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Exploring the Anticonvulsant Potential of Cannabaceae Family: A Focus on GABAergic Modulation and Epilepsy Treatment

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ABSTRACT

This review explored the anticonvulsant potential of various species from the Cannabaceae family, including *Cannabis sativa*, *Humulus lupulus*, *Celtis integrifolia*, *Celtis tournefortii*, and *Trema orientalis*. Epilepsy is a complex neurological condition influenced by multiple factors such as genetics, structural abnormalities, infections, metabolic disturbances, and immune system dysfunctions. Phytochemicals like cannabidiol (CBD) and tetrahydrocannabinol (THC) from *Cannabis sativa*, along with other bioactive compounds from *Humulus lupulus*, have shown significant anticonvulsant effects by regulating GABAergic neurotransmission. Additionally, *Celtis integrifolia* and *Celtis tournefortii* have demonstrated potential in mitigating oxidative stress, a key factor in the onset of seizures. While these findings from preclinical studies are promising, the lack of extensive clinical trials limits their immediate application in treating epilepsy in humans. This review highlighted the necessity for further research focused on isolating active compounds, studying their pharmacokinetics, and conducting clinical trials to validate their potential as effective treatments for epilepsy.

Keywords: *Anticonvulsant activity, Cannabaceae family, GABAergic modulation, Epilepsy, Seizure*

1. INTRODUCTION

Epilepsy

Epilepsy is the second most common neurological disorder across the world. Convulsion occurs in the grey matter of the brain where there is excessive and sudden discharge of cerebral neurons[1]. Nearly 5 million people are found to be affected by epilepsy each year. In India, there are more than 12 million persons with epilepsy which accounts for one-sixth of the global population affected by epilepsy[2]. Unbalances between the excitation and inhibition of cortical neurons diminish seizures, which are characterized by neuronal synchronization and death.

This results in loss of feeling, brushing, and unconsciousness[3.] Epileptogenesis is the slow process that affects brain development. Changes in neuron structure and interconnection may result from alterations in the brain parenchyma, which leads to gliosis, neurodegeneration, axonal damage, breaking down of the blood-brain barrier, etc. Research on neuronal genes and mutations is crucial in understanding the genetic etiology of various disorders, including epilepsy, which can be influenced by family history, genetic variants, and clinical findings[4]. Structural factors in neuroimaging, including CNV, can cause seizures due to genetic or acquired causes, including stroke, trauma, and hypoxic-ischemic encephalopathy[5]. Seizure is often triggered by metabolic disturbances in which defective GABA metabolism can be due to genetic disorders or deficiencies[6]. The epilepsies, often triggered by immunological disorders, a condition characterized by inflammation in the CNS[7]. There are three primary types of seizures: generalized onset seizures, which happen in both cerebral hemispheres and spread to every part of the neuronal network; unknown onset seizures, which happen during sleep or by themselves and may impair awareness; and focal onset seizures, which start in one area of the brain and spread to other areas[8].

Mechanisms of epilepsy

GABA, the inhibitory neurotransmitter, prevents the impulses from passing by binding itself with $GABA_A$ or $GABA_B$ receptors. $GABA_A$ receptors allow the permeability of chloride ions, hyperpolarizing the membrane. On the other hand,

$GABA_A$ receptors would activate the potassium channels via second messengers, also causing hyperpolarization. Glutamate, the excitatory neurotransmitter, binds with N-methyl-D-aspartate (NMDA), alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA), and kainate receptors that result in sodium influx and potassium efflux causing depolarization and generation of action potential. Seizures result from imbalances between excitatory and inhibitory neurotransmitters, altered ion flows due to changes in receptor function. Two principal factors are implicated in seizure initiation: high-frequency bursts of action potentials and hyper synchronization in the neuronal network. Bursts result from a long duration of depolarization by influxes of extracellular calcium, which increase sodium entry, followed by repetitive bursts of action potentials. This sequence, termed a paroxysmal depolarizing shift, is a cycle of depolarization, repolarization, and hyperpolarization. Activation of neighboring neurons establishes the spread across brain regions that causes epilepsy[9]. The following figure (**Figure. 1**) illustrates the mechanisms of seizure initiation, focusing on neurotransmitter roles and imbalances in neuronal signalling.

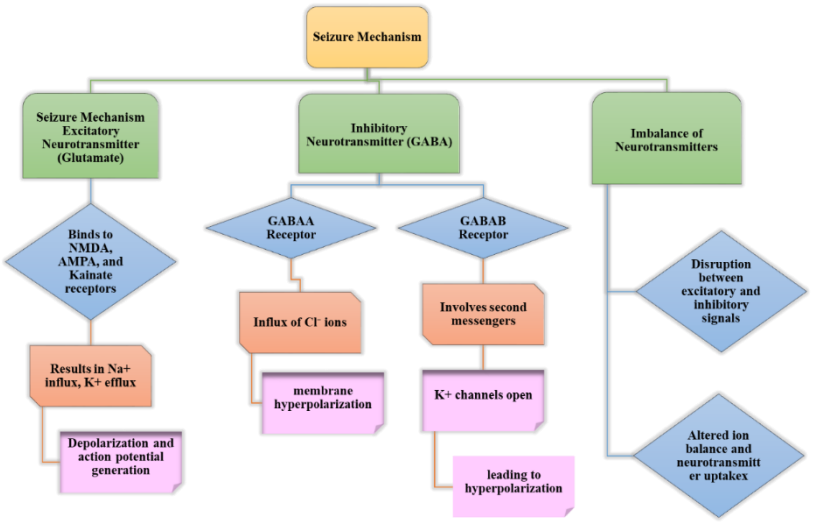

Figure. 1. Mechanisms of seizure initiation

Endocannabinoid System

The ECS (Endocannabinoid System) regulates neural progenitor growth, axon guidance, and synaptic plasticity, crucial for brain development[10]. ECS dysfunction is linked to epilepsy, as it modulates synaptic activity via endocannabinoids, involving cannabinoid receptors, endocannabinoids, and related enzymes[11]. Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are endocannabinoids migrating from the post- to pre-synaptic site to modulate synaptic transmission via retrograde signaling[12]. The primary receptors, CB1, CB2, and GPR55, affect different neural areas: CB1 in the hippocampus and cerebellum; CB2 in microglia and immune cells; GPR55 in the peripheral nervous system, enhancing intracellular calcium and neuronal excitability[13]. Dysregulated endocannabinoid signalling in epilepsy shows CB1 receptor downregulation and low AEA in cerebrospinal fluid, and CYP enzymes impact downstream signalling of these receptors[14]. Antiepileptic drugs, including sodium and calcium channel blockers, reduce glutamate but have adverse effects and resistance issues[15]. Herbal treatments offer alternative anticonvulsant activity, though more studies are needed for standardization[16].

