Review

Modulating Neural Excitability in Epilepsy: A Systems-Level Perspective on Cannabinoid–Terpene Signaling

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Abstract

Epilepsy is increasingly understood as a disorder of neural circuit hyperexcitability arising from disruptions in the balance between excitatory glutamatergic and inhibitory GABAergic signaling. In many forms of epilepsy, recurrent seizures are associated with excessive glutamate release and calcium influx, along with inflammatory signaling, oxidative stress, and maladaptive changes in synaptic transmission. These processes can further destabilize vulnerable networks, particularly within hippocampal and cortical circuits. Endogenous mechanisms that normally constrain hyperexcitability—including endocannabinoid signaling through CB1 receptors—may become insufficient or dysregulated in chronic epilepsy, creating conditions that favor recurrent seizure generation. Here, we propose that multi-phytocompound combinations may influence neural balance in epilepsy by engaging several molecular systems that regulate neuronal excitability and seizure threshold. Cannabinoids and terpenes derived from Cannabis sativa interact with diverse molecular targets implicated in epilepsy, including CB1 receptors, GPR55, transient receptor potential (TRP) channels, $GABA_A$ receptors, voltage-gated ion channels, glycine and serotonergic receptors, as well as endocannabinoid metabolic pathways. Through these convergent mechanisms, phytocannabinoids and terpenes may influence excitatory and inhibitory signaling, limit excitotoxic processes, and modulate pathways associated with neuroinflammation and oxidative stress. Within this context, we outline a theoretical multi-compound approach composed of a dozen cannabinoids and terpenes selected for their potential synergy and interactions with pathways implicated in seizure generation, synaptic transmission, and neuroprotection, yielding testable predictions for future experimental and clinical investigation. This perspective provides a systems-level model for understanding how coordinated, multi-target modulation of neural signaling pathways may influence circuit stability in epilepsy and offers a foundation for future experimental validation of multi-compound strategies.

Keywords: epilepsy; neural excitability; excitatory–inhibitory balance; cannabinoids; terpenes; synaptic plasticity; endocannabinoid signaling; neuropharmacology

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Background

Ancient Chinese Emperor Fu Hsi described cannabis as having yin and yang properties that restore balance within the body[1]. In modern neuroscience, this balance reflects excitatory and inhibitory neural signaling, whose dynamic ratio is essential for maintaining stable neuronal excitability and circuit function. Imbalances in excitatory and inhibitory signaling are central to current models of epilepsy, where shifts toward excitation promote network hyperexcitability and seizure generation[1–3]. Within this context, cannabis has been explored for its potential effects on seizure activity, with both historical accounts and modern studies describing anticonvulsant properties[4,5].

Over the past several decades, scientific investigation has begun to elucidate the cellular and molecular mechanisms underlying these effects. Early studies demonstrated that the two most

abundant cannabinoids in the cannabis plant—cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC)—each exhibit anticonvulsant properties[6–12]. Since then, additional cannabinoids, including cannabidivarin (CBDV)[13–17] and cannabinol (CBN)[18,19], as well as terpenes such as linalool[19–21] and caryophyllene[22,23], have demonstrated anticonvulsant effects. Cannabinoids exhibit anti-inflammatory and antioxidant properties[24–26], as well as neuroprotective effects[27], which may be particularly relevant in the context of seizure-associated neuroinflammation and excitotoxic stress. In specific contexts, cannabinoids have also demonstrated anti-cancer[28] and anti-tumor[29] activity, which may indirectly influence seizure activity associated with tumor-related neural dysfunction. In addition, cannabinoids have been reported to exert analgesic[30–32] and neuromodulatory effects, and may influence a range of biological processes through interactions with diverse receptor systems and signaling pathways[33–35]. Collectively, these properties suggest that cannabinoids engage multiple complementary mechanisms that may modulate physiological and neurobehavioral function.

