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Traditional Chinese medicine treatment for epilepsy: Focusing on voltage-gated ion channels

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ABSTRACT

Ethnopharmacological relevance: Epilepsy (EP) is a chronic neurological disease, and the clinical treatment of EP is dominated by modern drugs, but one-third of the patients have drug-resistant reactions, which seriously affects the quality of patients' survival. Traditional Chinese medicine (TCM), however, as a promising resource, plays a unique advantage in improving the clinical symptoms of EP and alleviating the adverse effects of modern drug therapy. A large number of studies in recent years have reported that TCM plays an important role in EP treatment by regulating voltage-gated ion channels (VGICs).

Aim of study: This study aims to examine the mechanisms by which VGICs influence EP, providing further elucidate the potential targets of TCM in treating EP by regulating VGICs, including traditional herbal formulas and active compounds. The objective is to offer fresh insights and strategies for the research and management of EP.

Methods: Literature information was obtained from the scientific databases PubMed, Web of Science, EMBASE, Cochrane library, and CNKI, built until June 2024, with search terms including "epilepsy", "voltage-gated ion channels ", "Chinese medicine" or "herbal medicine", "medicinal plants", "natural plants "and "herbal medicine".

Results: The results suggest that TCM can affect VGICs by influencing the opening of these channels, thereby regulating the currents and concentrations of sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}). Additionally, TCM modulates the expression of VGIC-related proteins, which in turn affects the release of neurotransmitters, including inflammatory mediators, oxidative stress markers, and glutamate. This process ultimately decreases neuronal excitability and helps inhibit the onset of EP.

Conclusions: By modulating key VGICs such as VGSCs, VGKCs, and VGCCs, TCM plays an important role in the treatment of EP, providing a novel therapeutic strategy based on traditional practices and modern science.

1. Introduction

Epilepsy (EP) is one of the most common chronic neurological disorders caused by excessive or hypersynchronized neuronal activity (Myers, 2022). Globally, the incidence of EP accounts for about 70 million people (Pong et al., 2023; Sands and Gelinas, 2024), while in Asia the number of EP accounts for about 23 million people (Trinka et al., 2019).2021 Epidemiologic studies have shown that there are about 10 million people with epilepsy in China, and the prevalence of epilepsy tends to increase with increasing years (Ding et al., 2021). Furthermore, patients with EP are most commonly comorbid with somatic and psychiatric conditions such as migraine, arrhythmia, anxiety, depression, and cognitive impairment (Ali, 2018; Yu et al., 2023), which severely affect quality of life. Currently, there are more than 30 clinically available antiepileptic drugs (AEDs) for treating EP, but up to one-third of the patients still face drug resistance and side effects persistently (Cai et al., 2024; Mesraoua et al., 2023). The rest of the patients had side effects such as abnormalities in the digestive system,

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central nervous system, hematopoietic system, urinary system and liver function (Su et al., 2023), presenting substantial obstacles to the comprehensive management and therapeutic interventions for EP. In light of this, new therapeutic strategies are urgently required, aimed at designing potent, safe, and longer-acting AEDs.

The recent years' research about EP has focused on revealing the drug resistance mechanism through regulation of voltage-gated ion channels (VGICs), neurotransmitter receptors, and glutamate receptors in order to improve the drug resistance in EP (Sills and Rogawski, 2020). With the development of molecular biology and single-channel current recording technique, the study of VGICs in the pathogenesis of EP is getting more and more attention by neuroscientists. VGICs are a large family of proteins, mainly including voltage-gated sodium channels (VGSCs), voltage-gated potassium channels (VGKCs), voltage-gated calcium channels (VGCCs), and Voltage-gated chloride channel (VGClCs) (Moreau et al., 2015; Shen et al., 2021). These channels can sense changes in the transmembrane potential of cell membranes and participate in various physiological processes, such as neurotransmitter transmission and muscle contraction, as well as secretion of hormones (Huang et al., 2024). When VGIC functions abnormally or is not properly regulated, it may cause the occurrence of diseases, such as EP, neuralgia, and arrhythmia, and in its extreme form, it may even cause sudden death (De Lera Ruiz and Kraus, 2015). Genetic research studies about EP have demonstrated gene mutations as the pathological basis for abnormal nerve cell discharges, which play important roles in the occurrence, development, and formation of drug-resistant EP (Prontera et al., 2018). Any kind of mutation in VGICs can prove to be a vulnerability for any proper function of channel proteins, causing an imbalance in the excitation-inhibition dynamics of the Central Nervous System, leading to unusual, synchronous nerve cell discharges and finally causing EP attacks (Symonds et al., 2017). Furthermore, it is worthwhile to note that various gene mutations may exert different functional effects on VGICs, mainly the phenotypes of loss-of-function (LoF) and gain-of-function (GoF), which lead to different clinical phenotypes and errors in the choice of a drug (Brunklaus et al., 2020).

Traditional Chinese medicine (TCM) is a promising resource with great chemical diversity and multi-target imperatives, appropriate for the regulation of different mechanisms linked to EP. In addition, TCM has a long history and rich experience in the treatment of EP. Traditional Chinese medicine pairing and compounding are the main means of treating the disease in TCM, which can treat the disease from the root and at the same time regulate the function of the body's internal organs and enhance the body's ability to resist the disease, with unique therapeutic efficacy and small adverse effects, effectively alleviating the extent of EP seizures, reducing the number of seizures, and mitigating the adverse effects of western drug treatment (Wang et al., 2016). The study showed that the combination of traditional Chinese medicine and western medicine significantly improved the clinical symptoms of EP compared with the western medicine anti-EP group alone (Yu et al., 2022). At present, the treatment principles often used in clinical practice include opening the orifices to awaken the mind, restraining wind and stopping spasm, clearing the liver and diarrhea, dispelling evil spirits and tonifying the deficiency, strengthening the spleen and resolving phlegm, activating blood circulation and removing blood stasis, nourishing the heart and tranquilizing the mind, and nourishing the liver and kidneys (Tian et al., 2016; Xia et al., 2019). Emerging preclinical evidence suggests that Traditional Chinese Medicine (TCM) may attenuate neuronal hyperexcitability through modulation of voltage-gated ion channel activity, ultimately inhibiting EP attacks through effects on VGICs opening, Na^+, K^+, Ca^{2+} currents and the concentration by regulating proteins expression linked to VGICs (Xiao et al., 2022; Zhao et al., 2022). Therefore, VGICs may be an important target for the therapeutic efficacy of TCM, and they will be summarized in respect to their role in the pathogenesis of EP and how TCM regulates VGICs to treat EP.

2. Pathogenesis of EP

The pathogenesis of EP is still not fully understood. It is said to be associated with these factors: neurotransmitters, VGICs, oxidative stress, a blood-brain barrier, glial cells, synaptic connection, genetic factors, and immune responses-all leading to an imbalance between the excitation and inhibition of neurons in the brain, which heightens neuronal excitability and abnormal synchronized discharges (Jacobs et al., 2009).

Neuroinflammation, mostly mediated by glial cells, is of great importance in the development of EP (Barker-Haliski et al., 2017). Glial cells express a variety of VGICs, and the activity of these channels might modulate microglia activation and its related physiological functions. For instance, the inflammatory cells, once activated, might have very important increased expression levels of the Kv1.3 channel for microglial proliferation, migration, and cytokine release (Irani and Vincent, 2016). Many studies have established that neuroinflammatory stimuli, such as lipopolysaccharides, via various membrane receptors, are able to activate the NF-κB pathway, which is induced by an M1-like activation state, promoting the upregulation of Kv1.3 and excessive production of pro-inflammatory factors that trigger seizures in EP models (Kołosowska et al., 2016).

Another important hypothesis of neuronal dysfunction in EP is excitotoxicity mediated by glutamic acid (Glu) (Mishima et al., 2021). Activation of Glu receptors increases the permeability of VGCCs, leading to enhanced intracellular Ca^{2+} concentration. Simultaneously, dysfunction of Ca^{2+}-ATPase removes the extrusion of Ca^{2+} from the cell and results in intracellular calcium overload, followed by overproduction of Glu, causing continuous excitotoxicity in neurons (Powell et al., 2014). Furthermore, high levels of Ca^{2+} can reduce the sensitivity of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) receptors, which in turn, through the activation of phospholipases and proteases, result in a delay in neuronal degeneration and necrosis, disturbing the balance between excitation and inhibition in the neural network (Meldrum and Rogawski, 2007).

The development of EP can lead to the loss of various brain cells, such as astrocytes and microglia, depolymerization of microtubules, dysfunction of the blood-brain barrier, and the induction of oxidative stress-based on (Spinelli et al., 2024). The opening of the transient receptor potential M2 channel (TRPM2), which is widely distributed in the central nervous system and highly expressed in neurons, astrocytes, and microglia, may be regulated by an increase in intracellular levels of Ca^{2+} and ADP-ribose and plays a role in neuronal death caused by oxidative stress (Wang et al., 2021). H_2O_2 and other peroxides activate poly ADP-ribose polymerase, which activates the TRPM2 ion channel, promoting the influx of Ca^{2+} and further disturbing intracellular Ca^{2+} homeostasis, aggravating EP (Çınar and Nazıroğlu, 2023).

Accumulating evidence over recent decades has demonstrated that VGICs may contribute to epileptogenesis through modulation of neuroinflammatory pathways, oxidative stress, and glutamate neurotoxicity, thus impacting the normal physiological functions of VGICs. Conversely, the occurrence of EP can exacerbate inflammation and oxidative stress, creating a vicious cycle (Debanne et al., 2024; Perucca and Taglialatela, 2025; Zheng and Chen, 2024) (Fig. 1). Therefore, maintaining the normal physiological functions of VGICs, regulating the currents and concentrations of Na^+, K^+, and Ca^{2+}, and modulating the expression of VGIC-related proteins may represent a breakthrough in the treatment of EP.

3. VGICs and EP

3.1. Mechanism of VGSCs regulating EP

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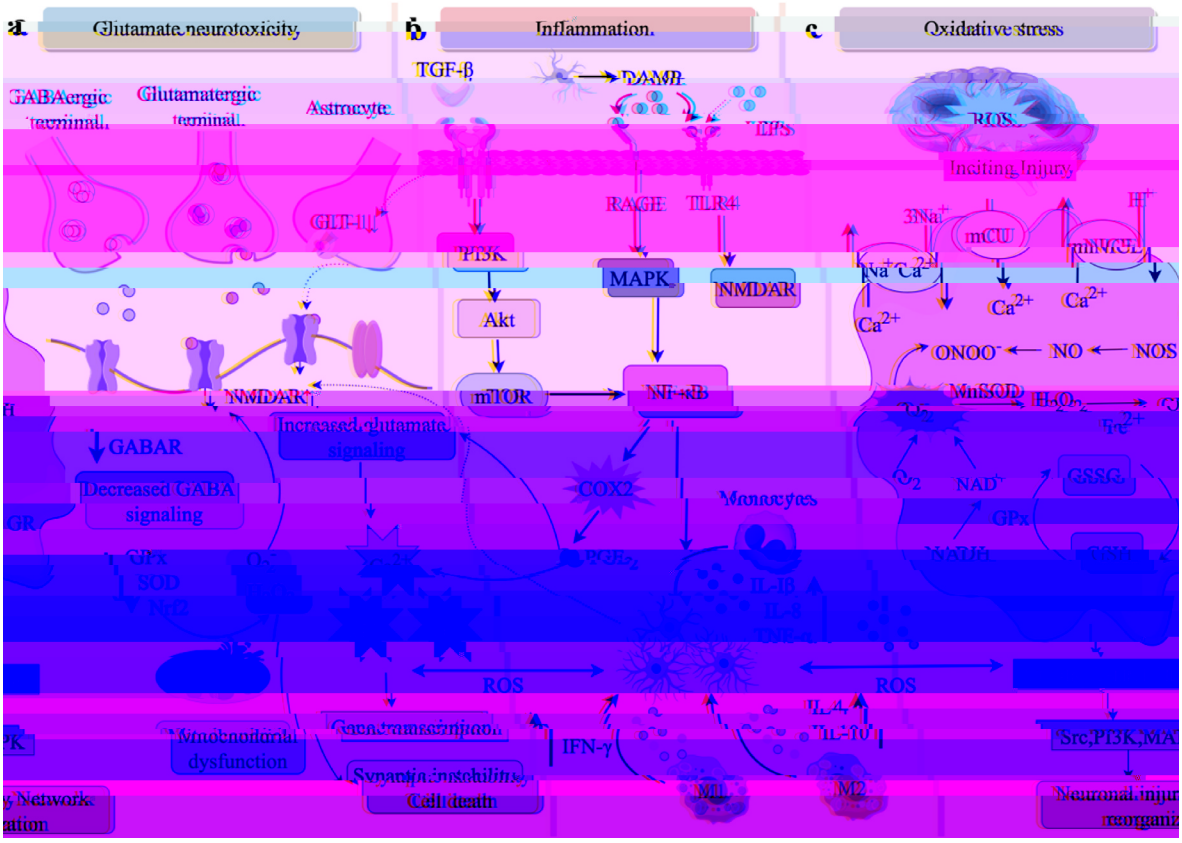

Fig. 1. Interaction of glutamate neuroexcitotoxicity, inflammation and oxidative stress leading to the main pathogenesis of EP. a. depicts the mechanism by which large accumulation of glutamate, impaired γ-aminobutyric acid production, and large accumulation of Ca^{2+} cause neuroexcitotoxicity leading to epilepsy; b. depicts the mechanism by which inflammatory stimuli can induce an activation state similar to that of M1 by affecting the NF-κB, PI3K/Akt, and other pathways, leading to the overproduction of proinflammatory factors, which then leads to epileptic seizures; c. depicts the mechanism by which oxidative stress leads to changes in Ca^{2+} influx, the mechanism by which EP is further exacerbated by changes in intracellular Ca^{2+} homeostasis.

syndromes (Chen et al., 2024). Voltage-gated Na^+ channels(Nav) consists of a large, pore-forming α subunit, comprising over 2000 residues, and two auxiliary β subunits. The α subunit acts as the functional unit and main component, whereas the β subunits serve a regulatory function (Bouza and Isom, 2018). There are nine subtypes of human sodium channel α subunits (Nav1.1 to Nav1.9), with only Nav1.1, Nav1.2, Nav1.3, and Nav1.6 predominantly expressed in the central nervous system (Catterall et al., 2005; Watanabe et al., 2000). The corresponding genes encoding these subtypes are SCN1A, SCN2A, SCN3A, and SCN8A (Claes et al., 2001; Larsen et al., 2015; Wolff et al., 2017; Zaman et al., 2018). Generally, VGSCs are considered crucial regulators of membrane potential fluctuations, existing in three main states: closed, open, and inactivated (Meisler et al., 2021). Studies have demonstrated that VGSCs open during excitatory processes, permitting a rapid influx of Na^+ into the cell. This influx may cause VGSCs to enter an inactivated state (prolonged opening). At this juncture, a residual persistent sodium current (INaP) remains when depolarization ceases, prompting neurons to stay excited and generate abnormal discharges, ultimately leading to EP episodes (Ednie and Bennett, 2012). Furthermore, numerous experimental studies have show that mutations in genes encoding VGSC proteins are the most common cause of hereditary EP, and approximately one-third of AEDs target the regulation of VGSCs (Bartolini et al., 2020).

