Exploring multi-omics strategies for herbal treatment of drug-resistant epilepsy: a comprehensive review

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Wasim M and Arain FM conceived the idea. Wasim M wrote the manuscript and revised the manuscript several times, Arain FM, Siddiqi HS, and Ahmad S improved and revised the manuscript. Wasim M and Arain FM revised the manuscript and approved it for the final submission.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
ASMs, anti-epileptic drugs; TLE-HS, temporal lobe epilepsy with hippocampus sclerosis; CA, cornu ammonis; GABA, γ-aminobutyric acid; NMR, nuclear magnetic resonance; TCM, traditional Chinese medicine; MS, mass spectrometry.

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Abstract
Epilepsy affects approximately 70 million people worldwide. Yet scientists have a partial understanding of the disease pathophysiology due to its heterogenic nature. About 70% of cases of epilepsy are treatable with FDA-approved anti-epileptic drugs while temporal lobe epilepsy with hippocampus sclerosis (TLE-HS) is drug resistant. Numerous herbs have been noted for their potential anti-convulsant properties. Yet, due to the scarcity of experimental data, there is an urgent need to conduct thorough investigations into these herbs for their practical use in treating TLE-HS. In-depth multi-omics research is needed for targeted TLE-HS therapy, focusing on cornu ammonis subregions, dentate gyrus, and also genetically glutamate, and γ-aminobutyric acid receptors. Animal models, due to the lack of human brain tissue, enable homogeneous sample selection, comparable groups, and ample tissue for in-vitro and ex-vivo studies. Consequently, it becomes feasible to examine the effectiveness of herbs on individual brain regions at the molecular level, paving the way for the potential development of drug interventions to treat TLE-HS.

Keywords: traditional medicine; GABA receptors; glutamate receptors; multi-omics; temporal lobe epilepsy

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Highlights
Herbs with anti-convulsant potential require further research for practical application in TLE-HS treatment. Essential multi-omics studies, targeting specific brain regions and genetics, are vital for precise therapy. Animal models offer a homogeneous platform to explore herb effectiveness at the molecular level, indicating potential drug development for TLE-HS treatment.

Medical history of objective
In Chinese medical history, the first known record of epilepsy in China is found in Huangdi Neijing, authored by a group of physicians around 770–221 B.C.E. In the article "Old remedies for epilepsy: Avicenna’s medicine", Asadi-Pooya AA et al. highlighted epilepsy’s historical roots spanning at least four millennia. Avicenna, born around 980 C.E. in Khorasan, and passing away in 1037 C.E. in Hamedan, provided numerous recommendations and proposed therapies for epilepsy in "The Canon of Medicine" (1025 C.E.).

Background
Epilepsy is a widespread chronic brain disorder affecting about 70 million people worldwide, with lot of complexity in the quality of life [1–3]. Among the wide spectrum of epilepsy disorders, temporal lobe epilepsy (TLE), frequently resistant to anti-epileptic drugs (ASMs). During the last 2 decades, more than 15 ASMs have been introduced with unique mechanisms of action [4]. Yet, around 30% epileptic patients are not treatable, while receiving ASMs either single or in combinations, with complex psychiatric, behavioral, cognitive, as well as social problems [5, 6]. In clinical settings, surgery is often employed for patients experiencing severe cases of TLE. A prevalent histopathological change observed in TLE is known as hippocampal sclerosis (TLE-HS). This condition is characterized by visible neuronal loss and reactive gliosis in the cornu ammonis (CA) regions. The anatomical regions involved include the dentate gyrus, CA1, CA2, and CA3, which are interconnected [7–9]. Hence, patients with psychiatric comorbidities and sclerosis contributes to seizures which prove resistant to both ASMs and epilepsy surgery [4, 10, 11]. Hence, there is an urgent requirement to delve into the potential of herbal remedies and employ multi-omics investigations on these crucial brain regions to develop specific treatment approaches.

