



A narrative review on traditional Chinese medicine prescriptions and bioactive components in epilepsy treatment

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Background and Objective: In traditional Chinese medicine (TCM), natural drugs and their bioactive components have been widely used to treat epilepsy. Epilepsy is a chronic disease caused by abnormal discharge of brain neurons that leads to brain dysfunction and cognitive impairment. Several factors are involved in the mechanisms of epilepsy, and the current treatments do not seem promising. The potential efficacy of natural drugs with lower toxicity and less side effects have attracted increasing attention.

Methods: We used the terms, “TCM”, “traditional Chinese medicine”, “herbal”, “epilepsy”, “seizure”, and the name of each prescription and bioactive components in the review to collect papers about application of TCM in epilepsy treatment from PubMed online database and Chinese database including Chinese National Knowledge Infrastructure (CNKI), Wanfang, and Weipu.

Key Content and Findings: We summarized some common TCM prescriptions and related active components used for the treatment of epilepsy. Six prescriptions (Chaihu Shugan decoction, Tianma Gouteng decoction, Kangxian capsules, Taohong Siwu decoction, Liujunzi decoction, Compound Danshen dropping pills) and nine main bioactive compounds (Saikosaponin A, Rhynchophylline, Tetramethylpyrazine, Gastrodin, Baicalin and baicalein, α -Asarone, Ginsenoside, Tanshinone, Paeoniflorin) were reviewed to provide a scientific basis for the development of potential antiepileptic drugs (AEDs).

Conclusions: The pharmacological effects and molecular mechanisms of TCM in the treatment of epilepsy are complex, targeting several pathological aspects of epilepsy. However, the limitations of TCM, such as the lack of standardized treatments, have prevented its clinical application in epilepsy treatment. Thus, additional clinical trials are required to further evaluate the effectiveness and safety of TCM prescriptions and their bioactive components in the future.

Keywords: Traditional Chinese medicine (TCM); epilepsy; antiepileptic drugs (AEDs); bioactive compound

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Introduction

Epilepsy is a common chronic disease of the nervous system, characterized by spontaneous and unprovoked recurrent seizures (1). According to various etiologies,

it is classified into idiopathic and acquired epilepsy (2). Idiopathic epilepsy is related to gene defects, also known as genetic epilepsy (3). In recent years, with the development of the genome revolution, such as second-generation sequencing technology, considerable progress has been

Table 1 The search strategy summary

Items	Specification
Date of search	2022.01.10–2022.05.01
Databases and other sources searched	PubMed, CNKI, Wanfang, Weipu
Search terms used	TCM, traditional Chinese medicine, herbal, epilepsy, seizure, Chaihu Shugan decoction, Tianma Gouteng decoction, Kangxian capsules, Taohong Siwu decoction, Liujuanzi decoction, Compound Danshen dropping pills, Saikosaponin A, Rhynchophylline, Tetramethylpyrazine, Gastrodin, Baicalin and baicalein, α -Asarone, Ginsenoside, Tanshinone, Paeoniflorin
Timeframe	2000–2022
Inclusion and exclusion criteria	Articles and reviews in English and Chinese were included
Selection process	FT and YC conducted the selection independently and discussed the results to get consensus

made in determining the genetic factors of epilepsy. Various gene mutations have been identified related to the occurrence of epilepsy, including those in ion channels and non-ion channels, which increases our understanding of the complex pathogenesis of genetic epilepsy (4,5). Alterations in the ion channel genes affect the channel function, change the electrical pulse and the excitability of neurons, and synchronize the neuronal network, resulting in seizures (6,7).

According to statistics, there are over 70 million epilepsy patients worldwide, and 5 million are diagnosed with epilepsy every year, making it one of the most common global neurological diseases. It affects the quality of life of patients severely and increases mortality (8). The current methods to treat epilepsy include drug therapy, surgical treatment (9), physical therapy (10), ketogenic diet therapy (11) and various devices, such as Responsive Neurostimulation System (RNS) (12,13). Drug therapy is the first choice for most patients. Although several antiepileptic drugs (AEDs) are available, almost 50% of patients do not show any improvement with the first use of AEDs, and about 33% of patients remain drug-resistant and develop into refractory epilepsy (14). Moreover, AEDs have side effects, leading to complications, such as headache, dizziness, and memory decline (15).