After decades of legal restrictions, *Cannabis sativa* has been approved for medicinal use in the majority of U.S. states. Patients are using cannabis-derived products for epilepsy, chronic pain, anxiety, neurodegenerative disorders, insomnia, and many other medical conditions. The safety and efficacy of cannabinoid-based therapeutics is highlighted by several FDA-approved drugs, including Marinol and Cesamet for cancer-associated nausea and Epidiolex for seizures. Epidiolex consists of purified CBD, which is safe and well tolerated even at large doses[36]. Purified CBD, however, may represent a more limited approach, as products containing multiple cannabinoids and terpenes could produce distinct or enhanced effects[1,37–40]. The synergetic interactions between cannabinoids and terpenes, their engagement of multiple neural receptors, and their modulation of diverse biological pathways (including components of the endocannabinoid system) are commonly referred to as the "entourage effect"—a concept proposing that combinations of phytocompounds may produce effects that differ from or exceed those of isolated constituents. Within this context, multi-compound approaches may engage a broader range of molecular targets—including G-protein–coupled receptors, ion channels, and signaling pathways involved in excitatory–inhibitory balance—thereby influencing neural circuit stability through convergent mechanisms. To examine this possibility, we propose a theoretical multi-compound system composed of a dozen cannabinoids and terpenes selected based on their reported interactions with pathways implicated in seizure generation and neural excitability. This framework provides a basis for evaluating whether such combinations may offer advantages over single-compound approaches in modulating neural function in epilepsy.

Mechanistic Basis of Multi-Compound Phytocannabinoid Signaling

CBD and Δ9-THC represent two primary phytocannabinoids relevant to the modulation of neural circuits involved in seizure generation. Several lines of evidence suggest that their combined effects may be more pronounced than those of isolated CBD or Δ9-THC alone[39,41–44]. Adverse effects in humans may also be more frequent in products containing purified CBD compared to extracts that include several cannabinoids and terpenes[39], suggesting a synergetic formula with multiple cannabinoids and terpenes may in some cases be better tolerated compared to products that only contain a single plant-derived compound. Some of the effects of Δ9-THC likely arise from its mechanism of action as a partial agonist of type-1 cannabinoid receptors (CB1Rs). CB1Rs are $G_{i/o}$-linked G-proteins that can powerfully modulate brain activity via several cellular and molecular cascades within neurons[45,46]. CB1Rs are the most prevalent G-proteins in the entire brain[47] and they are strategically located in neural circuits that generate seizures, such as the hippocampus[48,49]. CB1Rs are activated by exogenous cannabinoids like Δ9-THC and endogenous cannabinoids (or endocannabinoids/eCBs) like 2-arachyldonylglycerol (2-AG) and anandamide. Data from experimental epilepsy models suggest that excess glutamate release from axon terminals during seizures may engage the eCB-CB1R system, which, in turn, operates to dampen overactive circuits[50]. In this 'circuit breaker' scenario, seizure activity and excessive release of the excitatory neurotransmitter glutamate promotes spillover of glutamate from the synaptic cleft. This excess

glutamate binds to extra-synaptic mGluR receptors and activates a molecular pathway that drives 2-AG synthesis. The endocannabinoid 2-AG is subsequently released from postsynaptic neurons and binds to CB1Rs on presynaptic glutamatergic axon terminals. This suppresses glutamate release and prevents the over-excited circuit from uncontrolled hyperexcitability that leads to seizures. The levels of both eCBs, 2-AG and anandamide, are increased in the brain shortly after acute insults[51–53] including seizures[54,55]. This transient surge in eCBs likely engages presynaptic CB1R signaling and may limit excessive excitation by decreasing glutamate release. However, chronic on-going epilepsy may lead to alterations in eCB synthesis pathways and decreased CB1R expression on glutamatergic axon terminals[1,49]. These changes in the eCB-CB1R system may functionally compromise the eCB-mediated negative feedback that normally works to protect against seizures. Consistent with this, the levels of anandamide and the 2-AG synthesizing enzyme, DAGLα, are significantly decreased in the brain and spinal fluid of those with chronic temporal lobe epilepsy[56,57]. The diminished production of eCBs may contribute to epileptic seizures, as excess glutamate release proceeds unchecked and the excitatory/inhibitory ratio (E/I ratio) shifts towards excitation. Exogenous CB1R agonists like Δ9-THC can engage the CB1R signaling system and potentially boost the circuit dampener when eCBs are diminished. In support of this notion, CB1R agonists are anticonvulsant in several animal models of epilepsy and hyperexcitability[55,58–61], perhaps by decreasing glutamatergic transmission and restoring a healthy E/I ratio. Δ9-THC could also act on CB1Rs to keep overactive synaptic plasticity, which facilitates seizures, in check, by dampening activity in hippocampal circuits prone to runaway excitatory activity[62].