The primary causes of TLE-HS include abnormal neuronal excitability and changes in cellular connections. Neuronal alterations in the hippocampus, particularly imbalances in inhibitory (GABA) and excitatory (glutamate) signaling, are reported as key factors in establishing ictal activities [12]. Major inhibitory and excitatory neurotransmitters are GABA and glutamate, and these neurotransmitters are targeted by several ASMs, but still TLE-HS is resistant to such ASMs. As of now, there is no effective long-term treatment for TLE-HS. Consequently, there is a necessity to conduct advanced medical research, particularly through multi-omics investigations, to address this form of epilepsy that does not respond well to treatment. Over the past decade, advancements in high-throughput molecular methods have revolutionized the field of biological sciences [14]. Multi-omics integration, using transcriptomics and proteomics, unravels complex biological system information. Transcriptomics gauges RNA levels, indicating transcript presence and abundance. Proteomics assesses peptide abundance, protein quantification, modifications, and interactions. This synergy provides a comprehensive understanding of biological pathways in disease progression [15–17]. This review presents a comprehensive overview of experimental and potential herbal treatment options with a primary focus on improving the quality of life for individuals, particularly those suffering from drug-resistant epilepsy through multi-omics investigations. The aim is to empower patients with TLE-HS to lead healthy and fulfilling lives.

Classification of epilepsy
Epilepsy is classified by seizure types into focal, generalized, combined focal and generalized, and unknown. It’s further categorized by etiology as genetic, immune, infectious, metabolic, structural, and unknown. Common epilepsy affects approximately 95% of the population, while the remaining 5% experience rare epilepsy [18–22]. Overall, these types of epilepsies are shown in Figure 1.

An urgent and in-depth investigation is imperative to unravel the potential causes of TLE-HS, as elaborated upon below.

Causes of TLE-HS
TLE-HS is marked by the selective death of pyramidal cells, predominantly in the hippocampus subregions CA1, CA3, and CA4, resulting in hippocampus sclerosis. In contrast, the Dentate Granule cells experience significantly less neuronal death compared to pyramidal cells. Studies suggest that the death of target neurons in the CA3 and CA4 regions is considered a potential trigger for TLE-HS, leading to the survival of granule cells. It has also been observed that CA2 and even CA1 region which is independently involve in the local cell loss [23–26]. Therefore, it is essential to conduct an in-depth exploration, focusing on the molecular intricacies of the affected regions using multi-omics techniques, particularly in animal models of TLE-HS epilepsy, as depicted in Figure 2.

GABA is the primary inhibitory neurotransmitter and should be in equilibrium with glutamate, an excessive amount of glutamate and/or insufficient GABA can cause overstimulation in the CNS, resulting in seizures [12, 27]. Hence, after the successful induction of TLE-HS in the animal model, the door opens to the exploration of potential diagnosis and targeted treatment options through multi-omics investigations.

Multi-omics
The emergence of multi-omics techniques has sparked significant interest in investigating the brain in the context of epilepsy [28, 29]. The application of multi-omics techniques, either individually or in combination, holds immense potential for elucidating key molecular pathways underlying the epileptic brain connection. For example, by integrating various multi-omics approaches, we can gain a more comprehensive understanding of the mechanisms regarding epileptic patients with different receptors like GABA and glutamate [30]. Furthermore, leveraging the power of multi-omics can enhance our understanding of how effective treatment can be developed [31–33]. For a deeper understanding, it is imperative to conduct investigations using genomics, proteomics, and metabolomics (collectively known as omics) for comprehensive analyses, as discussed below.

Genomics
Numerous epilepsy mechanisms are associated with gene variations in crucial components such as axons, pre-synapses, neuroglia, and post-synapses. These variations can result in synaptic dysfunction, DNA repair issues, transcriptional dysregulation, and chromatin remodeling. Some of the genes listed in Table 1 can influence neurotransmitter production, disrupting the balance between inhibitory and excitatory neurotransmitters and causing neuronal hyperexcitability [18, 34, 35]. The multi-omics investigation of the overall functions and cytogenetic locations of pertinent genes, as outlined in Table 1, should be conducted in animal models of TLE-HS both before and after herbal treatment.