Recently, traditional Chinese medicine (TCM) has been widely used in chronic diseases, including epilepsy. The potential efficacy of natural drugs with lower toxicity and less side effects have attracted increasing attention (16,17). Chinese medicine has a long history of treating epilepsy for 2000 years. Interestingly, epilepsy is recorded in one of China's medical classic "Yellow Emperor's Internal Classic"

but is limited to generalized seizures due to limitations of the understanding of this disease (18). According to TCM, the causes of epilepsy include wind, fire, phlegm, stasis, and deficiency. Therefore, these TCM compounds utilized for the treatment of epilepsy have the functions of calming the liver, opening the orifices, nourishing, reducing fever, relieving exterior syndrome and promoting blood circulation.

Herein, we searched several database for papers about application of TCM in epilepsy treatment by the strategy in *Table 1* and reviewed some TCM prescriptions for the treatment of epilepsy in detail, with their compositions listed in *Table 2*. The scientific, generic, with Chinese names of botanicals in these prescriptions are also listed in *Table 3*. In addition, we summarized the effects and molecular mechanisms of some bioactive components of the TCM prescriptions in the treatment for epilepsy. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3306/rc>).

Methods

Relevant papers about application of TCM in epilepsy treatment were obtained from PubMed online database using terms including "TCM", "traditional Chinese medicine", "herbal", "epilepsy", "seizure", and the name of each prescription and bioactive components in the review. In addition, online Chinese database including Chinese National Knowledge Infrastructure (CNKI), Wanfang, and Weipu were also searched with above key words (*Table 1*).

Table 2 TCM prescriptions commonly used in epilepsy treatment and their components and main bioactive compounds

Prescriptions	Components	Bioactive compounds
Chaihu Shugan decoction	Radix Paeoniae Alba (<i>Paeonia lactiflora</i>), Radix Bupleuri (<i>Bupleurum chinense</i>), Rhizoma chuanxiong (<i>Ligusticum wallichii</i>), Fructus Aurantii (<i>Citrus aurantium</i>), Pericarpium Citri Reticulatae (<i>Citrus reticulata</i>), Uncariae Ramulus Cum Uncis (<i>Uncaria rhynchophylla</i>), Radix Glycyrrhizae (<i>Glycyrrhiza uralensis</i>)	Saikosaponin A (SSa), Paeoniflorin (PF)
Tianma Gouteng decoction	Rhizoma Gastrodiae (<i>Gastrodia elata</i>), Uncariae Ramulus Cum Uncis (<i>Uncaria rhynchophylla</i>), Fructus Gardeniae (<i>Gardenia jasminoides</i>), Poria (<i>Poria cocos</i>), Radix Scutellariae (<i>Scutellaria baicalensis</i>), Cortex Eucommiae (<i>Eucommia ulmoides</i>), Radix Achyranthis Bidentatae (<i>Achyranthes bidentata</i>), Caulis Polygoni Multiflori (<i>Polygonum multiflorum</i>)	Rhynchophylline (RIN), Baicalin and baicalein
Kangxian capsules	Rhizoma Gastrodiae (<i>Gastrodia elata</i>), Rhizoma Pinelliae (<i>Pinellia ternata</i>), Rhizoma Acori Tatarinowii (<i>Acorus tatarinowii</i>), Bombyx Batryticatus (<i>Bombyx mori</i>), Bulbus Fritillariae Cirrhosae (<i>Fritillaria cirrhosa</i>), Poria (<i>Poria cocos</i>), Radix Polygalae (<i>Polygala tenuifolia</i>), Radix Salviae Miltiorrhizae (<i>Salvia miltiorrhiza</i>), Radix Ophiopogonis (<i>Ophiopogon japonicus</i>)	Gastrodin, α -Asarone
Taohong Siwu decoction	Semen Persicae (<i>Prunus persica</i>), Flos Carthami (<i>Carthamus tinctorius</i>), Radix Angelicae Sinensis (<i>Angelica sinensis</i>), Radix Paeoniae Alba (<i>Paeonia lactiflora</i>), Rhizoma chuanxiong (<i>Ligusticum wallichii</i>), Radix Rehmanniae Preparata (<i>Rehmannia glutinosa</i>)	Tetramethylpyrazine (TMP)
Liujunzi decoction	Radix Et Rhizoma (<i>Panax ginseng</i>), Radix Glycyrrhizae (<i>Glycyrrhiza uralensis</i>), Atractylodis Macrocephalae (<i>Atractylodes macrocephala</i> Rhizoma), Poria (<i>Poria cocos</i>), Rhizoma Pinelliae (<i>Pinellia ternata</i>)	Ginsenoside
Compound Danshen dropping pills	Radix Salviae Miltiorrhizae (<i>Salvia miltiorrhiza</i>), Radix et Rhizoma Notoginseng (<i>Panax notoginseng</i>), Borneolum Syntheticum (<i>Synthetic borneol</i>)	Tanshinone

TCM, traditional Chinese medicine.