3.1.1. SCN1A

SCN1A encodes the sodium ion channel α1 subunit Nav1.1, which is variably expressed in cerebellar Purkinje fibers, inhibitory GABAergic neurons in the hippocampus, intermediate neurons in the hypothalamus, and the cerebral cortex (Misonou, 2018). It primarily enables inhibitory GABAergic neurons to generate sodium currents. Moreover, mutations in SCN1A can occur at the C-terminus, transmembrane segments, intracellular segments, and N-terminus of Nav1.1 (Menezes et al., 2020). Research has shown that mutations in the SCN1A gene are the most frequent mutation targets in genetic EP syndromes, with an incidence of approximately 1 in 12,200 (Escayg and Goldin, 2010). These variants can lead to conditions such as Dravet syndrome (DS), genetic epilepsy with febrile seizures plus ($GEFS^+$), febrile seizures (FS), developmental and epileptic encephalopathies (DEE), and familial hemiplegic migraine (FHM) (Scheffer and Nabbout, 2019). SCN1A is highly expressed during critical periods of human brain development, specifically between 7 and 9 months postnatally. This expression correlates with the age-dependent characteristics of EP associated with SCN1A mutations, as affected children often exhibit symptoms by 6 months of age (Liu et al., 2018).

Most mutations in the SCN1A gene are de novo, predominantly missense mutations (Sadleir et al., 2017). Studies have demonstrated that most SCN1A mutations result in LoF variants. These range from mild, self-limiting FS and $GEFS^+$ to relatively milder forms such as childhood absence EP and myoclonic-atonic EP, and up to the most severe form, severe infantile myoclonic EP like DS (Chilcott et al., 2022). Conversely, GoF mutations, mainly resulting from missense mutations, are linked with type 3 FHM and severe DEE, albeit less frequently. Notably, hereditary mutations typically manifest with milder phenotypes, whereas de novo mutations are associated with more severe manifestations. Approximately 80 % of DS patients have SCN1A mutations, with 90 % of these being de novo mutations (Brunklaus and Lal, 2020).

3.1.2. SCN2A

SCNA2 is found on human chromosome 2, 2q24.3, encoding a protein that consists of 2005 amino acids, which join to form the α subunit of VGSCs Nav1.2. It is located primarily in the axons of excitatory neurons and highly expressed in all parts of the brain, in particular the cortex, hippocampus, striatum, and midbrain (Sanders et al., 2018). Thus, Nav1.2 is restricted mainly to the first three months of life after the expression of which it is completely substituted by Nav1.6. A gene that seems to play a very important role in normal central nervous system functioning is SCN2A, which is strongly associated with neurodevelopment (Meisler et al., 2021). It has recently been described that mutations in SCN2A cause a broad range of clinical phenotypes of EP, including infantile epilepsy with migrating focal seizures (EIMFS), and benign familial neonatalinfantile seizures (BFNIE) (Sugawara et al., 2001). The more severe phenotypes may develop into epileptic encephalopathy (EE) and include DS, developmental and DEE and unclassified EE (Epifanio et al., 2021). There are also reports that identify episodic ataxia, autism spectrum disorder, and intellectual ability as important phenotypes caused by variations in this gene (Heron et al., 2002). To date, the treatment of SCN2A gene mutation includes multi-drug therapy of AEDs, but the effect differs because the mutation positions are different (Yang et al., 2021).

Research has established that SCN2A mutations can disturb the function of the encoded VGSCs, resulting in GoF and LoF or both in one mutation, with missense mutations being the most common. Patients with GoF-type EP generally present at an earlier age, often within three months, while those with LoF mutations typically experience a later onset (Kim et al., 2020; Zeng et al., 2022). Mutations associated with BFNIE are GoF mutations that result in increased neuronal excitability (Lauxmann et al., 2018). DEE related to SCN2A mutations can be categorized into early-onset (before 3 months) and late-onset (after 3 months). Early-onset DEE mutations typically enhance Nav1.2 function, and patients often respond well to sodium channel blockers (SCBs). In contrast, late-onset DEE is usually caused by LoF mutations, and patients may not respond to SCBs, sometimes experiencing worsening conditions (Reynolds et al., 2020). LoF mutations in SCN2A can also lead to autism spectrum disorder (ASD) or intellectual disability (ID), frequently accompanied by epileptic seizures. Notably, SCBs can effectively treat patients with GoF-type EP, while patients with LoF-type EP may show poor or no response, and sometimes their seizures may worsen (Hedrich et al., 2019). Additionally, unlike SCN1A mutations, SCN2A mutation-related EP is less often associated with heat sensitivity phenomena.

3.1.3. SCN3A

The SCN3A gene, which encodes the Nav1.3 channel, is located on the same chromosome as SCN1A and SCN2A. It is expressed in the cell bodies and dendrites of neurons, and mutations in this gene can lead to increased excitability of pyramidal neurons (Meisler et al., 2010). SCN3A is highly expressed during embryonic development but maintains low levels postnatally. Reports indicate that the Nav1.3 channel encoded by SCN3A has a lower firing threshold or a higher firing frequency, making it susceptible to epileptic seizures (Vanoye et al., 2014). In 2020, Zaman T et al. discovered that cortical malformations are a characteristic feature of SCN3A-related neurodevelopmental disorders. These malformations, including diffuse or focal polymicrogyria, cortical dysplasia, and agenesis of the corpus callosum, are observed in over 75 % of affected children. Therefore, it is recommended to describe the disease spectrum caused by SCN3A mutations as SCN3A-related neurodevelopmental disorders, which include developmental and DEE with or without cortical malformations, mild focal EP with cortical malformations, and isolated cortical malformations without EP (Zaman et al., 2020).

Currently, limited reports on SCN3A mutations causing EP make it difficult to infer the relationship between mutation types and phenotypes. However, most severe phenotypes tend to be associated with GoF mutations, such as early-onset epileptic encephalopathy (EOEE), while milder phenotypes are often linked to LoF mutations, such as focal EP with normal intellectual development (Zaman et al., 2018). Case studies have shown that SCN3A variants are associated with familial focal epilepsy with variable foci (FFEVF) and DEE (Miyatake et al., 2018). Functional studies indicate that variants causing these two conditions lead to increased persistent sodium current (INaP) or impaired inactivation of VGSCs, categorizing them as GoF mutations (Holland et al., 2008). Additionally, SCN3A gene mutations are associated with intellectual disability, with most affected children exhibiting severe cognitive impairment.

3.1.4. SCN8A

The SCN8A gene, located on chromosome 12q13.13, encodes the VGSC Nav1.6. This channel is primarily distributed in the axon initial segments and nodes of Ranvier of both excitatory and inhibitory neurons, with high expression levels observed in cerebellar granule cells and hippocampal pyramidal and granule cells (Feng et al., 2019). The Nav1.6 channel protein is embedded within the cell membrane and has the typical structure of four domains, each with a voltage sensor and an ion channel pore. The Nav1.6 functions in this respect to portray the change in membrane potential to alter the states of VGSCs (Talwar and Hammer, 2021). Of the SCN8A mutations reported to date, the majority of these were located within the transmembrane segments, inactivation gates, and C-terminus of Nav1.6. These mutations have increased or decreased the expression of Nav1.6 in neurons and have electrophysiological consequences that include early channel opening, impaired inactivation of the channel, and increased recovery currents. Changes in neuronal excitability might now promote the occurrence of EP (Meisler et al., 2016). Studies have shown that SCN8A mutations account for 3 % of patients with EOEE, which includes conditions such as infantile spasm (IS), ohtahara syndrome (OS), DS, early myoclonic encephalopathy, and unspecified non-specific epileptic encephalopathy (Conecker et al., 2024).

Research indicates that most SCN8A mutations are de novo and often lead to GoF effects (Meisler et al., 2021). The clinical phenotypes associated with these mutations vary widely, ranging from BFNIE and mild cognitive impairments to severe DEE (Barker et al., 2016; Bunton--Stasyshyn et al., 2019). In 2012, Veeramah et al. first documented the link between SCN8A mutations and epileptic encephalopathy (Veeramah et al., 2012). SCN8A-related epileptic seizures typically manifest early, around 4 months of age, and are accompanied by varying degrees of cognitive, language, and intellectual impairments (Kim et al., 2019). Previous studies have reported that 10 % of patients may experience sudden unexpected death in EP, but recent data suggest that the mortality rate associated with SCN8A mutations may be lower than that observed in DS, accounting for less than 50 % of causes of infant mortalitys.

In summary, mutations in VGSC genes can lalter channel permeability and conductivity, enhancing cellular excitability and precipitating epileptic seizures. SCBs that target the voltage/frequency-dependent properties of VGSCs can suppress abnormal neuronal discharges by blocking the rapid inactivation state of VGSCs, thus reducing or eliminating abnormal discharges and controlling the onset of epileptic seizures (Wirrell et al., 2017).

3.2. The regulation mechanism of VGKCs in EP

VGKCs are the most diverse ion channels, encoded by over 100 genes. They play a crucial role in regulating neuronal excitability, maintaining resting membrane potential, and mediating cell membrane repolarization processes (Kole and Stuart, 2012). Mutations in VGKC genes are closely associated with EP. When these mutations cause membrane protein dysfunction, normal potassium current activity across the cell membrane is disrupted. This disruption leads to abnormal depolarization and repolarization processes, which increase neuronal

excitability and trigger EP (Richards et al., 2004). Thus, the pathophysiological mechanism for the occurrence of EP was the abnormal increase or decrease in potassium current. In fact, it has been shown that LoF mutations, mainly acting through decreased channel opening ability, increased activation voltage, or decreased protein expression, are found in many children with VGKC-related EP. GoF mutations can be observed with the main feature of abnormally increased potassium current (Boßelmann et al., 2022). Common EP mutation genes include KCNQ2, KCNA2, and KCNT1 (Fan et al., 2018).

3.2.1. *KCNQ2*

The KCNQ2 gene was located at chromosome 20q13.3 and coded for the Kv7.2 channel, which was highly expressed both in the central and peripheral neurons. It was highly expressed in the axon initial segment and played a very crucial role in the stabilization of neurons and regulation of neuronal excitability (Casas-Alba et al., 2023). Mutations of the KCNQ2 gene result in a malfunction or dysfunction of VGKCs, changing the electrophysiological characteristics of neurons and, hence, provoking EP (Hahn and Neubauer, 2009). Children with mutations of the KCNQ2 gene showed early onset of EP; in most cases, this started during the neonatal period or infancy with very diverse clinical manifestations. Notably, the KCNQ2 protein forms heteromeric channels with the Kv7.3 subunit encoded by the KCNQ3 gene, mediating the M-current (Wang et al., 1998). The latter is activated at membrane potentials close to the action threshold, enabling cellular hyperpolarization and dampening repetitive neuronal firing (Steinlein et al., 1999). Mutations in the KCNQ2 gene may reduce the amplitude of the M-current by 20 %–30 %, thereby inducing abnormal neuronal excitability (Schroeder et al., 1998). The phenotypic spectrum of the KCNQ2 mutation ranges from benign familial neonatal epilepsy (BFNE) to early-onset epileptic encephalopathy, including OS and atypical EOEE (Falsaperla et al., 2023). Benign EP usually presents with LoF mutations, which usually are hereditary. These result in decreased protein expression, hence milder symptoms often controlled within months. While de novo missense mutations causing severe functional impairment in VGKC typically present with EOEE in the neonatal period and often accompany significant developmental delays and ASD, GoF and LoF mutations will be viewed in both EOEE; GoF mutations usually present worse than LoF mutations (Borggraefe and Wagner, 2023).

GABA agonists have also found widespread application in the treatment of EP caused by KCNQ2 gene mutations. Assorted drugs increase antiepileptic effects mainly through promoting GABA synthesis and inhibiting its degradation, hence increasing the levels of the inhibitory neurotransmitter in the tissue (Uchida et al., 2017). Commonly used drugs include sodium valproate and phenobarbital, with GABA agonists preferred for treating benign EP associated with KCNQ2 mutations (Kuersten et al., 2020). Currently, retigabine, a selective activator of M-channels, is reported to be a targeted antiepileptic drug for treating LoF mutations in KCNQ2 and KCNQ3 (Fontán-Lozano et al., 2011).