Hence, there is a critical requirement to undertake comprehensive research on epilepsy genetics on a broader scale, including the establishment of patient registries and the expansion of multi-center, randomized, and controlled trials. These initiatives are instrumental in bridging the gap between epilepsy patients, healthcare providers, and the research community, ultimately promoting the advancement of precision medicine in epilepsy.
Figure 1 Common and rare types of epilepsy based on prevalence. GGE, genetic generalized epilepsy; CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; TLE, temporal lobe epilepsy; DS, Dravet syndrome; LRS, Lafora Rett syndrome; CFD, cerebral folate deficiency; PDE, pyrodoxine dependent epilepsy; LE, limbic encephalitis; GE, gelastic epilepsy; SS, Sturge-Weber syndrome; VE, viral encephalitis; DS, Doose Syndrome; LKS, Landau Kleffner syndrome.

Figure 2 Comparison of normal and sclerosed hippocampus after the extraction of rat brain with vital regions

<table>
<thead>
<tr>
<th>Symbol of gene</th>
<th>Complete name of gene</th>
<th>Cytogenetic location</th>
<th>Function and variants</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN1B</td>
<td>Sodium voltage-gated channel, type 1, beta subunit</td>
<td>19q13.11</td>
<td>Generation and propagation of action potentials in muscle and neuronal cells. Variants linked to generalized epilepsy with febrile seizures plus, TLE, and cardiac arrhythmias, including Brugada syndrome and atrial fibrillation.</td>
<td>[36, 37]</td>
</tr>
<tr>
<td>SCN2A</td>
<td>Sodium voltage-gated channel, alpha subunit 2</td>
<td>2q24.3</td>
<td>Generation and propagation of action potentials in neurons and muscle. Epilepsy caused by SCN2A variants mostly starts in early childhood and has a wide phenotypic spectrum, ranging from self-limited epilepsy with a favorable outcome to developmental and epileptic encephalopathy, and most of them respond well to sodium channel blockers.</td>
<td>[38, 39]</td>
</tr>
<tr>
<td>SCN8A</td>
<td>Sodium voltage-gated channel, alpha subunit 8</td>
<td>12q13.13</td>
<td>Essential for the rapid membrane depolarization that occurs during the formation of the action potential in excitable neurons. Mutations in this gene are associated with cognitive disability, pancerebellar atrophy and ataxia.</td>
<td>[40, 41]</td>
</tr>
<tr>
<td>SCN3B</td>
<td>Sodium voltage-gated channel, beta subunit 3</td>
<td>11q24.1</td>
<td>Generation and propagation of action potentials in neurons and muscle. It play an important role in the progression of epilepsy through sodium channels.</td>
<td>[42, 43]</td>
</tr>
<tr>
<td>KCNJ3</td>
<td>Potassium channel, inwardly rectifying, subfamily J, member 3</td>
<td>2q24.1</td>
<td>Contributes to inward rectifier potassium channel activity. Involved in potassium ion import across plasma membrane. Part of voltage-gated potassium channel complex. These multimeric G-protein-gated inwardly rectifying potassium (GIRK) channels may play a role in the pathophysiology of epilepsy, addiction, Down’s syndrome, ataxia, and Parkinson’s disease.</td>
<td>[44, 45]</td>
</tr>
<tr>
<td>KCNJ10</td>
<td>Potassium channel, inwardly rectifying, subfamily J, member 10</td>
<td>1q23.2</td>
<td>This gene encodes a member of the inward rectifier-type potassium channel family, characterized by having a greater tendency to allow potassium to flow into, rather than out of, a cell. Mutations in this gene have been associated with seizure susceptibility of common idiopathic generalized epilepsy syndromes.</td>
<td>[46, 47]</td>
</tr>
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### Table 1 Prevalent genes involved to cause epilepsy (Continued)