Discussion

Clinical application of TCM prescription in epilepsy

Chaihu Shugan decoction

Chaihu Shugan decoction originates from the “General decree of Medicine.” The decoction is composed of Radix Paeoniae Alba (*Paeonia lactiflora*), Radix Bupleuri (*Bupleurum chinense*), Rhizoma chuanxiong (*Ligusticum wallichii*), Fructus Aurantii (*Citrus aurantium*), Pericarpium Citri Reticulatae (*Citrus reticulata*), Uncariae Ramulus Cum Uncis (*Uncaria rhynchophylla*) and Radix Glycyrrhizae (*Glycyrrhiza uralensis*), and is commonly used in a modern clinic to treat chronic gastritis and improve the depressive symptoms (19,20).

In the concept of TCM, the liver plays a critical role in mental health. The theory of “treating epilepsy from the liver” was mentioned in the ancient medical book “Internal Classic.” From the perspective of TCM, stagnation of liver “Qi”, depression, phlegm covering, and clearing orifices are the symptoms of epilepsy. Therefore, in the treatment of epilepsy, we should first calm the liver and extinguish the “wind” using the representative TCM formula, Chaihu Shugan decoction (19). In this prescription, Radix Bupleuri

is the main component that clears the heat and has a calming effect on the liver, wind, and mind. The decoction significantly prolongs the latency of generalized tonic-clonic seizures (GTCS) in pentylenetetrazole (PTZ)-induced epileptic rats, upregulates the level of glutamate transporter (GLT-1), and the activity of glutamine synthetase (GS) to achieve the antiepileptic effect (21). The Chaihu Shugan decoction also can be combined with other AEDs, including carbamazepine (CBZ), sodium valproate, and levetiracetam, which achieved a significant effect in the clinical treatment of refractory epilepsy by reducing seizure frequency (22).

Based on Chaihu Shugan decoction, Chaihu Longgu oyster decoction and Chaihu Guizhi decoction are effective for epilepsy treatment (23). Reportedly, Chaihu Longgu oyster decoction reduces the seizure frequency of patients with refractory epilepsy, and the antioxidant effect might be one of the underlying mechanisms (23). The administration of this decoction shortens the duration of epilepsy in a dose-dependent manner and exerts a protective effect on brain neurons in the PTZ-induced epilepsy mouse model (24). The Chaihu Guizhi decoction was applied in the treatment of liver injury (25) and gastric ulcers (26), while Chaihu

Table 3 Scientific, generic and Chinese names of botanicals in TCM used in epilepsy therapy

Scientific name	Generic name	Pinyin/Chinese name
<i>Paeonia lactiflora</i>	Radix Paeoniae Alba	Baishao/ 白芍
<i>Bupleurum chinense</i>	Radix bupleuri chinensis	Chaihu/ 柴胡
<i>Ligusticum wallichii</i>	Rhizoma chuanxiong	Chuanxiong/ 川芎
<i>Citrus aurantium</i>	Fructus Aurantii	Zhike/ 枳壳
<i>Citrus reticulata</i>	Pericarpium Citri Reticulatae	Chenpi/ 陈皮
<i>Uncaria rhynchophylla</i>	Uncariae Ramulus Cum Uncis	Gouteng/ 钩藤
<i>Glycyrrhiza uralensis</i>	Radix Glycyrrhizae	Gancao/ 甘草
<i>Gastrodia elata</i>	Rhizoma Gastrodiae	Tianma/ 天麻
<i>Gardenia jasminoides</i>	Fructus Gardeniae	Zhizi/ 栀子
<i>Poria cocos</i>	Poria	Fuling/ 茯苓
<i>Scutellaria baicalensis</i>	Radix Scutellariae	Huangqin/ 黄芩
<i>Eucommia ulmoides</i>	Cortex Eucommiae	Duzhong/ 杜仲
<i>Achyranthes bidentata</i>	Radix Achyranthis Bidentatae	Niuxi/ 牛膝
<i>Polygonum multiflorum</i>	Caulis Polygoni Multiflori	Heshouwu/ 何首乌
<i>Pinellia ternata</i>	Rhizoma Pinelliae	Banxia/ 半夏
<i>Acorus tatarinowii</i>	Rhizoma Acori Tatarinowii	Shichangpu/ 石菖蒲
<i>Bombyx mori</i>	Bombyx Batryticatus	Jiangcan/ 僵蚕
<i>Fritillaria cirrhosa</i>	Bulbus Fritillariae Cirrhosae	Chuanbeimu/ 川贝母
<i>Polygala tenuifolia</i>	Radix Polygalae	Yuanzhi/ 远志
<i>Salvia miltiorrhiza</i>	Radix Salviae Miltiorrhizae	Danshen/ 丹参
<i>Ophiopogon japonicus</i>	Radix Ophiopogonis	Maidong/ 麦冬
<i>Prunus persica</i>	Semen Persicae	Taoren/ 桃仁
<i>Carthamus tinctorius</i>	Flos Carthami	Honghua/ 红花
<i>Angelica sinensis</i>	Radix Angelicae Sinensis	Danggui/ 当归
<i>Rehmannia glutinosa</i>	Radix Rehmanniae Preparata	Shudi/ 熟地
<i>Panax ginseng</i>	Radic Et Rhizoma	Renshen/ 人参
<i>Atractylodes macrocephala Rhizoma</i>	Atractylodis Macrocephalae	Baishu/ 白术
<i>Panax notoginseng</i>	Radix et Rhizoma Notoginseng	Sanqi/ 三七
<i>Synthetic borneol</i>	Borneolum Syntheticum	Bingpian/ 冰片

