilepsy. However, to completely comprehend CBD's mechanics and therapeutic advantages for epilepsy and other illnesses, more study is necessary[51,52].

4.2 Δ9-tetrahydrocannabinolic acid (Δ9-THC)

Numerous investigations have been conducted into Δ9-THC, the principal psychotropic component found in cannabis. It primarily interacts with the CB1R and CB2R endocannabinoid receptors, acting at low doses as a partial agonist[53,55]. CB1 receptors, predominantly in vital brain regions, regulate neurotransmitter release within central nervous system (CNS) neurons. Through the dynamic regulation of endogenous ligands, including anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), these receptors contribute to the modulation of synaptic plasticity[54].

Activation of CB2 receptors results in immunosuppressive responses, which are mostly seen in immune cells and peripheral organs.While these receptors are minimally distributed in specific CNS neurons, their activation impacts neuronal excitability, particularly in regions such as the brainstem and hippocampus[55]. Δ9-THC not only targets endocannabinoid receptors but also exerts influence on various other receptors and channels, including TRP channels (TRPA1, TRPV2, TRPM8), GPR55, 5-HT3A receptor, PPARγ, opioid receptors, adrenoreceptors, as well as specific types of calcium, potassium, and sodium channels[54,56]. However, the precise effects of Δ9-THC's interaction with these targets in living organisms remain incompletely understood[57].

5. Clinical Evidence of Safety and Efficacy

This article examines the clinical data supporting the use of cannabinoids—more specifically, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in the treatment of epilepsy. Utilizing information from observational studies and randomized controlled trials highlights improvements to the general qualities of life and decreases in seizure frequency. In the study of Senn et al. (2020) the medicinal interest in THC and CBD has grown due to their shown ability to reduce epileptic seizures in several preclinical trials. Neuronal circuits containing the ECS and related ligands and receptors can have their excitability regulated by them[73]. This emphasizes the increased curiosity on THC and CBD as potential therapeutic agents.

5.1 Cannabidiol (CBD)

Devinsky *et al.* (2017) conducted a study on Dravet syndrome and discovered that it greatly decreased the number of seizures experienced by the patients when compared to a placebo. Almost 40% of the participants who received CBD reported a half or greater decrease in seizure frequency[58]. Devinsky *et al.* (2018) discovered additional proof of the efficacy of CBD therapy for Lennox-Gastaut Syndrome, with a significant decrease in drop seizures observed in patients. Moreover, caregivers noticed positive changes in overall health and improving the standard of living for kids who have epilepsy[59]. Thiele *et al.* (2018) conducted a phase 3 trial, which was randomized, double-blind, and placebo-controlled, and demonstrated that CBD medication effectively decreased the occurrence of motor seizures. Interestingly, more than 85% of patients reported an overall improvement in their quality of life, and nearly 5% became seizure-free[60].

Another study done by Gaston et al. (2017) explored potential drug interactions, providing essential insights into the safety profile of CBD when used alongside common antiepileptic drugs, thus addressing concerns related to co-administration. Additionally, improvements in behavior, sleep, and alertness were reported. This is further discussed by Strzelczyk and Schubert-Bast (2021) about the specific drug interactions between CBD and common antiepileptic drugs (AEDs) such as clobazam and valproate which is used in Lennox-Gastaut syndrome (LGS). When coadministered with other antiepileptic drugs (AEDs), potential drug interactions may occur. Patients taking simultaneous clobazam and cannabidiol saw the biggest improvements in seizure control and also saw greater efficacy when compared to a placebo. CBD, a substrate of these enzymes, may experience increased plasma concentrations when coadministered with valproate. This interaction could lead to elevated CBD levels and influence its effects on (LGS)[74]. Both studies have a unique contribution that lies in their emphasis on the safety aspect, fostering a more comprehensive understanding of CBD's place in epilepsy treatment it only not highlights the potential efficacy of cannabis-derived compounds in seizure management but also more refinement and holistic perspective on their role in comprehensive epilepsy care[61].

5.2 Δ9-Tetrahydrocannabinol (THC)

THC, also known as Δ9-Tetrahydrocannabinol,is cannabis' primary psychotropic ingredient. It functions by binding to the central nervous system and brain cannabinoid receptors, causing the inebriating effects commonly associated with marijuana use[3]. Drawing on the research by Reddy and Golub (2016), cannabinoids exert their effects through CB1 and CB2 receptors. The CB1 receptor, primarily responsible for psychoactive effects, sees THC's partial agonist action as a key mediator of its anti-seizure effectiveness[70]. Perruca's study (2017) highlighted Δ9-tetrahydrocannabinolic acid's (THC) anticonvulsant properties in early preclinical investigations without inducing undesirable psychoactive effects. Notably, THC has gained renewed attention in the USA, occasionally being employed for its anti-seizure benefits, potentially offering a more accessible and cost-effective alternative to CBD [35].