3.2.2. *KCNT1*

KCNT1 is located on human chromosome 9q34.3 and encodes the sodium-activated potassium channel KNa1.1, currently the largest known VGKC (Yuan et al., 2003). It is expressed in the olfactory bulb, cortex, brainstem, and hippocampus, mediating sodium-activated potassium currents responsible for the slow hyperpolarization following repetitive discharges (Barcia et al., 2012). All reported mutations in KCNT1 are missense mutations that increase channel activity, accelerate neuronal repolarization, and heighten neuronal excitability. These mutations may prolong the hyperpolarization of inhibitory neurons. Consequently, excitatory neurons exhibit relatively high excitability, leading to an imbalance between excitation and inhibition, which can trigger EP (Burbano et al., 2022). Children with EP due to KCNT1 gene mutations typically present early, predominantly with focal seizures, and exhibit severe symptoms with poor responsiveness to AEDs (Martin et al., 2014). Research indicates that EP associated with KCNT1 mutations often coexists with intellectual disability. The disease phenotypes include autosomal dominant nocturnal frontal lobe epilespy (ADNFLE), EIMFS, OS, and IS, and are also linked with arrhythmias and leukoencephalopathy. KCNT1 is acknowledged as the most significant pathogenic gene for ADNFLE to date (Bonardi et al., 2021).

Furthermore, electrophysiological studies have shown that mutations in the KCNT1 gene enhance VGKC function. Quinidine, a Class I antiarrhythmic and antimalarial drug, acts as a VGKC antagonist and may mitigate the functional impairments caused by KCNT1 mutations (Liu et al., 2023). A patient with EIMFS carrying a KCNT1 mutation experienced a substantial reduction in the frequency of EP seizures and improvement in psychomotor development during quinidine treatment. However, reports of treatment failures with quinidine in patients with KCNT1 gene mutations also exist (Mullen et al., 2018).

3.2.3. *KCNA2*

The KCNA2 gene, located on human chromosome 1p13.3, encodes the Kv1.2 channel. This channel is primarily located in Purkinje neurons, dendrites, and the hippocampus. It plays a crucial role in the later stages of neuronal action potentials, facilitating neuronal repolarization (Pena and Coimbra, 2015). Functional studies have identified three subtypes of KCNA2 gene mutations: LoF, GoF, and GoF combined with LoF. These mutations can overlap in clinical phenotypes. LoF mutations typically present with milder symptoms, often manifesting in infancy or early childhood as focal seizures, which are relatively easy to control. They may also present as myoclonic seizures during fever and require differentiation from DS. Electroencephalograms (EEGs) show characteristic features, including discharges in the Rolandic area and potentially evolving into a state of continuous epileptic activity during sleep (ESES), ultimately leading to benign EP with centrotemporal spikes in children (Syrbe et al., 2015). The most common LoF mutation site is P450L. In contrast, GoF mutations (notably E157K, R297Q, L298F) and GoF combined with LoF mutations (notably L290R, L293H, L328V, T374A) are associated with more severe phenotypes, beginning in the neonatal period. These cases often present with severe, intractable seizures, significant ataxia, and intellectual disabilities, with cerebellar involvement being a primary feature (Masnada et al., 2017).

In summary, mutations in VGKCs may cause dysfunction in membrane proteins, disrupting the normal activities K^+ currents across cell membranes. This disruption leads to atypical depolarization and repolarization processes, increasing neuronal excitability, which :

et al., 2021). Genetic studies in pediatric EP have frequently identified mutations in CACNA1A, CACNA1H, and CACNA2D2, with CACNA1A being the most thoroughly investigated.

3.3.1. CACNA1A

The CACNA1A gene is responsible for producing the α1 subunit of the Cav2.1 (P/Q-type calcium channel), a presynaptic channel protein essential for calcium-mediated neurotransmitter release at synapses and nerve terminals, facilitated through interactions with SNARE proteins (Zamponi et al., 2010). Cav2.1 is prevalently expressed across both central and peripheral synaptic sites and plays a significant role in neurotransmission and synaptic plasticity, influencing neuronal excitability (Heck et al., 2021). Mutations in CACNA1A are known to heighten neuronal excitability, leading to EP and cognitive impairments, predominantly within the scope of DEE, which are primarily focal, early-onset, and often evolve into status epilepticus (SE), with associated developmental delays and ataxia that are typically resistant to treatments (Damaj et al., 2015). These pathogenic mutations are linked to various neurological phenotypes, including episodic ataxia type 2 (EA2), spinocerebellar ataxia type 6 (SCA6), and familial hemiplegic migraine type 1 (FHM1) (Le Roux et al., 2021). Despite ongoing research, effective treatments for EP induced by CACNA1A mutations remain elusive. Studies involving Cav2.1 knockout mice have revealed deficits in hippocampal glutamatergic synaptic transmission and spatial learning and memory impairments (Angelini et al., 2019). Additionally, mutations in the CACNA1H gene, associated with pediatric EP characterized by FS plus, temporal lobe EP, and childhood absence EP, often respond favorably to lamotrigine treatment (Lipman et al., 2022).

3.3.2. CACNA1H

The CACNA1H gene, which encodes the T-type calcium channel Cav3.2, is located on chromosome 16p13.3. It is highly expressed in the brain, thalamus, amygdala, basal ganglia, and Purkinje cells of the cerebellum, where it mediates ion transport across membranes and influences cellular excitability (Stringer et al., 2021; Tjaden et al., 2021). Variants in CACNA1H increase neuronal excitability by enhancing the function of T-type calcium channels, thus facilitating the occurrence of EP and playing a crucial role in hereditary EP disorders. The phenotypic spectrum of EP associated with this gene includes juvenile myoclonic EP, juvenile absence EP, and generalized EP with GEFS$^+$ (Becker et al., 2017). Studies have demonstrated that polymorphisms in the CACNA1H gene are linked to susceptibility to EP and the efficacy of treatments (Kang et al., 2004). Research confirms that GoF mutations in CACNA1H are common among patients with absence EP, highlighting its significant role in the pathogenesis of this condition (Wang et al., 2017).

3.3.3. CACNA2D2

The CACNA2D2 gene encodes the auxiliary α2δ-2 subunit of high-voltage-gated calcium channels known as VGCCs, which is considered a major active regulator in synaptogenesis and plasticity (Dolphin, 2012). The α2δ protein performs multiple postsynaptic functions in driving synapse formation, mediating synaptic communication, and modulating glutamate receptor function (Brockhaus et al., 2018), and has been implicated in EP, movement disorders, and schizophrenia (Danis et al., 2023; Edvardson et al., 2013). Expression studies revealed the highest levels of expression in lungs and testes, followed by high but somewhat lower levels in the brain, heart, and pancreas (Gao et al., 2000). In the brain, CACNA2D2 is predominantly expressed in Purkinje cells of the cerebella (Punetha et al., 2019) but also in cerebral cortex, hippocampus, cerebellum, pons, and medulla (Klugbauer et al., 1999). The involvement of CACNA2D2 as a disease gene remains ambiguous. Deletion of CACNA2D2 has been associated with increased sensitivity to pentylenetetrazol-induced seizures (Barclay et al., 2001). The most common clinical phenotypes are represented by early-onset EP and congenital ataxia although pathogenic variants in CACNA2D2 were reported in three families with DEE (Zamponi et al., 2015) and in one family with pure congenital ataxia.

In summary, VGCCs are the primary pathway for Ca^{2+} entry into neurons. Mutations in these genes can disrupt the hyperpolarization of the cell membrane and the transmission of excitatory postsynaptic potentials, as well as alter the activity and function of calcium-activated VGCCs, leading to EP. The mechanism of EP regulation by VGICs is shown in Fig. 2. In addition, the coding genes, tissue distribution and function of VGICs and the relationship between functional and clinical phenotypes are shown in Table 1, Table 2.

4. The influence of TCM in regulating VGICs on EP

EP is classified as "Xian Zheng" in TCM. TCM theory suggests that EP arises from brain damage, dysfunction of internal organs, accumulation of phlegm-heat, and disturbances of internal wind, resulting in disordered Qi movement that impacts the clear orifices of the mind. TCM has a long history of treating EP, supported by a diverse array of herbal formulas that have cultivated a comprehensive theoretical and clinical framework. In recent years, the popularity of TCM has increased among patients due to its sustained effectiveness, minimal side effects, and reduced recurrence rates. Currently, active components of herbal medicine and TCM formulas are being explored as potential alternative treatments for EP.

4.1. Herbal formulas regulating VGICs in treating EP

Recent experimental studies have significantly advanced our understanding of herbal formulas used in treating EP, particularly their effects on VGICs and hippocampal neuronal cells. Classical and modified herbal decoctions, proven effective in clinical settings, regulate VGICs to treat EP. Common formulations include Guishao Zhenxian tablets (Zhao et al., 2023), Shigan powder (Li et al., 2016), Shouerzhi capsules (Ding, 2012), Xifeng capsules, Rongchang capsules, Kangxian capsules (Ma et al., 2015), Yuxian Ling granules (Wang et al., 2003), and Anxianning infusion (Song et al., 2002).

According to the 2020 edition of the Chinese Pharmacopeia, Guishao Zhenxian tablets are indicated for various types of EP. For example, Zhao et al. reported that the primary active components, baicalin and oroxylin A, regulate VGKCs and influence genes such as SCN5A, KCNH2, and SLC6A3, thus inhibiting apoptosis-related genes, protecting neurons, and reducing EP episodes (Zhao et al., 2023). Furthermore, Li et al. found that Shigan powder considerably reduces the amplitude of INap in mouse hippocampal neurons ($P < 0.01$) and increases the amplitude of IA transient outward K^+ channel current ($P = 0.047$), demonstrating its effectiveness in slowing depolarization rates, reducing neuronal firing, and decreasing neuronal excitability (Li et al., 2016). Previous research by Li et al. also confirmed that Shigan powder modulates VGICs, suppresses neuronal firing, and enhances the expression of brain-derived neurotrophic factor (BDNF) to protect nerve cells.

Research by Ding et al. indicated that Shouerzhi capsules can decrease the peak L-type calcium current while shifting the I-V curve upwards, suggesting a suppressive effect on the L-type calcium current in hippocampal neurons, which may contribute to its neuroprotective effects (Ding, 2012). Furthermore, Ma et al. observed that herbal formulas such as Xifeng capsules, Rongchang capsules, and Kangxian capsules can reduce NMDA receptor channel currents, decrease intracellular Ca^{2+} concentrations, and inhibit repetitive high-frequency firing of hippocampal neurons, thereby alleviating excitotoxicity caused by Ca^{2+} overload (Ma et al., 2015). Moreover, Lu et al. discovered that Xifeng capsules could reduce VGSCs current, enhance VGSCs inactivation, and prolong recovery time to decrease abnormal VGSC activation, thus reducing spontaneous EP episodes (Lu et al., 2019).

Yuxianling granules, primarily composed of blood-activating and stasis-removing herbs, have been shown to provide protective effects against pathological damage in the temporal lobe and hippocampus of seizure-prone rats (Wang et al., 2003). Wang et al. found that Yuxianling

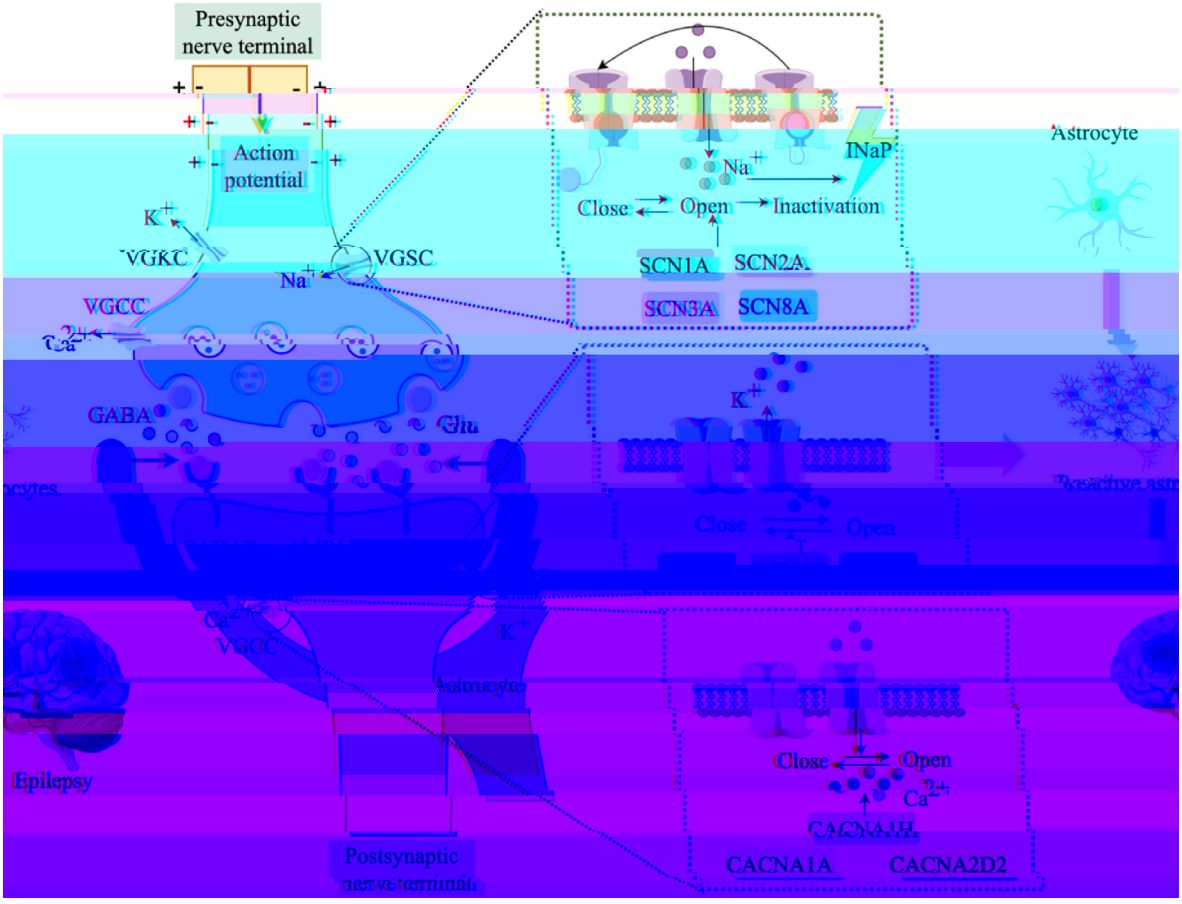

Fig. 2. Mechanisms of VGIC regulation of EP. mutations in ion channels such as VGSCs, VGKCs, and VGCCs may alter the normal function of channel proteins, leading to an imbalance in the excitation-inhibition dynamics of the CNS, resulting in abnormally synchronized neuronal firing, and ultimately leading to EP episodes.