TCM, traditional Chinese medicine.

Longgu oyster decoction has a history of use in the treatment of depression (27). Chaihu Guizhi decoction and Guishao Zhenxian tablet were utilized to treat various types of epilepsy, especially GTCS and generalized absence seizures. It not only corrects “Ying Wei” disharmony and relieves “wind evil” but also clears the liver and

gallbladder. Clinically, Guishao Zhenxian tablet alone has a poor therapeutic effect. It is often supplemented with other antiepileptic drugs, such as CBZ, to reduce epileptic symptoms and decrease the expression of pro-inflammatory factors (28). These findings further proved that the liver calming effect contributes to the effectiveness of Chaihu

Shugan decoction in the treatment of epilepsy.

Tianma Gouteng decoction

Tianma Gouteng decoction consists of Rhizoma Gastrodiae (*Gastrodia elata*), Uncariae Ramulus Cum Uncis (*Uncaria rhynchophylla*), Fructus Gardeniae (*Gardenia jasminoides*), Poria (*Poria cocos*), Radix Scutellariae (*Scutellaria baicalensis*), Cortex Eucommiae (*Eucommia ulmoides*), Radix Achyranthis Bidentatae (*Achyranthes bidentata*) and Caulis Polygoni Multiflori (*Polygonum multiflorum*). *Uncaria rhynchophylla* and *Gastrodia elata* calm the liver wind. *Polygonum multiflorum* and *Poria cocos* are sedative drugs. *Gardenia jasminoides* and *Scutellaria baicalensis* are antipyretic drugs. This prescription clears heat, as well as calms the liver, wind and mind. It also confers neuroprotection against cerebral ischemia *in vitro* and *in vivo* (29) and is mainly used to treat headaches, insomnia, and dizziness. A study has shown that adjustment with Tianma Gouteng decoction combined with AEDs in the treatment of epilepsy reduces the frequency and the symptoms of seizures and improves the quality of life of patients who cannot tolerate antiepileptic drugs, such as sodium valproate and CBZ (30).

Kangxian capsules

Kangxian capsules originated from the “Medical enlightenment” during the Qing Dynasty. Xiong Jibai, a master of TCM, proposed that the pathogenesis of epilepsy lies in the latent “phlegm evil” in the body, which occurs repeatedly. Kangxian capsules used to treat patients with wind phlegm obstruction (31) are composed of Rhizoma Gastrodiae (*Gastrodia elata*), Rhizoma Pinelliae (*Pinellia ternata*), Rhizoma Acori Tatarinowii (*Acorus tatarinowii*), Bombyx Batryticatus (*Bombyx mori*), Bulbus Fritillariae Cirrhosae (*Fritillaria cirrhosa*), Poria (*Poria cocos*), Radix Polygalae (*Polygala tenuifolia*), Radix Salviae Miltiorrhizae (*Salvia miltiorrhiza*) and Radix Ophiopogonis (*Ophiopogon japonicus*). *Polygala tenuifolia* and *Acorus tatarinowii* are classic sedatives. *Salvia miltiorrhiza*, *Ophiopogon japonicus* and *Fritillaria cirrhosa* are “yin”-nourishing drugs. Therefore, the combination of these drugs can improve the mental function of patients with epilepsy. Furthermore, Kangxian capsules can be combined with some AEDs to treat drug-resistant epilepsy (wind phlegm blocking type). The capsules also relieve the clinical symptoms, such as weakening the frequency and duration of seizures and reducing the expression of pro-inflammatory factors compared to AEDs alone (32). A clinical study reported that Kangxian capsules combined with levetiracetam are used in children with

