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MULTI TARGET MODULATION OF EPILEPTOGENIC PATHWAYS BY PLANT-DERIVED COMPOUNDS: A MECHANISTIC REVIEW FOR DRUG-RESISTANT EPILEPSY

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Abstract

Epilepsy represents a major neurological burden affecting approximately 100 million individuals worldwide, with one-third of cases remaining drug resistant despite available antiseizure medications. This resistance stems from the multifactorial nature of epileptogenesis, involving interconnected pathological processes including neurotransmitter imbalances (glutamate/GABA dysregulation), chronic neuroinflammation (astrocyte and microglia activation), mTOR pathway hyperactivation, and ion channel dysfunction. Current pharmacotherapies predominantly target single mechanisms, underscoring the need for multi target approaches. This review evaluates six plant derived compounds Cannabis sativa (cannabidiol, Δ^9-THC), Curcuma longa (curcumin), Acorus tatarinowii (asarones), Valeriana officinalis (valerenic acid), Citrus sinensis (hesperidin, nobiletin), and Cymbopogon winterianus (citronellal, geraniol) for their polypharmacological potential against these epileptogenic pathways. These botanicals demonstrate simultaneous modulation of multiple targets, offering a promising strategy for developing disease-modifying therapies. However, translational challenges including poor bioavailability, standardization issues, and limited clinical evidence must be addressed through advanced formulation strategies, systems pharmacology approaches, and mechanistically-informed clinical trials. Integrating ethnopharmacological knowledge with contemporary neuroscience may yield novel therapeutic avenues for drug resistant epilepsy.

INTRODUCTION

Epilepsy is a neurological disease, defined by recurrent seizures due to abnormal, excessive, or synchronized neuronal activity in the brain (Moshé et al., 2015). Epilepsy stands as one of the most prevalent chronic neurological disorders worldwide. Its global burden is high, with an estimated 100 million individuals expected to experience the condition during their lifetime (Helmstaedter et al., 2010)(Reynolds, 2002) . The lifetime risk of epilepsy and unprovoked seizures in industrialized nations is approximately 3.1% and 4.1%, respectively ("Series Editors," 2008), with a notably higher prevalence and associated treatment gap in less developed regions (Camfield

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& Camfield, 2015). This disorder transcends mere seizure occurrence, imparting significant neurological, cognitive, emotional, and social challenges that severely compromise quality of life (Beghi, 2019). The impact is particularly acute among older adults, who face a 2–3 times higher mortality rate compared to the general population (Brodie & Kwan, 2005).

Despite decades of pharmacological advancement, the management of epilepsy remains a formidable clinical challenge. Approximately one-third of patients develop drug-resistant epilepsy, experiencing uncontrolled seizures despite optimized antiseizure medication (ASM) regimens (Galanopoulou et al., 2012). Achieving seizure control is often a protracted process, requiring multiple therapy adjustments over several years (Alarcón & Valentín, 2012), while comorbidities further complicate care and diminish patient well-being. A critical limitation of current ASMs is that they primarily function as symptomatic treatments, suppressing seizures without addressing the underlying pathogenic processes that drive epileptogenesis (Tandon et al., 2024).

This review argues that a narrow shift towards targeting these core mechanisms of epileptogenesis including neurotransmitter imbalances (Zhou & Danbolt, 2014), neuroinflammatory cascades (Augusto-Oliveira et al., 2020), dysregulated mTOR signaling (Meng et al., 2013), and ion channel dysfunction (Kumar et al., 2016) that offer the most promising sites for developing disease modifying therapies. Concurrently, there is a resurrection of interest in plant derived compounds, which historically have served as sources of neuroactive agents and often exhibit polypharmacological profiles capable of modulating multiple pathological pathways simultaneously (He et al., 2024).

Therefore, the primary objective of this work is to synthesize contemporary understanding of key molecular mechanisms in epilepsy and critically evaluate the potential of selected plant derived compounds (Cannabis sativa, Curcuma longa, Acorus tatarinowii, Valeriana officinalis, Citrus sinensis, and Cymbopogon winterianus) to intervene in these processes. By bridging modern neurobiology with ethnopharmacology, this review aims to provide a mechanistic rationale for exploring novel, multi target botanical interventions that could potentially overcome the limitations of current monolithic therapies and address the unmet needs of patients with drug resistant epilepsy (He et al., 2024).