Cannabaceae family

The Cannabaceae family initially comprised two main genera, Humulus and Cannabis. Subsequently, eight additional genera from the Celtidaceae family were included: *Celtis*, *Pteroceltis*, *Aphananthe*, *Chaetachme*, *Gironniera*, *Lozanella*, *Trema*, and *Parasponia*. Among these, the species that have exhibited anticonvulsant activity and are discussed in this review are *Cannabis sativa*, *Humulus lupulus*, *Celtis integrifolia*, *Celtis tournefortii*, and *Trema orientalis*. The in vivo studies of Anticonvulsant activity of phytochemicals in the Cannabaceae plant family is shown in Table 1. The following figure (Fig. 2) depicts the phylogenetic relationships of the Cannabaceae family, highlighting species with potential anticonvulsant properties.

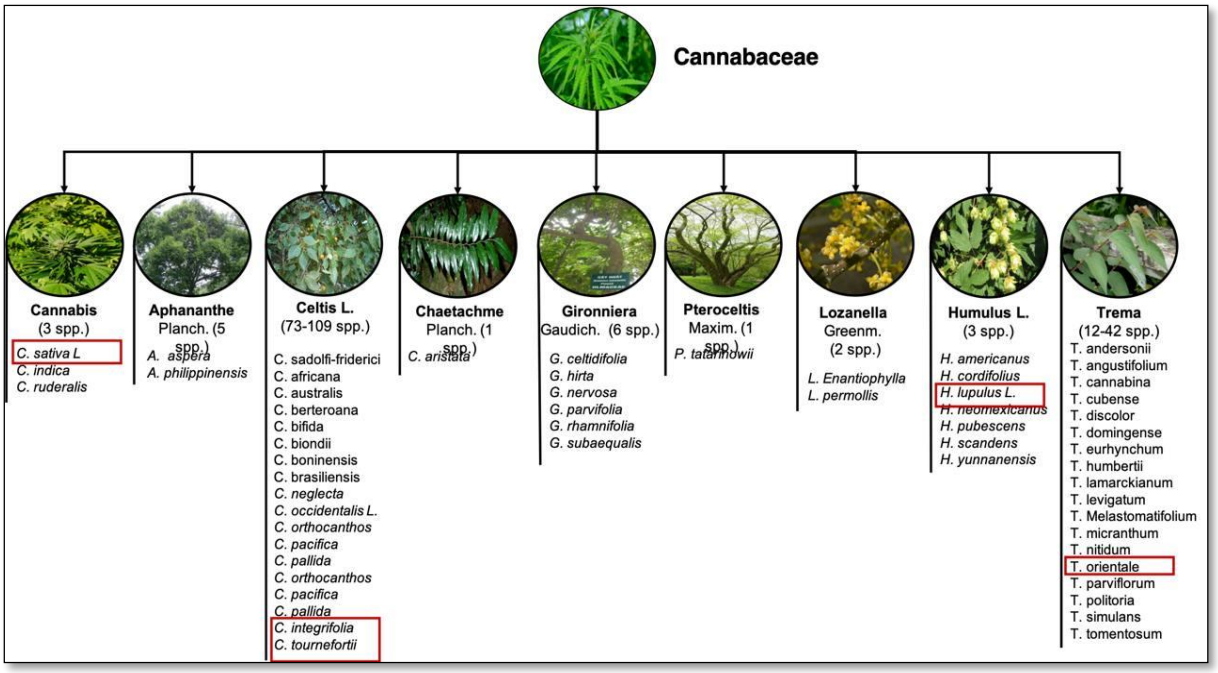

Figure. 2. Cannabaceae family tree with highlighted anticonvulsant species

Cannabis sativa

Cannabis sativa, a historically significant plant in the Cannabaceae family, has been utilized for food, paper, textiles, and rope production due to its fiber content[17] . Medicinally, the primary varieties are *C. sativa ssp. sativa var. sativa* (medical marijuana source) and *C. sativa ssp. indica var. indica*. The extract of this plant was found to be rich in terpenes, flavonoids, phenolic derivatives, polyphenols, etc. showing good fungicide, insecticide and therapeutic properties[18]. The plant's primary active components are phytocannabinoids such as cannabinolic acid and cannabidiolic acid, whose effects are amplified by the "entourage effect" of synergistic phytochemicals[19]. Its leaves, flowers, trichomes, and oils exhibit cytotoxic, antimicrobial, antipyretic, and free-radical scavenging activities. Additionally, the antioxidant properties of flower extracts are utilized in treating chronic diseases like cancer and liver disease[20].

Celtis integrifolia

Celtis integrifolia, a plant from the Ulmaceae family, is traditionally used in Northern Nigeria by the Hausa tribe to treat epilepsy, utilizing the leaves, roots, and bark[21]. The plant contains bioactive compounds like proline, GABA, gallic acid, and leucocyanidin, contributing to its therapeutic effects. Studies have demonstrated the anticonvulsant potential of the methanolic stem bark extract in various seizure models, including those induced by pentylenetetrazole, 4-aminopyridine, and maximal electroshock[22]. The plant's therapeutic effects are believed to stem from its ability to modulate GABAergic neurotransmission, essential for controlling seizures. Phytochemical analysis revealed flavonoids, alkaloids, tannins, and saponins, all contributing to the plant's central nervous system-modulating effects. These findings support *Celtis integrifolia* as a promising candidate for natural epilepsy treatments.

Celtis tournefortii

Celtis tournefortii (oriental hackberry) is a Mediterranean perennial used traditionally in Turkey for ailments such as diarrhea, dysentery, peptic ulcers, kidney sand, epilepsy, wound healing, and menstrual disorders. Known for its sedative and digestive benefits, it has gained attention for potential neuroprotective and anticonvulsant applications due to its antioxidant properties, which counteract oxidative stress a factor in seizure pathogenesis[23]. Bioactive compounds, including flavonoids, phenolic acids, sterols, and lipid-soluble vitamins, make *C. tournefortii* promising for further research into its antioxidant and anticonvulsant effects[24].

Humulus lupulus

Humulus lupulus (hops), commonly used in brewing, has a history in traditional medicine for its sedative and anxiolytic effects[25]. Modern research emphasizes its potential as an anticonvulsant, focusing on its interactions with gamma-aminobutyric acid (GABA), a key inhibitory neurotransmitter linked to epilepsy. Studies indicate that hop extracts can effectively modulate GABAergic activity, which may reduce neural excitability without the severe side effects of

conventional treatments. Electrophysiological studies confirmed the inhibitory action of GABA on neural transmission, while biochemical assays and radioligand binding studies demonstrated the affinity of hop compounds for GABAA receptor sites, particularly the benzodiazepine site, vital for GABAergic transmission.