epilepsy (phlegm fire disturbing God syndrome) to control the seizures effectively and improve cognitive functions. This combination had a safe and reliable curative effect (33).

Ditan decoction is from Kangxian capsules and is composed of Rhizoma Pinelliae (*Pinellia ternata*), Arisaema biradiatifolium (*Arisaema erubescens*), Poria (*Poria cocos*), Radic Et Rhizoma (*Panax ginseng*), Rhizoma Acori Tatarinowii (*Acorus tatarinowii*), Radix Glycyrrhizae (*Glycyrrhiza uralensis*), Rhizoma Zingiberis (*Zingiber officinale*) and Fructus Aurantii (*Citrus aurantium*). It is an effective prescription for calming shock and eliminating phlegm. Among these, *Pinellia ternata*, *Arisaema erubescens*, *Citrus aurantium* and *Acorus tatarinowii* are drugs for resuscitation and rejuvenation. Previous clinical study has reported that modified Ditan decoction is effective on drug-resistant epilepsy with cognitive impairment, and increases insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF) post-treatment, which might be responsible for the decline in epileptic symptoms (34).

Children’s Kangxian capsule is developed based on Ditan decoction combined with modern pharmacological research of TCM on the childhood epilepsy. The mechanisms of Kangxian capsule in the treatment of epilepsy include weakening the N-methyl-D-aspartic acid (NMDA) receptor channel current, reducing the intracellular Ca²⁺ concentration, and inhibiting the excitation of hippocampal neurons, thus exerting neuroprotective effects (35).

Taohong Siwu decoction

Taohong Siwu decoction is a classic blood-activating prescription, composed of Semen Persicae (*Prunus persica*), Flos Carthami (*Carthamus tinctorius*), Radix Angelicae Sinensis (*Angelica sinensis*), Radix Paeoniae Alba (*Paeonia lactiflora*), Rhizoma chuanxiong (*Ligusticum wallichii*), and Radix Rehmanniae Preparata (*Rehmannia glutinosa*). *Prunus persica* is clinically used to treat gynecological (36), cardiovascular and cerebrovascular diseases (37,38). Modern medicine speculated that the cardiovascular system is closely related to the nervous system (39), while according to TCM, “phlegm” and “stasis” can affect each other. The lack of “phlegm” dissolved in the body leads to poor “Qi” and blood, and the long-term lack of smooth “Qi” and blood will change into “stasis,” leading to the failure of normal circulation of body fluid in the body. The vicious circle of “phlegm” and “stasis” leads to repeated seizure onset. This phenomenon also indicated that Taohong Siwu decoction could be used for the symptomatic treatment of epilepsy. It reduces the permeability of the vascular barrier, increases

the expression of tight junction protein (a vital part of the blood-brain barrier), and reduces the seizure onset of the PTZ-induced epileptic rat model. The combination of AEDs with Taohong Siwu decoction also synergistically controlled the seizure onset and improved the therapeutic effect (40,41).

Liujunzi decoction

Liujunzi decoction is composed of Radic Et Rhizoma (*Panax ginseng*), Radix Glycyrrhizae (*Glycyrrhiza uralensis*), Atractylodis Macrocephalae (*Atractylodes macrocephala Rhizoma*), Poria (*Poria cocos*) and Rhizoma Pinelliae (*Pinellia ternata*), among which *Panax ginseng*, *Atractylodes macrocephala* and *Glycyrrhiza uralensis* are drugs with nutritional effects. Traditional AEDs cause some side effects, including damage to the liver, spleen, stomach, and other organs, in turn affecting the growth and development of children with epilepsies. Liujunzi decoction enhances the physique of children, making the spleen and stomach vigorous and alleviating seizures (42). A study proposed that the pathogenesis of childhood epilepsy is that “phlegm subdues the brain collaterals and Qi goes against the wind.” The application of Liujunzi decoction achieves “Qi” smoothing and “phlegm” clearing, which improves the clinical syndrome of childhood epilepsy with fewer side effects (43).