2. Core Mechanisms of Epileptogenesis: Underlying Pathogenic Processes

The development and persistence of epilepsy, known as epileptogenesis, involves a complex interplay of molecular and cellular dysregulations. Moving beyond symptomatic control requires targeting these core pathogenic processes, which serve as interconnected hubs for therapeutic intervention.

2.1. Neurotransmitter Imbalance: Glutamate and GABA Dysregulation

A fundamental mechanism in epilepsy is the disruption of the delicate balance between excitatory and inhibitory neurotransmission in the brain.

Glutamate serves as the principal excitatory neurotransmitter in the mammalian central nervous system and is profusely present within neuronal cells (Zhou & Danbolt, 2014). It plays a critical role in controlling various higher-order functions such as cognition, learning, and memory consolidation (Sarlo & Holton, 2021) .The release of glutamate from glutamatergic neurons is triggered through the activation of calcium channels, allowing it to enter the extracellular space, where it interacts with either ionotropic or metabotropic glutamate receptors to exert its effects (Sarlo & Holton, 2021) .To prevent excessive neuronal excitation, which can be detrimental, astrocytes and specific transporter systems facilitate the reuptake of glutamate from the synaptic cleft (Zhou & Danbolt, 2014).

In contrast, GABA functions as the chief inhibitory neurotransmitter within the brain and also plays an inhibitory role in the spinal cord (Chen & Sharma, 2025)(Pedrón et al., 2019). It acts primarily at postsynaptic GABA receptors, regulating ion channel activity and suppressing the generation of action potentials. A disturbance in the balance between excitatory (glutamate) and

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inhibitory (GABA) signaling specifically, elevated glutamate alongside reduced GABA can lead to excitotoxicity and is associated with the onset of seizures. This dysregulation is closely linked to disruptions in the glutamatergic pathway, which may result from receptor dysfunction, impaired transporter activity, or deficiencies in key enzymes involved in glutamate and GABA metabolism.

2.2. Neuroinflammation: Astrocyte and Microglia Activation

Chronic inflammation within the central nervous system (CNS) is now recognized as a key driver and sustainer of epileptic activity. Astrocytes, the principal supportive cells of the CNS, perform a wide spectrum of homeostatic and regulatory functions essential for maintaining neuronal health (Augusto-Oliveira et al., 2020; Lee et al., 2022). However, under conditions of cellular stress or injury, astrocytes undergo reactive astrogliosis, becoming hypertrophic and dysfunctional. Critically, their capacity to regulate extracellular ion concentrations and effectively clear excess glutamate becomes significantly impaired. The resulting accumulation of extracellular glutamate leads to excitotoxicity, further contributing to neurodegeneration and disease progression.

Simultaneously, microglias that are the resident immune cells of the CNS are transitioned from a surveillant to an activated state (Verkhratsky et al., 2021). Their functional response is highly variable; upon mild activation, they can exhibit neuroprotective effects. However, when exposed to severe stimuli, microglia transition to a proinflammatory phenotype, releasing cytokines, complement proteins, and other mediators that exacerbate neuroinflammation and can induce neuronal injury (Kwon & Koh, 2020; Lee et al., 2021). Astrocyte-microglia crosstalk represents a key mechanism in regulating CNS inflammation. The hyperactivation of NMDA-type glutamate receptors in neurons triggers the release of ATP, activating microglia to release proinflammatory mediators. These mediators subsequently activate astrocytes, leading to a feed forward production of additional chemokines and cytokines (Jha et al., 2019; Liu et al., 2020). Furthermore, microglia can increase extracellular glutamate levels through their own release mechanisms. When combined with the impaired glutamate uptake by reactive astrocytes, this synergistic effect substantially elevates excitotoxic risk and amplifies the inflammatory environment (Linnerbauer et al., 2020).