Trema orientalis

Trema orientalis, native to Africa and parts of Asia, is traditionally used in treating ailments like asthma, diarrhoea, and epilepsy, with various plant parts valued for their medicinal properties[26]. Recent studies highlight its potential anticonvulsant effects through modulation of the GABA neurotransmitter system, which reduces neuronal excitability and helps prevent seizures. The traditional use of *T. orientalis* in epilepsy treatment suggests bioactive compounds that may influence GABAergic pathways, presenting a promising approach for seizure management.

Celtis tetrandra

Celtis tetrandra, called the Nilgiri elm, is a species of flowering plant in the hackberry genus Celtis, family Cannabaceae. It is widely distributed across the Indian Subcontinent, southern China, Southeast Asia, and western Indonesia.

This plant is a large tree growing up to 20 m in deciduous forest. There is no information of C. tetrandra in traditional medicinal purpose in Thailand and phytochemical constituent of this plant has not yet been reported his genus contains many classified phytoconstituents, such as terpenoids, organic acids, flavonoids, and volatile compounds. Their extracts and pure substances have been shown to have the same anticancer, antibacterial, anti-inflammatory, antioxidant, hepatoprotective, cardioprotective, urease-inhibiting, and antidiarrheal properties as their traditional uses. Some phytoconstituents (for instance, kaempferol, myricetin, quercetin, and eugenol) and extracts (for example, leaves, seeds, and ripe fruits extracts of C. australis) showed tremendous results in preliminary testing with promising antimicrobial, anticancer, and urease inhibitory effects. Ethnopharmacological investigations found the Celtis genus helped fight infection, inflammation, and cancer.

2. METHODOLOGY

This review systematically examined peer-reviewed studies from databases like PubMed, Scopus, and Google Scholar, focusing on the anticonvulsant properties of Cannabaceae plants through GABAergic mechanisms in epilepsy. Studies up to September 2023 were included if they explored seizure reduction via GABA pathways. Findings compared plant species, extracts, and efficacy, highlighting strengths, limitations, and research gaps, with recommendations for future research.

3. RESULTS

Targets of seizures

Epileptic seizures stem from disrupted electrical bursts and altered neuronal excitability. Normally, voltage-gated sodium channels trigger action potentials, followed by potassium channel-driven repolarization. Persistent sodium channels (INaP) may stay open, affecting neuronal firing at subthreshold levels, with electrical discharge continuing through synaptic connections, ensuring synchronized neuronal activity. Ion channels regulate intracellular ion concentrations and come in voltage-gated and ligand-gated forms. Imbalances in cation or anion channels (channelopathies) lead to epileptogenesis, as seen with slow sodium channel closure or mutations causing prolonged sodium influx and disrupting neuronal signalling. Sodium-channel-targeting drugs like Phenytoin and Rufinamide are commonly used to control seizures[27].

Mutations in calcium channels can raise intracellular calcium, causing excessive neurotransmitter release, disrupting neurotransmission; drugs like Pregabalin and Gabapentin control these effects. Potassium channel mutations affect membrane potential maintenance, with Retigabine as an anticonvulsant that reduces neuronal hyperexcitability[28]. The excitatory receptors NMDAR (The excitatory receptors NMDAR and AMPAR are targeted by drugs like Valproate and Perampanel to prevent seizure-induced hyperexcitability) and AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) are targeted by drugs like Valproate and Perampanel to prevent seizure-induced hyperexcitability. Inhibitory GABA receptors (GABAA and GABAB) prevent neuron excitability, with around 35% of anticonvulsants like Diazepam and Clonazepam acting as GABAR agonists to prolong inhibitory effects. Around 35% of anticonvulsants, including Diazepam, Clonazepam, and Vigabatrin, are GABA receptor agonists that extend channel opening to enhance inhibitory effects[29]. The following figure (Fig. 3) illustrates the pathways of ion channel and receptor dysfunctions leading to epileptic seizures and the associated drug interventions.

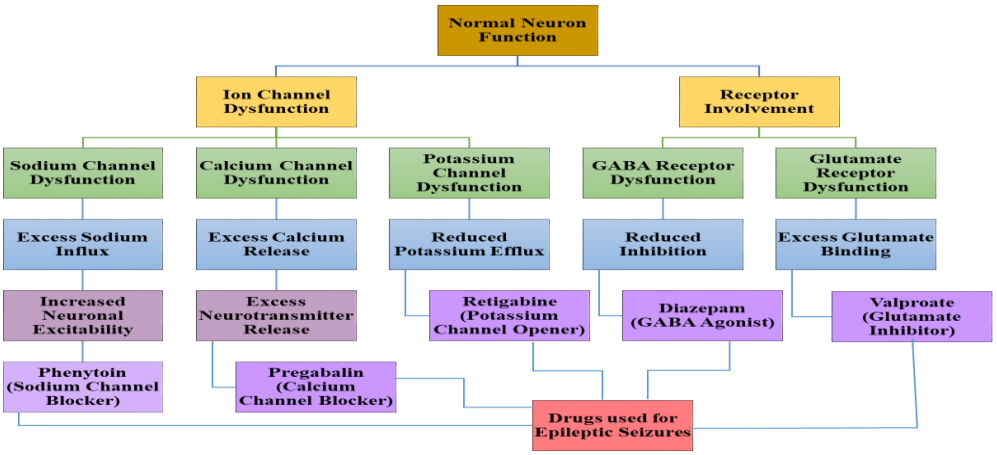

Figure. 3. Mechanisms of epilepsy and targeted drug interventions

Phytocompounds in Cannabis sativa with antiepileptic/anticonvulsant activity

The phytochemicals in Cannabis sativa, known as cannabinoids, feature a C21 terpene phenolic structure. These phytocannabinoids, including cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC), originate from plant-based meroterpenoids with a resorcinyl core and various side chains. The biosynthesis begins with geranyl diphosphate (GPP) and involves the enzyme GPP olivetolate geranyltransferase, leading to the formation of precursors like cannabigerolic acid (CBGA) and cannabigerovaric acid (CBGVA). This pathway facilitates the production of various cannabinoids such as Δ9-tetrahydrocannabivarin (Δ9-THCV), cannabidivarin (CBDV), cannabinol (CBN), cannabigerol (CBG), and cannabichromene (CBC). These compounds are classified into "THC-like", "CBD-like", and "CBC-like" phytocannabinoids. The therapeutic application of these cannabinoids, particularly in treating seizures, is attributed to their interaction with cannabinoid receptors (CB1 and CB2) in the brain. The network pharmacological targets and the clinical efficacy of these cannabinoids against seizures are detailed in Fig. 4 and Table 2 respectively, underlining their potential in seizure management.