Supporting this, Dulgosz et al. (2023) conducted comprehensive animal seizure models affirming THC's antiseizure properties. In their study, they assessed the efficacy of CBD and THC individually, as well as in combination (CBD+THC at a ratio of 15:1) in the maximal electroshock (MES) model in mice. The findings suggest that treatment options for generalized-onset seizures may involve CBD alone or the combination of CBD+THC[71]. However, it was noted that the advantages of combining THC with CBD might be more limited when treating focal-onset seizures[72].

Gaston et al. (2017) stated that Δ9-THC may possess analgesic properties, rendering it advantageous for treating persistent pain syndromes[62]. Due to its antiemetic qualities, it can help reduce nausea and vomiting brought on by some medical procedures, like chemotherapy[63]. A randomized controlled trial (RCT) was carried out by Abrams et al. (2007) to look at the analgesic effects of smoked cannabis on patients with neuropathic pain.The findings suggest that Δ9-THC possesses analgesic properties. The study provided evidence for the analgesic effect of Δ9-THC by showing a substantial decrease in the level of pain in the cannabis group relative to the placebo group[64].

6. Discussion

Epilepsy, characterized by recurrent seizures, poses multifaceted challenges with diverse causes[1]. Cannabinoids, specifically Cannabidiols and Δ9-tetrahydrocannabinol, show promise in epilepsy treatment, primarily for their potential anticonvulsant properties and neuroprotective effects[3-5,38]. CBD-based medication exhibits significant efficacy in reducing seizures, particularly in Dravet syndrome and Lennox–Gastaut syndrome[59]. Seizures, varying in type and duration, require an accurate diagnosis for targeted treatment[22]. Despite advancements, concerns persist about the identification of novel therapies and targets, especially for drug-resistant seizures. Herbal medicines, with their broad spectrum, offer potential avenues, drawing from traditional knowledge[33].

The utility of phytochemicals like CBD (cannabidiol) and THC (Δ9-tetrahydrocannabinol) varies depending on the specific medical conditions they are employed to address[65]. CBD has medicinal benefits without the euphoric symptoms that THC is commonly associated with, it is frequently considered to be the more adaptable and advantageous of the two[66]. CBD, widely acknowledged for its potential therapeutic applications, finds use in treating diverse medical conditions, including epilepsy, anxiety, pain management, and inflammation[62,64]. An essential distinction lies in the fact that CBD does not induce intoxication, making it suitable for patients seeking relief without experiencing the psychoactive high associated with THC[67].

On the other hand, THC, being the psychoactive component in cannabis, is responsible for the euphoric sensation linked to marijuana use[68]. While THC does possess therapeutic properties such as pain relief and appetite stimulation, its psychoactive effects can limit its applicability, particularly for individuals who seek treatment without cognitive impairment[69]. Its anticonvulsant properties have gained attention, potentially offering a more

accessible and cost-effective alternative to CBD. Studies have shown that THC's antiseizure properties can be achieved through CBD alone or in combination with THC[71]. However, the advantages of combining THC with CBD might be limited for focal-onset seizures[72]. Δ9-THC may also possess analgesic properties, making it beneficial for treating persistent pain syndromes and reducing nausea and vomiting caused by medical procedures like chemotherapy[73].

For instance, in the context of epilepsy, CBD has undergone extensive study for its effectiveness in treating medication-resistant epilepsy conditions like Dravet syndrome and Lennox-Gastaut syndrome. Clinical studies have revealed noteworthy reductions in seizure frequency among patients treated with CBD[51,60]. This highlights the potential of CBD as a promising therapeutic agent in managing challenging medical conditions.

