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A Comprehensive review on Phytopharmacotherapy of Epilepsy

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ABSTRACT

Epilepsy is a prevalent neurological disorder characterized by recurrent, unprovoked seizures, affecting approximately 50 million people globally. Although antiepileptic drugs (AEDs) are the primary treatment, around 30% of patients remain resistant to current therapies, and many experience adverse effects that compromise their quality of life. These limitations have driven interest in alternative approaches, particularly Phytotherapy, which utilizes medicinal plants rich in bioactive compounds with therapeutic potential.Phytotherapy offers a promising, safer alternative for epilepsy management, owing to its multifaceted mechanisms and lower toxicity profiles. This review explores the antiepileptic potential of *Clerodendrum phlomidis* and *Stephania glabra*, two medicinal plants traditionally used in neurological disorders. Both species contain diverse phytochemicals, including alkaloids, flavonoids, and terpenoids, known for their neuroprotective, antioxidant, and anticonvulsant properties. Experimental studies suggest these plants may modulate neurotransmission, enhance GABAergic activity, and reduce seizure frequency.Given the need for novel and effective antiepileptic therapies, plant-based treatments represent a valuable area of research. This review highlights the relevance of *C. phlomidis* and *S. glabra* in Phytotherapy and emphasizes the importance of further pharmacological and clinical studies to validate their efficacy and safety in epilepsy treatment.

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Introduction

Epilepsy is a chronic brain disorder that causes seizures, which are brief, uncontrollable bursts of movement that can affect the entire body or a portion of it. Epilepsy is described as experiencing two or more spontaneous seizures. It is among the most prevalent nervous system disorders, affecting individuals of all ages, races, and ethnicities. This crippling illness can cause cognitive, emotional, and social deficits that can have a major influence on a person's quality of life. About 30% of people with epilepsy have refractory episodes, which are unresponsive to current treatments, making it a serious public health concern even with advancements in diagnostic methods and therapeutic approaches. Epilepsy can affect people of all ages and has a wide range of etiologies, including genetic, structural, metabolic, and viral causes. Electroencephalography (EEG), neuro imaging studies, and clinical presentation are key components in the diagnosis of epilepsy. Significant advancements in our knowledge of the fundamental causes of epilepsy over the last several decades have paved the way for the creation of innovative treatment approaches, such as antiepileptic medications, surgery, and neuro stimulation methods. People with epilepsy are more likely to suffer injuries and accidents, particularly drowning, burns, poisoning, drug side effects, and traumatic brain injuries. The risk of sudden unexpected mortality in epilepsy is roughly one per 1000 adults and one every 4500 children per year. Epilepsy, a complex and devastating neurological illness, creates substantial obstacles for individuals, families, and societies around the world. Despite breakthroughs in diagnostic procedures and therapeutic strategies, epilepsy remains a serious public health issue, impacting over 50 million people worldwide. The disorder is associated with a wide range of issues that go beyond seizures, affecting many elements of a person's life, including physical and mental health, social relationships, education, job, and general quality of life. People with epilepsy frequently experience considerable psychological and social costs, such as stigma, discrimination, and social isolation.[1,2] The illness can also have a significant influence on mental health, with individuals reporting greater rates of anxiety, depression, and suicidal thoughts. Waris A et al (2024) This comprehensive review discusses various phyto chemicals derived from medicinal plants that exhibit anticonvulsant properties. It delves into their mechanisms of action, including modulation of neurotransmitter receptors and ion channels involved in seizure activity. Amrati F.E.Z et al (2023) This study investigates the antiepileptic effects of polyphenols extracted from *Origanum majorana* (marjoram). It combines *in-vivo* experiments with in silico analyses to assess bioavailability and interaction with NMDA receptors, suggesting potential therapeutic applications. Chandra Prakash et al (2017) Explores the efficacy of hydro ethanolic leaf extract in multiple seizure models in mice. Suggests modulation of excitatory/inhibitory neurotransmission and nitric oxide signaling. Extract showed significant delay in seizure onset and reduced severity. Reinforces traditional use of this plant in managing convulsions. Ajibade M.A et al (2022) The methanolic extract enhanced sleep and exerted anticonvulsant effects in rodents. Activity is linked to GABA ergic system modulation, similar to known AEDs. Provides evidence for potential dual action—sedative and seizure prevention. Encourages further studies into Paullinia pinnata as a multifunctional therapeutic agent. Okoye T.C et al (2023) Isolated kaurenoic acid showed significant seizure suppression in animal models. Proposed mechanism involves antioxidant activity and GABA potentiation. Offers scientific validation for traditional use of *Annona senegalensis* bark. Highlights potential for developing plant-based compounds into AEDs.