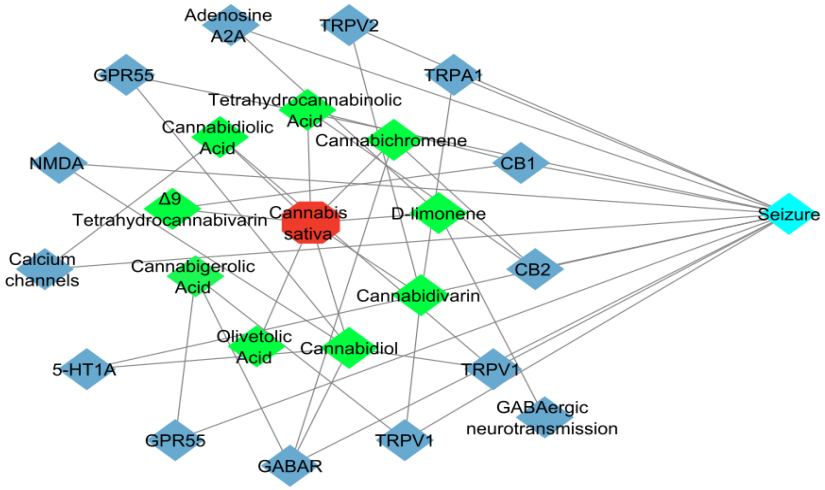

Figure. 4. Pharmacological targets of different phytochemicals in Cannabis sativa in Seizure

Cannabidiol

Cannabidiol (CBD), a non-psychoactive phytocannabinoid in *Cannabis sativa*, is widely used as an antiepileptic agent, with preclinical studies supporting its anticonvulsant properties[30]. CBD acts as an agonist or antagonist for various ion channels, neurotransmitter transporters, and 7-transmembrane receptors. Beyond seizure control, CBD demonstrates neuroprotective effects, preventing neuronal death and restoring hippocampal interneuron function in temporal lobe epilepsy[31]. CBD's antagonism of GPR55 was studied by Rosenberg et al. (2018), who found that CBD counters LPI-induced GPR55 activity, which enhances its anticonvulsant potential. CBD's effect on adenosine levels aids in seizure regulation by upregulating adenosine signalling. It also desensitizes TRPV1, an effect confirmed in both in vitro studies and hippocampal rat slices, indicating its potential to reduce epileptiform bursts[32]. In a randomized, placebo-controlled study in children with Lennox-

Gastaut syndrome, CBD (10 or 20 mg/kg/day for 14 weeks) reduced seizure frequency, though 14 patients experienced elevated liver aminotransferase levels. Similarly, a multicentre study on febrile infection-related epilepsy (25 mg/kg/day for 4 weeks) showed reduced seizure duration and frequency. In a randomized, placebo-controlled study in children with Lennox-Gastaut syndrome, CBD (10 or 20 mg/kg/day for 14 weeks) reduced seizure frequency, though 14 patients experienced elevated liver aminotransferase levels [33]. Another randomized study in children with Dravet syndrome (5–20 mg/kg/day for three weeks) noted seizure improvement, though side effects like pyrexia and drowsiness occurred. An open-label study with treatment-resistant epilepsy patients with CDKL5 deficiency, Aicardi, Doose, and Dup15q syndromes showed a decrease in seizures over 12–48 weeks with Epidiolex (5–50 mg/kg/day). Another large-scale open-label study of 607 patients showed reduced seizure frequency after CBD (2–10 mg/kg/day or up to 50 mg/kg/day for 48 weeks), with diarrhea and somnolence as notable side effects[34]. Another randomized placebo-controlled, double-blind study was performed on 198 children with Dravet syndrome in which 10 or 20 mg/kg/day of CBD was given for 14 weeks. A significant reduction in seizures and some adverse events such as loss of appetite and hypertransaminasemia were seen.

Δ9 Tetrahydrocannabinol

The primary acidic cannabinoid in *Cannabis sativa*, Δ9-tetrahydrocannabinolic acid (THCA), shows anticonvulsant activity by acting as a partial agonist on the CB1 receptor. In a Dravet syndrome mouse model, intraperitoneal administration of low-dose THC (0.1 and 0.3 mg/kg) demonstrated anticonvulsant effects by raising the temperature threshold for hyperthermia-induced seizures, though oral THC showed no effect on seizure onset or frequency. Co-administration of 12 mg/kg CBD with 0.1 mg/kg THC enhanced anticonvulsant effects, but higher doses (25, 100, or 3,500 mg CBD with 70 mg/kg THC) showed no additional therapeutic benefits in reducing seizure frequency.

Cannabidivarin

Cannabidivarin (CBDV) exhibits anticonvulsant activity in various epilepsy models. In vitro, CBDV reduced the amplitude and duration of epileptiform activities in rat hippocampal slices at concentrations ≥10 µM. In vivo studies showed that doses ≥100 mg/kg effectively controlled seizures in maximal electroshock (mES) and audiogenic models, and were also effective in pentylenetetrazole (PTZ) models at 100 and 200 mg/kg. However, it was ineffective in pilocarpine-induced seizures unless administered at 400 mg/kg or combined with valproic acid or ethosuximide, which enhanced its efficacy. CBDV was safe in neonatal and childhood seizure models, showing effectiveness mainly in older rat pups (P20), and was non-toxic at doses up to 200 mg/kg. Clinical trials confirmed its safety and efficacy, with significant seizure reduction in children with drug-resistant epilepsy, demonstrating tolerable side effects[35].

Cannabigerolic Acid (CGBA)

Cannabigerolic acid (CBGA) is the acid of form of cannabigerol which is primarily involved in the synthesis of Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol. In order to identify whether this compound possesses anticonvulsant properties, in vivo studies were carried out in the $Scn1a^{+/-}$ mouse model of Dravet syndrome. 30mg/kg i.p. of CBGA was found to exert significant anticonvulsant activity against hyperthermia-induced seizures and MES test. At a higher dose, CBGA shows to be a proconvulsant where there is an increased frequency of spontaneous seizures in the generalized tonic-clonic seizure model. In combination with clobazam (1mg/kg), CBGA (30 mg/kg) shows a synergistic effect in reducing the onset of seizures. The mechanism of anticonvulsant activity of CBGA is determined using in vitro studies using HEK293 cells and it was found that CBGA inhibits the activation of GRP55 (non-competitive antagonist) by both LPI and ML-186, at IC_{50} of 4.8 µM and 5.7 µM, inhibits TRPV1 at IC_{50} of 22 µM. CBGA also acts as a positive allosteric modulator of the GABAA receptor with EC_{50} of 910nM and also causes desensitization of receptors at higher concentrations. These interactions confer for the anticonvulsant and proconvulsant activity of CGBA.