7. Conclusion

THC and CBD are two cannabinoids that have demonstrated promise in treating epilepsy because of their neuroprotective and anticonvulsant qualities. CBD is well known for its capacity to lessen seizures, especially in those with Lennox-Gastaut syndrome and Dravet syndrome. Its therapeutic uses are flexible and beneficial for managing a range of illnesses. Although THC, which is well-known for its psychoactive effects, may have anticonvulsant effects, people without cognitive impairment may not be able to benefit from it due to its psychoactive effects. Both THC and CBD may have analgesic effects; however, THC may be able to lessen chronic pain as well as the nausea and vomiting that come with medical procedures. Numerous studies have demonstrated the efficacy of CBD, especially in cases of medication-resistant epilepsy, which emphasizes the substance's promise as a therapeutic agent for the treatment of difficult medical disorders.

The increasing interest in cannabis highlights the necessity for additional study to fully realize their therapeutic potential and establish them as competitive alternatives to existing pharmaceutical options. Even with these encouraging results, the incorporation of cannabis products into treatment is still in its infancy, and more research is needed in several areas, such as the best ways to administer the medicine, how much to take, any possible drug interactions, and patient response biomarkers. The review emphasizes the need for extensive, long-term studies in further investigations and clinical trials to determine cannabinoid-based medicines' long-term efficacy and safety. With the potential to revolutionize seizure control and improve the overall quality of life for patients, this coordinated initiative seeks to establish cannabinoids—in particular, CBD—as durable and dependable choices for the efficient treatment of epilepsy.

Acknowledgments

We want to express our sincere gratitude to Professor Jacqueline Padilla, RPh, MSPharm, our esteemed advisor in the Drug Discovery Laboratory. Professor Padilla's profound expertise and insights have been pivotal in shaping the content of our journal review, ensuring the overall quality of our work. Without her invaluable guidance and unwavering support, the successful completion of this review would not have been possible. She has played a significant and indispensable role in accomplishing this project, and we extend our heartfelt appreciation for her steadfast commitment to enhancing our knowledge in this field.

References

1. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR: Incidence of epilepsy: a systematic review and meta-analysis. Neurology. 2011, 77:1005-1012. 10.1212/WNL.0b013e31822cfc90

2. Kwan P, Schachter SC, Brodie MJ: Drug-resistant epilepsy. N Engl J Med. 2011, 365:919-926.10.1056/NEJMra1004418

3. Rosenberg EC, Tsien RW, Whalley BJ, Devinsky O. Cannabinoids and Epilepsy. Neurotherapeutics. 2015 Oct;12(4):747-68. doi: 10.1007/s13311-015-0375-5. PMID: 26282273; PMCID: PMC4604191. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4604191/

4. Devinsky O, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55:791-802.

5. Rogawski MA. The intrinsic severity hypothesis of pharmacoresistance to antiepileptic drugs. *Epilepsia.* 2013;54(Suppl. 2):33–40. doi: 10.1111/epi.12182.

6. *Mechanisms Behind Epileptic Seizures*. (2020, April 28). News-Medical.net. https://www.news-medical.net/health/Mechanisms-Behind-Epileptic-Seizures.aspx

7. Bromfield, E. B., Cavazos, J. E., & Sirven, J. I. (2006). Basic Mechanisms Underlying Seizures and Epilepsy. In www.ncbi.nlm.nih.gov. American Epilepsy Society. https://www.ncbi.nlm.nih.gov/books/NBK2510/#:~:text=Epilepsy%20can%20result%20from%20processes

8. Scharfman, H. E. (2007). The neurobiology of epilepsy. Current Neurology and Neuroscience Reports, 7(4), 348–354. https://doi.org/10.1007/s11910-007-0053-z

9. Staley, K. (2015). Molecular mechanisms of epilepsy. Nature Neuroscience, 18(3), 367–372. https://doi.org/10.1038/nn.3947

10. Goldensohn ES, Porter RJ, Schwartzkroin PA. The American Epilepsy Society: An historic perspective on 50 years of advances in research. Epilepsia. 1997;38:124–150.

11. Moran, N. F., Poole, K., Bell, G., Solomon, J., Kendall, S., McCarthy, M., McCormick, D., Nashef, L., Sander, J., & Shorvon, S. D. (2004). Epilepsy in the United Kingdom: seizure frequency and severity, anti-epileptic drug utilization and impact on life in 1652 people with epilepsy. Seizure, 13(6), 425–433. https://doi.org/10.1016/j.seizure.2003.10.002

12. Macdonald, R. L., & Kang, J.-Q. (2012). mRNA surveillance and endoplasmic reticulum quality control processes alter biogenesis of mutant GABAAreceptor subunits associated with genetic epilepsies. Epilepsia, 53, 59–70. https://doi.org/10.1111/epi.12035