<table>
<thead>
<tr>
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<th>Function and variants</th>
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</thead>
<tbody>
<tr>
<td>KCNN3</td>
<td>Potassium channel, calcium-activated, intermediate/small conductance, subfamily N, member 3</td>
<td>1q21.3</td>
<td>Plays a role in neural excitability, and mutations in this gene does not show epilepsy but seizures have been seen in patient.</td>
<td>[48-50]</td>
</tr>
<tr>
<td>KCNMB3</td>
<td>Potassium channel, calcium-activated, large conductance, subfamily M, beta 3</td>
<td>3q26.32</td>
<td>The gene encoding large conductance calcium-sensitive potassium channels represents a positional and functional candidate gene for idiopathic generalized epilepsy.</td>
<td>[51, 52]</td>
</tr>
<tr>
<td>CACNA1H</td>
<td>Calcium channel, voltage-dependent, T type, alpha-1H subunit</td>
<td>16p13.3</td>
<td>This gene encodes a T-type member of the alpha-1 subunit family, a protein in the voltage-dependent calcium channel complex. Studies suggest certain mutations in this gene lead to childhood absence epilepsy.</td>
<td>[53, 54]</td>
</tr>
<tr>
<td>AQP4</td>
<td>Aquaporin 4</td>
<td>18q11.2</td>
<td>AQP4 is the predominant water channel in the brain and has an important role in brain water homeostasis. Studies reported that AQP4 has a potential role in the development of epilepsy.</td>
<td>[55, 56]</td>
</tr>
<tr>
<td>CACNA1A</td>
<td>Calcium channel, voltage-dependent, P/Q type, alpha-1A subunit</td>
<td>19p13.13</td>
<td>Mutations in this gene is potentially associated with pure epilepsy and the spectrum of epileptic phenotypes such as absence epilepsy or partial epilepsy.</td>
<td>[57, 58]</td>
</tr>
<tr>
<td>CACNG3</td>
<td>Calcium channel, voltage-dependent, gamma-3 subunit</td>
<td>16p12.1</td>
<td>This gene is a susceptibility locus for childhood absence epilepsy.</td>
<td>[59]</td>
</tr>
<tr>
<td>CACNB4</td>
<td>Calcium channel, voltage-dependent, beta-4 subunit</td>
<td>2q23.3</td>
<td>This gene encodes a member of the beta subunit family of voltage-dependent calcium channel complex proteins. Certain mutations in this gene have been associated with idiopathic generalized epilepsy, and juvenile myoclonic epilepsy.</td>
<td>[60, 61]</td>
</tr>
<tr>
<td>CHRNA4</td>
<td>Cholinergic receptor, neuronal nicotinic, alpha polypeptide 4</td>
<td>20q13.33</td>
<td>Mutations in this gene linked to autosomal dominant nocturnal frontal lobe epilepsy, are also found in patients with predominantly sleep-related insular epilepsy.</td>
<td>[62]</td>
</tr>
<tr>
<td>GRM4</td>
<td>Glutamate receptor, metabotropic, 4</td>
<td>6p21.31</td>
<td>Mutation in this gene is associated with generalized epilepsy.</td>
<td>[63]</td>
</tr>
<tr>
<td>LGI1</td>
<td>Leucine-rich, glioma-inactivated, 1</td>
<td>10q23.33</td>
<td>This gene encodes a secreted leucine-rich protein that is expressed in brain and plays a role in regulating postnatal glutamatergic synapse development. Mutations in this gene result in autosomal dominant lateral temporal epilepsy.</td>
<td>[64]</td>
</tr>
<tr>
<td>ASIC1a</td>
<td>Acid-sensing ion channel, subunit 1</td>
<td>12q13.12</td>
<td>Cell and animal studies have shown that ASIC1a play different roles in seizures and the termination of epilepsy.</td>
<td>[65]</td>
</tr>
<tr>
<td>STX1B</td>
<td>Syntaxin 1B</td>
<td>16p11.2</td>
<td>The protein encoded by this gene belongs to a family of proteins thought to play a role in the exocytosis of synaptic vesicles. Mutations in this gene have been identified as one cause of fever-associated epilepsy syndromes.</td>
<td>[66, 67]</td>
</tr>
<tr>
<td>SYN2</td>
<td>Synapsin II</td>
<td>3p25.2</td>
<td>This gene encodes neuronal phosphoproteins which associate with the cytoplasmic surface of synaptic vesicles. Polycomb complexes are associated with abnormal presynaptic function and related neuronal disorders, including autism, epilepsy, bipolar disorder, and schizophrenia.</td>
<td>[68]</td>
</tr>
<tr>
<td>SLC12A5</td>
<td>Solute carrier family 12 (potassium/chloride transporter), member 5</td>
<td>20q13.12</td>
<td>Mutations in this gene causes a severe infantile onset pharmacoresistant epilepsy syndrome, and epilepsy of infancy with migrating focal seizures.</td>
<td>[69]</td>
</tr>
<tr>
<td>ME2</td>
<td>Malic enzyme 2</td>
<td>18q21.2</td>
<td>This gene encodes a mitochondrial NAD-dependent malic enzyme, a homotetrmeric protein, which catalyzes the oxidative decarboxylation of malate to pyruvate. Certain single-nucleotide polymorphism haplotypes of this gene have been shown to increase the risk for idiopathic generalized epilepsy.</td>
<td>[70, 71]</td>
</tr>
<tr>
<td>ALDHSA1</td>
<td>Aldehyde dehydrogenase 5 family, member A1</td>
<td>6p22.3</td>
<td>Mutations in this gene have a role in seizures and epilepsy.</td>
<td>[72, 73]</td>
</tr>
<tr>
<td>GABA-A receptor</td>
<td>Gamma-aminobutyric acid receptor, alpha-1</td>
<td>5q34</td>
<td>This gene encodes a GABA receptor. Mutations in this gene cause juvenile myoclonic epilepsy and childhood absence epilepsy type 4.</td>
<td>[74, 75]</td>
</tr>
</tbody>
</table>
Table 1 Prevalent genes involved to cause epilepsy (Continued)

