Ind. J. Pharm. Edu. Res., 2024; 58(1):15-20.
https://www.ijper.org

Review Article

Enlightening Pharmacological Mechanisms of Cannabidiol in Epilepsy: A Comprehensive Review on their Neuroprotective Potential

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ABSTRACT

Cannabinoids interact with Cannabinoid Receptors (CBRs) and some related non-cannabinoid transcription factors within neurological and non-neuronal-specific receptors. The current review has covered pharmacological molecular mechanisms during an epileptic attack and provided a beneficial therapeutic approach for the treatment of neurological disorders. CBRs and new targets may be involved in Cannabidiol (CBD) effects. Although it has a low affinity for both CB1 and CB2 receptors, CBD can effectively block CB1 receptors when concentrations are high. The following are numerous potential CBD goals: (A) Blocking GPR55 receptors; (B) Systematic desensitization of TRPV1 channels; (C) Suppressing adenosine re-uptake transporters; (D) Regulating GABA production; and (E) Influencing the Endocannabinoid networks. According to the current review, numerous outstanding cannabis formulations are currently being developed and proven in numerous clinical studies. Nevertheless, more research is urgently needed to determine the best dosage and proportions of cannabinoids for reducing seizure frequency. This study needs to take place in huge, rising randomized clinical trials that really can reveal the rewards and drawbacks of cannabinoids in controlled patients. Furthermore, there is a lot of significant variation in the experimental approaches performed, particularly when it comes to the length of immunosuppressive drugs, dosages, and delivery methods in animal models. So, reproducing the existing results using comparable methods will be one of the biggest challenges in the additional investigation.

Keywords: Cannabinoids, Epilepsy, Experimental Models, Preclinical Study, Pharmacological Mechanism, Neuroprotective Potential.

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Received: 15-04-2023;
Revised: 26-06-2023;
Accepted: 26-10-2023.

INTRODUCTION

Epilepsy is a chronic brain disorder that affects young adults and kids. Globally, 65 million people suffer from epilepsy.[1] Anti-Seizure Medications (ASMs) are still the primary form of therapy for acute and severe epilepsy. Notwithstanding, the continuing research into new ASMs, especially when several drugs are used (offers a large number), 30% of respondents experienced no seizure response.[2] This is evident when utilizing suitable ASMs for the majority of cases (single agent). In these individuals, non-responsiveness to every subsequent ASMs diminishes the probability of a subsequent therapeutic outcome.[3] CBD has various other pharmacological activities (shown in Figure 1). A selectivity in preclinical studies and ASMs discovery towards the modification of specific epileptogenesis abnormalities, such as a focus on minimizing neuronal excitability via intracellular signaling modification or a focus on a single clinical manifestation, could be the explanation for this large number of individuals with refractory epilepsy.[4]

The species *Cannabis sativa* L., which has been utilized for medicinal purposes for many centuries, generates a wide range of components that together are known by the term cannabis.[5] Cannabis ingestion is associated with psychoactive properties, such as a "high" or feeling of euphoria. Scientists have discovered a category of substances referred to as cannabinoids, which may be classified into three primary groups: Phytocannabinoids, endogenous cannabinoids, and synthetic CBD. Hemp, a type of *Cannabis sativa* L., contains insignificant levels of both 9-Tetrahydrocannabinol (THC), which has the potential to establish itself as an ingredient, and CBD, a non-euphorigenic cannabinoid.[6] Hemp has traditionally been grown for its useful fiber components found in its stems and seeds. Cold crushing can be used to extract hemp oil or hempseed oil from cannabis seeds; however, the oils of cannabinoid content have limited Side effects. Inversely, THC and CBD are extracted from the hemp plant's

DOI: 10.5530/ijper.58.1.2

(flowering parts) and absorbed in a wide range of solvents, most frequently moderate fatty acids like sesame or olive oil.[7] THC has to be either completely absent from or present in very small quantities in cannabis oil when it has been carefully extracted and separated, but the separation of these two ingredients requires rigorous standardization and production standards during the extraction method.[8] CBD has high potency to easily pass the blood-brain barrier (Figure 2). CBD has been shown to have therapeutic potential.[9]