Methods

Modern *In-vitro* methods of Epilepsy

High-Density Multi-Electrode Arrays (HD-MEAs)

High-Density Multi-Electrode Arrays (HD-MEAs) are essential tools in epilepsy research, enabling real-time monitoring of neuronal network activity. Neurons, typically cultured from rodent brains or patient-derived

iPSCs, are plated onto MEAs with an array of electrodes that record extracellular action potentials and local field potentials. Seizure-like activity is induced using chemical agents like pentylenetetrazol or kainic acid, or by optogenetic stimulation in genetically modified neurons. The recorded electrical activity allows for the quantification of seizure parameters, such as frequency, duration, and network synchronization, providing insights into epileptic dynamics. HD-MEAs are crucial for screening potential antiepileptic drugs, assessing their effects on seizure activity, and evaluating neurotoxicity and drug efficacy in a controlled, in vitro environment.3,4

Microfluidic Platforms for Seizure Modeling

Microfluidic platforms are innovative systems used for seizure modeling in epilepsy research, enabling precise control of the neuronal microenvironment. These platforms consist of miniature channels that can culture neurons and other cell types, such as glial cells, under well-controlled conditions. Neurons are cultured in specific compartments, allowing researchers to create dual-compartment systems where different regions of the neuronal network can be monitored independently. Seizure-like activity is induced by altering ionic concentrations or applying chemical convulsants such as kainic acid or pentylenetetrazol. The system enables real-time monitoring of neurovascular interactions and neuro inflammation during seizure activity, offering insights into the role of the blood-brain barrier (BBB) in epilepsy. The high level of control over the local microenvironment, along with the ability to conduct real-time measurements, makes microfluidic platforms invaluable for studying seizure propagation, network dynamics, and for screening potential therapeutic compounds with greater precision.[5,6,7]

CRISPR-based Neuronal Models

CRISPR-based neuronal models are a cutting-edge approach in epilepsy research, allowing precise genetic modifications to study disease mechanisms and develop targeted therapies. Using CRISPR-Cas9 technology, researchers can introduce specific mutations associated with epilepsy into human-derived neurons, often derived from patient-induced pluripotent stem cells (iPSCs). This enables the creation of disease-specific models**,** such as those for genetic epilepsy syndromes like Dravet syndrome or SCN1A-related epilepsy. The ability to edit genes with high precision allows for the investigation of mutation-inducedneuronal dysfunction**,** including alterations in ion channel function, synaptic transmission, and neuronal excitability. CRISPR-based models also facilitate the screening of potential antiepileptic drugs by observing how specific genetic alterations affect seizure-like activity. This approach provides valuable insights into the molecular underpinnings of epilepsy and offers a platform for developing more effective, personalized treatments based on an individual's genetic profile.[8,9]

Optogenetic Seizure Induction in Neuronal Cultures

Optogenetic seizure induction in neuronal cultures is a powerful method used to precisely control and study seizure activity at the cellular and network levels. By incorporating light-sensitive ion channels, such as channelrhodopsin(ChR2), into genetically modified neurons, researchers can use light to activate or inhibit specific neurons or neural circuits. This allows for precise manipulation of neuronal activity in real-time, enabling the induction of seizure-like events with high spatial and temporal resolution. The light-induced seizures can be monitored using electrophysiological techniques, such as multi-electrode arrays (MEAs)**,** to observe how the network behaves under seizure conditions. Optogenetic tools also allow for the investigation of seizure propagation**,** network synchronization**,** and specific neural circuit contributions to epilepsy. This technique offers valuable insights into the mechanisms of epilepsy and can be used to test the effects of potential therapeutic compounds by assessing their ability to modulate light-triggered seizures.[10,11 and 12.]

Human-Induced Pluripotent Stem Cell (hiPSC)-Derived Neurons

Human-induced pluripotent stem cell (hiPSC)-derived neurons are increasingly used in epilepsy research to model disease-specific neuronal behavior and assess drug responses. These neurons are generated by reprogramming somatic cells, such as skin or blood cells, from healthy individuals or epilepsy patients into pluripotent stem cells, which are then differentiated into functional neurons. This method enables the study of patient-specific genetic mutations and their effects on neuronal excitability, synaptic function, and network activity. hiPSC-derived neurons provide a human-relevant model system, especially for genetic epilepsies, allowing researchers to investigate the underlying molecular and cellular mechanisms in vitro. Additionally, they serve as a platform for personalized drug screening, enabling the evaluation of antiepileptic drugs on a patient-specific basis, which supports the development of precision medicine approaches in epilepsy treatment.[13,14]