<table>
<thead>
<tr>
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<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GABA-B</td>
<td>Gamma-amino butyric acid B receptor 1</td>
<td>6p22.1</td>
<td>This gene encodes a receptor for GABA, which is the main inhibitory neurotransmitter in the mammalian central nervous system. Defects in this gene may underlie brain disorders such as schizophrenia and epilepsy.</td>
<td>[74, 75]</td>
<td></td>
</tr>
<tr>
<td>PCDH7</td>
<td>Protocadherin 7</td>
<td>4p15.1</td>
<td>This gene belongs to the protocadherin gene family, a subfamily of the cadherin superfamily. The gene encodes a protein with an extracellular domain containing 7 cadherin repeats. The gene product is an integral membrane protein that is thought to function in cell-cell recognition and adhesion. PCDH7 is highly expressed in the brain and has been linked to CNS disorders, including epilepsy.</td>
<td>[76]</td>
<td></td>
</tr>
<tr>
<td>CPA6</td>
<td>Carboxypeptidase A6</td>
<td>8q13.2</td>
<td>The gene encodes a member of the peptidase M14 family of metalloendopeptidases. Mutations in this gene may be linked to epilepsy and febrile seizures.</td>
<td>[77]</td>
<td></td>
</tr>
<tr>
<td>EFHC1</td>
<td>EF-hand domain (C-terminal)-containing protein 1</td>
<td>6p12.2</td>
<td>This gene encodes an EF-hand-containing calcium binding protein. The encoded protein likely plays a role in calcium homeostasis. Mutations in this gene have been associated with susceptibility to juvenile myoclonic epilepsy and juvenile absence epilepsy.</td>
<td>[78, 79]</td>
<td></td>
</tr>
<tr>
<td>BRD2</td>
<td>Bromodomain-containing protein 2</td>
<td>6p21.32</td>
<td>This gene encodes a transcriptional regulator that belongs to the BET (bromodomains and extra terminal domain) family of proteins. This gene has been implicated in juvenile myoclonic epilepsy, a common form of epilepsy that becomes apparent in adolescence.</td>
<td>[80]</td>
<td></td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain-derived neurotrophic factor</td>
<td>11p14.1</td>
<td>BDNF was found to increase excitatory synaptic transmission and decrease the inhibitory effect of inhibitory neurotransmitters on activated synapses, thereby enhancing the transmission of epileptiform discharges in neural networks.</td>
<td>[81, 82]</td>
<td></td>
</tr>
</tbody>
</table>