2.3. The mTOR Pathway: A Central Signaling Hub in Epileptogenesis

The mechanistic target of rapamycin (mTOR) pathway is a crucial intracellular signaling cascade whose hyperactivation is intimately linked to the development of structural and functional brain abnormalities that underlie epilepsy. mTOR is a serine/threonine protein kinase that forms part of two intracellular signaling complexes, mTORC1 and mTORC2 (elmegiri & El-Sayed, 2022; Meng et al., 2013). In the brain, mTOR signaling controls neuronal functions, such as synaptic plasticity, learning, and memory. As a result, dysregulation of mTOR signaling has been implicated in several neurodevelopmental and neuropsychiatric disorders (Gerasimenko et al., 2023). mTOR exerts control over the expression of diverse ion channels and neurotransmitter receptors, as well as influencing synaptic plasticity, neuronal morphology, and synaptic transmission (Sumadewi et al., 2023).

The key role of the mTOR pathway in epileptogenesis is best exemplified by tuberous sclerosis complex (TSC) and focal cortical dysplasia (FCD). mTOR hyperactivation due to mutations in phosphatase and tensin homolog (PTEN) and TSC1/2 genes leads to epileptogenesis in human samples and mouse models; conversely, inhibition of mTOR prevents the development of epilepsy and underlying neuronal alterations (Limanaqi et al., 2020). Loss-of-function mutations or removal of negative regulators like PTEN or TSC1/2 leads to an up regulation of mTOR signaling (Lasarge & Danzer, 2014).

Emerging studies have demonstrated that over activated mTOR induces the pathogenesis of epilepsy by disrupting the formation of neural circuits and altering existing neural networks (Zhao et al., 2023). Thus, excessive activation of

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mTOR signaling is linked to the development of cortical malformations and epilepsy (Citraro et al., 2016).

2.4. Ion Channel Dysfunction: Voltage-Gated Channelopathies

Ion channels are critical for neuronal excitability, and their dysfunction is a primary cause of both genetic and acquired forms of epilepsy. Ion channels are divided into two major classes: (i) voltage-gated (Na+, K+, Ca2+, and Cl−) and (ii) ligand gated (e.g., GABA, NMDA receptors) (Kumar et al., 2016). Molecular studies have demonstrated that specific ion channels play an important role in both genetic and acquired forms of epilepsy. There are three main ways in which ion channels are involved: specific mutations in familial idiopathic epilepsies; specific antibodies in acquired disorders; and changes in ion channel expression and function associated with modification of seizure activity (Lerche et al., 2013).

Voltage Gated Sodium Channels (VGSCs): VGSCs play a critical role in the generation and propagation of action potentials (APs) in neurons. Genetic alterations in VGSC genes (SCN1A/NaV1.1, SCN2A/NaV1.2, SCN3A/NaV1.3, and SCN8A/NaV1.6) are considered to be associated with epileptogenesis (Tao et al., 2019). Mutations can lead to defects in inactivation gating, enhancing persistent sodium currents and neuronal firing, resulting in epilepsy (Agbo et al., 2023).

Voltage Gated Calcium Channels (VGCCs): VGCCs mediate Ca2+ influx in response to action potentials and sub threshold depolarizing signals (Mayo et al., 2023).T-type VGCCs (Cav3.1–3.3) are important for the repetitive firing of action potentials in rhythmically firing cells. T-type VGCC abnormalities in expression and function have been linked to a range of neurological diseases, including absence seizure and epilepsy (Xu & Tang, 2018).

Voltage-Gated Potassium Channels (VGKCs): Potassium channels comprise the largest group of ion channels and regulate neuronal spike waveform and firing patterns by repolarizing and hyperpolarizing membrane potentials to prevent hyperactivity (Weng et al., 2022). Potassium channelopathies include those affecting the KV, KCa and Kir families, a significant proportion of which have been implicated in neurological disease (Allen et al., 2020). For instance, KCNQ2 potassium channel (Kv7.2) mutations that result in reduction or loss of channel activity cause benign familial neonatal convulsions (Li et al., 2013). In summary, the dysfunction of these ion channels destabilizes neuronal membrane potential and network synchrony, creating a hyper excitable state primed for seizure generation.

