Review Article

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

Feng Tao[1#], Yong Cai[2#], Chunyan Deng[3], Zehao Chen[3], Yuntian Shen[3], Hualin Sun[3]

[1]Nantong University Informatization Center, Nantong University, Nantong, Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China; [2]Department of Neurology, People's Hospital of Binhai County, Yancheng, China; [3]Key Laboratory of Neuroregeneration of Jiangsu and Ministry of Education, Co-innovation Center of Neuroregeneration, Nantong University, Nantong, China

Contributions: (I) Conception and design: F Tao, Y Cai, H Sun; (II) Administrative support: H Sun; (III) Provision of study materials or patients: F Tao, Y Cai, H Sun; (IV) Collection and assembly of data: F Tao, Y Cai, C Deng, Z Chen, Y Shen; (V) Data analysis and interpretation: F Tao, Y Cai, H Sun; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Hualin Sun, PhD. Nantong University, 19 Qixiu Road, Nantong 226001, China. Email: sunhl@ntu.edu.cn.

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

Submitted Jun 27, 2022. Accepted for publication Nov 06, 2022. Published online Dec 13, 2022.
doi: 10.21037/atm-22-3306
View this article at: https://dx.doi.org/10.21037/atm-22-3306

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, Liujunzi 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 (*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*), Radix Glycyrrhizae (*Glycyrrhiza uralensis*)	Saikosaponin A (SSa), Paeoniflorin (PF)
Tianma Gouteng decoction	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*), Caulis Polygoni Multiflori (*Polygonum multiflorum*)	Rhynchophylline (RIN), Baicalin and baicalein
Kangxian capsules	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*), Radix Ophiopogonis (*Ophiopogon japonicus*)	Gastrodin, α-Asarone
Taohong Siwu decoction	Semen Persicae (*Prunus persica*), Flos Carthami (*Carthamus tinctorius*), Radix Angelicae Sinensis (*Angelica sinensis*), Radix Paeoniae Alba (*Paeonia lactiflora*), Rhizoma chuanxiong (*Ligusticum wallichii*), Radix Rehmanniae Preparata (*Rehmannia glutinosa*)	Tetramethylpyrazine (TMP)
Liujunzi decoction	Radic Et Rhizoma (*Panax ginseng*), Radix Glycyrrhizae (*Glycyrrhiza uralensis*), Atractylodis Macrocephalae (*Atractylodes macrocephala Rhizoma*), Poria (*Poria cocos*), Rhizoma Pinelliae (*Pinellia ternata*)	Ginsenoside
Compound Danshen dropping pills	Radix Salviae Miltiorrhizae (*Salvia miltiorrhiza*), Radix et Rhizoma Notoginseng (*Panax notoginseng*), Borneolum Syntheticum (*Synthetic borneol*)	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
Paeonia lactiflora	Radix Paeoniae Alba	Baishao/ 白芍
Bupleurum chinense	Radix bupleuri chinensis	Chaihu/ 柴胡
Ligusticum wallichii	Rhizoma chuanxiong	Chuanxiong/ 川芎
Citrus aurantium	Fructus Aurantii	Zhike/ 枳壳
Citrus reticulata	Pericarpium Citri Reticulatae	Chenpi/ 陈皮
Uncaria rhynchophylla	Uncariae Ramulus Cum Uncis	Gouteng/ 钩藤
Glycyrrhiza uralensis	Radix Glycyrrhizae	Gancao/ 甘草
Gastrodia elata	Rhizoma Gastrodiae	Tianma/ 天麻
Gardenia jasminoides	Fructus Gardeniae	Zhizi/ 栀子
Poria cocos	Poria	Fuling/ 茯苓
Scutellaria baicalensis	Radix Scutellariae	Huangqin/ 黄芩
Eucommia ulmoides	Cortex Eucommiae	Duzhong/ 杜仲
Achyranthes bidentata	Radix Achyranthis Bidentatae	Niuxi/ 牛膝
Polygonum multiflorum	Caulis Polygoni Multiflori	Heshouwu/ 何首乌
Pinellia ternata	Rhizoma Pinelliae	Banxia/ 半夏
Acorus tatarinowii	Rhizoma Acori Tatarinowii	Shichangpu/ 石菖蒲
Bombyx mori	Bombyx Batryticatus	Jiangcan/ 僵蚕
Fritillaria cirrhosa	Bulbus Fritillariae Cirrhosae	Chuanbeimu/ 川贝母
Polygala tenuifolia	Radix Polygalae	Yuanzhi/ 远志
Salvia miltiorrhiza	Radix Salviae Miltiorrhizae	Danshen/ 丹参
Ophiopogon japonicus	Radix Ophiopogonis	Maidong/ 麦冬
Prunus persica	Semen Persicae	Taoren/ 桃仁
Carthamus tinctorius	Flos Carthami	Honghua/ 红花
Angelica sinensis	Radix Angelicae Sinensis	Danggui/ 当归
Rehmannia glutinosa	Radix Rehmanniae Preparata	Shudi/ 熟地
Panax ginseng	Radic Et Rhizoma	Renshen/ 人参
Atractylodes macrocephala Rhizoma	Atractylodis Macrocephalae	Baishu/ 白术
Panax notoginseng	Radix et Rhizoma Notoginseng	Sanqi/ 三七
Synthetic borneol	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 ternate*), 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 Ca^{2+} 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-1β (IL-1β) 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 pirocarpine 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-κB) 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 Mg^{2+}-induced neuron injury by activating the Nrf2/ARE pathway (83). Ginsenoside Rg3 interacts with $GABA_A$ receptor γ2 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.