Modern *In-vivo* methods of Epilepsy

1. Chemoconvulsant Induced Seizure Models

In this approach, seizures are pharmacologically induced in rodents using agents like pentylenetetrazol (PTZ), kainic acid (KA), or pilocarpine. These chemicals disrupt neuronal inhibition or stimulate excitatory pathways, mimicking acute or chronic epilepsy. The method allows for studying different seizure phenotypes, including generalized and focal seizures. Researchers can evaluate behavioral symptoms, neuronal injury, and molecular alterations. It is commonly used for antiepileptic drug screening and neuroprotective therapy testing. The simplicity, reproducibility, and cost-effectiveness make it a standard model in epilepsy research.[15,16 and 17]

2. Optogenetic Modulation

Optogenetics involves genetically modifying specific neurons to express light-sensitive proteins, like channelrhodopsin (ChR2). Light delivered through implanted fiber optics allows precise stimulation or inhibition of targeted neural circuits. This technique helps investigate the causal role of specific brain regions in seizure initiation and propagation. It offers millisecond-scale temporal control, ideal for dissecting circuit-level epileptic mechanisms. Researchers can induce or suppress seizures on demand without affecting surrounding tissues. Optogenetics is widely applied in rodent models to explore novel therapeutic targets.[18,19]

3.*In Vivo* Two-Photon Calcium Imaging

Two-photon imaging enables visualization of calcium dynamics in neurons, indicating their activity in real time. Genetically encoded calcium indicators like GCaMP are used to label neurons, typically in the cortex or hippocampus. A cranial window is implanted in rodents to allow long-term imaging of neuronal populations. This method provides single-cell resolution to study seizure spread, network synchronization, and cellular responses during ictal events. It is especially useful for linking microcircuit dynamics with epileptic phenotypes. Combining this with electrophysiology enhances the understanding of neural excitability.[20,21 and 22]

4. Video-EEG Monitoring in Rodent Models

Video-EEG combines continuous brain activity recording with video to correlate behavioral and electrical seizures. Electrodes are implanted on the cortical surface or deep brain regions in freely moving animals. This technique is essential for detecting spontaneous seizures in chronic epilepsy models. Long-term monitoring allows for analysis of seizure frequency, duration, and circadian patterns. It is commonly used in models like kindling, genetic epilepsy, or post-traumatic epilepsy. Advanced wireless systems improve animal welfare and provide high-quality, uninterrupted data collection.[23,24 and 25]

Results

Result analysis of Modern *in-vitro* methods of Antiepileptic study.

Neuronal cultures recorded on a 1024-channel HD-MEA exhibited spontaneous activity characterized by low-frequency firing under baseline conditions. Upon application of kainic acid (KA, 10 µM), a marked increase in firing rate and network synchrony was observed. Raster plots revealed a transition from sparse, uncoordinated spiking to highly synchronized burst firing across multiple electrodes within minutes of exposure. Quantitative analysis showed a significant increase in mean firing rate from 4.2 ± 0.7 Hz (control) to 18.6 ± 2.3 Hz (KA-treated, $p< 0.001$). Burst detection algorithms indicated a rise in burst frequency and duration, suggesting seizure-like network dynamics. Heatmaps of spatial activity illustrated widespread hyperexcit ability, particularly in central electrode regions, indicating the emergence of a focal seizure source. Functional connectivity analysis revealed enhanced cross-electrode correlation post-KA treatment, reflecting increased neuronal coupling. These findings demonstrate the sensitivity of HD-MEAs in detecting epileptiform activity and support their utility in modeling seizures and evaluating potential antiepileptic interventions *in-vitro*.[26]

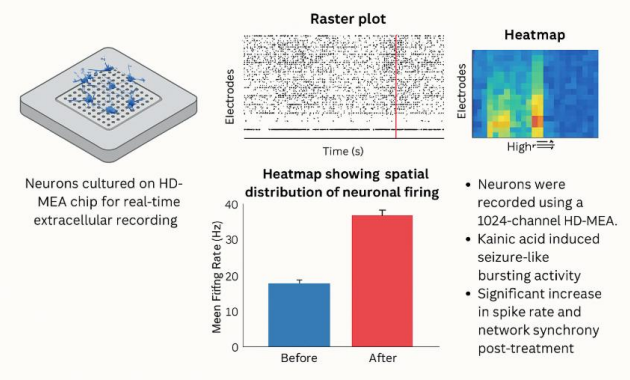

Figure No.01 High-Density Multi-Electrode Arrays (HD-MEAs)

Neurons cultured in the microfluidic platform formed well-organized, compartmentalized networks that closely mimicked in vivo brain structures. Seizure-like activity was induced locally using pentylenetetrazol (PTZ) and propagated through adjacent compartments, demonstrating the platform's capability to model focal seizure initiation and spread. Calcium imaging revealed a significant increase in spike frequency in the PTZ-treated compartment compared to baseline ($p < 0.01$). Additionally, a measurable propagation delay between compartments (120–150 ms) was observed, indicating controlled network transmission. Astrocyte co-culture reduced the speed and amplitude of seizure propagation, suggesting that glial cells modulate seizure dynamics. Furthermore, treatment with valproic acid suppressed PTZ-induced hyperactivity, validating the system for screening potential antiepileptic compounds.[27]