Table 1
Coding genes, tissue distribution and functions of VGICs.

VGICs	Coding gene	Chromosme	Deactivation rate/Current type	Organizational distribution	Cell distribution and Function	Reference
Nav1.1	SCN1A	2q24.3	Sharp	Brain, Spinal cord	Located in inhibitory interneurons, involved in inhibitory networks	(Misonou,2018)
Nav1.2	SCN2A	2q24.3	Sharp	Brain, Kidney	Located proximal to the axon initiating segment (AIS) of excitatory neurons, dendrites, involved in the retrograde propagation of action potentials	(Sanders et al., 2018)
Nav1.3	SCN3A	2q24.3	Sharp	Brain	Located in fetal and neonatal neurons, involved in development	(Meisler et al., 2010)
Nav1.6	SCN8A	12q13.13	Sharp	Brain	Located in the distal AIS and Langfeld's ganglion of neurons involved in the initiation and propagation of action potentials	(Feng et al., 2019)
Kv7. 2	KCNQ2	20q13. 3	Sharp	Central and peripheral neurons	Located in central and peripheral neurons, responsible for stabilizing neurons and regulating neuronal excitability	(Casas-Alba et al., 2023)
KNal.1	KCNT1	9q34. 3	Sharp	Cerebral olfactory bulb, Cortex, Brainstem and Hippocampus	Located in the olfactory bulb, cortex, brainstem, and hippocampus of the brain, responsible for slow hyperpolarization after repetitive discharges	(Yuan et al., 2003)
Kv1. 2	KCNA2	1p13. 3	Slowly	Purkinje nerve, Dendritic and Hippocampal areas	Located in the Purkinje nerve, dendritic and hippocampal regions, responsible for late repolarization of neuronal action potentials	(Pen and Coimbra,2015)
Cav2.1	CACNA1A	19p13.13	P/Q type	Cerebellum, Caudate nucleus, Brain	Located in the presynaptic membrane of central and peripheral nerves, it is responsible for regulating transmitter release at synapses and nerve endings	(Zamponiet al.,2010)
Cav3.2	CACNA1H	16p13.3	T type	Cerebral, Thalamic, Amygdala, Basal ganglia region, Cerebellar purkinje cells	Located in the brain, thalamus, amygdala, and basal ganglia regions, responsible for increasing neuronal excitability	(Stringer et al., 2021; Tjaden et al., 2021)
Cav1.3	CACNA2D2	3p21.3	L type	Brain, Inner hair cells and Cardiac organs	Regulation of contraction, secretion, neurotransmission and gene expression	(Dolphin,2012; Brockhaus et al., 2018)

Table 2
Relationship between functional and clinical phenotypes of VGICs.

Gene	LoF-induced diseases	GoF-induced diseases	Reference
SCN1A	GEFS^{+} FS、DS	Non-DS FHM、DEE	(Brunklaus et al., 2022)
SCN2A	Evening hair DEE、ASD、ID	Early hair DEE、BFNIE、EA、EIMFS	(Wolff et al., 2019)
SCN3A	ASD、ID	FFEVF、DEE、EOEE	(Kwan et al., 2008)
SCN8A	ASD、ID	DEE、BFNIE	(Conecker ? 20J

granules alleviate calcium overload in the brains of PTZ-chronic kindled rats, indicating that while reducing neuronal Ca^{2+}, they can increase Ca^{2+} concentrations in the cerebrospinal fluid, likely due to the granules' hindrance of extracellular Ca^{2+} entry into neurons, thereby increasing the membrane potential difference and reducing abnormal neuronal firing, ultimately achieving therapeutic effects on EP (Wang et al., 2005). Anxianning infusion has sedative and anticonvulsant effects. Song et al. reported that administering Anxianning infusion could reduce malondialdehyde (MDA) levels in the brain homogenate of penicillin-induced EP mice while enhancing superoxide dismutase (SOD) activity, indicating that its anti-EP effects are related to antioxidative stress and maintaining the dynamic balance of Na^{+}, K^{+}, and Ca^{2+} ions (Song et al., 2002).

4.2. Regulation of VGICs by active components of TCM in the treatment of EP

TCM and its active components have been used for thousands of years. Numerous studies have shown that Chinese herbs and their active ingredients, such as hawthorn acid, white stigmata extract, saikosaponin a, and leucovorin, have been shown to have a significant effect on the treatment of EP in animal experiments and clinical trials, and in view of the lack of clinical trials in humans, their effects may be related to the protection of neurons through the reduction of inflammation, oxidative stress, and neurotoxicity via the modulation of VGICs, and thus the control of EP episodes(Xiang, 2021; Hu, 2021; Cheng et al., 2021).

Kumar et al. discovered that curcumin counteracts the downregulation of two channel proteins, CACNA1A and GABRD, associated with EP (Kumar and Sharma, 2020). In models of iron-induced EP, the expression of the sodium channel Nav1.1 was upregulated, while curcumin was found to reduce the expression of cortical Nav1.1, contributing to its antiepileptic effects (Kumar et al., 2019). Additionally, the natural terpenoid maslinic acid may reduce the excitability of cortical pyramidal neurons by increasing M-current. Further research by Xiang Jiayao et al. showed that hawthorn acid can affect the basic properties of Nav1.2 and Nav1.7, inhibiting persistent sodium currents (INaP), and modifying neuronal excitability to produce therapeutic effects against EP (Xiang, 2021). As an animal-derived medicine in traditional Chinese medicine, proteins and peptides (polypeptides) are the main chemical components unique to bombyx batryticatus. Studies have indicated that bombyx batryticatus protein offers protection against glutamate-induced PC-12 cells, and the bombyx batryticatus extract can modulate N-methyl-D-aspartate receptors (NMDAR), glutamate receptor ion genes (GRIN1), and Bax, while enhancing Bcl-2, thereby mitigating glutamate toxicity (Hu, 2021).

Saikosaponin A has demonstrated potential in anti-tumor, anti-inflammatory, and antiepileptic applications (Cheng et al., 2021). Research by Yu et al. revealed that saikosaponin A achieves its antiepileptic effects by selectively modulating different subunits of VGSCs and VGKCs (Yu, 2013). Additionally, Xie et al. identified that the antiepileptic effect of saikosaponin A is realized by significantly inhibiting the increase of Ca^{2+} activated by glutamate, and reducing the levels of interleukin-6 (IL-6) in the extracellular fluid of astrocytes activated by glutamate (Xie et al., 2008). Furthermore, succinic acid, an intermediate metabolite of the tricarboxylic acid cycle, exhibits various pharmacological effects, including sedation, analgesia, and anticonvulsant effects. Cong et al. determined that succinic acid can dose-dependently inhibit high-voltage-activated (HVA) calcium currents without affecting low-voltage-activated (LVA) currents, suggesting that succinic acid may reduce calcium influx by inhibiting HVA calcium currents and modulating the excitability of neurons in the hippocampal CA1 region, thereby inhibiting the development of EP (Cong and Yue, 2009). Moreover, Fu et al. demonstrated that schisandrin A significantly inhibits voltage-activated VGSCs and VGCCs currents in hippocampal neurons, decreasing their excitability, while piperine can effectively inhibit synchronized electrical activity in neuronal networks (Fu, 2009). It is noteworthy that the efficacy of Schisandra can vary based on its origin, source, and cultivation conditions, which directly influenc the content and ratio of its active components, including schisandrin A and schisandrin B.

The main active component of Uncaria rhynchophylla is indole alkaloids, and its water extract has been proven to exhibit antiepileptic activity in rats. It has long been utilized to treat central nervous system diseases (Li and Lou, 2021). Research by Shao et al. found that rhynchophylline can downregulate the expression of Nav1.6, thereby inhibiting INaP, which effectively improves seizure occurrences in EP rats (Shao et al., 2016). Additionally, Xie et al. discovered that rhynchophylline can suppress the spontaneous firing frequency of action potentials in hippocampal neurons and exhibits inhibitory activity on VGSCs and VGKCs (Xie, 2020). Notably, rhynchophylline shows a stronger inhibitory effect on potassium currents in hippocampal neurons compared to sodium channels, demonstrating significant antiepileptic activity. The inward rectifier potassium channel blocker kushenin has also been reported to have sedative, hypnotic, and anti-seizure properties. Ligustrazine, a large-conductance calcium-activated potassium channel opener, is one of the more thoroughly studied active ingredients for promoting blood circulation and removing blood stasis. Jia et al. using kushenin and ligustrazine, demonstrated that both compounds inhibited induced seizures and decreased the incidence of MES-induced seizures, thus indicating that calcium-activated VGKCs may play a role in the mechanisms of EP and antiepileptic properties of kushenin and ligustrazine can be related, at least partially, to the opening of VGKCs (Jia, 2007).

Besides, triptolide displays intense physiological activity, shows prominent antiapoptotic, anti-inflammatory, and immune-regulatory activity, and passes through the blood-brain barrier, making it very clinically used. Pan et al. showed that triptolide could decrease neuronal apoptosis for the EP rats by enhancing the expression of kv1.1 protein in the CA3 region of hippocampus to provide neuroprotection (Pan et al., 2012). Zhang et al. discovered that polysaccharides from Ganoderma lucidum can indirectly inhibit NF-κB from entering the nucleus by reducing intracellular Ca^{2+} influx, thereby decreasing neuronal excitability and significantly countering the occurrence of EP (Zhang et al., 2008). Furthermore, octyl gallate has been shown to strongly inhibit Ca^{2+} influx in GH4C1 rat cells. Guo et al. reported that octyl gallate inhibits Ca^{2+} release activated by RyR and IP3R, protecting cells from excitotoxic damage and thereby controlling EP (Guo, 2013). Research indicates that Qingyangshen glycosides exhibit a notable antagonistic effect on FeSO4-induced EP, demonstrating significant antiepileptic effects. Additionally, Li et al. observed that Qingyangshen glycosides may

exacerbate PTZ-induced EP, potentially due to their ability to elevate the expression of KCNAl, Camk2b, and Pcx in the hippocampus while reducing SCN1B expression (Li, 2005).

The dried whole scorpion, derived from Buthus martensii, is rich in neurotoxic peptides (scorpion venom) and possesses various pharmacological effects, including antiepileptic, anti-seizure, and immune-regulatory properties. Liu et al. found that scorpion tail extracts exhibit effective activity against Kv1.2, Kv1.3, and Kv4.1 channels (Liu, 2019). Furthermore, Wang et al. discovered that these scorpion venom peptides can inhibit the excitability of hippocampal neurons, providing neuroprotective effects (Wang et al., 2014). Jonas P et al. concluded from experiments with frogs that the toxin γ in scorpion venom affects the activation and inactivation of VGSCs in neuronal membranes (Jonas et al., 1986). Additionally, Li et al. found that osthole can accelerate the inactivation of VGKCs recorded in hippocampal neurons and, at lower concentrations, can hasten the inactivation of delayed rectifier potassium channels Kv1.1, Kv1.2, Kv1.3, and Kv2.1, suggesting that osthole may exert antiepileptic effects by converting delayed rectifier potassium channels into functional A-type potassium channels, thus reducing the excitability of pyramidal neurons (Li, 2016). Therefore, both herbal formulas and active components of TCM can inhibit EP episodes by modulating VGICs, as shown in Fig. 3,Table 3,Table 4.

5. Conclusions and prospects

The essence of EP is excessive abnormal synchronization of neuronal discharges in the brain, and the relevant VGICs such as sodium, potassium and calcium ions are the basis for regulating neuronal excitability and play an important role in this process. Mutations in the genes encoding the above mentioned ion channels can affect the normal physiological function of neurons and thus lead to the EP episodes, with the wide application of second-generation sequencing, the EP associated with mutations in the genes of VGICs are also With the wide application of second-generation sequencing, EPs associated with mutations in VGICs genes have also been gradually discovered and recognised, e.g., VGSCs, as the basis of excitatory activity in the nervous system, are the main causative genes and important candidate genes for a variety of EP syndromes and are responsible for the generation and propagation of action potentials, which play an important role in the process of neural excitation, and potassium channels are the most important ion channel regulating the excitability of neurons, and the mutations in VGKCs genes are closely associated with EP, and the mutations in VGCCs are associated with VGCCs are closely related to the overall electrical excitability of neurons and abnormal neuronal discharge, and selective or non-selective T-type calcium channels are potential therapeutic targets for EP. In addition, the clinical treatment of EP is dominated by western drugs, but it produces large adverse reactions, which can lead to abnormalities in the digestive system, central nervous system, hematopoietic system, urinary system and liver function to varying degrees, and the drug resistance is strong, which is not conducive to the long-term use of patients.