Mechanisms Underlying CBD activity

The hypothetical CBD activity is (shown in Figure 3). In addition, while THC has a far or higher binding affinity for orthostatic regions on the endocannabinoid receptor, CBD has a significantly lower potential.[10] Preclinical findings suggest that many sites, including intracellular signal modulation and unknown targets, may be involved in the anticonvulsant effects of CBD. CBD may interact with several receptors, and the precise molecular pathways by which CBD applies to humans are still unknown.[11] Similarly to the therapeutically used of ASMs ethosuximide and zonisamide, which inhibit T-type calcium influx and obstruct sodium and T-type calcium gates, CBD has been reported to block calcium influx through T-type voltage-gated calcium channels.[12] Cannabidiol's (CBD) effects on the brain are complicated and engage both synaptic and neuronal pathways. CBD impacts endocannabinoid receptors and generates neurological benefits.[13] To adjust overall network excitability and neurological inflammation, CBD and additional cannabinoid constituents regulate distinct cannabis receptors by emphasizing pathways in a network of neurons and non-neuronal microglial systems.[14] These, along with additional actions, may regulate the neural pathways responsible for hyperactivity and epileptic fits, which could consequently decrease the expression of comorbidity symptoms. Endocannabinoid pathway stimulation by CBD relieves discomfort, inflammatory processes, oxidative stress, and neuronal degeneration.[15] Anti-inflammatory, antioxidant, neurogenic, anxiolytic, painkiller, and neuroprotective capabilities belong to the additional properties (Figure 1).[16]

Pharmacological neuroprotective mechanism of cannabidiol

In targeted cells, both neuronal and non-neuronal, cannabinoids interact with receptors (CBRs) alongside various non-cannabinoid signaling mechanisms.[17,18] CBRs and novel objectives may be associated with its actions. While having a low sensitivity for the CB1 as well as the CB2 receptors, CBD might indirectly suppress the CB1 receptors when concentrations are high or enough.[19] These are some additional CBD target mechanisms (detailed mechanisms are shown in Figure 3): (a) regulating GABA production; (b) desensitizing TRPV1 channels; (c) inhibiting adenosine reuptake carriers; (d) altering the functioning of the endocannabinoid system; (e) suppression of GPR55 receptors

Regulating GABA production

CBD is associated with cannabinoids that influence $GABA_A$ receptors primarily in the brain and through CB1 and CB2 receptor stimulation. Both excitatory and synaptic terminals possess these CBD sites. By influencing postsynaptic CBRs and improving postsynaptic GABAergic action, CBD may regulate GABA production. It accomplishes this by strengthening $GABA_A$ receptor-mediated current through direct modifications, including persistence at membrane areas by regulating calcineurin-linked phosphorylation.[20]

Desensitizing TRPV1 channels

CBD works on a Transient Receptor Potential Vanilloid-1 (TRPV1) as an agonist, quickly desensitizing nonselective ion channels that have elevated Calcium (Ca^{2+}) sensitivity. The subsequent reduction in the influx of calcium decreases neurotransmission and reduces the occurrence of convulsions.[21]

Inhibiting adenosine reuptake carriers

Endogenous intrinsic purine neuromodulator extracellular adenosine, which has anti-inflammatory and anticonvulsive activities, gets enhanced by CBD. It can block the adenosine reuptake transporters on microglial as well as on astrocyte cells. Stimulation at 5-HT1A receptors, rapid receptor potential the ankyrin 1 (TRPA1), and TRPV2, as well as sodium channel variants, are alternative candidates.[22,23]

Altering the functioning of the endocannabinoid system

Anandamide additionally referred to as Arachidonoyl ethanolamide (AEA), and 2-arachidonoylglycerol (2-AG), are

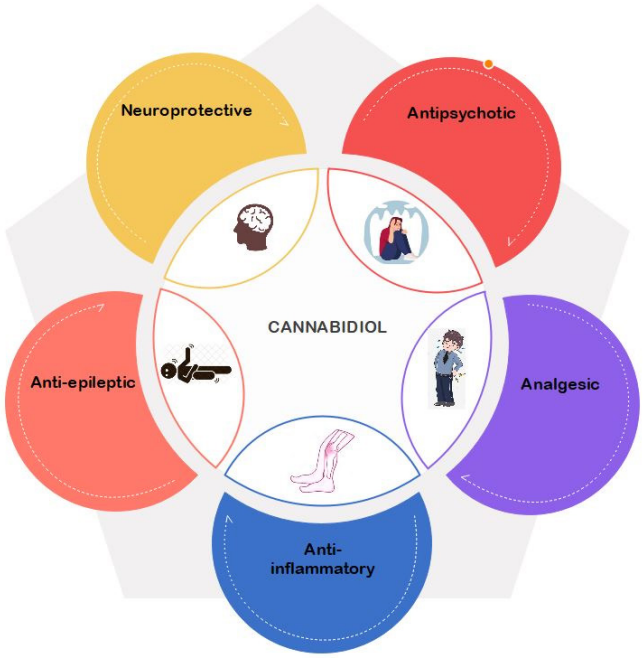

Figure 1: Therapeutic Efficacy of CBD in Various Neurological Conditions.