3. Plant-Derived Compounds as Multi-Target Therapeutic Agents

The limitations of current single target ASMs highlight the need for polypharmacological approaches. Plant derived compounds, with their inherent chemical diversity and multi target profiles, present a compelling strategy for modulating the interconnected pathogenic networks underlying epilepsy (Efferth & Koch, 2011). This section evaluates selected botanicals Cannabis sativa, Curcuma longa, Acorus tatarinowii, Valeriana officinalis, Citrus sinensis, and Cymbopogon winterianus through the lens of the core mechanisms outlined in Section 2, highlighting their potential as disease modifying agents.

3.1. Cannabis sativa: Modulation of the Endocannabinoid System and Beyond

Cannabis, commonly referred to as marijuana, has been utilized since the 19th century for the management of epileptic seizures. Cannabis sativa and its derivatives have garnered significant interest for treatment-resistant epilepsies, exemplified by the FDA approval of cannabidiol (CBD) for specific syndromes (Reddy & Golub, 2016).

Primary Active Compounds: Cannabidiol (CBD), Δ^9-tetrahydrocannabinol (THC) (Verrotti et al., 2016).

Mechanistic Targets:

Neurotransmitter Balance: CBD modulates the endocannabinoid system. Activation of presynaptic cannabinoid receptor 1 (CB1R) by

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endogenous ligands like anandamide reduces glutamate release, countering excitotoxicity. CBD also influences GABAergic signaling, helping restore inhibitory tone (Gray & Whalley, 2020).

Neuroinflammation: Both CBD and THC possess notable anti-inflammatory properties. They suppress pro-inflammatory cytokine release from activated microglia and astrocytes, directly targeting the neuroinflammatory cascade central to epileptogenesis (Kozela et al., 2010).

Ion Channel Dysfunction: CBD modulates voltage-gated sodium (Na^+) and T-type calcium (Ca^{2+}) channels, stabilizing neuronal membrane potential and reducing aberrant firing (Iannotti et al., 2014).

3.2. Curcuma longa (Turmeric): A Potent Anti-Inflammatory and Antioxidant Agent

Curcuma longa, widely recognized as turmeric, is a perennial herbaceous plant that is part of the Zingiberaceae family. The oil derived from Curcuma longa, along with its active compounds such as curcuminoids and bisabolene sesquiterpenoids, has shown potential in exhibiting anti-seizure effects (Choo & Shaikh, 2021).

Primary Active Compounds: Curcumin, bisdemethoxycurcumin (Orellana-Paucar et al., 2012).

Mechanistic Targets:

Neuroinflammation: Curcumin is a potent suppressor of NF-κB and other pro-inflammatory pathways, reducing astrocyte and microglial activation and the subsequent release of cytokines like IL-1β and TNF-α (Zafar et al., 2025).

Oxidative Stress: It scavenges reactive oxygen species (ROS) and up regulates endogenous antioxidant defenses (e.g., glutathione), mitigating oxidative damage that exacerbates neuronal hyper excitability.

Neurotransmitter Balance: Curcumin enhances GABAergic inhibition in the hippocampus and may modulate the L-arginine-NO pathway, contributing to reduced neuronal excitability (Mehla et al., 2010).

3.3. Acorus tatarinowii and Valeriana officinalis: Enhancing GABAergic Inhibition

The rhizome of Acorus tatarinowii, referred to as Shi-Chang-Pu in Chinese, has been employed in clinical practice for the management of various disorders affecting the central nervous system (CNS) (Liu et al., 2015). Valeriana officinalis L., a member of the Valerianaceae family, has been utilized as a medicinal herb for thousands of years, with its dried roots and rhizomes being particularly valued, this plant contains over 150 identified chemical constituents within its essential oils, with variations in these constituents observed depending on the harvest conditions. These plants are traditional nervines with well-characterized GABA-enhancing effects.

Primary Active Compounds: α- and β-asarone (Acorus), valerenic acid and valepotriates (Valeriana) (Wang et al., 2023)(Torres-Hernández et al., 2015).

Mechanistic Targets:

Neurotransmitter Balance: Both plants strongly potentiate GABAergic transmission. Asarones increase GABA levels by up regulating glutamic acid decarboxylase (GAD) and inhibiting GABA transaminase (GABA-T) (Kim et al., 2022)(He et al., 2023). Valerian compounds inhibit GABA degradation and reuptake, and may act as ligands at $GABA_a$-benzodiazepine receptor sites (Malva et al., 2004). Neuroinflammation: Secondary anti-inflammatory properties of these compounds help reduce associated inflammatory damage in chronic epilepsy models.