In recent years, TCM has shown distinct advantages in treating EP. Experimental results from animal models of EP suggest that blocking VGSCs or enhancing VGKCs can effectively manage seizures. Modulating VGIC-related genes and proteins may be a key mechanism by which TCM ameliorates EP. Active components from traditional herbs, such as maslinic acid, bombyx batryticatus extract, and saikosaponin A, as well as traditional formulations like Guishao Zhenxian tablets, Shigan powder, and Shouerzhi capsules, can regulate VGICs, affecting their activation, managing the currents and concentrations of Na^+, K^+, and Ca^{2+},

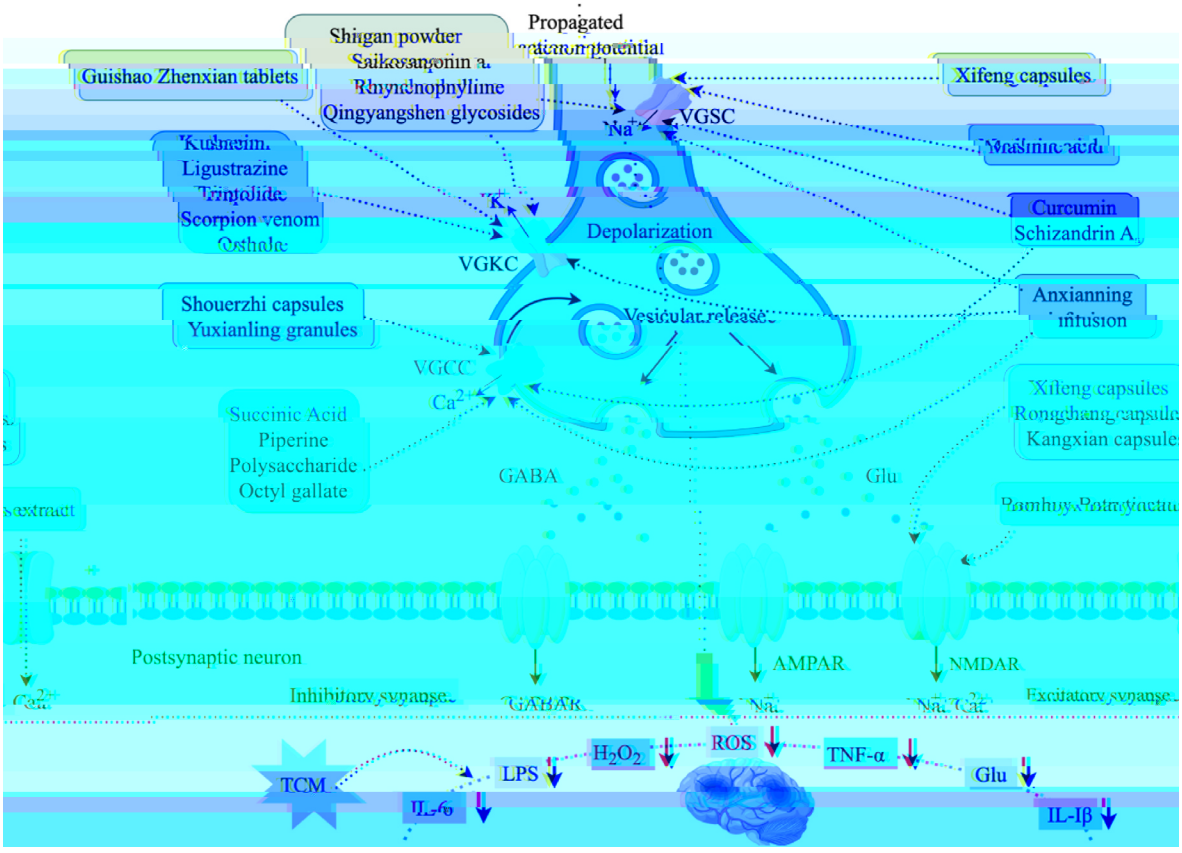

Fig. 3. TCM modulates the effect of VGICs on EP. By acting on VGICs (VGSCs, VGKCs and VGCCs) and ion channel-related receptors, TCM (TCM formulations and TCM active ingredients) reduce inflammation, oxidative stress and Glu neuroexcitotoxicity responses, thus reducing neuronal excitability and maintaining the balance of excitatory-inhibitory system of the neural network, and ultimately preventing and controlling EP.

Table 3
Modulation of VGICs by herbal formulas in the treatment of epilepsy.

Herbal formula	Traditional use	Herbal composition	Preclinical Study subjects	Impact on VGICs	Impact on epilepsy	Reference
Guishao Zhenxian tablets	Various seizure types of epilepsy (Chinese pharmacopeia,2020)	Cinnamomi Ramulus, Codonopsis Radix, Glycyrrhizae Radix et Rhizoma, Ziziphus jujuba Mill, Paeoniae Radix Alba, Pinellia ternata, Scutellaria baicalensis Georgi, Bupleuri Radix, Zingiberofficinale Roscoe	–	Regulation of VGKCs function	Inhibition of apoptosis-related genes to protect neurons	(Zhao et al., 2023)
Shigan powder	Antiepileptic(Li,2023)	Acorus tatarinowii, Nardostachys chinensis	Pentylenetetrazol rat epilepsy model	Downward adjustment of INap amplitude and upward adjustment of instantaneous outward VGKCs current amplitude	Inhibits neuronal discharge and reduces neuronal excitability	(Li et al., 2016)
Shouer zhi capsules	Alzheimer's disease and antiepileptic(Ding and Wu,2012)	Scutellaria baicalensis Georgi, Ligusticum chuanxiong hort, Acorus tatarinowii, Polygala tenuifolia, Plastrum testudinis	Japanese White Rabbit with Large Ears and 12-15d cells	Suppression of L-type calcium currents	Protection of nerve cells	(Ding,2012)
Rong chang capsules	Antiepileptic and anticonvulsant (Guo et al., 2021)	Cervi Cornu Pantotri chum, Acorus tatarinowii, Cuscuta chinensis, Arisaema cum Bile, Gastrodia elata Bl,Scorpio, Bombyx Batryticatus, Pinellia ternata, Citri reticulatae pericarpium, Poria, Borneolum Syntheticum, Glycyrrhizae Radix et Rhizoma	A model of magnesium-free induced hippocmpal neuronal firing	Reduces intracellular Ca^{2+} concentration	Reduces Glu neuroexcitotoxicity and protects nerve cells	(Ma et al., 2015)
Kangxian capsules	Antiepileptic(Geng et al., 2021)	Pseudostellariaeradix, Poria, Citri reticulatae pericarpium, Pinellia ternata, Acorus tatarinowii, Arisaema cum Bile, Poncirus trifoliata, Platycodon grandiflorus, Gastrodia elata Bl,Ligusticum chuanxiong hort, Aquilariae Lignum Resinatum	A model of magnesium-free induced hippocampal neuronal firing	Reduces intracellular Ca^{2+} concentration	Reduces Glu neuroexcitotoxicity and protects nerve cells	(Ma et al., 2015)
Xifeng capsules	Antiepileptic(Lu,2022)	Placenta hominis, Gastrodia elata Bl, Acorus tatarinowii, Bombyx Batryticatus, Scorpio, Curcumae radix, Ligusticum chuanxiong hort	Lithium chloride-pilocarpine rat epilepsy model	Reduced VGSCs current and enhanced VGSCs inactivation	Reducing recurrent spontaneous seizures	(Lu et al., 2019)
Yuxianling granules	Antiepileptic(Li et al., 2010)	Eleutherococcus senticosus, Ligusticum chuanxiong hort, Acorus tatarinowii, Scorpio, Chilopoda, Bambusae caulis in taenias, Pheretima, Scutellaria baicalensis Georgi, Carthami Flos, Micae Lapis Aureus, Borneolum Syntheticum	Pentylenetetrazol rat epilepsy model	Reduction of"calcium buildup"in nerve cells	Reduced abnormal neuronal discharge	(Wang et al., 2005)
Anxianning infusion	Antiepileptic(Zhao and Zhao,2003)	Bupleuri Radix, Paeoniae radix alba, Arisaema cum Bile, Poria, Piper Nigrum L	Penicillin-induced epilepsy model in mice	Maintaining the dynamic equilibrium of Na^{+}, K^{+}, Mg^{2+}, Ca^{2+}	Reducing oxidative stress	(Song et al., 2002)

and modulating the expression of VGIC-related proteins to reduce hippocampal neuronal excitability. Therefore, further research into TCM may offer a promising avenue for developing VGIC-based therapeutic strategies for EP. In view of this, we have explored the distribution of voltage-gated ion channel (VGIC) encoding genes, their roles, and the mechanisms by which they influence EP. The relationship between the functional types of VGICs and clinical phenotypes is also examined. Most importantly, we have systematically summarized how TCM impacts VGICs to mitigate inflammation, oxidative stress, and glutamate excitotoxicity, thereby reducing neuronal excitability and maintaining the balance of excitation and inhibition in neural networks, ultimately contributing to the treatment of EP.

It is noteworthy that due to the complexity of the mechanisms underlying EP, in conjunction with TCM's pathogenesis, several challenges remain. First, a lack of rigorous design in clinical studies persists, including the need for large sample sizes and multi-center research. This is further compounded by significant individual variability among patients, long treatment cycles, and poor patient compliance, which pose difficulties for research. Second, TCM's therapeutic effects are achieved through multiple targets and pathways, yet specific research on molecular pathways and precise targets is lacking. The exact mechanisms of TCM in treating EP require further investigation, necessitating a more systematic and integrative approach to studying these mechanisms. Third, gene-targeted therapies, which are more precise compared to other treatment modalities, are gradually being applied in channelopathies, but safety remains a primary concern. Additionally, genetic testing lays the foundation for precise diagnosis and treatment of EP, but functional testing at the cellular or animal level is needed to provide

Table 4
Modulation of VGICs by herbal active components in the treatment of epilepsy.

Active component	TCM	Study subjects	Impact on VGICs	Impact on epilepsy	Reference
Curcumin	Turmeric	$FeCl_3$-induced epilepsy in rat	Attenuated down-regulation of CACNA1A and GABRD and down-regulated Nav1.1 expression	Reduces neuroexcitotoxicity	(Kumar and Sharma,2020; Kumar et al., 2019)
Maslinic acid	Hawthorn	Pentylenetetrazol-induced zebrafish	Suppression of INaP by affecting the fundamental properties of Nav1.2 and Nav1.7	Altered neuronal excitability	(Xiang,2021)
Bombyx Batryticatus extract	Bombyx Batryticatus	–	Attenuates the toxic effects of Glu and reduces intracellular Ca^{2+} concentration	Anticonvulsive	(Hu,2021)
Saikosaponin a	Chinese thorowax root	Glutamate Activation of rat hippocampal astrocytes	Suppressing VGSCs current amplitude and up-regulating VGKCs current amplitude	Selective modulation of different VGSCs, VGKCs subunits exerts antiepileptic effects	(Yu,2013; Xie et al., 2008)
Succinic Acid	Amber	SD rat pups	Inhibition of HVA calcium current reduces Ca^{2+} inward flow	Influence on the excitability of neurons in the CA1 region of the hippocampus	(Cong and Yue,2009)
Schizandrin A	Schisandrachinensis	SD rats	Suppression of VGSCs and VGCCs currents	Decreased excitability of hippocampal neurons	(Fu,2009)
Piperine	Pepper	SD rats	Inhibition of spontaneous synchronization of calcium oscillations in hippocampal neuronal networks	Inhibition of synchronized electrical activity in neuronal networks	(Fu,2009)
Rhynchophylline	Uncaria	Maximal Electroconvulsive and 6-Hz Induced Epilepsy Models	Inhibition of voltage-gated VGSCs, VGKCs activity	Reducing the frequency and prolonging the duration of action potential issuance in rat hippocampal neurons	(Shao et al., 2016; Xie,2020)
Kushenin	Sophora alopecuroides	Electrical stimulation of the amygdala ignites a chronic epilepsy model	VGKCs open	Suppression of ignition seizures and reduction in the incidence of convulsions with maximal electroconvulsions	(Jia,2007)
Ligustrazine	Chuanxiong Rhizoma				
Triptolide	Tripterygium wilfordii	Kelvinic acid	Increased expression of kv1.1 protein	Reduction of neuronal apoptosis in epileptic rats	(Pan et al., 2012)
Polysaccharide	Ganoderma lucidum	Pentylenetetrazol rat epilepsy model	Reduced Ca^{2+} inward flow in nerve cells	Reduces excitability of nerve cells	(Zhang et al., 2008)
Octyl gallate	Turkish gall	–	Inhibition of Ca^{2+} release	Protects cells from excitatory damage	(Guo,2013)
Qingyangshen glycosides	Cynanchum otophyllum	Pentylenetetrazol rat epilepsy model	Elevation of KCNAl, Camk2b and Pcx Expression and Reduction of SCNlB Expression in Hippocampal Sites	Suppression of strong noise-induced audiogenic convulsive seizures	(Li,2005)
Scorpion venom	Scorpion	–	Good activity against Kv1.2, Kv1.3 and Kv4.1	Inhibition of hippocampal neuron excitability	(Liu,2019) (Wang T et al., 2014) (Jonas et al., 1986)
Osthole	Cnidii Fructus	Maximal electroshock and pentylenet etrazole-induced epilepsy model	Accelerated deactivation of Kv1.1, Kv1.2, Kv1.3, Kv2.1 currents	Decreased excitability of pyramidal neurons	(Li,2016)

evidence for pathogenicity. Fourth, significant research gaps persist regarding the relationship between genotype, phenotype, and function in ion channel diseases. How to guide medication based on different genotypes and assess patient prognosis requires further exploration. Fifth, as TCM compounding consists of multiple herbal formulations with different components and active ingredients and potential inconsistencies in study doses, the development of standardized TCM protocols for the treatment of EP is a key scientific issue that needs to be addressed. Sixth, the treatment of EP with TCM may have side effects such as excitatory neurotoxicity, blood-brain barrier competition and developmental toxicity in children. Seventh, VGSCs, VGKCs, VGCCs, etc., as key targets for the treatment of EP, may provide new ideas and new approaches for the development of EP treatment guidelines.

With technological advances in genetics, neuroimaging, and increasing research into the etiology of EP, therapies targeting specific etiologies are emerging, which has brought about a dramatic change in the clinical EP treatment paradigm. We believe that the search for novel AEDs with new mechanisms of action is the key to treating DRE. Future EP-related research can be conducted in the following areas: ① More case reports and more in-depth results of basic and clinical studies are expected to further elucidate the pathogenesis of EP associated with VGICs gene variants, the correlation between the clinical phenotype and genotype; ② A standardized system of"multi-dimensional quality control, intelligent dose optimization and global regulatory synergy"must be constructed for the treatment of EP with Chinese medicine, and clinical applicability will be improved through the establishment of a library of antiepileptic ingredients of Chinese medicine, the development of adaptive drug delivery systems and drug genome testing kits; ③ We are actively conducting multi-center, large-sample, prospective clinical studies on EP to provide new evidence-based evidence for the diagnosis and treatment of EP with TCM and to develop individualized EP treatment protocols by combining multiple treatment modalities, to improve the inhibition rate of clinical EP, and to place more emphasis on precision medicine to prevent EP episodes in a patient-centered manner.