Δ9 Tetrahydrocannabivarin

Δ9-Tetrahydrocannabivarin (THCV), a propyl analog of Δ9-THC, exhibits anticonvulsant effects in both in vitro and in vivo studies. In rat piriform cortex slices, THCV (5-50 µM) reduced epileptiform activity dose-dependently, with significant reduction at 50 µM. Pre-treatment with 10 µM THCV also decreased epileptiform activity. THCV binds to the CB1 receptor with a moderate affinity (Ki = 286 ± 43 nM). In PTZ-induced seizure mouse models, intraperitoneal THCV (0.025-2.5 mg/kg) delayed seizure onset in a dose-dependent manner[36].

Cannabidiolic Acid (CBDA)

Cannabidiolic acid is a terpenophenolic compound that is found in the seed-oil and fiber of hemp varieties. This compound is derived from cannabigerolic acid by undergoing stereoselective oxidocyclization by cannabidiolic acid synthase. CBDA shows anticonvulsant effects in Dravet syndrome mouse models, significantly inhibiting hyperthermia-induced seizures at doses of 10 and 30 mg/kg. Pharmacokinetic studies of CBDA and other phytocannabinoids THCA, CBCA, CBDVA, CBGA, and CBGVA demonstrated rapid blood absorption (tmax of 15–45 mins) but limited brain penetration, with CBDA exhibiting a brain-plasma ratio of 0.04. To enhance CBDA's stability and anticonvulsant effects, Goerl et al. enriched CBDA with

magnesium ions (Mg-CBDA) and compared it to Chylobinoid, which contains CBD (4.7%), THCA (1.9%), and THC (0.3%). Administered at 140 mg/kg (Mg-CBDA) and 80 mg/kg (Chylobinoid), both compounds reached peak effect at 1 hour. Chylobinoid proved more effective in maximal electroshock (MES)-induced seizures than Mg-CBDA, with an ED50 of 102.97 mg/kg, likely due to the entourage effect of CBDA with other cannabinoids[37]. However, the exact mechanism of CBDA is not well understood.

Δ9 Tetrahydrocannabinolic acid (THCA-A)

The binding affinity of THCA-A with CB1 and CB2 receptors was measured using a competition binding assay with the transfected HEK cells and it was found that THCA-A exhibits binding affinity with either of the receptors with Ki values of 3.1 and 12.5μM respectively[38]. The anticonvulsant activity of THCA-A in different models of seizure shows that THCA-A does not have any effect on hyperthermia-induced seizures even at the highest dose. However, the combination of THCA-A and THC exhibits anticonvulsant activity in 6-Hz seizure model at a dose of 100mg/kg with a greater CC50 value as compared to that of the vehicle. Pure THCA-A (200mg/kg, i.p) was ineffective against seizure in 6-Hz electroshock. THCA-A readily undergoes decarboxylation to form THC when exposed to light or heat therefore, it is unstable and cannot be stored for a longer duration. THCA-A acts as a proconvulsant when 200mg/kg is injected prior to the MEST test. But the mixture of THCA-A and THC was ineffective. Finally, combined THCA-A and THC were found to increase the severity of seizure in a dose-dependent manner (250 and 2000mg/kg) and decrease the lifespan of $Scn1a^{+/-}$ mice in spontaneous seizure model.

Cannabichromene

Cannabichromene (CBC), a non-psychoactive cannabinoid, acts as a CB2 receptor agonist. In *in vitro* studies using AtT20 cells, CBC induced dose-dependent CB2 activation and hyperpolarization at 30 μM, signalling via Gi/o G proteins and causing receptor desensitization. In an open-label trial, a Cannabis extract with 4% CBC demonstrated anticonvulsant effects in children with intractable epilepsy, supported by elevated CBC plasma levels. Anderson et al. tested CBC and related compounds in Dravet syndrome models, finding anticonvulsant effects and brain penetration with a brain-plasma ratio of 0.2 to 5.8. CBC also enhances GABAA receptor activity, with an EC50 of 10.83 μM in Xenopus oocytes, binding via the β2 subunit at residue V436. Whole-cell patch-clamp studies show that 20 μM CBC has no effect on KCNT1, Nav1.2, and Nav1.6, confirming its role as a $GABA_A$ receptor modulator. In zebrafish, CBC reduces PTZ-induced seizure hyperactivity dose-dependently, with greater efficacy than CBD or CBN at similar doses. The calcium channel inhibitory potential of phytocannabinoids such as CBCA, CBCVA, CBGA, CBGVA, and CBDVA was analysed in HEK-293 cells. Only CBGVA and CBDVA at 10 μM significantly inhibited Cav 3.1 and Cav 3.2 channels with IC50 values of 6 and 2 μM, respectively, explaining their anticonvulsant effects by targeting calcium channels[39].

Olivetolic acid

Olivetolic acid, a biosynthetic precursor to cannabigerolic acid (CBGA), shows modest anticonvulsant effects in a Dravet syndrome mouse model, reducing hyperthermia-induced

seizures at 100 mg/kg, though it exhibits low brain penetration (1%). The CBGA methyl ester lacks anticonvulsant activity, and neither compound inhibits GPR55 or T-type calcium channels in HEK293 cells.

Terpenes

The resins of *Cannabis sativa* are rich in terpenes, primarily mono- and sesquiterpenes, with triterpenes found in roots, seed oil, and fibers. α-Pinene, β-pinene, linalool, and d-limonene are the most abundant terpenes. In pentylenetetrazole (PTZ)-induced seizures, 400 mg/kg of β-pinene and a mixture of α- and β-pinene decreased seizure intensity by lowering hippocampal nitrite and striatal dopamine and norepinephrine levels. Linalool's anticonvulsant effects include NMDA receptor antagonism, demonstrated by dose-dependent inhibition of L-[^{3}H] glutamate binding in rat cortex, delaying seizures in NMDA- and quinolinic acid-induced convulsions at increasing doses.

D-limonene showed anticonvulsant properties in PTZ-induced seizures, with pretreatment reducing seizure onset and score in a dose-dependent manner. It also decreased mossy fiber sprouting and NPAS4 expression, while acting as an adenosine A2A receptor agonist, altering GABAergic transmission[40]. The figure (Fig. 5) provides an overview of phytocompounds in *Cannabis sativa* and their roles in modulating seizure mechanisms.