Acknowledgments

Funding: This work was supported by the National Natural Science Foundation of China (No. 81901933), the Major Natural Science Research Projects in Universities of Jiangsu Province (No. 20KJA310012), the "QingLan Project" in Jiangsu Universities, and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3306/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3306/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sirven JI. Epilepsy: A Spectrum Disorder. Cold Spring Harb Perspect Med 2015;5:a022848.
2. Zuberi SM, Wirrell E, Yozawitz E, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia 2022;63:1349-97.
3. McWilliam M, Al Khalili Y, Idiopathic (Genetic) Generalized Epilepsy. In StatPearls, Treasure Island (FL), 2022.
4. Kang JQ. Defects at the crossroads of GABAergic signaling in generalized genetic epilepsies. Epilepsy Res 2017;137:9-18.
5. Symonds JD, Zuberi SM, Johnson MR. Advances in epilepsy gene discovery and implications for epilepsy diagnosis and treatment. Curr Opin Neurol 2017;30:193-9.
6. Nikitin ES, Vinogradova LV. Potassium channels as prominent targets and tools for the treatment of epilepsy. Expert Opin Ther Targets 2021;25:223-35.
7. Ceska K, Danhofer P, Horak O, et al. Phenotypic spectrum of the SCN1A mutation (from febrile seizures to Dravet syndrome). Bratisl Lek Listy 2022;123:483-6.
8. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:459-80.
9. Rapport F, Shih P, Mitchell R, et al. Better evidence for earlier assessment and surgical intervention for refractory epilepsy (The BEST study): a mixed methods study protocol. BMJ Open 2017;7:e017148.
10. Chambers A, Bowen JM. Electrical stimulation for drug-resistant epilepsy: an evidence-based analysis. Ont Health Technol Assess Ser 2013;13:1-37.
11. D'Andrea Meira I, Romão TT, Pires do Prado HJ, et al. Ketogenic Diet and Epilepsy: What We Know So Far. Front Neurosci 2019;13:5.
12. Roa JA, Abramova M, Fields M, et al. Responsive Neurostimulation of the Thalamus for the Treatment of Refractory Epilepsy. Front Hum Neurosci 2022;16:926337.
13. Chen B, Lundstrom BN, Crepeau AZ, et al. Brain responsive neurostimulation device safety and effectiveness in patients with drug-resistant autoimmune-associated