CRediT authorship contribution statement

Jialin Zhong: Writing – review editing, Writing – original draft, Investigation, Data curation. **Maofu Zhang:** Writing – original draft, Visualization. **Shuang Huang:** Investigation, Data curation. **Jingxi Yao:** Investigation, Data curation. **Bing Jiang:** Visualization, Investigation, Data curation. **Lv Gao:** Investigation, Formal analysis, Data curation. **Zhenggang Shi:** Supervision, Project administration, Methodology, Investigation, Conceptualization.

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Declaration of competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

(ADNFLE) Autosomal dominant nocturnal frontal lobe epilespy
(AEDs): Antiepileptic drugs
(ASD): Autism spectrum disorder
(BDNF) Brain-derived neurotrophic factor
(BFNE) Benign familial neonatal epilepsy
(BFNIE) Benign familial neonatalinfantile seizures
(DEE) Developmental and epileptic encephalopathies
(DS) Dravet syndrome
(EA2) Episodic ataxia type 2
(EE) Epileptic encephalopathy
(EEGs) Electroencephalograms
(EIMFS) Infantile epilepsy with migrating focal seizures
(EOEE) Early-onset epileptic encephalopathy
(EP) Epilepsy
(ESES) Electrical status epilepticus during sleep
(FFEVF) Familial focal epilepsy with variable foci
(FHM) Familial hemiplegic migraine
(FS) Febrile seizures
(GABA) γ-aminobutyric acid
(GEFS^{+}): Genetic epilepsy with febrile seizures plus
(Glu): Glutamic acid
(GoF) Gain-of-function
(GRIN1) Glutamate receptor ion genes
(HVA): High-voltage-activated
(ID) Intellectual disability
(IL-6) Interleukin-6
(INaP) Residual persistent sodium current
(IS) Infantile spasm
(LoF) Loss-of-function
(MDA) Malondialdehyde
(MES) maximal electroshock seizure
(NMDAR) N-methyl-D-aspartate receptors
(OS) Ohtahara syndrome
(SCBs) Sodium channel blockers
(SE) Status epilepticus
(SOD) Superoxide dismutase
(TCM) Traditional Chinese medicine
(TRPM2) Transient receptor potential M2 channel
(VGCCs) Voltage-gated calcium channels
(VGICs) Voltage-gated ion channels
(VGKCs) Voltage-gated potassium channels
(VGSCs) Voltage-gated sodium channels

Data availability

No data was used for the research described in the article.

References

Ali, A., 2018. Global health: Epilepsy. Semin. Neurol. 38, 191–199.
Angelini, C., Van Gils, J., Bigourdan, A., Jouk, P.S., Lacombe, D., Menegon, P., Moutton, S., Riant, F., Sole, G., Tournier-Lasserve, E., Trimouille, A., Vincent, M., Goizet, C., 2019. Major intra-familial phenotypic heterogeneity and incomplete penetrance due to a CACNA1A pathogenic variant. Eur. J. Med. Genet. 62, 103530.
Barcia, G., Fleming, M.R., Deligniere, A., Gazula, V.R., Brown, M.R., Langouet, M., Chen, H., Kronengold, J., Abhyankar, A., Cilio, R., Nitschke, P., Kaminska, A., Boddaert, N., Casanova, J.L., Desguerre, I., Munnich, A., Dulac, O., Kaczmarek, L.K., Colleaux, L., Nabbout, R., 2012. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat. Genet. 44, 1255–1259.
Barclay, J., Balaguero, N., Mione, M., Ackerman, S.L., Letts, V.A., Brodbeck, J., Canti, C., Meir, A., Page, K.M., Kusumi, K., Perez-Reyes, E., Lander, E.S., Frankel, W.N., Gardiner, R.M., Dolphin, A.C., Rees, M., 2001. Ducky mouse phenotype of epilepsy and ataxia is associated with mutations in the Cacna2d2 gene and decreased calcium channel current in cerebellar purkinje cells. J. Neurosci. 21, 6095–6104.
Barker, B.S., Ottolini, M., Wagnon, J.L., Hollander, R.M., Meisler, M.H., Patel, M.K., 2016. The SCN8A encephalopathy mutation p.Ile1327Val displays elevated sensitivity to the anticonvulsant phenytoin. Epilepsia 57, 1458–1466.
Barker-Haliski, M.L., Loscher, W., White, H.S., Galanopoulou, A.S., 2017. Neuroinflammation in epileptogenesis: insights and translational perspectives from new models of epilepsy. Epilepsia 58, 39–47.
Bartolini, E., Campostrini, R., Kiferle, L., Pradella, S., Rosati, E., Chinthapalli, K., Palumbo, P., 2020. Epilepsy and brain channelopathies from infancy to adulthood. Neurol. Sci. 41, 749–761.
Becker, F., Reid, C.A., Hallmann, K., Tae, H.S., Phillips, A.M., Teodorescu, G., Weber, Y. G., Kleefuss-Lie, A., Elger, C., Perez-Reyes, E., Petrou, S., Kunz, W.S., Lerche, H., Maljevic, S., 2017. Functional variants in HCN4 and CACNA1H May contribute to genetic generalized epilepsy. Epilepsia Open 2, 334–342.
Boßelmann, C.M., Hedrich, U.B.S., Müller, P., Sonnenberg, L., Parthasarathy, S., Helbig, I., Lerche, H., Pfeifer, N., 2022. Predicting the functional effects of voltage-gated potassium channel missense variants with multi-task learning. EBioMedicine 81, 104115.
Bonardi, C.M., Heyne, H.O., Fiannacca, M., Fitzgerald, M.P., Gardella, E., Gunning, B., Olofsson, K., Lesca, G., Verbeek, N., Stamberger, H., Striano, P., Zara, F., Mancardi, M.M., Nava, C., Syrbe, S., Buono, S., Baulac, S., Coppola, A., Weckhuysen, S., Schoonjans, A.S., Ceulemans, B., Sarret, C., Baumgartner, T., Muhle, H., Portes, V.D., Toulouse, J., Nougues, M.C., Rossi, M., Demarquay, G., Ville, D., Hirsch, E., Maurey, H., Willems, M., de Bellescize, J., Altuzarra, C.D., Villeneuve, N., Bartolomei, F., Picard, F., Hornemann, F., Koolen, D.A., Kroes, H.Y., Reale, C., Fenger, C.D., Tan, W.H., Dibbens, L., Bearden, D.R., Møller, R.S., Rubboli, G., 2021. KCNT1-related epilepsies and epileptic encephalopathies: phenotypic and mutational spectrum. Brain 144, 3635–3650.
Borggraefe, I., Wagner, M., 2023. Precision therapy in KCNQ2-Related epilepsy. Neuropediatrics 54, 295–296.
Bouza, A.A., Isom, L.L., 2018. Voltage-gated sodium channel β subunits and their related diseases. Handb. Exp. Pharmacol. 246, 423–450.
Brockhaus, J., Schreitmüller, M., Repetto, D., Klatt, O., Reissner, C., Elmslie, K., Heine, M., Missler, M., 2018. α-Neurexins together with α2δ-1 auxiliary subunits regulate Ca2+ influx through Cav2.1 channels. J. Neurosci. 38, 8277–8294.
Brunklaus, A., Du, J., Steckler, F., Ghanty, I.I., Johannesen, K.M., Fenger, C.D., Schorge, S., Baez-Nieto, D., Wang, H.R., Allen, A., Pan, J.Q., Lerche, H., Heyne, H., Symonds, J.D., Zuberi, S.M., Sanders, S., Sheidley, B.R., Craiu, D., Olson, H.E., Weckhuysen, S., DeJonge, P., Helbig, I., Van Esch, H., Busa, T., Milh, M., Isidor, B., Depienne, C., Poduri, A., Campbell, A.J., Dimidschstein, J., Møller, R.S., Lal, D., 2020. Biological concepts in human sodium channel epilepsies and their relevance in clinical practice. Epilepsia 61, 387–399.
Brunklaus, A., Lal, D., 2020. Sodium channel epilepsies and neurodevelopmental disorders: from disease mechanisms to clinical application. Dev. Med. Child Neurol. 62, 784–792.
Bunton-Stasyshyn, R.K.A., Wagnon, J.L., Wengert, E.R., Barker, B.S., Faulkner, A., Wagley, P.K., Bhatia, K., Jones, J.M., Maniaci, M.R., Parent, J.M., Goodkin, H.P., Patel, M.K., Meisler, M.H., 2019. Prominent role of forebrain excitatory neurons in SCN8A encephalopathy. Brain 142, 362–375.
Burbano, L.E., Li, M., Jancovski, N., Jafar-Nejad, P., Richards, K., Sedo, A., Soriano, A., Rollo, B., Jia, L., Gazina, E.V., Piltz, S., Adikusuma, F., Thomas, P.Q., Kopsidas, H., Rigo, F., Reid, C.A., Maljevic, S., Petrou, S., 2022. Antisense oligonucleotide therapy for KCNT1 encephalopathy. JCI Insight 7, e146090.
Cai, Y., He, X., Ao, L., Liu, Y., Zhang, Y., Yang, H., Zhang, L., 2024. Efficacy and safety of traditional Chinese medicine for the treatment of epilepsy by wind quenching and phlegm resolving: a systematic review and meta-analysis. Medicine (Baltim.) 103, e39942.
Casas-Alba, D., Aguilar, A., Alonso, I., García, M.T., Cilio, M.R., Fons, C., 2023. BIO-KCNQ2- Spanish study group. Relationship between epileptic activity and developmental outcome in KCNQ2-Related epilepsy. Pediatr. Neurol. 144, 11–15.
Catterall, W.A., Goldin, A.L., Waxman, S.G., 2005. International union of pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. Pharmacol. Rev. 57, 397–409.
Cheng, Y.P., Jiang, L.L., Wang, Y.Z., Ren, P.Y., Gao, N., Wang, Bo, 2021. Research progress on pharmacology of saikosaponin a. Chinese Archives of Traditional Chinese Medicine 39, 24–27.
Chen, H., Xia, Z., Dong, J., Huang, B., Zhang, J., Zhou, F., Yan, R., Shi, Y., Gong, J., Jiang, J., Huang, Z., Jiang, D., 2024. Structural mechanism of voltage-gated sodium channel slow inactivation. Nat. Commun. 15, 3691.
Chilcott, E., Díaz, J.A., Bertram, C., Berti, M., Karda, R., 2022. Genetic therapeutic advancements for Dravet syndrome. Epilepsy Behav. 132, 108741.

Çınar, R., Nazıroğlu, M., 2023. TRPM2 channel inhibition attenuates amyloid β42-Induced apoptosis and oxidative stress in the hippocampus of mice. Cell. Mol. Neurobiol. 43, 1335–1353.
Claes, L., Del-Favero, J., Ceulemans, B., Lagae, L., Van Broeckhoven, C., De Jonghe, P., 2001. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am. J. Hum. Genet. 68, 1327–1332.
Conecker, G., Xia, M.Y., Hecker, J., Achkar, C., Cukiert, C., Devries, S., Donner, E., Fitzgerald, M.P., Gardella, E., Hammer, M., Hegde, A., Hu, C., Kato, M., Luo, T., Schreiber, J.M., Wang, Y., Kooistra, T., Oudin, M., Waldrop, K., Youngquist, J.T., Zhang, D., Wirrell, E., Perry, M.S., 2024. Global modified Delphi consensus on diagnosis, phenotypes, and treatment of SCN8A-related epilepsy And/Or neurodevelopmental disorders. Epilepsia 65, 2322–2338.
Cong, H.Q., Yue, W., 2009. Effect of succinic acid on voltage-dependent calcium currents in rat hippocampal CA1 area neurons. Prog. Mod. Biomed. 9, 444–447.
Damaj, L., Lupien-Meilleur, A., Lortie, A., Riou, É., Ospina, L.H., Gagnon, L., Vanasse, C., Rossignol, E., 2015. CACNA1A haploinsufficiency causes cognitive impairment, autism and epileptic encephalopathy with mild cerebellar symptoms. Eur. J. Hum. Genet. 23, 1505–1512.
Danis, A., Gallagher, A.A., Anderson, A.N., Isakharov, A., Beeson, K.A., Schnell, E., 2023. Altered hippocampal activation in seizure-prone CACNA2D2 knockout mice. bioRxiv 10 [Preprint] 2023.11.08.565511.
Debanne, D., Mylonaki, K., Musella, M.L., Russier, M., 2024. Voltage-gated ion channels in epilepsies: circuit dysfunctions and treatments. Trends Pharmacol. Sci. 45, 1018–1032.
De Lera Ruiz, M., Kraus, Rl, 2015. Voltage-gated sodium channels: structure, function, pharmacology, and clinical indications. J. Med. Chem. 58, 7093–7118.
Ding, D., Zhou, D., Sander, J.W., Wang, W., Li, S., Hong, Z., 2021. Epilepsy in China: major progress in the past two decades. Lancet Neurol. 20, 316–326.
Ding, Y.B., 2012. Effects of shourezi containing serum on L-type calcium channel currents in rabbit hippocampal neuronal cells. Hubei Journal of Traditional Chinese Medicine 34, 20–21.
Dolphin, A.C., 2012. Calcium channel auxiliary α2δ and β subunits: trafficking and one step beyond. Nat. Rev. Neurosci. 13, 542–555.
Ednie, A.R., Bennett, E.S., 2012. Modulation of voltage-gated ion channels by sialylation. Compr. Physiol. 2, 1269–1301.
Edvardson, S., Oz, S., Abulhijaa, F.A., Taher, F.B., Shaag, A., Zenvirt, S., Dascal, N., Elpeleg, O., 2013. Early infantile epileptic encephalopathy associated with a high voltage gated calcium channelopathy. J. Med. Genet. 50, 118–123.
Epifanio, R., Giorda, R., Merlano, M.C., Zanotta, N., Romaniello, R., Marelli, S., Russo, S., Cogliati, F., Bassi, M.T., Zucca, C., 2021. SCN2A pathogenic variants and epilepsy: heterogeneous clinical, genetic and diagnostic features. Brain Sci. 12, 18.
Escayg, A., Goldin, A.L., 2010. Sodium channel SCN1A and epilepsy: mutations and mechanisms. Epilepsia 51, 1650–1658.
Falsaperla, R., Criscione, R., Cimino, C., Pisani, F., Ruggieri, M., 2023. KCNQ2-Related epilepsy: genotype-phenotype relationship with tailored antiseizure medication (ASM)-A systematic review. Neuropediatrics 54, 297–307.
Fan, Z., Feng, X., Fan, Z., Zhu, X., Yin, S., 2018. Immunotherapy by targeting of VGKC complex for seizure control and prevention of cognitive impairment in a mouse model of epilepsy. Mol. Med. Rep. 18, 169–178.
Feng, Y., Zhang, S., Zhang, Z., Guo, J., Tan, Z., Zhu, Y., Tao, J., Ji, Y.H., 2019. Understanding genotypes and phenotypes of the mutations in voltage-gated sodium channel α subunits in epilepsy. CNS Neurol. Disord.: Drug Targets 18, 266–272.
Fontán-Lozano, A., Suárez-Pereira, I., Delgado-García, J.M., Carrión, A.M., 2011. The M-current inhibitor XE991 decreases the stimulation threshold for long-term synaptic plasticity in healthy mice and in models of cognitive disease. Hippocampus (New York, N. Y.) 21, 22–32.
Fu, M., 2009. Study of the inhibitory effect of ... on epileptiform ... in hippocampal ... Neuronal Networks. Tsinghua University.
Gao, B., Sekido, Y., Maximov, A., Saad, M., Forgacs, E., Latif, F., Wei, M.H., Lerman, M., Lee, J.H., Perez-Reyes, E., Bezprozvanny, I., Minna, J.D., 2000. Functional properties of a new voltage-dependent calcium channel alpha(2)delta auxiliary subunit gene (CACNA2D2). J. Biol. Chem. 275, 12237–12242.
Geng, L.J., Wang, B.H., Zhang, X.E., Ma, N., Li, J., Li, S.Q., Jiang, M., 2021. Clinical study on Xiao'er kangxian capsules combined with sodium valproate in treatment of primary systemic tonic-clonic seizure epilepsy in children and its effect on the levels of GFAP and S100β. Drugs Clinic 36, 995–999.
Guo, Y.J., 2013. Does octyl