Compound Danshen dropping pills

Compound Danshen dropping pills are composed of Radix Salviae Miltiorrhizae (*Salvia miltiorrhiza*), Radix et Rhizoma Notoginseng (*Panax notoginseng*) and Borneolum Syntheticum (*Synthetic borneol*). *Panax notoginseng* dissolves blood stasis and collaterals, and *Synthetic borneol* is an aromatic resuscitation drug. *Salvia miltiorrhiza* is a tonic medicine. The combination of the above three herbs promotes blood circulation and the removal of blood stasis. This prescription is commonly used to treat angina pectoris (44). The combination of compound Danshen dropping pills and antiepileptic drugs achieved the clinical therapeutic effect by reducing the expression of pro-inflammatory factors and the production of lipid peroxidation product MDA (45). In kainic acid (KA)-induced epileptic rats, compound Danshen dropping pills combined with CBZ reduces the frequency of seizures, improves cognitive impairment, and prevents hippocampal neuron damage. The underlying mechanisms could be related to the anti-apoptosis effect and upregulation of the expression of glial cell-derived neurotrophic factor (GDNF) (46).

Antiepileptic effect of bioactive components of TCM and the underlying mechanisms

Saikosaponin A (SSa)

SSa is a triterpenoid saponin extracted from *Bupleurum chinense*. In the pilocarpine-induced rat epilepsy model, SSa reduces the expression of multidrug resistance protein P-glycoprotein (P-gp), decreases the level of glutamate stimulation, and releases Ca^{2+} and interleukin-6 (IL-6) from rat hippocampal astrocytes (47). In the PTZ-induced rat model, SSa promotes the expression of glutamate aspartate transporter (GLAST) and uptake of glutamate via the expression of Activator Protein 1 (AP-1) and miR-155, thus ameliorating epilepsy (48). SSa also exerts a protective effect on PTZ-induced seizures and hippocampal neuronal apoptosis by inhibiting the mammalian target of rapamycin (mTOR) signaling pathway (49). In addition, it also has an inhibitory effect on the NMDA receptor current and Kv4.2-mediated A-type voltage-gated potassium current that decreases the epileptiform discharge induced by four action potentials (50,51).

Rhynchophylline (RIN)

RIN is a compound extracted from *Uncaria rhynchophylla*. It has anticonvulsive effects and can alleviate KA-induced seizures by reducing the expression of phosphorylated c-Jun amino-terminal kinase (p-JNK) in the mitogen-activated protein kinase (MAPK) signaling pathway in the cerebral cortex and hippocampus (52). In the acute stage of status epilepticus in pilocarpine-induced temporal lobe epilepsy (TLE) rat model, both RIN pre- and post-treatment reduce the degree of epilepsy and inhibit the excitability of neurons by inhibiting the continuous process of opening of sodium and NMDA receptor channels (53). Immune regulation is also involved in the anticonvulsive effects of RIN. In KA-induced rats, RIN regulates the toll-like receptor (TLR) and neurotrophin signaling pathways, and inhibits the expression of interleukin-1 β (IL-1 β) and *BDNF* genes (54). These findings indicated that RIN targeted multiple biological processes and pathways and shaped a multiple-layer network to exert systematic anticonvulsive effects on epilepsy (55).

Tetramethylpyrazine (TMP)

TMP is an alkaloid extracted from *Ligusticum wallichii*. In combination with traditional antiepileptic drugs, TMP improves the therapeutic effects in the clinical treatment of traumatic epilepsy (56). It prevents the epileptogenesis

progression of corneal electrical kindling models of TLE by regulating hippocampal excitatory neurotransmitter transmission and calcium channel repression in a dose-dependent manner (57). It also inhibits KA-induced epilepsy model *in vivo* and *in vitro*, and the underlying mechanisms involved neuroprotective effects, including the stabilization of the mitochondrial function, declining oxidative damage, and prevention of the loss of neurons in the hippocampal CA3 region (58). The enhanced hippocampal BDNF/ERK signaling alleviates the neuropsychiatric comorbidities in neurological diseases (59). In addition, TMP reduces pro-inflammatory factors, such as IL-2, IL-6, and tumor necrosis factor- α (TNF- α), which in turn decreases the PTZ-induced seizures in rat models (60).