13. Yu, F. H., Mantegazza, M., Westenbroek, R. E., Robbins, C. A., Kalume, F., Burton, K. A., Spain, W. J., McKnight, G. S., Scheuer, T., & Catterall, W. A. (2006). Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. Nature Neuroscience, 9(9), 1142–1149. https://doi.org/10.1038/nn1754

14. Ran, X., Li, J., Shao, Q., Chen, H., Lin, Z., Sun, Z. S., & Wu, J. (2014). EpilepsyGene: a genetic resource for genes and mutations related to epilepsy. Nucleic Acids Research, 43(D1), D893–D899. https://doi.org/10.1093/nar/gku943

15. Goldenberg, M. M. (2010). Overview of drugs used for epilepsy and seizures: etiology, diagnosis, and treatment. *P & T : A Peer-Reviewed Journal for Formulary Management*, *35*(7), 392–415. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2912003/

16. Bazil CW, Morrell MJ, Pedley TA. Epilepsy. In: Rowland LP, editor. Merritt's Neurology. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 990–1008.

17. Lowenstein DH. Seizures and epilepsy. In: Fauci AS, Kasper DL, Longo DL, editors. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008. pp. 2498–2512. Section 2: Diseases of the Central Nervous System

18. Epilepsy Foundation About epilepsy and seizures. Available at: www.epilepsyfoundation.org/about/statistics.cfm. Accessed December 14, 2023

19. The 2017 ILAE classification of seizure types and the epilepsies: what do people with epilepsy and their caregivers need to know? Brodie MJ, Zuberi SM, Scheffer IE, Fisher RS. Epileptic Disord. 2018;20:77–87.

20. Instruction manual for the ILAE 2017 operational classification of seizure types. Fisher RS, Cross JH, D'Souza C, et al. *Epilepsia*. 2017;58:531–542.

21. Sarmast, S. T., Abdullahi, A. M., & Jahan, N. (2020). Current Classification of Seizures and Epilepsies: Scope, Limitations and Recommendations for Future Action. *Cureus*, *12*(9). https://doi.org/10.7759/cureus.10549

22. Bromfield E.B., Cavazos J.E., Sirven J.I. American Epilepsy Society; 2006. An introduction to epilepsy. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2513/

23. McNamara JO. Drugs effective in the therapy of the epilepsies. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw-Hill; 1999. pp. 461–486.

24. Elwes RDC, Johnson AL, Shorvon SD, Reynolds EH. The prognosis for seizure control in newly diagnosed epilepsy. N Engl J Med. 1984;311:944–947.

25. Stephen LJ, Brodie MJ. Selection of antiepileptic drugs in adults. Neurol Clin. 2009;27:967–992.

26. Scottish Intercollegiate Guidelines Network (SIGN)Guideline No 70. Diagnosis and Management of Epilepsy in Adults Edinburgh, U.K.SIGN; 2003Available at: www.sign.ac.uk. Accessed April 2009

27. Perucca E., Meador K.J. Adverse effects of antiepileptic drugs. Acta Neurol Scand Suppl. 2005;181:30–35.

28. Engel J. What can we do for people with drug-resistant epilepsy? The 2016 Wartenberg Lecture. Neurology. 2016;87:2483–2489.

29. Sriranjini S.J., Sandhya K., Mamta V.S. Ayurveda and botanical drugs for epilepsy: Current evidence and future prospects. . Epilepsy Behav., . 2015;(52Part B):290–296.

30. Shetty A.K., Upadhya D. GABA-ergic cell therapy for epilepsy: Advances, limitations and challenges. Neurosci. Biobehav. Rev. 2016;62:35–47. [http://dx.doi.org/10.1016/j.neubiorev.2015.12. 014].

31. Al Asmi A., Al Maniri A., Al-Farsi Y.M., Burke D.T., Al Asfoor F.M., Al Busaidi I., Al Breiki M.H., Lahiri S., Braidy N., Essa M.M., Al-Adawi S. Types and sociodemographic correlates of complementary and alternative medicine (CAM) use among people with epilepsy in Oman. Epilepsy Behav. 2013;29(2):361–366. [http://dx.doi.org/10.1016/j.yebeh.2013.07.022]. [PMID: 24011398].

32. Sucher N.J., Carles M.C. A pharmacological basis of herbal medicines for epilepsy. 2015.

33. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: . United States. Natl Health Stat Report. 2007. pp. 1–23.

34. Kakooza-Mwesige A. The importance of botanical treatments in traditional societies and challenges in developing countries. 2015.