Years of anecdotal evidence suggests cannabis derivatives with "some THC", are more effective at treating seizures than pure CBD alone and that a 20:1 CBD:THC ratio may be favorable[1,4]. One comprehensive review that examined 34 studies conducted in 6 animal species found Δ9-THC was anticonvulsant in over 60% of seizure models[1]. There is also evidence that Δ9-THC has anti-convulsant properties in humans[63]. Aside from CB1Rs, the anticonvulsant mechanism of Δ9-THC could involve transient receptor potential (TRP) channels. Δ9-THC can activate and subsequently desensitize TRPA1, TRPV1, and TRPV2 channels[64–66]. Through desensitization of calcium-permeable TRP channels, Δ9-THC may contribute to the modulation of neuronal excitability and calcium-dependent processes implicated in neurotoxicity and seizure generation. Δ9-THC may also help regulate neuronal excitability via the inhibition of T-type voltage-gated Ca^{2+} channels[67]. Given T-type calcium channels are expressed in thalamic, cortical, and hippocampal neurons[68] where they support low-threshold burst firing and network synchronization[69], inhibition of these channels by Δ9-THC may reduce neuronal excitability by limiting burst generation, disrupting pathological oscillations, and stabilizing hyperexcitable circuits implicated in seizure activity. Δ9-THC also has potent anti-inflammatory and antioxidant properties and is neuroprotective against toxicity in multiple biological models[70–77]. Since CB1Rs may be several-fold more strongly coupled to downstream signaling pathways on glutamatergic neurons than on GABAergic neurons[78,79], relatively low levels of Δ9-THC may preferentially engage CB1R signaling at excitatory neuron terminals while limiting strong CB1R-mediated effects on inhibitory neurons (even if they express higher levels of CB1Rs[80]). This differential coupling may allow CB1R activation to reduce excitation while preserving inhibition, supporting the concept that lower relative levels of THC may be advantageous in multi-compound cannabinoid approaches.

Since it was first isolated in 1940[81], CBD has been reported to exhibit antioxidant, anti-inflammatory, anxiolytic, and antidepressant properties[77,82]. It has also been shown to reduce seizure frequency and severity in several mouse models of epilepsy and in human patients with the disease[12,83–97]. In preclinical models, CBD reduced spontaneous recurrent seizures[91] and regulated excitatory–inhibitory (E/I) ratio in acute seizures[92,93]. In humans, CBD showed efficacy in treating Dravet syndrome[83,94,95], Lennox-Gastaut syndrome[96] and tuberous sclerosis[97], which led to FDA approval of highly purified, plant-derived CBD for epilepsy. CBD can modulate brain activity by engaging multiple cellular pathways. One proposed anticonvulsant mechanism involves interference with LPI–GPR55 signaling at presynaptic boutons of excitatory glutamatergic

neurons in the hippocampus[98]. GPR55 is a G-protein coupled receptor that mediates increases in intracellular Ca^{2+} within neurons, leading to subsequent neurotransmitter release from axon terminals[99]. Lysophosphatidylinositol (LPI) is a lipid signaling molecule that has pro-excitatory actions when it binds to GPR55. The binding of LPI to GPR55 causes presynaptic Ca^{2+} rise in glutamatergic axon terminals and the release of glutamate[99]. LPI-GPR55 interactions can also decrease inhibitory neural signaling in the hippocampus, therefore shifting the E/I ratio in favor of excitation two ways. Seizures were found to elevate LPI and GPR55 levels in the brain, putting the cellular substrates in place to perpetuate a harmful positive-feedback loop of hyperactivity that could lead to more seizures. In experimental models of epilepsy, CBD was found to block LPI-GPR55 signaling, thereby decreasing LPI's ability to enhance excitation, reduce inhibition, and generate seizures[98]. Given that healthy brain function relies on a balance between excitatory and inhibitory neural signaling (Figure 1), CBD's ability to modulate excitatory–inhibitory (E/I) balance and limit neuronal hyperexcitability likely contributes to its prominence as one of the most well-studied cannabinoids in epilepsy. The therapeutic action of CBD may also rely on CBD's modulation of several other ion channels and G-proteins in the brain.