Gastrodin

Gastrodin is the main active component of *Gastrodia elata*. In recent years, several studies have focused on the antiepileptic mechanisms of Gastrodin (61-63). It inhibits the degradation of γ -aminobutyric acid (GABA) in the synaptic space to reverse the declining GABA level (44). In the PTZ-induced zebrafish epilepsy model, Gastrodin significantly prolongs the latency of epilepsy and shortened the duration of epilepsy; this effect is related to the upregulated antioxidant enzyme activity and the expression of oxidative stress-related genes (64). In the PTZ-induced epileptic mice, Gastrodin inhibits the production of pro-inflammatory factors IL-1 and TNF- α to alleviate the seizure onset, and the effect is mediated by the MAPK signaling pathway (65). On the other hand, Gastrodin prolongs the latency of epilepsy and shortens the duration of epilepsy by activating the GABA_A receptors (66).

Baicalin and baicalein

Baicalin and baicalein are two flavonoids with anticonvulsant effects extracted from *Scutellaria baicalensis* (67,68). In the rat model, Baicalin has significant anticonvulsant and neuroprotective effects on status epilepticus induced by picrocarpine or PTZ. The cognitive dysfunction could also be improved by Baicalin. The mechanisms involved in the neuroprotective effects might be related to the increased level of glutathione (GSH) and activity of superoxide dismutase (SOD), reduced expression of pro-inflammatory factors in the hippocampus and regulation of apoptosis-related genes. The antiepileptic effects of Baicalin are effectuated via activation of the TLR4/MYD88/Caspase-3 pathway (69,70). Also, it has a significant therapeutic effect on the rat model with epilepsy phenotype similar to

TLE patients, which improves the cognitive impairment and hippocampal injury by inhibiting oxidative stress and inflammatory response. This phenomenon affects the expression of actin-related proteins, suppresses ferroptosis, regulates insulin-like growth factor 1 receptor (IGF1R), and intervenes in glucocorticoid synthesis and metabolism (71,72).

α -Asarone

α -Asarone is an essential oil component of *Acorus tatarinowii* that possesses sedation and anticonvulsant activity. It antagonizes maximal electroshock seizure (MES) and PTZ-induced seizures in mice, lithium-pilocarpine-induced status epilepticus (SE), and spontaneous recurrent seizures in rats (73). The anticonvulsant mechanism of α -Asarone is related to the modulation of GABA_A receptors and altering ionic currents through ion channels (74-77). In addition, α -Asarone improves the cognitive function of pilocarpine-induced status epilepticus rats by reducing the activation of nuclear factor kappa-B (NF- κ B) and reducing microglial inflammation. It also protects the neurons by regulating expression of neurotrophic factors in astrocytes (78,79). In addition, methyleugenol and eudesmin are monomers that have anticonvulsant effects and are isolated from *Acorus tatarinowii*. Eudesmin upregulates the expression of GABA and glutamic acid decarboxylase 65 (GAD65), and downregulates the expression of Caspase-3, thus inhibiting neuronal apoptosis in the brain (80). A recent study demonstrated that some α -Asarone derivatives exerted neuroprotective effects against epilepsy using PTZ-induced seizure models both *in vitro* and *in vivo*, providing primary data for the applying these derivatives as potential anti-seizure drugs (81). These findings suggest that α -Asarone may be used as a natural supplementary remedy to manage convulsions and epilepsy.

Ginsenoside

Ginsenoside is a steroid compound extracted from *Panax ginseng*. It exerts biological activities, including antitumor, anti-inflammatory, antioxidation and inhibition of apoptosis, which is widely used to prevent and treat neurological diseases (82). Ginsenoside Rb1 was reported to confer neuroprotective effects against PTZ-induced seizure and Mg²⁺-induced neuron injury by activating the Nrf2/ARE pathway (83). Ginsenoside Rg3 interacts with GABA_A receptor γ 2 subunit to activate the GABA_A receptor and enhance GABA_A receptor-mediated inward currents, thereby inhibiting neuronal excitation, which

might be one of the molecular bases of Ginsenoside in epilepsy treatment (84). Recently, there has been a study on Ginsenoside complex K (GCK), the primary metabolite of Ginsenoside Rb1, Rb2 and Rc in the intestinal microbiota. GCK reduces the severity and prolongs the latency of seizures by increasing the content of GABA and enhancing the GABAergic inhibitory neurotransmitters (85). GCK also mitigates sodium valproate-induced hepatotoxicity via antioxidant effect, regulation of peroxisome pathway and iron homeostasis (86).