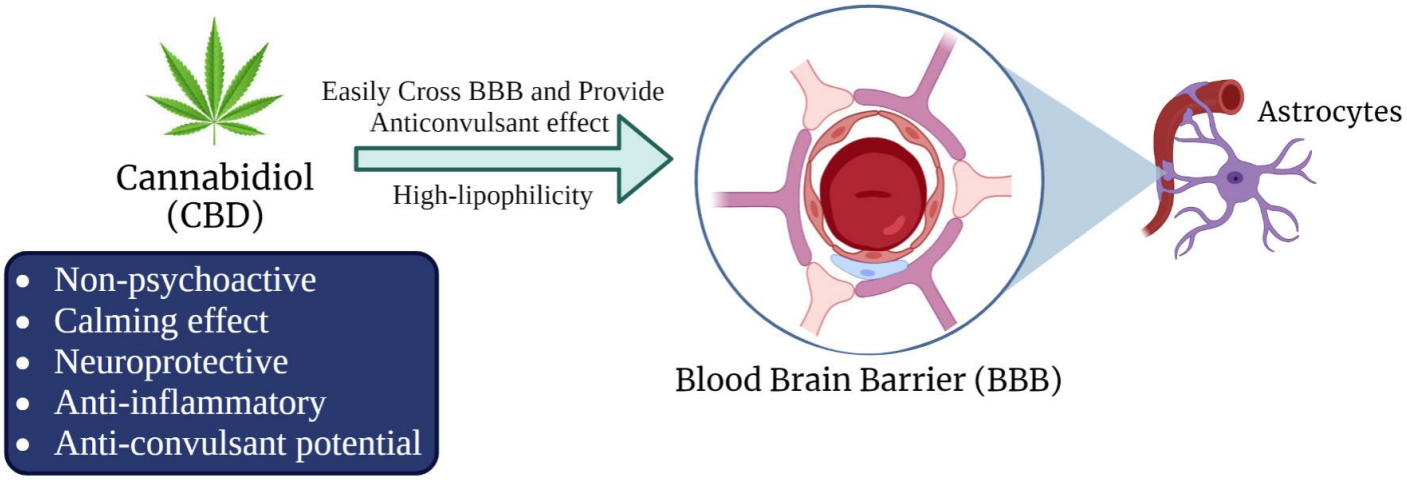

Figure 2: Graphically represented CBD can easily across BBB and exhibit various pharmacological effects.