Proteomics

Scientists have conducted recent studies in which they analyzed the proteomic profile of hippocampal tissue obtained from patients with drug-resistant TLE-HS [83, 84]. The obtained tissue was compared to tissue from autopsy. To identify differentially expressed proteins, the scientists employed advanced analytical techniques, such as liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) [85, 86]. Notably, the expression of glutathione S-transferase P (GSTP1) protein was detected solely in the hippocampal tissue of patients with TLE-HS, and not in the tissue obtained from autopsy. Therefore, the anomalous expression of GSTP1 in the hippocampal tissue of TLE-HS patients may be associated with pharmacoresistance mechanisms. Furthermore, a study reported that both GSTP1 and PARK7 were exclusively present in TLE-HS patients and were absent in the control group, and GSTP1 was linked to drug resistance [28, 84]. Researchers compared the proteomic profiles of hippocampal tissue from drug-resistant and drug-responsive patients with TLE-HS, and identified differentially expressed proteins involved in energy metabolism, synaptic plasticity, and inflammation. The results highlighted potential molecular markers and therapeutic targets for drug-resistant epilepsy [87]. Biomarkers identifications have also been reported through proteomics, there is a great potential to discover biomarkers using such advanced proteomics analyses [88]. Researchers have compiled an exhaustive catalog of proteins predominantly expressed in epilepsy, specifically TLE-HS, as shown in Figure 3 [84, 89]. Consequently, the levels of expression should be monitored before and after herbal treatment in TLE-HS models through multi-omics strategies.

Metabolomics

Metabolomics provides a powerful tool to pinpoint metabolites or pathways that are associated with a disease, which can then be translated into clinical applications [90–93]. Researchers employed metabolomic profiling of plasma samples from TLE-HS patients, identifying alterations in various metabolic pathways, including amino acid metabolism, lipid metabolism, and energy metabolism. The findings provided insights into the complex metabolic dysregulation associated with epileptogenesis [94]. It has also been reported that the potential of NMR spectroscopy as a powerful tool for metabolomic analysis and biomarker discovery in epilepsy research [95]. Various metabolomics methods have been utilized to investigate epilepsy, supplying a wealth of data to enhance diagnosis, treatment, and individualized patient care like: NMR spectroscopy, mass spectrometry (MS), high-resolution mass spectrometry, imaging mass spectrometry, and stable isotope tracing [95–99].

However, despite the technological advances in recent years, there remains a notable research gap in the application of metabolomics to epilepsy. This gap is a key reason behind the lack of effective treatments for drug-resistant TLE-HS cases. Therefore, a comprehensive exploration of all metabolites involved in epilepsy is imperative. Advanced analytical tools such as LC-MS/MS, GC-MS, and NMR are available, but their potential in developing novel, effective drugs for TLE-HS is largely untapped. Figure 4 illustrates the overall process of targeted drug development using multi-omics.