Tanshinone

Tanshinone is extracted from *Salvia miltiorrhiza* and can pass through the blood-brain barrier. The antiepileptic effect is achieved by regulating the ion channels (87). The increased channel activity inhibits the calcium influx and the activity of MAPK, thereby decreasing the glutamate release and the excitation of the nervous system (88). In addition, Tanshinone II-A improves PTZ-induced zebrafish seizures by activating the GABA_A receptors (89). A study has shown that Tanshinone IIA significantly improves synaptic transmission in the hippocampal CA1 area of epileptic rats, and hippocampal synaptic plasticity, restores long-term potentiation (LTP) inhibition, and reduces cognitive impairment (75). Sodium sulfonate (DS-201) is a water-soluble derivative of Tanshinone II-A, which selectively targets the sporogenesis of the human BKCa channel to enhance channel activity and increase the expression and transport of this subunit (90).

Paeoniflorin (PF)

Paeoniflorin is a major bioactive component of *Paeonia lactiflora* which has been used for neurological disorders, such as epilepsy, neurodegeneration disease and developmental defects (91-93). PF could directly reduce the neuroexcitation to deserve anticonvulsive effects by preventing metabotropic glutamate receptor 5 (mGluR5)—dependent calcium influx (94) and modulation of NMDA receptors, specifically the NR2B subunit (95). In addition, PF shows protective effects on neuron damage in a rat cobalt focus epilepsy model (93). The anticonvulsive effects combined with the neuroprotective effects of PF make it a potential candidate for the treatment of epilepsy.

Herb-herb and herb-drug interactions in epilepsy treatment

As each TCM prescription contains multiple herbs and

TCM is often combined with AEDs to treat epilepsy, herb-herb and herb-drug interactions should be fully understood before clinical application. Herb-herb and herb-drug interactions might change metabolism of herb medicines and AEDs, as well as directly change the effect on seizure threshold. Unpredictable herb-herb and herb-drug interactions might occur in the brain and other organs (96). However, there is a lack of research on synergistic or antagonistic herb-herb interactions in epilepsy treatment, making it difficult to recommend TCM for the treatment of epilepsy. It is a challenge to understand herb-herb interactions at the molecular, cellular and organism levels with modern technologies (97).

On the other hand, pharmacokinetic and pharmacodynamic interactions of some herbal medicines and AEDs have been investigated. Herbs might have variable actions on the metabolism, absorption and transport of AEDs (96). For example, several studies have reported pharmacokinetic interactions of CBZ with different herbal medicines, such as *Rhizoma Gastrodiae* (98,99). Pharmacokinetic study in rats indicated that *Rhizoma Gastrodiae* could reduce the auto-induction of CBZ and increase the plasma concentration of CBZ and its metabolite, demonstrating an herb-drug interaction of *Rhizoma Gastrodiae* with CBZ which will provide implications for epilepsy treatment in clinic (98). On the contrary, *Panax ginseng* was reported to unlikely interfere with the pharmacokinetic of CBZ in rabbits (100). The complicated herb-drug interactions indicated that additional caution should be taken when combination treatment with TCM and AEDs are performed.

Summary

The abnormal discharge of neurons during seizures is related to several factors: abnormal neurotransmitter transmission, ion channel mutation, glial dysfunction, synaptic connection dysfunction and heredity. Various pathological mechanisms are involved in epilepsy, indicating the complexity of the therapeutic effects of antiepileptic drugs. Traditional antiepileptic drugs target only one ion channel or neurotransmitter, while the chemically bioactive components in TCM possess multi-target and multi-level pharmacological effects, which is advantageous in epilepsy treatment. Typically, the molecular mechanisms of TCM in the treatment of epilepsy include regulating the neurotransmitters and receptors, regulating the ion channels, regulating the expression of inflammatory factors,

regulating the expression of apoptosis-related genes and antagonizing oxidative stress.

Although TCM has a long history in treating epilepsy, the lack of understanding of standardized treatment methods, exact molecular compositions and mechanisms, and herb-herb/drug interactions have always been an obstacle to the development of TCM for clinical application. Thus, improving the quality control of TCM prescriptions and their bioactive components is imperative. Also, appropriate animal models are required to screen the anticonvulsant effects of the drugs. Substantially large randomized clinical trials are also essential to evaluate the efficiency and safety of TCM prescriptions and their bioactive components.

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Footnote

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