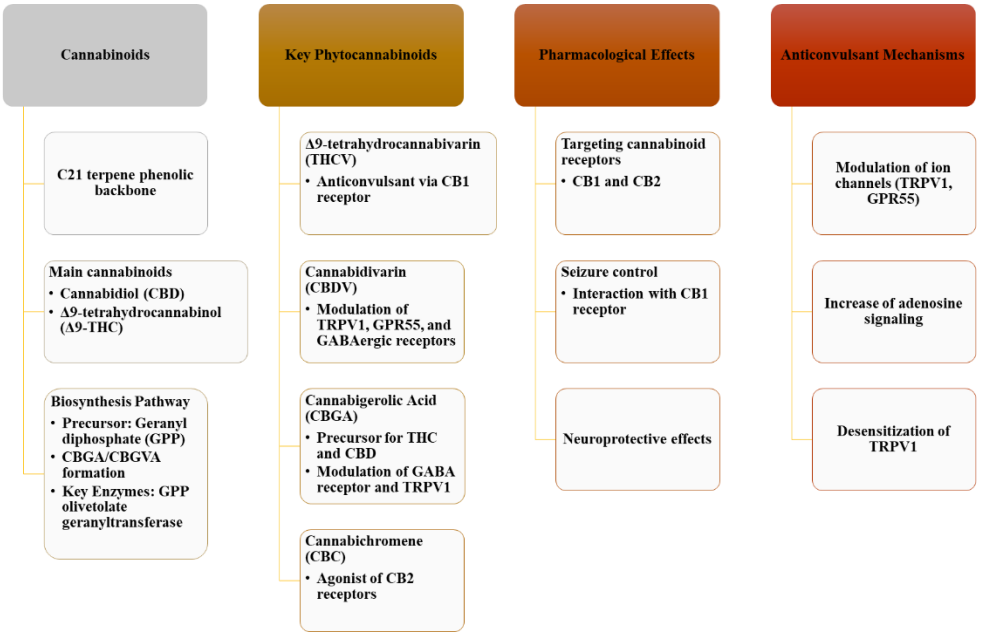

Figure. 5. Overview of Cannabis Phytocompounds.

Celtis integrifolia's Extract

The methanol stem bark extract of Celtis integrifolia has demonstrated significant anticonvulsant properties, as observed in several experimental seizure models. The bioactive compounds such as alkaloids, flavonoids, tannins, saponins, and glycosides with the CNS-modulating effect of the methanol stem bark extract of Celtis integrifolia showed significant anticonvulsant activity in different seizure models. In a PTZ-induced seizure model simulating petit mal epilepsy, extract dosing at 400 mg/kg resulted in 33.3% protection by delaying the onset of seizure and an increase in latency to death, and results were suggestive of an enhancement of GABAergic inhibition. The extract's effectiveness in this model indicates its potential to increase inhibitory neurotransmission and reduce seizure susceptibility. Similarly, in the 4-aminopyridine (4-AP)-induced seizure model, which interferes with potassium channels involved in neuronal excitability, the extract delayed the onset of seizures and provided 16.7% protection at the 200mg/kg dose. This suggests that the extract may modulate potassium channels, which play a significant role in maintaining the resting membrane potential and regulating neuronal excitability In contrast, the extract demonstrated no significant anticonvulsant effects in the strychnine-induced convulsion test, where it specifically impacted the GABAergic and potassium channels. In the MES (Maximal Electroshock Seizure) model of tonic-clonic seizures, whose ionic mechanisms are ascribed to dysfunction in sodium channels, the extract conferred no protection but significantly delayed the onset of seizures; therefore, it should be concluded to have low efficacy for sodium channel-related seizures. This indicates that Celtis integrifolia may not be effective in treating seizures associated with sodium channel dysfunction, as the MES model primarily evaluates sodium channel modulation.

Celtis tournefortii

Aqueous extracts and ethanol extracts of Celtis tournefortii have shown significant antioxidant activity, with the aqueous extract outperforming BHT in free radical scavenging, thus implying a promising anticative role in protection against oxidative stress: this is a major contributor to neuronal damage in epilepsy.

Phytochemicals of C. tournefortii

Phytochemical analysis of *Celtis tournefortii* shows high levels of antioxidants, including α-tocopherol (2.65 mg/kg), vitamin D (10.05 mg/kg), ergosterol (78.70 mg/kg), and stigmasterol (185.90 mg/kg), along with 74.47% unsaturated fatty acids, contributing to its strong antioxidant properties. Gas chromatography identified essential fatty acids like palmitic, oleic, linoleic, and caprylic acid methyl esters, supporting cell membrane integrity and protecting against oxidative damage Although specific anticonvulsant effects were not examined, the rich antioxidant and neuroprotective content, especially flavonoids and phenolic acids, suggests that *C. tournefortii* may reduce oxidative damage linked to epilepsy. Given the role of oxidative stress in seizure pathogenesis, *C. tournefortii* may offer neuroprotection by neutralizing reactive oxygen species (ROS), supporting its traditional use in epilepsy treatment and justifying further research on its anticonvulsant potential.

Anticonvulsant Effects of Humulus lupulus

The anticonvulsant effects of *Humulus lupulus* were demonstrated in PTZ-induced seizure mouse models, with aqueous

extracts (400–800 mg/kg) reducing seizure duration and severity in a dose-dependent manner. This activity is attributed to bioactive compounds like humulone and lupulone, which modulate GABAA receptors, enhancing GABA-induced chloride currents and acting as positive allosteric modulators. Xanthohumol, another key component, inhibits GABA transaminase, raising CNS GABA levels. It reduces kainic acid (KA)-induced seizures at doses of 10–50 mg/kg, lowers glutamate levels, mitigates CA3 neuronal death, and influences the expression of apoptotic markers (Mfn-2, Bcl-2, Apaf-1, and caspase-3)[41].

In PTZ-induced seizures in rats, oral *Humulus lupulus* extracts (200–600 mg/kg) increased seizure latency and reduced severity, with neuroprotective benefits noted in reducing excitotoxic neuronal damage. Binding assays reveal that humulone and related compounds interact with the benzodiazepine site on GABAA receptors, displacing flumazenil, suggesting GABAergic modulation without benzodiazepine-related side effects. Consequently, *Humulus lupulus* may offer a safer alternative for patients who are resistant to or intolerant of conventional anticonvulsants.