Li, Z.X., Xie, J.T., Wang, J.J., Yin, Y., Li, J.A., Huang, Y.F., Ding, Z.G., Zhu, B.K., Li, Z.G., 2010. Effects of yuxianling granule on bdnf expression and cognitive dysfunction in ptz- induced epileptic rats. Chinese Journal of Traditional Medical Science and Technology 17, 484-486+471-472.
Lu, Y.L., Fang, Y.Y., Li, X.M., Sun, D., Ma, L.T., Han, Y.W., 2019. Research of the effect of xifeng capsule on the function of voltage-gated sodium channel in epileptic rats induced by pilocarpine. Tianjin J. Traditional Chin. Med. 36, 1001–1005.
Martin, H.C., Kim, G.E., Pagnamenta, A.T., Murakami, Y., Carvill, G.L., Meyer, E., Copley, R.R., Rimmer, A., Barcia, G., Fleming, M.R., Kronengold, J., Brown, M.R., Hudspith, K.A., Broxholme, J., Kanapin, A., Cazier, J.B., Kinoshita, T., Nabbout, R., Wgs, Consortium, Bentley, D., McVean, G., Heavin, S., Zaiwalla, Z., McShane, T., Mefford, H.C., Shears, D., Stewart, H., Kurian, M.A., Scheffer, I.E., Blair, E., Donnelly, P., Kaczmarek, L.K., Taylor, J.C., 2014. Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis. Hum. Mol. Genet. 23, 3200–3211.
Ma, R., Yang, C.Q., Liu, Q.H., Ren, X.Q., Zhang, X.L., Rong, P., 2015. Effects of wind-extinguishing capsule, fuzzy calamus capsule and Anti-eclampsia capsule on NMDA receptor currents and intracellular free calcium in hippocampal neurons. Pharmacol. Clinics of Chin. Materia Medica 31, 140–142.
Masnada, S., Hedrich, U.B.S., Gardella, E., Schubert, J., Kaiwar, C., Klee, E.W., Lanpher, B.C., Gavrilova, R.H., Synofzik, M., Bast, T., Gorman, K., King, M.D., Allen, N.M., Conroy, J., Ben Zeev, B., Tzadok, M., Korff, C., Dubois, F., Ramsey, K., Narayanan, V., Serratosa, J.M., Giraldez, B.G., Helbig, I., Marsh, E., O'Brien, M., Bergqvist, C.A., Binelli, A., Porter, B., Zaeyen, E., Horovitz, D.D., Wolff, M., Marjanovic, D., Caglayan, H.S., Arslan, M., Pena, S.D.J., Sisodiya, S.M., Balestrini, S., Syrbe, S., Veggiotti, P., Lemke, J.R., Møller, R.S., Lerche, H., Rubboli, G., 2017. Clinical spectrum and genotype-phenotype associations of KCNA2-related encephalopathies. Brain 140, 2337–2354.
Meisler, M.H., Helman, G., Hammer, M.F., Fureman, B.E., Gaillard, W.D., Goldin, A.L., 2016. SCN8A encephalopathy: research progress and prospects. Epilepsia 57, 1027–1035.
Meisler, M.H., Hill, S.F., Yu, W., 2021. Sodium channelopathies in neurodevelopmental disorders. Nat. Rev. Neurosci. 22, 152–166.
Meisler, M.H., O'Brien, J.E., Sharkey, L.M., 2010. Sodium channel gene family: epilepsy mutations, gene interactions and modifier effects. J. Physiol. 588, 1841–1848.
Meldrum, B.S., Rogawski, M.A., 2007. Molecular targets for antiepileptic drug development. Neurotherapeutics 4, 18–61.
Menezes, L.F.S., Sabiá Júnior, E.F., Tibery, D.V., Carneiro, L.D.A., Schwartz, E.F., 2020. Epilepsy-related voltage-gated sodium channelopathies: a review. Front. Pharmacol. 11, 1276.
Mesraoua, B., Brigo, F., Lattanzi, S., Abou-Khalil, B., Al Hail, H., Asadi-Pooya, A.A., 2023. Drug-resistant epilepsy: definition, pathophysiology, and management. J. Neurol. Sci. 452, 120766.
Mishima, T., Fujiwara, T., Kofuji, T., Saito, A., Terao, Y., Akagawa, K., 2021. Syntaxin 1B regulates synaptic GABA release and extracellular GABA concentration, and is associated with temperature-dependent seizures. J. Neurochem. 156, 604–613.
Misonou, H., 2018. Precise localizations of voltage-gated sodium and potassium channels in neurons. Dev. Neurobiol. 78, 271–282.
Miyatake, S., Kato, M., Sawaishi, Y., Saito, T., Nakashima, M., Mizuguchi, T., Mitsuhashi, S., Takata, A., Miyake, N., Saitsu, H., Matsumoto, N., 2018. Recurrent SCN3A p.Ile875Thr variant in patients with polymicrogyria. Ann. Neurol. 84, 159–161.
Moreau, A., Gosselin-Badaroudine, P., Chahine, M., 2015. Gating pore currents, a new pathological mechanism underlying cardiac arrhythmias associated with dilated cardiomyopathy. Channels 9, 139–144.
Mullen, S.A., Carney, P.W., Roten, A., Ching, M., Lightfoot, P.A., Churilov, L., Nair, U., Li, M., Berkovic, S.F., Petrou, S., Scheffer, I.E., 2018. Precision therapy for epilepsy due to KCNT1 mutations: a randomized trial of oral quinidine. Neurology 90, e67–e72.
Myers, K.A., 2022. Genetic epilepsy syndromes. Continuum (Minneap.Minn) 28, 339–362.
Pan, X., Zou, Z.F., Zeng, C.X., Cui, J.H., Hu, B., Li, Y.W., 2012. Effect of tretinoinol on the expression of voltage-gated potassium channel kv1.1 in epileptic rats. J. Int. Neurol. Neurosurg. 39, 108–113.
Pena, S.D., Coimbra, R.L., 2015. Ataxia and myoclonic epilepsy due to a heterozygous new mutation in KCNA2: proposal for a new channelopathy. Clin. Genet. 87, e1–e3.
Perucca, E., Taglialatela, M., 2025. Targeting Kv7 potassium channels for epilepsy. CNS Drugs 39, 263–288.
Pong, A.W., Xu, K.J., Klein, P., 2023. Recent advances in pharmacotherapy for epilepsy. Curr. Opin. Neurol. 36, 77–85.
Powell, K.L., Lukasiuk, K., O'Brien, T.J., Pitkänen, A., 2014. Are alterations in transmitter receptor and ion channel expression responsible for epilepsies? Adv. Exp. Med. Biol. 813, 211- 29.
Prontera, P., Sarchielli, P., Caproni, S., Bedetti, C., Cupini, L.M., Calabresi, P., Costa, C., 2018. Epilepsy in hemiplegic migraine: genetic mutations and clinical implications. Cephalalgia 38, 361–373.
Punetha, J., Karaca, E., Gezdirici, A., Lamont, R.E., Pehlivan, D., Marafi, D., Appendino, J.P., Hunter, J.V., Akdemir, Z.C., Fatih, J.M., Jhangiani, S.N., Gibbs, R. A., Innes, A.M., Posey, J.E., Lupski, J.R., 2019. Biallelic CACNA2D2 variants in epileptic encephalopathy and cerebellar atrophy. Ann. Clin. Transl. Neurol. 6, 1395–1406.
Reynolds, C., King, M.D., Gorman, K.M., 2020. The phenotypic spectrum of SCN2A-related epilepsy. Eur. J. Paediatr. Neurol. 24, 117–122.
Richards, M.C., Heron, S.E., Spendlove, H.E., Scheffer, I.E., Grinton, B., Berkovic, S.F., Mulley, J.C., Davy, A., 2004. Novel mutations in the KCNQ2 gene link epilepsy to a dysfunction of the KCNQ2-calmodulin interaction. J. Med. Genet. 41, e35.
Sadleir, L.G., Mountier, E.I., Gill, D., Davis, S., Joshi, C., DeVile, C., Kurian, M.A., Ddd, Study, Mandelstam, S., Wirrell, E., Nickels, K.C., Murali, H.R., Carvill, G., Myers, C.T., Mefford, H.C., Scheffer, I.E., 2017. Not all SCN1A epileptic encephalopathies are Dravet syndrome: early profound Thr226Met phenotype. Neurology 89, 1035–1042.
Sanders, S.J., Campbell, A.J., Cottrell, J.R., Moller, R.S., Wagner, F.F., Auldridge, A.L., Bernier, R.A., Catterall, W.A., Chung, W.K., Empfield, J.R., George Jr., A.L., Hipp, J. F., Khwaja, O., Kiskinis, E., Lal, D., Malhotra, D., Millichap, J.J., Otis, T.S., Petrou, S., Pitt, G., Schust, L.F., Taylor, C.M., Tjernagel, J., Spiro, J.E., Bender, K.J., 2018. Progress in understanding and treating SCN2A-Mediated disorders. Trends Neurosci. 41, 442–456.
Sands, T.T., Gelinas, J.N., 2024. Epilepsy and encephalopathy. Pediatr. Neurol. 150, 24–31.
Scheffer, I.E., Nabbout, R., 2019. SCN1A-related phenotypes: Epilepsy and beyond. Epilepsia 3, S17–S24.
Schroeder, B.C., Kubisch, C., Stein, V., Jentsch, T.J., 1998. Moderate loss of function of cyclic- AMP-Modulated KCNQ2/KCNQ3 K+ channels causes epilepsy. Nature 396, 687–690.
Shao, H., Yang, Y., Mi, Z., Zhu, G.X., Qi, A.P., Ji, W.G., Zhu, Z.R., 2016. Anticonvulsant effect of rhynchophylline involved in the inhibition of persistent sodium current and NMDA receptor current in the pilocarpine rat model of temporal lobe epilepsy. Neuroscience 337, 355–369.
Shen, K.F., Yang, X.L., Liu, G.L., Zhu, G., Wang, Z.K., Shi, X.J., Wang, T.T., Wu, Z.F., Lv, S.Q., Liu, S.Y., Yang, H., Zhang, C.Q., 2021. The role of voltage-gated chloride channels in the epileptogenesis of temporal lobe epilepsy. EBioMedicine 70, 103537.
Sills, G.J., Rogawski, M.A., 2020. Mechanisms of action of currently used antiseizure drugs. Neuropharmacology 168, 107966.
Simms, B.A., Zamponi, G.W., 2014. Neuronal voltage-gated calcium channels: structure, function, and dysfunction. Neuron (Camb., Mass.) 82, 24–45.
Siwek, M., Henseler, C., Broich, K., Papazoglou, A., Weiergräber, M., 2012. Voltage-gated Ca(2+) channel mediated Ca(2+) influx in epileptogenesis. Adv. Exp. Med. Biol. 740, 1219–1247.
Song, L.Q., Xiao, H.B., Zhao, D.Y., Song, S.J., 2002. Effects of An-epileptin punch on MDA, SOD, and ATPase in brain tissues of mouse epilepsy model. Chin. J. Exp. Tradit. Med. Formulae 2002, 44–46.
Spinelli, S., Remigante, A., Liuni, R., Mantegna, G., Legname, G., Marino, A., Morabito, R., Dossena, S., 2024. Oxidative stress-related cellular aging causes dysfunction of the Kv3.1/KCNC1 channel reverted by melatonin. Aging Cell 23, e14185.
Stefani, A., Spadoni, F., Bernardi, G., 1997. Voltage-activated calcium channels: targets of antiepileptic drug therapy? Epilepsia 38, 959–965.
Steinlein, O.K., Stoodt, J., Biervert, C., Janz, D., Sander, T., 1999. The voltage gated potassium channel KCNQ2 and idiopathic generalized epilepsy. Neuroreport 10, 1163–1166.
Stringer, R.N., Jurkovicova-Tarabova, B., Souza, I.A., Ibrahim, J., Vacik, T., Fathalla, W. M., Hertecant, J., Zamponi, G.W., Lacinova, L., Weiss, N., 2021. De novo SCN8A and inherited rare CACNA1H variants associated with severe developmental and epileptic encephalopathy. Mol. Brain 14, 126.
Su, F.Z., Sun, Y.P., Bai, C.X., Zhang, W.S., Yang, B.Y., Wang, Q.H., Kuang, H.X., 2023. Epilepsy treated by traditional Chinese medicine based on syndrome differentiation: a review. Chin. J. Exp. Tradit. Med. Formulae 29, 200–211.
Sugawara, T., Tsurubuchi, Y., Agarwala, K.L., Ito, M., Fukuma, G., Mazaki-Miyazaki, E., Nagafuji, H., Noda, M., Imoto, K., Wada, K., Mitsudome, A., Kaneko, S., Montal, M., Nagata, K., Hirose, S., Yamakawa, K., 2001. A missense mutation of the na+ channel alpha II subunit gene Na(v)1.2 in a patient with febrile and afebrile seizures causes channel dysfunction. Proc. Natl. Acad. Sci. USA 98, 6384–6389.
Symonds, J.D., Zuberi, S.M., Johnson, M.R., 2017. Advances in epilepsy gene discovery and implications for epilepsy diagnosis and treatment. Curr. Opin. Neurol. 30, 193–199.
Syrbe, S., Hedrich, U.B.S., Riesch, E., Djémié, T., Müller, S., Møller, R.S., Maher, B., Hernandez Hernandez, L., Synofzik, M., Caglayan, H.S., Arslan, M., Serratosa, J.M., Nothnagel, M., May, P., Krause, R., Löffler, H., Detert, K., Dorn, T., Vogt, H., Krämer, G., Schöls, L., Mullis, P.E., Linnankivi, T., Lehesjoki, A.E., Sterbova, K., Craiu, D.C., Hoffman-Zacharska, D., Korff, C.M., Weber, Y.G., Steinlin, M., Gallati, S., Bertsche, A., Bernhard, M.K., Merkenschlager, A., Kiess, W., Gonzalez, M., Züchner, S., Palotie, A., Suls, A., De Jonghe, P., Helbig, I., Biskup, S., Wolff, M., Maljevic, S., Schüle, R., Sisodiya, S.M., Weckhuysen, S., Lerche, H., Lemke, J.R., 2015. De novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy. Nat. Genet. 47, 393–399.
Talwar, D., Hammer, M.F., 2021. SCN8A epilepsy, developmental encephalopathy, and related disorders. Pediatr. Neurol. 122, 76–83.
Tian, R., He, L., Chen, H.F., Zhao, W.J., 2016. Analysis on composition principles of ancient prescriptions for epilepsy based on canopy clustering. J. Li-shizhen Traditional Chin. Med. 27, 2782–2785.
Tjaden, J., Eickhoff, A., Stahlke, S., Gehmeyr, J., Vorgerd, M., Theis, V., Matschke, V., Theiss, C., 2021. Expression pattern of T-Type Ca2+ channels in cerebellar purkinje cells after VEGF treatment. Cells 10, 2277.
Trinka, E., Kwan, P., Lee, B., Dash, A., 2019. Epilepsy in Asia: disease burden, management barriers, and challenges. Epilepsia 60, 7–21.
Uchida, T., Lossin, C., Ihara, Y., Deshimaru, M., Yanagawa, Y., Koyama, S., Hirose, S., 2017. Abnormal γ-aminobutyric acid neurotransmission in a Kcnq2 model of early onset epilepsy. Epilepsia 58, 1430–1439.
Vanoye, C.G., Gurnett, C.A., Holland, K.D., George, A.L., Kearney, J.A., 2014. Novel SCN3A variants associated with focal epilepsy in children. Neurobiol. Dis. 62, 313–322.