Possible treatment options for TLE-HS

TLE-HS is a common form of drug-resistant epilepsy for which surgery is often considered. While surgical intervention can offer a safer therapeutic option for many patients, particularly those with TLE-HS, advanced diagnostic tools and therapeutic technologies can help avoid or revise complicated cases where surgery is not beneficial. Despite the significant technological advancements, the improvements in surgical outcomes have not yet kept pace. Therefore, the reasons behind the failure of TLE-HS surgery remain uncertain. Known causes of surgery failure in TLE-HS patients include the spread of the epileptogenic zone to adjacent regions, the structural causes of TLE-HS, as well as post-surgical complications such as memory impairments, delayed hydrocephalus, intracranial hematoma, subdural empyema, and visual field defects [100–102]. One promising direction for the future is the adoption of targeted medicine for TLE-HS [103–105].

In treating TLE-HS, the goal is to manage seizures and enhance quality of life. Herbal remedies show promise, but their effectiveness varies, emphasizing the need for consultation with healthcare professionals due to potential interactions. The ketogenic diet, altering the brain’s energy source, and surgical options like temporal lobectomy offer additional avenues. Lifestyle changes and a tailored approach combining ASMs, herbal remedies, and neurostimulation
techniques are crucial. Collaborating with healthcare professionals is essential for developing personalized treatment plans, and ongoing research may bring further innovations to TLE-HS management. Therefore, we propose a potential treatment mechanism for TLE-HS, which is illustrated in Figure 5.
Herbal interventions
Despite having great potential to effectively treat epilepsy, herbal extracts are still underexplored as a possible treatment option for TLE-HS. Although several herbs with anti-convulsant effects have been reported, they have not been tested on actual epileptic animal models such as the Li-Pi epileptic animal model. Various herbs have shown potential to control or terminate seizures, as reported in studies, but little clinical studies have been conducted [106]. Several herbal remedies have been studied for their potential antiepileptic effects, and while the evidence is limited, some herbs have shown promise in managing TLE with HS. It’s essential to highlight that herbal treatments should be a subject of consultation with a certified healthcare practitioner. Their expertise can guide individuals regarding safety, recommended dosages, and potential interactions with ASMs. Natural compounds, exemplified by cannabidiol (CBD), rapamycin, and huperzine A, have exhibited significant promise in the therapeutic landscape of epilepsy. Notably, these compounds showcase distinctive mechanisms of action and have received approvals for addressing drug-resistant epilepsy. Furthermore, the therapeutic potential of natural products, specifically those capable of stimulating the vagus nerve like CBD, has emerged as a noteworthy aspect in combating drug-resistant epilepsy [107]. A parallel avenue of exploration involves the utilization of herbal extracts as a viable treatment approach for drug-resistant epilepsy. Research findings underscore the potential of herbal extracts as a valuable reservoir, presenting novel mechanisms of action for potential anti-epileptic drug candidates [108]. In the discourse surrounding the treatment of drug-resistant epilepsy, discussions have centered on the application of natural compounds, with CBD taking a prominent role. This discourse underscores the necessity to consider unconventional targets, exemplified by P-glycoprotein, as part of the comprehensive strategy for addressing drug-resistant epilepsy [109]. In summation, the current body of research strongly implies that natural compounds derived from herbal sources hold considerable promise in effectively managing drug-resistant epilepsy. However, to comprehensively unravel their therapeutic potential, further investigative efforts are warranted to delve into their intricate structures, target points, and underlying mechanisms of action [107–109].

It has been reported that, CBD has shown promise in managing seizures associated with TLE. Several clinical trials have reported a reduction in seizure frequency and improved quality of life in TLE patients treated with CBD [110, 111]. However, further research is needed to determine the optimal dosage and long-term effects of cannabis-based products. Moreover, other herbs Xianyaosan and Wendan decoction, have shown anticonvulsant effects in animal models of TLE. However, rigorous clinical trials are required to assess the efficacy and safety of herbal medicines in TLE patients [112]. In our previous reported review article, a list of herbs has mentioned with anti-convulsant effects [106]. Moreover, herbs with the properties and mode of actions have been discussed in Figure 6 [112–128].