3.4. Citrus sinensis and Cymbopogon winterianus: Flavonoid and Terpenes Mediated Actions

Citrus sinensis, commonly known as sweet orange, belongs to the Rutaceae family and is extensively cultivated worldwide. Two significant flavonoids, Hesperidin (Hsd) and its aglycone Hesperetin (Hst), exhibit neuroprotective properties associated with citrus flavonoids, demonstrating important biological effects. Research indicates that the anticonvulsant effect of hydro-ethanolic leaf extract of Citrus sinensis is more pronounced at a dosage of 100 mg/kg compared to 50 mg/kg.

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This suggests that the hydro-ethanolic leaf extract may exert its anticonvulsant action by enhancing the levels of gamma amino butyric acid (GABA), an inhibitory neurotransmitter in the central nervous system. Cymbopogon winterianus Jowitt, commonly referred to as java citronella or "capim-citronela" in Brazil, is a member of the Poaceae family. This plant is utilized in Brazilian traditional medicine for its analgesic, anxiolytic, and anticonvulsant effects. These plants contribute a range of bioactive molecules with complementary mechanisms.

Primary Active Compounds: Hesperidin, nobiletin, tangeretin (Citrus); citronellal, geraniol (Cymbopogon).

Mechanistic Targets:

Neurotransmitter Balance: Extracts from both plants demonstrate GABA-enhancing activity. Citrus flavonoids can act as benzodiazepine receptor ligands, while Cymbopogon constituents like citronellal and geraniol potentiate $GABA_a$ receptor function (de Sousa et al., 2006; Hanrahan et al., 2011).

Ion Channel Dysfunction: Citronellol from Cymbopogon exhibits voltage-dependent sodium channel blockade, reducing neuronal excitability at the membrane level (Maher, 2019).

Antioxidant Effects: The high flavonoid content in Citrus spp. provides robust antioxidant activity, protecting against oxidative stress-induced neuronal damage (de Sousa et al., 2006).

Plant Source	Key Bioactive Compounds	Targeted Epileptogenic Pathway	Specific Molecular Action	Proposed Therapeutic Effect	Representative References
Cannabis sativa	Cannabidiol (CBD), Δ^9-THC	1. Neurotransmitter Imbalance 2. Neuroinflammation 3. Ion Channel Dysfunction	• CB1R activation → ↓ glutamate release • ↓ Proinflammatory cytokines (IL-1β, TNF-α) • Modulation of T-type Ca^{2+} channels	Multi-target anticonvulsant; FDA-approved for specific epileptic syndromes	(Gray & Whalley, 2020)
Curcuma longa (Turmeric)	Curcumin, curcuminoids	1. Neuroinflammation 2. Neurotransmitter Imbalance 3. Oxidative Stress	• NF-κB pathway inhibition • ↑ GABAergic transmission • ROS scavenging, ↑ glutathione	Anti-inflammatory, antioxidant, potential disease-modifying agent	(Choo & Shaikh, 2021; Mehla et al., 2010)
Acorus tatarinowii	α-Asarone, β-Asarone	1. Neurotransmitter Imbalance (Primary) 2. Neuroinflammation	• ↑ GAD activity (GABA synthesis) • ↓ GABA-T activity (GABA degradation) • Anti-inflammatory effects	GABA-enhancing anticonvulsant	(Kim et al., 2022; Liu et al., 2015)
Valeriana officinalis	Valerenic acid, valepotriates	1. Neurotransmitter Imbalance	• $GABA_a$ receptor modulation • ↓ GABA reuptake/degradation	Anxiolytic, sedative, anticonvulsant through GABAergic system	(Benke et al., 2009)(Malva et al., 2004)
Citrus sinensis	Hesperidin, nobiletin, tangeretin	1. Neurotransmitter Imbalance 2. Oxidative Stress	• $GABA_a$ receptor ligand activity	Antioxidant neuroprotection	(Hanrahan et al., 2011)

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			• Flavonoid-mediated antioxidant effects	with GABAergic modulation	
Cymbopogon winterianus	Citronellal, geraniol	1. Ion Channel Dysfunction 2. Neurotransmitter Imbalance	• Voltage-gated Na^+ channel blockade • $GABA_a$ receptor potentiation	Anticonvulsant via membrane stabilization and GABA enhancement	(de Sousa et al., 2006)

Table 1: Mechanistic profiles of selected plant derived compounds against epileptogenic pathway.