35. Perucca E. Cannabinoids in the treatment of epilepsy: hard evidence at last? J Epilep Res. 2017;7:61–76

36. Ahuja, A. S. (2019). Cannabis-based treatments as an alternative remedy for epilepsy. *Integrative Medicine Research*, *8*(3), 200–201. https://doi.org/10.1016/j.imr.2019.07.003

37. Brodie M.J. Antiepileptic drug therapy the story so far. Seizure. 2010;19(10):650–655. [http://dx.doi.org/10.1016/j.seizure.2010. 10.027]

38. Gray, R.A. and Whalley, B.J. (2020), The proposed mechanisms of action of CBD in epilepsy. Epileptic Disorders, 22: S10-S15. https://doi.org/10.1684/epd.2020.1135

39. Oka S, Nakajima K, Yamashita A, Kishimoto S, Sugiura T. Identification of GPR55 as a lysophosphatidylinositol receptor. Biochemical and biophysical research communications. 2007 Nov 3;362(4):928-34.

40. Sylantyev S, Jensen TP, Ross RA, Rusakov DA. Cannabinoid-and lysophosphatidylinositol-sensitive receptor GPR55 boosts neurotransmitter release at central synapses. Proceedings of the National Academy of Sciences. 2013 Mar 26;110(13):5193-8

41. Straiker A, Dvorakova M, Zimmowitch A, Mackie K. Cannabidiol inhibits endocannabinoid signaling in autaptic hippocampal neurons. Molecular pharmacology. 2018 Jul 1;94(1):743-8.

42. Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 2001;134:845–52.

43. Ligresti A, Moriello AS, Starowicz K, Matias I, Pisanti S, De Petrocellis L, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther 2006;318:1375–87.

44. Chen CY, Li W, Qu KP, et al. Piperine exerts anti-seizure effects via the TRPV1 receptor in mice. Eur J Pharmacol. 2013;714:288–294.

45. Manna SS, Umathe SN. A possible participation of transient receptor potential vanilloid type 1 channels in the antidepressant effect of fluoxetine. Eur J Pharmacol. 2012;685:81–90.

46. Iannotti FA, Hill CL, Leo A, et al. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. ACS Chem Neurosci.

47. Sebastião AM, Macedo MP, Ribeiro JA. Tonic activation of A2A adenosine receptors unmasks, and of A1 receptors prevents, a facilitatory action of calcitonin gene-related peptide in the rat hippocampus. British journal of pharmacology. 2000 Jan;129(2):374-80.

48. Ribeiro A., Ferraz-de-Paula V., Pinheiro M.L., et al. Cannabidiol, a non-psychotropic plant-derived cannabinoid, decreases inflammation in a murine model of acute lung injury: role for the adenosine A(2A) receptor. Eur J Pharmacol. 678 1-3 2012; 78–85

49. Boison D. The biochemistry and epigenetics of epilepsy: focus on adenosine and glycine. Front Mol Neurosci. 9 2016; 26

50. Weltha L, Reemmer J, Boison D. The role of adenosine in epilepsy. Brain Res Bull 2019; 151: 46–54.

51. Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55:791–802.

52. Rimmerman N, Ben-Hail D, Porat Z, Juknat A, Kozela E, Daniels MP, et al. Direct modulation of the outer mitochondrial membrane channel, voltage-dependent anion channel 1 (VDAC1) by cannabidiol: a novel mechanism for cannabinoid-induced cell death. Cell Death Dis 2013;4:e949.

53. Atakan, Z. (2012). Cannabis, a complex plant: different compounds and different effects on individuals. Therapeutic Advances in Psychopharmacology, 2(6), 241–254. https://doi.org/10.1177/2045125312457586

54. Kendall, D. A., & Yudowski, G. A. (2017). Cannabinoid Receptors in the Central Nervous System: Their Signaling and Roles in Disease. Frontiers in Cellular Neuroscience, 10. https://doi.org/10.3389/fncel.2016.00294

55. Bie, B., Wu, J., Foss, J. F., & Naguib, M. (2018). An overview of the cannabinoid type 2 receptor system and its therapeutic potential. Current Opinion in Anaesthesiology, 31(4), 407–414. https://doi.org/10.1097/aco.0000000000000616

56. Morales, P., Hurst, D. P., & Reggio, P. H. (2017). Molecular targets of the phytocannabinoids: A complex picture. Progress in the Chemistry of Organic Natural Products, 103, 103–131. https://doi.org/10.1007/978-3-319-45541-9_4