CBD can inhibit transient receptor potential (TRP) channels by stimulating and then desensitizing them[100–102], which may help put a brake on excitotoxic calcium entry into neurons, excitatory depolarization, and TRP-mediated synaptic plasticity. CBD also functions as an agonist of 5HT1A serotonin receptors[103], which can evoke inhibitory actions in neurons via its G-protein signaling cascades. CBD is also an agonist of glycine receptors[104], which mediate fast inhibitory synaptic transmission between neurons. CBD's action on glycine receptors may contribute to enhancing inhibitory tone within neural circuits. CBD is an antagonist of TRPM8 receptors[64] and inhibits voltage-gated Ca^{2+} channels[67] and voltage-gated Na^{+} channels[105]. The inhibitory action of CBD on ion channels could potentially protect against excitotoxicity and excessive glutamate release from synaptic terminals. CBD's ability to reduce neuronal excitability by enhancing K^{+} channel currents may also contribute to its ability to help prevent seizures[106]. By inhibiting the uptake of anandamide and fatty acid amide hydrolase (the enzyme that breaks it down), CBD can also increase extracellular anandamide levels[101,107,108], which may have anti-epileptic effects. Collectively, these mechanisms highlight CBD as a key modulator of neuronal excitability within multi-compound approaches targeting epileptic circuits (Figure 2).

Cannabinoid–Terpene Synergy

Dr. Raphael Mechoulam, widely regarded as the father of cannabinoid research, was among the first to propose that whole-plant cannabis extracts may produce pharmacological effects distinct from isolated constituents. These effects may arise from synergistic modulatory interactions among cannabinoids, terpenes, and other phytochemicals that converge on multiple receptor systems and endogenous cannabinoid signaling pathways[42,109]. Around the time Mechoulam was elucidating the structures of CBD and THC, and isolating THC and anandamide, he postulated that multiple cannabinoids and terpenes could enhance the body's endogenous cannabinoid signaling system. This may occur through coordinated effects on receptor activity, endocannabinoid synthesis and degradation, and synaptic release dynamics, which collectively shape retrograde signaling and circuit-level excitability[109]. Building on this concept, Wagner and Ulrich-Merzenich[110] proposed 4 potential synergistic mechanisms for phytotherapeutics using cannabis as an example: 1) multitarget effects (e.g., cannabinoids and terpenes engaging a variety of ion channels and G-proteins); 2) pharmacokinetic effects (e.g., enhanced bioavailability or modulation of endocannabinoid levels, such as increased anandamide via reduced degradation[107]); 3) improved bacterial resistance; and 4) modulation of adverse events (e.g., CBD's ability to counteract the psychoactive effects of Δ9-THC[35]). Within this framework of multi-target synergy, individual phytocannabinoids can be understood as contributing distinct yet complementary mechanisms to the overall functional profile.

Cannabidivarin (CBDV) represents a secondary phytocannabinoid of interest within this framework, with potential to complement the pharmacological effects of both Δ9-THC and CBD. Preclinical studies demonstrate that CBDV can reduce seizure activity in multiple preclinical models of epilepsy[13–15], and emerging clinical data suggest it may also reduce seizure burden in human patients while remaining generally safe and well tolerated in both adult and pediatric populations[16,111]. At the molecular level, CBDV appears to exert anticonvulsant effects through multi-target modulation of neuronal excitability. CBDV modulates intracellular calcium dynamics via transient receptor potential (TRP) channels, including TRPV1, TRPV2, and TRPA1[64,65]. These channels regulate calcium influx and play a central role in controlling neuronal firing and network excitability, providing a mechanistic basis for CBDV's effects on hyperexcitable neural circuits. Emerging evidence suggests that CBDV may indirectly influence excitatory and inhibitory neurotransmission through its effects on neuronal excitability and gene expression, potentially contributing to a shift in excitatory–inhibitory (E/I) balance toward a more stable state[13–16]. Together, these mechanisms suggest that CBDV may complement the effects of other cannabinoids (Figure 2).