4. Discussion

The comprehensive review of epileptogenesis mechanisms and plant derived therapeutics reveals a compelling convergence. Many botanical compounds intrinsically target multiple pathways involved in epilepsy's pathogenesis. This discussion synthesizes these findings, evaluates the therapeutic implications, addresses translational challenges, and proposes a future research framework.

4.1. The Multi-Target Advantage in Complex Neurological Disorders

Epilepsy's multifactorial nature encompassing excitotoxicity, neuroinflammation, aberrant signaling, and channel dysfunction, presents a fundamental challenge to single target pharmacotherapy. Current ASMs typically address one aspect, often GABA enhancement or sodium channel blockade, which explains both their efficacy limitations and high rate of therapeutic failure (up to 30%) (Galanopoulou et al., 2012). In contrast, plant derived compounds often exhibit polypharmacology (the ability to modulate multiple targets simultaneously) which aligns with systems biology approaches to complex diseases (Efferth & Koch, 2011).

For instance, curcumin from Curcuma longa demonstrates this advantage clearly: it simultaneously suppresses neuroinflammation (via NF-κB inhibition), enhances GABAergic inhibition, and provides antioxidant protection (Choo & Shaikh, 2021; Iannotti et al., 2014). Similarly, CBD from Cannabis sativa modulates glutamate release, reduces inflammatory cytokines, and affects voltage-gated ion channels (Gray & Whalley, 2020). This multi target profile may provide broader therapeutic coverage, potentially addressing both seizure control and disease modification a critical unmet need in epilepsy management.

4.2. Mechanistic Synergies and Pathway Convergence

The reviewed plants demonstrate remarkable convergence on key epileptogenic hubs. The GABAergic system emerges as a particularly common target, with multiple plants (Acorus tatarinowii, Valeriana officinalis, Citrus sinensis, Cymbopogon winterianus) employing different strategies to enhance inhibitory tone. This redundancy across species suggests an evolutionarily conserved pathway for neurological modulation.

Equally significant is the concurrent targeting of neuroinflammation by several compounds. Chronic inflammation is now recognized not merely as a consequence but as a driver of epileptogenesis (Vezzani et al., 2019). Plants like Curcuma longa and Cannabis sativa offer direct anti-inflammatory action through distinct but complementary mechanisms curcumin via NF-κB pathway inhibition and CBD through endocannabinoid mediated cytokine regulation. This simultaneous modulation of both neuronal excitability and inflammatory environment represents an important approach absent from most conventional ASMs.

4.3. Translational Challenges and Limitations

Despite promising mechanistic evidence, significant barriers hinder the clinical translation of plant based epilepsy therapies:

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4.3.1. Bioavailability and Blood-Brain Barrier Penetration

Many promising compounds, particularly curcumin and flavonoids, suffer from poor oral bioavailability and limited CNS penetration due to extensive metabolism, rapid elimination, and efflux transporter activity (Anand et al., 2007). For instance, curcumin bioavailability is exceptionally low (<1% in some studies), necessitating advanced delivery systems for therapeutic efficacy.

4.3.2. Standardization and Quality Control

Botanical preparations face inherent variability due to genetic differences, growing conditions, harvest times, and extraction methods. The chemical complexity of plant extracts containing hundreds of compounds with potentially synergistic or antagonistic effects complicates standardization, dosing, and reproducibility (Heinrich et al., 2020). This contrasts sharply with the precise chemical definitions required for pharmaceutical development.

4.3.3. Dose-Dependent and Context-Specific Effects

Several compounds exhibit bidirectional or dose-dependent effects. Δ^9-THC demonstrates anticonvulsant properties at lower doses but can be proconvulsant at higher concentrations (Rosenberg et al., 2017). Similarly, some flavonoids show GABAergic enhancement at certain concentrations but inhibition at others. This complexity requires precise therapeutic windows that may vary between individuals and epilepsy types.