Neuroprotective Effects of Humulus lupulus Extracts

Oral supplementation with hop extracts decreased seizure onset and increased latency. Additionally, these extracts prevent or delay neuronal damage in the hippocampal CA3 region, which is selectively damaged by seizure activity. Such results would mean that hop extracts should protect the brain from the effects of recurrent seizures detrimental to the brain in the long term and make neuroprotection a part of therapeutic interventions in epilepsy. This dual functionality anticonvulsant and neuroprotective highlights the therapeutic potential of *Humulus lupulus* in managing epilepsy.

Implications for Epilepsy Treatment

Humulus lupulus compounds, particularly humulone and xanthohumol, enhance GABAA receptor modulation and inhibit GABA transaminase, supporting sustained inhibitory neurotransmission, reducing seizure propagation, and presenting a potential epilepsy treatment. Unlike benzodiazepines, these hop-derived compounds offer fewer side effects, potentially avoiding tolerance and dependence. Similarly, *Trema orientalis*, rich in terpenes, improves GABAA receptor function in the CNS, reducing PTZ- and KA-induced seizures in mice, indicating a promising role in anticonvulsant therapy.

Table 1. In vivo studies of Anticonvulsant activity of phytochemicals in the Cannabaceae plant family

No.	Plant	Phytochemical	Model used	Animal Used	Dose	Mechanism	Inference	Reference
1	Cannabis sativa	Cannabidiol (CBD)	Maximal electroshock threshold model	TRPV1 Knockout Mice	10-100 mg/kg	Desensitizes TRPV1 and regulates adenosine signaling	Decreased seizure threshold due to the partial anticonvulsant activity	42
		Δ9-Tetrahydrocannabinolic acid (THCA)	Dravet syndrome model	Scn1a +/− mice	0.1 and 0.3 mg/kg	Significant increase in the GTCS temperature threshold	Shows anticonvulsant activity	9
		THC (Δ9 Tetrahydrocannabinol) + CBD	Dravet syndrome model	Scn1a +/− mice	0.1 mg/kg THC + 12 mg/kg CBD (i.p.); 3,500 mg CBD + 70	Increases temperature threshold for hyperthermia-induced seizures	Shows anticonvulsant activity	9

					mg/kg Δ9-THC (oral)			
		Cannabidivarin (CBDV)	Maximal electroshock and audiogenic seizure model	Mouse	50-200 mg/kg	Reduction in hindlimb extension and seizure severity	Shows anticonvulsant activity	36
			PTZ- and pilocarpine-induced seizure models	Rats	50-200 mg/kg	Reduction in seizure frequency. Effective in pilocarpine-induced seizure models at a higher dose (400 mg/kg orally).	Shows anticonvulsant activity	36
		Cannabidivarin (CBDV)	PTZ-, MES-DMCM, KA-, hypoxia-, and NMDA-induced seizure models	P10 and P20 rat pups	50-200 mg/kg	Effective in P20 rat pups for controlling seizures in PTZ- and MES-induced seizures.	Shows anticonvulsant activity	43
			Neurotoxicity model	Pediatric rat	200 mg/kg	Modest neurotoxicity and safe to use in pediatrics	Safe to be used as an anticonvulsant agent in pediatrics	43
		Cannabigerolic Acid (CBGA)	Dravet syndrome model	Scn1a+/- mouse	30 mg/kg	Decreased seizure in hyperthermia-induced seizures and MES test.	Significant anticonvulsant activity	7
			Generalized tonic-clonic	Mouse	100 mg/kg	Increased frequency of	Proconvulsant activity	7

			seizure model			spontaneous seizures		
			Generalized tonic-clonic seizure model	Mouse	1400-2500 mg/kg	Increased frequency of spontaneous seizures	Proconvulsant activity	7
			Dravet syndrome model	Scn1a+/- mouse	30 mg/kg i.p. + Clobazam (1 mg/kg)	Reduction in the onset of seizures.	Synergistic anticonvulsant effect	7
		Cannabidivarinic acid (CBDVA)	Generalized tonic-clonic seizure model	Mouse	100 mg/kg	Increases the temperature threshold.	Show anticonvulsant activity	7
		Cannabigerovarinic acid (CBGVA)	Generalized tonic-clonic seizure model	Mouse	100 mg/kg	Increases the temperature threshold.	Show anticonvulsant activity	7
		Δ9 Tetrahydrocannabivarin (THCV)	PTZ-induced seizure	Mice	0.025, 0.25, 2.5 mg/kg	Reduces seizure onset in a concentration-dependent manner.	Show anticonvulsant activity	36
		Olivetolic Acid	Dravet syndrome model	Scn1a+/- mouse	100 mg/kg	Reduces hyperthermia-induced seizure.	Shows modest anticonvulsant activity	10
		Cannabidiolic acid (CBDA)	Dravet syndrome model	Scn1a+/- mouse	1, 10, 30 mg/kg	Inhibits hyperthermia-induced seizures	Show anticonvulsant activity	8
		Δ9-Tetrahydrocannabinolic acid (THCA), cannabichromenic acid (CBCA), Cannabidi	Pharmacokinetic study		10 mg/kg	Rapid absorption (tmax = 15-45 min) with short half-lives of <4 hours.	Good absorption	8

		varinic acid (CBDVA), Cannabigerolic Acid (CBGA), Cannabigerovarinic acid (CBGVA)						
		Mg-CBDA	Maximal electroshock threshold model	Rats	140 mg/kg	(ED50 = 124.34 mg/kg).	Shows anticonvulsant activity	37
		Chylobinoid	Maximal electroshock threshold model	Rats	80 mg/kg	Reducing seizures when compared to Mg-CBDA and CBD (ED50 = 102.97 mg/kg).	Shows anticonvulsant activity	37
		Mg-CBDA, Chylobinoid	Maximal electroshock threshold model	Rats	140 mg/kg (Mg-CBDA), 80 mg/kg (Chylobinoid)	Decrease in seizure	Shows entourage effect with improved anticonvulsant activity	37
		Δ9 Tetrahydrocannabinolic acid (THCA-A)+ THC	6-Hz seizure model	Scn1a+/- mice	100 mg/kg (i.p.)	Decreases seizures	Shows anticonvulsant activity	15
		THCA-A	MEST model	Scn1a+/- mice	200 mg/kg (i.p.)	An increase in the severity of seizures in a dose-dependent manner when combined with THC.	Acts as a proconvulsant	15