Cannabigerol (CBG) may interact with multiple neurotransmitter systems, receptors, ion channels, and intracellular signaling pathways[112,113]. CBG can inhibit voltage-gated Na^+ channels[112], which could potentially reduce high-frequency neuronal firing and limit the initiation and propagation of action potentials—key processes underlying seizure generation and spread. Phytocannabinoids including CBG modulate multiple transient receptor potential (TRP) channels, including TRPV1, TRPV2, and TRPA1, key regulators of calcium influx and neuronal excitability[64–66]. In addition, CBG has been shown to interact with cannabinoid receptors, acting as a low-affinity agonist at CB1 and CB2 receptors[114]. CB1 receptor engagement is relevant to epilepsy because CB1 receptors are positioned on presynaptic terminals where they suppress neurotransmitter release, such as glutamate release in hyperexcitable circuits. CB2 receptor signaling is less directly tied to fast synaptic transmission, but it may still be therapeutically relevant through modulation of neuroinflammatory pathways, which are increasingly recognized as contributors to seizure susceptibility and epileptogenesis. Taken together, even relatively weak or low-affinity CBG activity at CB1 and CB2 could complement other cannabinoids by adding both circuit-dampening and anti-inflammatory effects. CBG is also believed to be an agonist of α2-adrenoceptors[115]. α2-adrenoceptor activation is especially attractive in an antiepileptic framework because these receptors are Gi/o-coupled and generally reduce neurotransmitter release, dampen neuronal firing, and oppose excessive excitatory drive[116]. Since α2-adrenoceptors are expressed by excitatory neurons throughout the hippocampus and cortex[117,118] and their activation can reduce glutamate release from hippocampal neurons[119], CBG's activation of these receptors may contribute to reductions in network excitability, which fits well with a multi-compound approach aimed at stabilizing hyperexcitable circuits. Since Cascio et al. found CBG to be a potent α2-adrenoceptor agonist, this may be one of the stronger mechanisms through which CBG contributes to seizure-threshold stabilization. In addition, CBG is thought to antagonize 5-HT1A serotonin receptors[115], which are Gi/o-coupled inhibitory receptors expressed on both excitatory pyramidal neurons and GABAergic interneurons within hippocampal (including CA1 and dentate gyrus) and cortical circuits[120]. CBG's antagonism of 5HT1A receptors may prevent serotonergic suppression of interneuron activity, thereby preserving inhibitory tone within hyperexcitable networks implicated in seizure generation. Through these combined mechanisms, CBG could support stabilization of excitatory–inhibitory balance and complement the effects of other cannabinoids within multi-compound combinations.

Cannabinol (CBN) has been reported to exhibit anticonvulsant-like effects in preclinical models of seizures and epilepsy[18,19]. Studies demonstrate that cannabis-derived constituents, including CBN, can reduce seizure-like behavior in both chemically induced and genetic models of epilepsy[19], although the effects of CBN appear less consistent than those of cannabidiol (CBD)[18]. At the molecular level, CBN has been reported to interact with cannabinoid receptors (CB1 and CB2)[121] and may influence synaptic transmission through effects on ion channel activity and

neurotransmitter release[1]. Emerging evidence suggests that CBN may modulate voltage-gated sodium channels by stabilizing inactivated channel states and reducing neuronal excitability[122], as well as interacting with TRP channels[64,65], mechanisms that could contribute to reduced neuronal excitability and calcium-dependent signaling. In addition, CBN exhibits anti-inflammatory and neuroprotective properties[1,53], which may help mitigate neuroinflammatory signaling and excitotoxic stress—processes that contribute to seizure initiation and propagation. Although clinical data in human epilepsy are limited, these convergent mechanisms suggest that CBN may contribute to seizure modulation, particularly when combined with other cannabinoids and terpenes targeting complementary pathways.

Cannabichromene (CBC) may have beneficial effects including anti-inflammatory, analgesic, and antidepressant activities[123]. CBC can also modulate the endocannabinoid system through multiple mechanisms, including activation of CB2 receptors[124] and interaction with transient receptor potential (TRP) channels such as TRPA1 and TRPV1[64,65], which are functionally integrated with endocannabinoid signaling pathways[125]. Emerging evidence also suggests that CBC possesses anticonvulsant properties. In preclinical models, CBC has been shown to reduce seizure activity and delay seizure onset in chemically induced epilepsy paradigms, including models of Dravet syndrome, indicating a direct effect on neuronal excitability[126]. Mechanistically, recent studies demonstrate that CBC can act as a positive allosteric modulator of $GABA_A$ receptors, enhancing inhibitory neurotransmission and increasing GABAergic tone—one of the primary mechanisms through which many anti-seizure medications exert their effects[127]. Through these combined actions—enhancing inhibitory signaling while modulating excitatory ion channel activity—CBC may contribute to stabilization of hyperexcitable neural circuits and elevation of seizure threshold. Interestingly, hemp extracts containing significant amounts of CBC, CBN, and CBD exhibited greater anticonvulsant activity than purified CBD alone[127], supporting the idea that multi-compound combinations may produce enhanced effects in experimental models.

Although clinical data in human epilepsy remain limited, CBC is frequently detected in cannabis-derived formulations used by patients with treatment-resistant epilepsy, and accumulating preclinical evidence supports its inclusion as a potentially active component within multi-compound cannabinoid therapies.