4.3.4. Limited Clinical Evidence

Despite extensive preclinical data, robust clinical trials remain sparse for most plant derived epilepsy treatments except CBD (in specific pediatric syndromes). The evidence for curcumin, asarones, and citrus flavonoids primarily derives from animal models, with few randomized controlled trials in human epilepsy populations.

4.4. Future Research Directions: A Translational Roadmap

4.4.1. Advanced Formulation Strategies

To overcome bioavailability limitations, future research should prioritize innovative delivery systems:

Nanotechnology: Lipid nanoparticles, polymeric nanocarriers, and nanoemulsions can enhance CNS delivery of compounds like curcumin and hesperidin (Hafezi et al., 2020).

Pro drug Development: Chemical modification to improve pharmacokinetic properties while maintaining therapeutic activity. Combination Formulations: Rational combinations of plant compounds with complementary mechanisms and pharmacokinetics.

4.4.2. Systems Pharmacology Approaches

Modern analytical techniques can elucidate the complex mechanisms of plant extracts:

Network Pharmacology: Mapping compound target disease networks to identify key nodes and synergistic combinations. Omics Technologies: Transcriptomics, proteomics, and metabolomics to characterize systemic effects beyond known targets. Computational Modeling: In silico screening of plant compound libraries against epileptogenesis related targets.

4.4.3. Mechanistically Informed Clinical Trial Design

Future clinical investigations should move beyond symptom focused endpoints:

Biomarker Driven Trials: Incorporate neuroimaging (MRS for GABA/glutamate), EEG biomarkers, and inflammatory markers (IL-1β, TNF-α) to demonstrate target engagement.

Population Stratification: Test compounds in patient subgroups most likely to benefit based on pathophysiology (e.g., anti-inflammatory agents in patients with elevated inflammatory markers).

Disease-Modification Endpoints: Assess impact on epileptogenesis biomarkers, cognitive outcomes, and neuroprotection in addition to seizure frequency.

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4.4.4. Integration with Conventional Therapies

Research should explore rational combination therapies where plant compounds complement conventional ASMs. Adjunctive Therapy Trials: Evaluate botanical supplements alongside standard ASMs, monitoring for synergistic effects and reduced side effects. ASM Sparing Strategies: Investigate whether multi target plant compounds can reduce requirements for conventional medications with significant adverse effects.

4.5. Ethical and Regulatory Considerations

The integration of traditional botanical knowledge into modern epilepsy therapy requires careful navigation. Intellectual Property and Benefit Sharing: Equitable models for developing traditional knowledge-based therapies (Heinrich et al., 2020).

Regulatory Harmonization: Development of appropriate regulatory frameworks for complex botanical products that acknowledge their unique characteristics while ensuring safety and efficacy.

Standardization Protocols: Establishment of internationally recognized standards for authentication, extraction, and quality control of medicinal plants for epilepsy.

5. Conclusion

This review has systematically examined the convergence between core mechanisms of epileptogenesis neurotransmitter imbalance, neuroinflammation, mTOR dysregulation, and ion channel dysfunction and the multi target profiles of selected plant derived compounds. The analysis reveals that plants like Cannabis sativa, Curcuma longa, Acorus tatarinowii, Valeriana officinalis, Citrus sinensis, and Cymbopogon winterianus contain bioactive constituents capable of simultaneously modulating multiple pathological pathways.

The polypharmacological nature of these botanical agents represents both their greatest therapeutic potential and their most significant translational challenge. Unlike conventional ASMs with singular mechanisms, these compounds engage epilepsy's complexity more holistically, potentially offering advantages for drug-resistant cases and disease modification. However, realizing this potential requires overcoming substantial barriers in bioavailability, standardization, and clinical validation.

The path forward necessitates a multidisciplinary approach combining ethnopharmacology with modern neuroscience, advanced formulation science, and innovative clinical trial design. By bridging traditional knowledge with contemporary molecular understanding, plant derived compounds may contribute to a new generation of epilepsy therapies that address not just symptoms but the underlying disease process. As research progresses, these natural products offer hope for developing more effective, better tolerated treatments for the millions worldwide living with uncontrolled epilepsy.

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