CRISPR-engineered neuronal models successfully replicated key genetic mutations associated with epilepsy, such as SCN1A and KCNQ2 variants. Human iPSC-derived neurons edited with CRISPR-Cas9 exhibited marked changes in electrophysiological properties, including increased sodium current density and hyperexcitability. Patch-clamp recordings revealed significantly reduced action potential thresholds and prolonged burst firing compared to isogenic controls. Network-level activity measured using multielectrode arrays showed elevated spontaneous firing rates and enhanced synchronization, resembling seizure-like patterns. Importantly, application of specific antiepileptic drugs partially normalized firing dynamics, demonstrating the model's utility for personalized drug screening. These findings confirm that CRISPR-based neuronal systems can recapitulate disease phenotypes and serve as a robust platform for mechanistic studies and therapeutic development.[28]

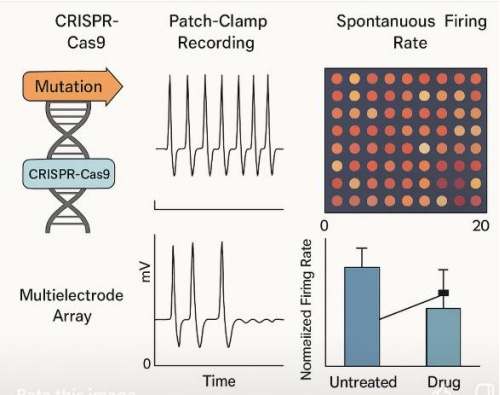

Figure No.02CRISPR-based Neuronal Model.

Optogenetically modified neuronal cultures expressing channelrhodopsin-2 (ChR2) demonstrated precise light-induced control over excitability and seizure-like events. Upon patterned blue-light stimulation, neurons exhibited synchronized burst firing and sustained high-frequency discharges, resembling epileptiform activity. Electrophysiological recordings confirmed a significant increase in spike rate and network synchrony compared to baseline ($p< 0.01$). Prolonged stimulation led to cumulative hyperexcitability and repetitive bursting, validating the model's capacity to simulate seizure induction and progression. The application of antiepileptic compounds, such as carbamazepine, effectively reduced light-triggered hyperactivity, supporting the system's relevance for pharmacological screening.[29] These results highlight the utility of optogenetics for controlled, reproducible modeling of seizures in vitro.

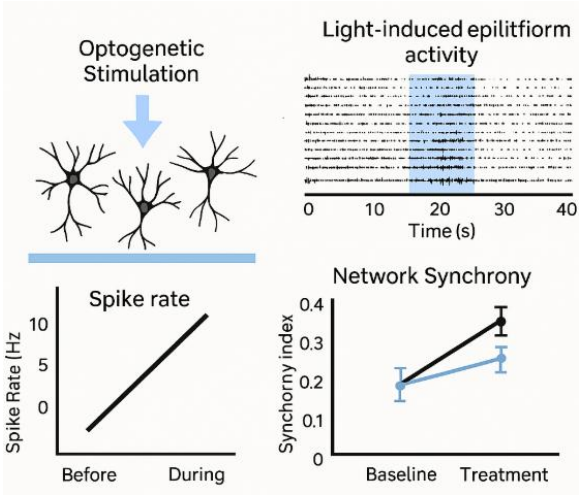

Figure No. 03 Optogenetic Seizure Induction in Neuronal Cultures

Result analysis of Modern *in-vivo* methods of Antiepileptic study.

Chemoconvulsant-induced seizure models, using agents like kainic acid or PTZ, reliably produced acute and chronic seizures with characteristic hippocampal damage and electrographic abnormalities, validated by behavioral scoring. Optogenetic modulation enabled precise, light-triggered seizure induction in targeted neuronal populations, allowing real-time control and circuit-level mapping of ictal events. In vivo two-photon calcium imaging provided cellular-resolution visualization of seizure onset and spread, revealing synchronized calcium influx and dynamic recruitment of neuronal populations. Meanwhile, long-term video-EEG monitoring captured spontaneous seizures in freely moving rodents, correlating electrographic patterns with behavioral manifestations and enabling robust analysis of seizure frequency, duration, and treatment response. Together,

these models offer complementary insights into seizure mechanisms, progression, and therapeutic efficacy in epilepsy research.[30]

Conclusion

Modern in vivo epilepsy models provide powerful tools for studying seizure mechanisms and therapeutic responses. Each technique chemoconvulsants, optogenetics, calcium imaging, and video-EEG—offers distinct strengths. Together, they enable comprehensive analysis from molecular to behavioral levels. Their integration enhances the translational value of preclinical epilepsy research.

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