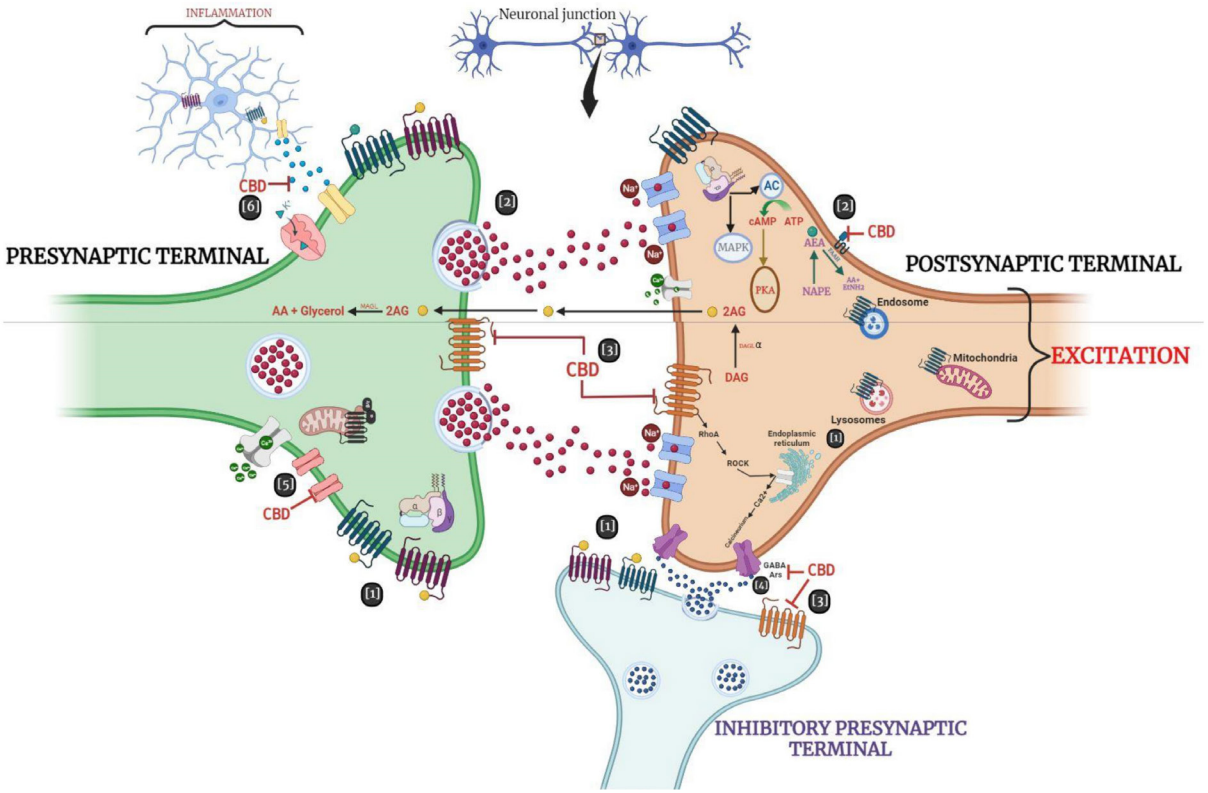

Figure 3: Potential molecular mechanisms of cannabidiol (CBD) on cannabinoid signaling pathways in the brain.

endocannabinoids that are synthesized and released on demand. They are involved in backward signaling by altering presynaptic receptors. Since they are lipophilic drugs, they easily pass through the cell membrane and proceed backward to stimulate cannabinoid receptors in presynaptic cells, microglia, and other glial cells.[24]

Suppression of GPR55 receptors

A newly identified target for CBD that might be relevant for some of its protective properties is the G Protein-coupled Receptor-55 [GPR55]. In the hippocampus and other regions, GPR55 receptors exist to regulate GABAergic neurotransmission. CBD inhibits the action of these receptors in the brain. Although the specific role of GPR55 signaling at inhibitory synapses is currently unknown, these receptors probably lead to the release of intracellular calcium and the formation of excitatory currents. Although CBD is a GPR55 antagonist, it diminishes the excitability of neurons and seizure activity by disrupting GPR55-mediated pro-excitatory or disinhibitory coordination.[25-27]

Table 1: Few experimentation animal studies of CBD with their efficacy on various models of epilepsy.

Sl. No.	Design of protocol	Animals	CBD Pharmacological effect	References
1.	Adolescents were subjected to early constraint anxiety, accompanied by an alternating alcohol delivery of 3 mg/kg for four days per week for four weeks.	Male rats	Onset delayed in myoclonic movement. Neuroprotective potential.	28
2.	A prolonged moderate stress model for animals was implemented, followed by a two-bottle selection paradigm using a 20% ethanol solution.	Male and female rats	Reduced period of Delayed the initiation of fits in epilepsy.	29
3.	Prolonged continuous ethanol intake at 10% (w/v) for fifteen days or periodic consumption of ethanol at 10% (w/v), five days per week for three weeks.	Male rats	The onset of seizures has improved. Increased CBD effect on $GABA_A$ receptor.	30
4.	Adolescent training in a two-bottle selection paradigm: 10% (v/v) ethylene oxide 24 hr per day for four weeks.	Male rats	Reduction in the frequency of seizures. Increased the sensitivity of the GABAA receptor.	31
5.	Adolescents who occasionally consume alcohol: 3 g/kg, i.p., for four consecutive days each week, for four weeks.	Male rats	Significant reduction in periodic seizures. In histopathology, inhibits neuronal death.	32,33
6.	Mice were given 2 mg/kg/d of ethylene oxide intravenously for a total of 21 days, and their movement behavior after their final injection was used to determine whether they were EtOH-high or EtOH-low animals.	Swiss Mice	Exhibit neuroprotective potential and improvement in TRPV1 functions.	34,35
7.	15 days of free use of EtOH (2–32% alcohol by volume, p.o.)	C57/Bj6 male mice	Mice exhibiting a higher tendency for alcohol mixture at a level of 16-32% had decreased CNR2 in the midbrain.	36