Collectively, these cannabinoids may converge on a shared neurobiological objective: stabilization of neural excitability through restoration of excitatory–inhibitory (E/I) balance. Dysregulation of this balance—characterized by excessive glutamatergic activity and/or insufficient GABAergic inhibition—is a central feature of epilepsy and related neurological conditions. Individual constituents within multi-compound approaches may target complementary nodes within this system. Importantly, these compounds do not act in isolation. Rather, their combined pharmacology suggests a systems-level modulation of neural circuits, simultaneously targeting presynaptic neurotransmitter release, postsynaptic receptor activity, ion channel conductance, intracellular signaling pathways, and neuroinflammatory processes. This multi-target approach may enable more robust stabilization of hyperexcitable networks compared to single-compound strategies, particularly in treatment-resistant epilepsy where multiple pathological mechanisms coexist. In this context, the "entourage effect" may be understood not simply as additive synergy, but as coordinated modulation of interconnected biological systems governing neuronal excitability, synaptic plasticity, and network homeostasis.

To further expand these complementary and potentially synergetic interactions, bioactive terpenes with neuromodulatory, anti-inflammatory, and anticonvulsant properties are also relevant. Linalool has neuroprotective, anxiolytic, and antidepressant actions[128,129], as well as direct anticonvulsant effects in preclinical models[20,21]. Linalool-rich preparations reduce seizure frequency and severity in both pentylenetetrazole (PTZ) and maximal electroshock (MES) models[20,21]. Studies suggest that linalool may increase $GABA_A$ currents[130] and inhibit both voltage-gated Ca^{2+} channels and voltage-gated Na^{+} channels[131], mechanisms that may contribute

to the stabilization of network activity by restoring inhibitory transmission and limiting excessive depolarization and Ca^{2+} entry.

β-Caryophyllene contributes anti-inflammatory and neuroprotective effects and has demonstrated antiseizure activity in rodent models, including reductions in recurrent seizure activity and attenuation of blood–brain barrier disruption following pilocarpine-induced status epilepticus[22,23]. As a CB2 receptor agonist[132], β-caryophyllene may also modulate neuroinflammatory pathways that contribute to seizure susceptibility and epileptogenesis, thereby indirectly supporting restoration of E/I balance.

Additional monoterpenes, including limonene, myrcene, and pinene, further expand mechanistic diversity. Limonene has been reported to exhibit antioxidant, anti-inflammatory, and anticancer properties[133,134]. Limonene has also been shown to suppress PTZ-induced seizures and kindling, potentially through adenosine A2A receptor–mediated modulation of GABAergic neuronal activity[135]. Through this mechanism, limonene may enhance inhibitory neurotransmission and reduce network hyperexcitability in circuits prone to seizure generation. Myrcene is believed to have anxiolytic, antioxidant, anti-inflammatory, and analgesic properties[136]. In PTZ-induced seizure models, β-myrcene increases latency to convulsion and improves survival, consistent with a reduction in network hyperexcitability[137]. Pinene-related effects appear structure-dependent, with β-pinene—but not α-pinene—reducing seizure severity and prolonging survival in PTZ models[138,139], while α-pinene potentiates $GABA_A$ responses through direct binding to $GABA_A$ receptors[140]. Both α-pinene and β-pinene can modestly increase $GABA_A$ receptor inhibitory currents[130], so both forms of the terpene may help boost inhibition in circuits prone to runaway excitation and seizure generation. Pinene may also inhibit acetylcholinesterase activity[141] which could contribute to anticonvulsant effects in a context-dependent manner by enhancing cholinergic tone, which can preferentially recruit inhibitory interneurons[142], drive glutamate/GABA balance towards inhibition[143] and promote desynchronization of hypersynchronous network activity[144]. Collectively, these findings suggest that terpene components complement cannabinoid actions by engaging convergent mechanisms that regulate neuronal excitability, including enhancement of inhibitory signaling, receptor-mediated neuromodulation, and suppression of inflammation-driven hyperexcitability. Through these combined effects, terpenes may help restore E/I balance and stabilize hyperexcitable neural circuits.

Given that epilepsy and autism are thought to share overlapping neurobiological features and etiological pathways[145], related mechanistic frameworks have been put forth suggesting that multi-compound cannabinoid–terpene interactions may influence circuit-level excitatory–inhibitory balance in autism[146]. These cross-condition parallels further support the relevance of multi-target approaches in modulating network-level excitability.