		THCA-A + THC	Spontaneous seizure model	Scn1a+/- mice	250 mg/kg, 2000 mg/kg	Combination of THCA-A and THC reduces lifespan of Scn1a+/- mice	Shows anticonvulsant activity	15
		β-Pinene	PTZ-induced convulsion model	Mice	400 mg/kg	Decreases intensity of seizures by reducing hippocampal nitrite and striatal dopamine and norepinephrine levels.	Shows anticonvulsant activity	44
		Linalool	NMDA-induced convulsions model	Mice	350 mg/kg	Delays the onset of seizure and protects against quinolinic acid-induced convulsion.	Shows anticonvulsant activity	45
			Quinolinic acid-induced convulsion	Mice	9.2 mM i.c.v. (up to 45 mM)	Provides 50–100% protection dose-dependently	Shows anticonvulsant activity	45
		D-Limonene	PTZ-induced kindling model	Mouse	10-60 mg/kg	Decreases mossy fiber sprouting in CA3, reduces axonal sprouting in hippocampus, lowers Npas4 expression	Shows anticonvulsant activity	40

2	Celtis integrifolia	Aqueous extract	PTZ-induced seizure model	Mice	400 mg/kg	Delays the onset of seizure by GABAergic inhibition	Shows anticonvulsant activity	22
		Aqueous extract	4-aminopyridine (4-AP)-induced seizure model	Mice	200 mg/kg	Delays the onset of seizure	Shows anticonvulsant activity	21
3	*Humulus lupulus*	Aqueous extract	PTZ-induced seizure model	Mice	*400 to 800 mg/kg*	Decreases the duration and severity of seizure	Shows anticonvulsant activity and neuroprotection	5

Table 2. Clinical studies of anticonvulsant activity of phytochemicals in Cannabis sativa

No.	Drug	Study Design	Dose	Study population	Outcome	Reference
1	Epidiolex	Open-label study	2-50 mg/kg/day	Patients with Dravet syndrome, Lennox-Gastaut syndrome, and intractable epilepsy within the age of 1-30 years	Improvement in seizure frequency	33
		Open-label study	25 mg/kg/day	Children with febrile infection-related epilepsy	Reduction in seizure frequency and duration	46
		Randomized, placebo-controlled, double-blind study	10-20 mg/kg/day	Children with Lennox-Gastaut syndrome	Reduction in seizure frequency	47
		Randomized, placebo-controlled study	5-20 mg/kg/day	Children (4-10 years) with Dravet syndrome	Improved seizure control	47
		Open-label study	5-50 mg/kg/day	Patients with treatment-resistant epilepsy	Reduction in seizure frequency	47
		Prospective, controlled,	5-50 mg/kg/day	Patients with refractory epilepsy	Reduction in seizure frequency	48

		open-label study				
		Randomized, placebo-controlled, double-blind study	10-20 mg/kg/day	Children with Dravet syndrome	Significant reduction in seizure	49
2	Cannabidivarin (CBDV)	Clinical Trial Phase 1 study	2.5 mg/kg/day, titrated up to 10 mg/kg/day	Female children with Rett syndrome and drug-resistant epilepsy	Significant reduction in the frequency of seizures with mild adverse effects.	35
		Clinical Trial Phase 2 study, randomized placebo-controlled trial	400 mg bid, titrated up to 800 mg bid	162 patients	40.5% seizure reduction with acceptable adverse events.	19
3	Cannabichromene (CBC)	Open-label trial	4.7 mg/kg	Children with intractable epilepsy	Significant reduction in seizure frequency	50

4. DISCUSSION

The paper "Plants with anticonvulsant properties in Cannabinaceae family: a review" is subjected to a critical evaluation in this review, which examines the methods, results, constraints, novelty, and potential avenues for further research. The Cannabinaceae family of plants, specifically Cannabis sativa, Celtis integrifolia, Celtis tournefortii, Humulus lupulus, and Trema orientalis, have been shown in the article to have anticonvulsant potential. These plants also have effects on GABAergic mechanisms, a crucial neurotransmitter pathway involved in preventing seizures.

The article concludes that the plants studied have anticonvulsant effects based on a range of preclinical studies, including animal models such as pentylenetetrazole (PTZ) and 4-aminopyridine (4-AP) induced seizures. The models of epilepsy used in the studies were appropriately selected since they mirror several features of human epileptic seizures. An instance of this can be seen with Trema orientalis and Humulus lupulus, which increase GABAergic transmission suggesting that such products could be used as therapeutic adjuncts for epilepsy. Some of the strengths of the study are also the exhaustive evaluation of bioactive such as flavonoids and terpenoids that probably have limited effects modifying GABA-ergic transmission and who can therefore have potential therapeutic applications.Although these studies are very informative, the models are limited in that they do not fully represent the complicated disease state of epilepsy. In addition, there are also no attempts made to fully characterize the pharmacokinetics of the studied compounds which create some portions that explain the low health benefits or efficacy of the herbs.

One of the main drawbacks is the lack of large-scale clinical study which would statistically support the preclinical results. Then, study sample sizes of experimental ones are generally inadequate to improve the statistical strength and relevance of the findings. Also, the investigation does not consider adverse events, toxicity or potential interactions with other antiepileptic drugs which are very important in respect to therapeutic strategies. Also, the action mechanisms for some bioactive compounds in the plants such as Celtis integrifolia and Celtis tournefortii are still imagined and thus there is need for further conceptual studies to provide factual proof.

This article contributes novel perspectives by exploring lesser-known species like *Celtis integrifolia* and *Celtis tournefortii*, which are not commonly investigated for their anticonvulsant properties. The discussion of how phytocannabinoids from *Cannabis sativa* and bioactive compounds from *Humulus lupulus* modulate GABAergic mechanisms adds a fresh perspective to the field of neuropharmacology. Additionally, the detailed exploration of *Trema orientalis* as a potential anticonvulsant through its interaction with GABA receptors underscores the plant's promise as a candidate for developing new antiepileptic drugs.

Future research should focus on isolating and characterizing specific bioactive compounds in the identified plants, especially those from *Trema orientalis* and *Humulus lupulus*, which demonstrate potent GABAergic activity. Clinical trials are essential to assess the safety and efficacy of these compounds in humans, along with determining appropriate dosing regimens. Mechanistic studies should further investigate how these compounds interact with GABA receptor subtypes and other ion

channels involved in seizure regulation. Additionally, the long-term effects, including neurotoxicity and potential side effects, need thorough investigation.

5. CONCLUSION

In summary, the review provides an in-depth critique of the anticonvulsant properties of plants in the Cannabinaceae family, highlighting *Cannabis sativa*, *Celtis integrifolia*, *Celtis tournefortii*, *Humulus lupulus*, and *Trema orientalis*. The article's strength lies in its exploration of bioactive compounds and their modulation of GABAergic mechanisms, offering potential alternative therapies for epilepsy. Future research should prioritize clinical trials, mechanistic studies, and toxicological evaluations to translate these preclinical findings into effective treatments for epilepsy and other neurological disorders.

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