The clinical application of herbs in the management of drug-resistant epilepsy has gained interest as an adjunctive or alternative treatment option. While the evidence supporting their efficacy is still evolving, some herbs have shown potential in reducing seizure frequency and improving seizure control in individuals with drug-resistant epilepsy.

The use of herbal treatments for drug-resistant epilepsy should be approached cautiously, under the guidance of a medical professional. Effectiveness, safety, and proper dosage may vary based on individual factors, such as medical history, specific epilepsy syndrome, and interactions with other medications. It’s recommended to consult a healthcare professional with expertise in epilepsy management before incorporating herbal remedies into the treatment plan. Additionally, further research, including well-designed clinical trials, is needed to determine the optimal clinical applications, dosages, and long-term effects of herbs in treating drug-resistant epilepsy. Applying traditional Chinese medicine (TCM) to specific brain regions shows potential neuroprotective and therapeutic benefits, particularly in addressing unique brain injuries or diseases. Using MLC901 in a rat model exemplifies evidence of TCM’s ability to safeguard against brain injury and deficits after global ischemia in the hippocampal CA1 region [129].

Moreover, TCM has been explored for its impact on brain ischemia-reperfusion injury (IRI), encompassing conditions like ischemic stroke and traumatic brain injury, demonstrating noteworthy therapeutic effects in preclinical studies involving diverse animal models [130]. Investigations into TCM’s role in treating neurological disorders, such as Parkinson’s disease, have revealed positive outcomes through modalities like acupuncture and deep brain stimulation [131]. Additionally, TCM has been recognized for its contribution to neural regeneration and repair in neurological disorders, including ischemic brain injury [132]. These findings suggest that employing TCM in a specific brain region may effectively target distinct pathological processes, offering neuroprotective and therapeutic advantages.

Recent omics studies in the herbal treatment of TLE-HS hold promise in identifying therapeutic options. Using genomics, proteomics, and metabolomics, researchers comprehensively investigate molecular mechanisms. Herbal remedies are explored for targeted treatments, but caution is advised. Consulting healthcare professionals is crucial due to variations in efficacy and potential interactions with anti-epileptic drugs [28–30, 97, 98, 112]. Despite these promising findings, more research and well-designed clinical trials are needed to establish the optimal clinical application, dosage, and long-term effects of herbal treatments for TLE-HS.

Figure 6 Various herbs possessing medicinal properties can contribute to the treatment of drug resistant epilepsy

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Conclusion

TLE-HS is a prevalent form of drug-resistant epilepsy, and patients affected by it continue to experience seizures despite using FDA-approved medications, either individually or in various combinations. Structural changes have been observed in TLE-HS, and at molecular level mostly changes investigated in CA regions and GABA neurotransmitters. However, to understand the pathophysiology of TLE-HS there is a need to explore such regions and neurotransmitters through multi-omics analyses, for this purpose animal models can play a crucial role. Numerous studies have explored the potential anticonvulsant effects of various herbs, but many of these studies primarily utilized seizure models rather than actual epileptic models. Using actual epileptic animal model, targeted herbal medicines (CBD, Ginkgo Folium, Bacopa Monnieri, passionflower, Valerian Root, curcumin, etc.), should be investigated with extensive experimentalizations, and pre-clinical and clinical trials. Particularly, by investigating clinical trials and evidence-based research, mechanistic studies and pharmacokinetic studies, standardization of herbal products, as well as long-term safety and tolerability, can play vital role in the field of herbal medicines for drug-resistant epilepsy. Hence it can contribute valuable insights and potentially expand the treatment options available for individuals with epilepsy. By employing multi-omics analyses and interventions, there is an opportunity to develop new, targeted treatment options that could offer long-term and effective solutions for individuals with TLE-HS, allowing them to lead healthy and fulfilling lives.

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