Conclusion

The perspective presented here integrates findings from preclinical models and mechanistic studies; however, direct evidence supporting the efficacy of specific multi-compound cannabinoid–terpene combinations in human epilepsy remains limited and requires validation in controlled clinical trials. Nevertheless, it yields several testable predictions: that multi-compound combinations may produce greater reductions in neuronal hyperexcitability and seizure frequency than isolated cannabinoids, more effectively restore excitatory–inhibitory balance within hippocampal and cortical circuits, and demonstrate improved tolerability through coordinated modulation of complementary molecular pathways. These predictions could be evaluated through electrophysiological recordings of excitatory–inhibitory balance, calcium imaging of network activity, and clinical assessments of seizure frequency and severity in controlled trials, as well as through molecular and transcriptomic analyses of pathways involved in synaptic plasticity and neuronal excitability.

More broadly, these findings raise the possibility that complex, multi-compound systems may harness coordinated interactions among phytocompounds to produce effects that extend beyond those of isolated constituents. Much like individual musical notes combining to form a symphony,

such interactions may give rise to emergent properties that stabilize neural circuit dynamics and support balanced network function. Together, this framework provides a mechanistically grounded and experimentally testable approach for investigating multi-compound cannabinoid–terpene interactions in the modulation of neural excitability in epilepsy.

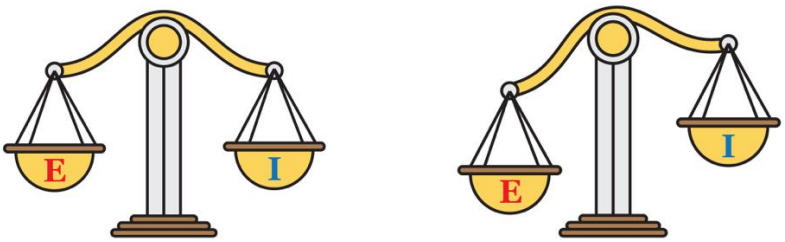

Figure 1. Excitatory–Inhibitory Balance in Neural Circuits. Healthy brain function depends on maintaining a balance between excitatory (E) and inhibitory (I) neural signaling (top left). Disruptions in this balance may contribute to neurological conditions such as epilepsy. For example, when activity shifts toward excitation (top right), network hyperexcitability may emerge and promote seizure generation.Excessive glutamatergic signaling and impaired GABAergic inhibition contribute to neuronal hyperexcitability and seizure generation.