57. Martínez, V., Iriondo De-Hond, A., Borrelli, F., Capasso, R., del Castillo, M. D., & Abalo, R. (2020). Cannabidiol and Other Non-Psychoactive Cannabinoids for Prevention and Treatment of Gastrointestinal Disorders: Useful Nutraceuticals? International Journal of Molecular Sciences, 21(9). https://doi.org/10.3390/ijms21093067

58. Devinsky, O., Cross, J. H., Laux, L., Marsh, E., Miller, I., Nabbout, R., & et al (May 25, 2017). Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. New England Journal of Medicine. Retrieved from https://www.nejm.org/doi/full/10.1056/NEJMoa1611618

59. Devinsky, O., Patel, A. D., Cross, J. H., Villanueva, V., Wirrell, E. C., Privitera, M., & et al (May 17, 2018). Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. New England Journal of Medicine. Retrieved from https://www.nejm.org/doi/full/10.1056/NEJMoa1714631

60. Thiele, E. A., Marsh, E. D., French, J. A., Mazurkiewicz-Beldzinska, M., Benbadis, S. R., Joshi, C., & et al (January 24, 2018). Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet, 391(10125), 1085-1096. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30136-3/fulltext

61. Gaston, T. E., Bebin, E. M., Cutter, G. R., & Liu, Y. (06 August 2017). Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia, 58(9), 1586-1592. Retrieved from https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13852

62. Pérez, R., Glaser, T., Villegas, C., Burgos, V., Ulrich, H., & Paz, C. (2022). *Therapeutic Effects of Cannabinoids and Their Applications in COVID-19 Treatment*. *12*(12), 2117–2117. https://doi.org/10.3390/life12122117

63. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy. 2013 Feb;33(2):195-209. doi: 10.1002/phar.1187. PMID: 23386598. https://pubmed.ncbi.nlm.nih.gov/23386598/

64. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007 Feb 13;68(7):515-21. doi: 10.1212/01.wnl.0000253187.66183.9c. PMID: 17296917.

65. National Academies of Sciences, Engineering, and Medicine. (2017, January 12). *Therapeutic Effects of Cannabis and Cannabinoids*. Nih.gov; National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK425767/

66. Bridgeman, M. B., & Abazia, D. T. (2017). Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. *P & T : A Peer-Reviewed Journal for Formulary Management*, *42*(3), 180–188. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5312634/

67. Bergamaschi, M. M., et al. (2011). Safety and side effects of cannabidiol, a Cannabis sativa constituent. Current Drug Safety, 6(4), 237-249.

68. Ng, T., & Gupta, V. (2022). *Tetrahydrocannabinol (THC)*. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK563174/

69. Grotenhermen, F. (2003). Pharmacokinetics and pharmacodynamics of cannabinoids. Clinical Pharmacokinetics, 42(4), 327-360.

70. Reddy, D. S., & Golub, V. M. (2016). The Pharmacological Basis of Cannabis Therapy for Epilepsy. Journal of Pharmacology and Experimental Therapeutics, 357(1), 45–55. https://doi.org/10.1124/jpet.115.230151

71. Dlugosz, L., Zhou, H. Z., Scott, B. W., & Burnham, M. (2023). The effects of cannabidiol and Δ9-tetrahydrocannabinol, alone and in combination, in the maximal electroshock seizure model. Epilepsy Research, 190, 107087. https://doi.org/10.1016/j.eplepsyres.2023.107087

72. Castel-Branco, M. M., Alves, G. L., Figueiredo, I. V., Falcao, A. C., & Caramona, M. M. (2009). The maximal electroshock seizure (MES) model in the preclinical assessment of potential new antiepileptic drugs. Methods and Findings in Experimental and Clinical Pharmacology, 31(2), 101. https://doi.org/10.1358/mf.2009.31.2.1338414

73. Senn, L., Cannazza, G., & Biagini, G. (2020). Receptors and Channels Possibly Mediating the Effects of Phytocannabinoids on Seizures and Epilepsy. *Pharmaceuticals*, *13*(8), 174. https://doi.org/10.3390/ph13080174

74. Strzelczyk, A., & Schubert-Bast, S. (2021). Expanding the Treatment Landscape for Lennox-Gastaut Syndrome: Current and Future Strategies. *CNS Drugs*, *35*(1), 61–83. https://doi.org/10.1007/s40263-020-00784-8