Pre-Clinical Investigation of Cannabidiol on Experimental Models of Epilepsy

Future Prospectives for Epilepsy Management

According to the current review, numerous excellent effects of cannabis compounds are currently being researched and confirmed in many clinical trials (shown in Table 1). However, additional investigation is desperately required to figure out the optimum administration and nature of cannabis for treating severe discomfort conditions. Such studies need to be carried out in huge, superior, randomized clinical investigations that can reveal both the benefits and drawbacks of cannabinoids in a regulated patient group.[37] To minimize their suffering while limiting unintended adverse consequences, collaborative efforts involving pharmacological and biopharmaceutical technical sciences have been implemented, supported by higher investments in studies. The production of superior, high-safety cannabis drugs will be dependent on the ethical, moral, and physiological components of enhanced regulations.[38]

CONCLUSION

The research evidence obtained in this narrative overview from animal and human studies emphasizes the modifications that occur in the key elements upon contact with drugs of harm, particularly during the initial stages of life or associated with separate dependent phases (acute or chronic exposure, reliance, withdrawal from substances, or relapse). It is significant to point out that the information currently available in the broader field suggests the possible advantages of determining receptor modifications for cannabinoid agonists or enzymes as indicators for enhancing the evaluation and categorization of patients with substance abuse disorders as well as the therapeutic effect of the drug. Furthermore, there is a lot of variation in the experimental approaches employed, especially when it comes to the duration of drug exposure, quantities, and methods of administration in animal models.[39] Therefore, reproducing the existing results using comparable methods will be one of the primary obstacles to future research. The pattern and their level of change in different

active constituents can only be precisely identified in this way, which plays an important role in the ongoing research for reliable biomarkers with therapeutic potential. An integrated research and experimental methods of models combining the latest technologies (such as genomics) with biological specimens from humans and animals is needed. This study needs to take place in huge, rising randomized clinical trials that really can reveal the rewards and drawbacks of cannabinoids in controlled patients.[40] Furthermore, there is a lot of variation in the experimental approaches performed, particularly when it comes to the length of immunosuppressive drugs, dosages, and delivery methods in animal models. So, reproducing the existing results using comparable methods will be one of the biggest challenges in the additional investigation. However, CBD neuroprotective effects have recently been stated, indicating that CBD may have the neuroprotective potential to become a safe and dynamic alternative cure. Some specific bioflavonoids and CBD could provide synergistic effects with ASMs in the investigation of new therapeutic approaches for the treatment of epilepsy.

ACKNOWLEDGEMENT

The authors are thankful to G.L.A University, Mathura, and the Institute of Professional Studies College of Pharmacy, Gwalior for their support.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

AEDs: Anti-epileptic drugs; **ASMS:** Anti-seizure medications; **AEA:** Arachidonoyl Ethanolamide; **BBB:** Blood-Brain Barrier; **CBD:** Cannabidiol; **CNS:** Central nervous system; **GABA:** Gamma-aminobutyric acid; **THC:** Tetrahydro cannabidiol.

SUMMARY

- The topics included in this review paper were summarized following an in-depth investigation of the efficacy of CBD and their drug delivery research with Anti-Seizure Medications (ASMs) used in various epilepsy experimental designs.
- CBD may also provide a synergistic effect with ASMs and also provide a good neuroprotective activity in epileptic conditions.
- CBD and THC are different compounds found in cannabis. But THC has psychoactive properties while CBD has non-psychoactive activity. Drug absorption into the brain is substantially limited by some factors, especially in the blood-brain barrier, which affects the potency of antiepileptic drugs to reach and remain inside the brain.
- The main objective of this review paper was to bring light to the molecular mechanism of CBD on synaptic junctions and their therapeutic effect during epileptic situations. Nanoparticles and their use in treating different epileptic disorders. This article might be useful to researchers looking into the effects of CBD on epileptic seizures.

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Cite this article: Shrivastava A, Gupta JK. Enlightening Pharmacological Mechanisms of Cannabidiol in Epilepsy: A Comprehensive Review on their Neuroprotective Potential. Indian J of Pharmaceutical Education and Research. 2024;58(1):15-20.