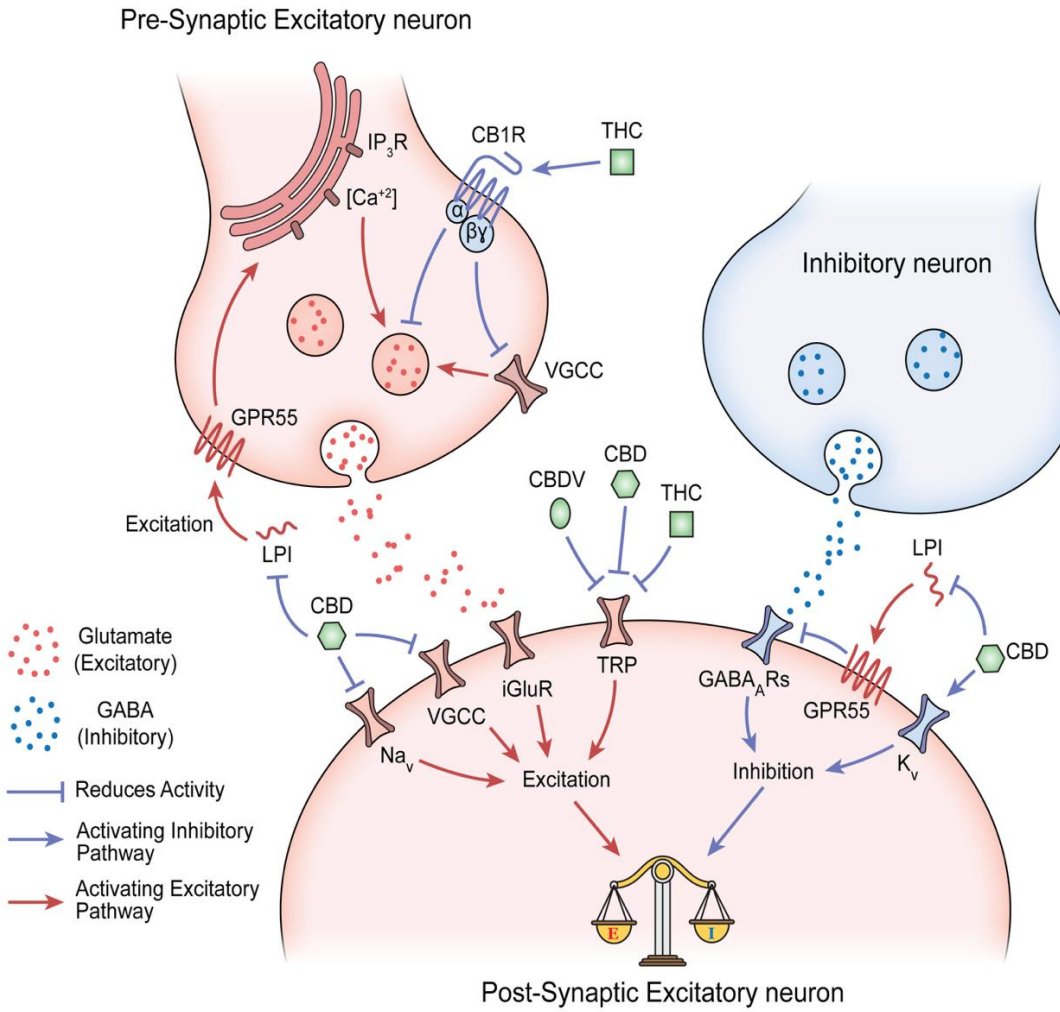

Figure 2. Cannabinoid modulation of synaptic transmission and excitatory–inhibitory (E/I) balance in epileptic circuits. Cannabidiol (CBD), cannabidivarin (CBDV), and Δ9-tetrahydrocannabinol (Δ9-THC) act on multiple molecular targets that may reduce excitatory drive and stabilize network activity.

Presynaptic activation of cannabinoid receptor type 1 (CB1R), particularly by Δ9-THC and endocannabinoids, inhibits neurotransmitter release via Gi/o-coupled signaling, reducing calcium (Ca^{2+}) influx through voltage-gated calcium channels (VGCCs) and suppressing glutamate release. CBD may further reduce glutamate release by interfering with lysophosphatidylinositol (LPI)–G protein-coupled receptor 55 (GPR55) signaling, thereby limiting presynaptic Ca^{2+} influx. Reduced glutamate release decreases activation of postsynaptic ionotropic glutamate receptors (iGluRs), including AMPA and NMDA receptors, which drive excitatory transmission and long-term plasticity.

CBD, CBDV, and Δ9-THC also modulate intracellular Ca^{2+} dynamics through transient receptor potential (TRP) channels (e.g., TRPV1, TRPV2, TRPA1), contributing to stabilization of neuronal excitability. In addition, CBD can inhibit voltage-gated sodium (Na_V) channels and VGCCs, while activating voltage-gated potassium (K_V) channels, further reducing neuronal firing.

Because GPR55 signaling has been associated with reduced γ-aminobutyric acid type A ($GABA_A$ receptor) expression, CBD-mediated interference with LPI–GPR55 pathways may help preserve inhibitory tone. Together, these complementary mechanisms may reduce network hyperexcitability, enhance inhibitory control, and increase seizure threshold, thereby supporting restoration of E/I balance in epileptic circuits. Schematic created by the author.

This article presents a mechanistic perspective informed by existing scientific literature. The content is intended for educational and scholarly purposes and should not be interpreted as medical advice or as evidence of clinical efficacy. Translation to clinical practice requires validation through rigorously controlled human studies.

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Abbreviations

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Ca^{2+}, calcium; CB1R, cannabinoid receptor type 1; CBD, cannabidiol; CBDV, cannabidivarin; Δ^9-THC, Δ^9-tetrahydrocannabinol; E/I balance, excitatory–inhibitory balance; $GABA_A$ receptor, γ-aminobutyric acid type A receptor; GPR55, G protein-coupled receptor 55; iGluR, ionotropic glutamate receptor; K_V, voltage-gated potassium channel; LPI, lysophosphatidylinositol; Na_V, voltage-gated sodium channel; NMDA, N-methyl-D-aspartate receptor; TRP, transient receptor potential; TRPV1/2, transient receptor potential vanilloid 1/2; TRPA1, transient receptor potential ankyrin 1; VGCC, voltage-gated calcium channel.

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