Veeramah, K.R., O'Brien, J.E., Meisler, M.H., Cheng, X., Dib-Hajj, S.D., Waxman, S.G., Talwar, D., Girirajan, S., Eichler, E.E., Restifo, L.L., Erickson, R.P., Hammer, M.F., 2012. De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. Am. J. Hum. Genet. 90, 502–510.

Wang, H.S., Pan, Z., Shi, W., Brown, B.S., Wymore, R.S., Cohen, I.S., Dixon, J.E., McKinnon, D., 1998. KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel. Science 282, 1890–1893.

Wang, H., Xu, M., Kong, Q., Sun, P., Yan, F., Tian, W., Wang, X., 2017. Research and progress on ClC-2. Mol. Med. Rep. 16, 11–22 (Review).

Wang, J.J., Han, M., Zhang, X.X., Wang, Y.H., Huang, Y., Liang, Y.G., 2005. Intervention of guaifenesin on calcium ions in pentylenetetrazol-ignited epileptic rats. China Journal of Traditional Chinese Medicine and Pharmacy 2005, 628–629.

Wang, J.J., Li, Z.G., Zhong, Y., Chen, B.Y., He, Q., Duan, Z.Z., 2003. Preprotective effect of guaifenesin on pathological damage of temporal lobe and hippocampus in epileptogenic rats. China Journal of Traditional Chinese Medicine and Pharmacy 18, 209–210.

Wang, Q., Liu, N., Ni, Y.S., Yang, J.M., Ma, L., Lan, X.B., Wu, J., Niu, J.G., Yu, J.Q., 2021. TRPM2 in ischemic stroke: structure, molecular mechanisms, and drug intervention. Channels 15, 136–154.

Wang, T., Wang, S.W., Zhang, Y., Wu, X.F., Peng, Y., Cao, Z., Ge, B.Y., Wang, X., Wu, Q., Lin, J.T., Zhang, W.Q., Li, S., Zhao, J., 2014. Scorpion venom heat-resistant peptide (SVHRP) enhances neurogenesis and neurite outgrowth of immature neurons in adult mice by up- regulating brain-derived neurotrophic factor (BDNF). PLoS One 9, e109977.

Wang, W., Li, H., Yu, J., Hong, M., Zhou, J., Zhu, L., Wang, Y., Luo, M., Xia, Z., Yang, Z.J., Tang, T., Ren, P., Huang, X., Wang, J., 2016. Protective effects of Chinese herbal medicine rhizoma drynariae in rats after traumatic brain injury and identification of active compound. Mol. Neurobiol. 53, 4809–4820.

Watanabe, E., Fujikawa, A., Matsunaga, H., Yasoshima, Y., Sako, N., Yamamoto, T., Saegusa, C., Noda, M., 2000. Nav2/NaG channel is involved in control salt-intake behavior in the CNS. J. Neurosci. 20, 7743–7751.

Wirrell, E.C., Laux, L., Donner, E., Jette, N., Knupp, K., Meskis, M.A., Miller, I., Sullivan, J., Welborn, M., Berg, A.T., 2017. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a north American consensus panel. Pediatr. Neurol. 68, 18–34.

Wolff, M., Johannesen, K.M., Hedrich, U.B.S., Masnada, S., Rubboli, G., Gardella, E., Lesca, G., Ville, D., Milh, M., Villard, L., Afenjar, A., Chantot-Bastaraud, S., Mignot, C., Lardennois, C., Nava, C., Schwarz, N., Gérard, M., Perrin, L., Doummar, D., Auvin, S., Miranda, M.J., Hempel, M., Brilstra, E., Knoers, N., Verbeek, N., van Kempen, M., Braun, K.P., Mancini, G., Biskup, S., Hörtnagel, K., Döcker, M., Bast, T., Loddenkemper, T., Wong-Kisiel, L., Baumeister, F.M., Fazeli, W., Striano, P., Dilena, R., Fontana, E., Zara, F., Kurlemann, G., Klepper, J., Thoene, J.G., Arndt, D.H., Deconinck, N., Schmitt-Mechelke, T., Maier, O., Muhle, H., Wical, B., Finetti, C., Brückner, R., Pietz, J., Golla, G., Jillella, D., Linnet, K.M., Charles, P., Moog, U., Õiglane-Shlik, E., Mantovani, J.F., Park, K., Deprez, M., Lederer, D., Mary, S., Scalais, E., Selim, L., Van Coster, R., Lagae, L., Nikanorova, M., Hjalgrim, H., Korenke, G.C., Trivisano, M., Specchio, N., Ceulemans, B., Dorn, T., Helbig, K.L., Hardies, K., Stamberger, H., de Jonghe, P., Weckhuysen, S., Lemke, J.R., Krägeloh-Mann, I., Helbig, I., Kluger, G., Lerche, H., Møller, R.S., 2017. Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. Brain 140, 1316–1336.

Xiang, J.Y., 2021. Study on the Antiepileptic Effect and Mechanism of the Natural Terpenoid Constituent Hawthornic Acid. Kunming University of Science and Technology.

Xiao, Q., Zhang, Z.P., Hou, Y.B., Qu, D.X., Tang, L.L., Chen, L.J., Li, G.Y., Ji, Y.H., Tao, J., Zhu, Y.D., 2022. Anti-Epileptic/Pro-Epileptic effects of sodium channel modulators from Buthus martensii karsch. Sheng Li Xue Bao 74, 621–632.

Xia, S.S., Yang, P., Li, L., Yu, Q., Lu, J., Shao, F., He, Z.M., Huang, H.Y., 2019. Research review on TCM treatment of syndromes differentiation of epilepsy. China Journal of Traditional Chinese Medicine and Pharmacy 34, 37–40.

Xie, W.Z., Wen, W.B., Yong, L.J., 2008. Inhibition of Increased Cā(2+) Concentration and IL-6 Release in glutamate-activated Rat Hippocampal Astrocytes by Chaihu Saponin a. Journal of Beijing University of Traditional Chinese Medicine 2008, pp. 756–758 +766.

Xie, Z.Q., 2020. Studies on the Effect of Crocus Sativus Alkaloids on the Ion Channels of Hippocampal Neurons and Their Antiepileptic Activity, 2020. Shanghai University of Chinese Medicine.

Yang, R., Qian, R., Chen, K., Yi, W., Sima, X., 2021. Genetic polymorphisms in SCN2A are not associated with epilepsy risk and AEDs response: evidence from a meta-analysis. Neurol. Sci. 42, 2705–2711.

Yuan, A., Santi, C.M., Wei, A., Wang, Z.W., Pollak, K., Nonet, M., Kaczmarek, L., Crowder, C.M., Salkoff, L., 2003. The sodium-activated potassium channel is encoded by a member of the slo gene family. Neuron (Camb., Mass.) 37, 765–773.

Yu, C., Deng, X.J., Xu, D., 2023. Microglia in epilepsy. Neurobiol. Dis. 185, 106249.

Yu, Y.H., 2013. Study on the Inhibitory Effect of Chaihu Saponin a on Epileptiform Discharges of Rat Hippocampal Neurons and the Modulation of Related Ion Channel Currents. Southern Medical University.

Yu, Y.Y., Yuan, C.X., Gu, C., 2022. Clinical efficacy and safety of removing blood stasis and resolving phlegm in the treatment of epilepsy with cognitive impairment: a systematic review and meta-analysis. Medicine (Baltim.) 101, e30212.

Zaman, T., Helbig, I., Božović, I.B., DeBrosse, S.D., Bergqvist, A.C., Wallis, K., Medne, L., Maver, A., Peterlin, B., Helbig, K.L., Zhang, X., Goldberg, E.M., 2018. Mutations in SCN3A cause early infantile epileptic encephalopathy. Ann. Neurol. 83, 703–717.

Zaman, T., Helbig, K.L., Clatot, J., Thompson, C.H., Kang, S.K., Stouffs, K., Jansen, A.E., Verstraete, L., Jacquinet, A., Parrini, E., Guerrini, R., Fujiwara, Y., Miyatake, S., Ben-Zeev, B., Bassan, H., Reish, O., Marom, D., Hauser, N., Vu, T.A., Ackermann, S., Spencer, C.E., Lippa, N., Srinivasan, S., Charzewska, A., Hoffman-Zacharska, D., Fitzpatrick, D., Harrison, V., Vasudevan, P., Joss, S., Pilz, D.T., Fawcett, K.A., Helbig, I., Matsumoto, N., Kearney, J.A., Fry, A.E., Goldberg, E.M., 2020. SCN3A-Related neurodevelopmental disorder: a spectrum of epilepsy and brain malformation. Ann. Neurol. 88, 348–362.

Zamponi, G.W., Lory, P., Perez-Reyes, E., 2010. Role of voltage-gated calcium channels in epilepsy. Pflügers Archiv 460, 395–403.

Zamponi, G.W., Striessnig, J., Koschak, A., Dolphin, A.C., 2015. The physiology, pathology, and pharmacology of voltage-gated calcium channels and their future therapeutic potential. Pharmacol. Rev. 67, 821–870.

Zeng, Q., Yang, Y., Duan, J., Niu, X., Chen, Y., Wang, D., Zhang, J., Chen, J., Yang, X., Li, J., Yang, Z., Jiang, Y., Liao, J., Zhang, Y., 2022. SCN2A-Related epilepsy: the phenotypic spectrum, treatment and prognosis. Front. Mol. Neurosci. 15, 809951.

Zhang, J.B., Zhang, C.B., Zhu, J.L., Ma, X.R., Lu, J.B., Kang, Y.M., Liu, S.A., Wang, S.Q., 2008. Effects of Ganoderma lucidum polysaccharides on NF-κB changes in pentylenetetrazol- activated hippocampal neuronal cells. Chin. J. Pathophysiol. 2008, 379–381.

Zhao, C., Lu, L., Liu, W., Zhou, D., Wu, X., 2022. Complementary and alternative medicine for treating epilepsy in China: a systematic review. Acta Neurol. Scand. 146, 775–785.

Zhao, X., Huang, B.Y., Wu, D., Zhang, M., 2023. The mechanism of guishaozhenxian tablet in the treatment of temporal lobeepilepsy based on network pharmacology and molecular docking. Shandong Sci. 36, 27–37.

Zheng, Y., Chen, J., 2024. Voltage-gated potassium channels and genetic epilepsy. Front. Neurol. 15, 1466075.