epilepsy. Epilepsy Res 2022;184:106974.
14. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314-9.
15. Shi MM, Piao JH, Xu XL, et al. Chinese medicines with sedative-hypnotic effects and their active components. Sleep Med Rev 2016;29:108-18.
16. He LY, Hu MB, Li RL, et al. Natural Medicines for the Treatment of Epilepsy: Bioactive Components, Pharmacology and Mechanism. Front Pharmacol 2021;12:604040.
17. Lin CH, Hsieh CL. Chinese Herbal Medicine for Treating Epilepsy. Front Neurosci 2021;15:682821.
18. Xiao F, Yan B, Chen L, et al. Review of the use of botanicals for epilepsy in complementary medical systems--Traditional Chinese Medicine. Epilepsy Behav 2015;52:281-9.
19. Qin F, Liu JY, Yuan JH. Chaihu-Shugan-San, an oriental herbal preparation, for the treatment of chronic gastritis: a meta-analysis of randomized controlled trials. J Ethnopharmacol 2013;146:433-9.
20. Yan L, Xu X, He Z, et al. Antidepressant-Like Effects and Cognitive Enhancement of Coadministration of Chaihu Shugan San and Fluoxetine: Dependent on the BDNF-ERK-CREB Signaling Pathway in the Hippocampus and Frontal Cortex. Biomed Res Int 2020;2020:2794263.
21. Yu Y, Xie W, Wang C. Chaihushugan decoction exerts antiepileptic effects by increasing hippocampal glutamate metabolism in pentylenetetrazole-kindled rats. J Tradit Chin Med 2015;35:659-65.
22. He QC, Chen W, Liu T, et al. Clinical Observation on Chaihu Shugan Decoction (柴胡疏肝汤) Combined with Zhebeimu (Fritillaria Thun bergii Miq.) and Western Medicine Treating 60 Patients with Intractable Epilepsy. Journal of Traditional Chinese Medicine 2016;57:1662-5.
23. Hung-Ming W, Liu CS, Tsai JJ, et al. Antioxidant and anticonvulsant effect of a modified formula of chaihu-longu-muli-tang. Am J Chin Med 2002;30:339-46.
24. Shan P, Zhang HJ, Gou YL, et al. Protective Effect of Chaihu Longgu Muli Decoction on Cerebral Neurons in Pentylenetetrazol-kindled Epileptic Mice. Liaoning Journal of Traditional Chinese Medicine 2019;46:2656-8.
25. Tatsuta M, Iishi H, Baba M, et al. Suppression by Chai-hu-gui-zhi-tang of the development of liver lesions induced by N-nitrosomorpholine in Sprague-Dawley rats. Cancer Lett 2000;152:31-6.
26. Chen CY, Kuo TL, Sheu SY, et al. Preventive effects of Chinese herb chai-hu-gui-zhi-tang extract on water immersion restraint stress-induced acute gastric ulceration in rats. J Vet Med Sci 2010;72:679-85.
27. Wang X, Zou Z, Shen Q, et al. Involvement of NMDA-AKT-mTOR Signaling in Rapid Antidepressant-Like Activity of Chaihu-jia-Longgu-Muli-tang on Olfactory Bulbectomized Mice. Front Pharmacol 2018;9:1537.
28. Zhang XH, Zhang SQ, Wu D, et al. Clinical study on Guishao Zhengxian Tablets combined with carbamazepine in treatment of epilepsy. Drugs & Clinic 2018;33:3139-42.
29. Wang ZH, Chen BH, Lin YY, et al. Herbal decoction of Gastrodia, Uncaria, and Curcuma confers neuroprotection against cerebral ischemia in vitro and in vivo. J Integr Neurosci 2020;19:513-9.
30. Cui F, Li F. Effect of Tianma Gouteng Decoction on symptomatic epilepsy. Guangming Journal of Chinese Medicine 2015;30:1736-7.
31. Nie HL, Yao XY. Chinese Medicine Master Xiong Jibo's Clinical Experience in Treating Epilepsy According to Phlegm Conditions. Journal of Hunan University of Chinese Medicine 2018;38:1363-5.
32. Chen Y, Guo Z, Chen Y, et al. Effect of Dingxiam Pill on Inflammatory Factor- Iron Metabolism Pathway in Patients with DRE of Wind and Phlegm obstruction. Zhong Yiyao Xuebao 2019;47:54-8.
33. Wang SL, Hou JH, Chen TY, et al. Clinical Efficacy of Modified Dingxianwan Combined with Levetiracetam on Syndrome of Phlegm-fire Disturbing Mind in Children with Epilepsy and Effect on Cognitive Function and Life Quality. Chinese Journal of Experimental Traditional Medical Formulae 2018; 24:171-6.
34. Zhou LZ, Li J, Chen CP, et al. Clinical observation of modified Ditan decoction′s efficacy in generalized tonic-clonic seisure with cognitive dysfunction. Shiyong Yixue Zazhi 2018;34:3474-7.
35. Ren XQ, Ma R, Yang CQ, et al. Kangxian capsules: Effects on convulsive injuries, N-methyl-d-aspartate (NMDA) receptor subunit expression, and free Ca(2+) concentration in a rat hippocampal neuron epileptic discharge model. Seizure 2016;40:27-32.
36. Zuo C, Zhang Y, Wang J, et al. Deciphering the intervention mechanism of Taohong Siwu Decoction following the abnormal uterine bleeding rats based on serum metabolic profiles. J Pharm Biomed Anal 2019;170:204-14.
37. Luo ZR, Li H, Xiao ZX, et al. Taohong Siwu Decoction Exerts a Beneficial Effect on Cardiac Function by Possibly Improving the Microenvironment and Decreasing Mitochondrial Fission after Myocardial Infarction. Cardiol

Res Pract 2019;2019:5198278.
38. Li L, Yang N, Nin L, et al. Chinese herbal medicine formula tao hong si wu decoction protects against cerebral ischemia-reperfusion injury via PI3K/Akt and the Nrf2 signaling pathway. J Nat Med 2015;69:76-85.
39. Dong Q, Xing W, Fu F, et al. Tetrahydroxystilbene Glucoside Inhibits Excessive Autophagy and Improves Microvascular Endothelial Dysfunction in Prehypertensive Spontaneously Hypertensive Rats. Am J Chin Med 2016;44:1393-412.
40. Xu LJ, Tang JY, Zhou XJ, et al. Study on anti-epileptic mechanism of Taohong Siwu Decoction. Chinese Traditional and Herbal Drugs 2017;48:3117-21.
41. Ren HT. Curative Effect Analysis of Taohong Siwu Decoction and Phlegm-removing Decoction on Epilepsy Patients. World Latest Medicne Information 2019;19:195-6.
42. Zhang JM, Qu JY. Clinical Observation on Liujunzi Decoction and Valproate in the Treatment of Pediatric Epilepsy. Guangming Journal of Chinese Medicine 2019;34:411-412.
43. Ma R, Zhang XL. The pathogenesis of "phlegm Fu Naoluo, Qi counter wind" in children with epilepsy. Journal of Traditional Chinese Medicine 2020;61:79-81.
44. Yao D, Wang C, Han L, et al. Compound danshen dripping pills combined with trimetazidine in treating unstable angina pectoris: Protocol for a systematic review of randomized controlled trials. Medicine (Baltimore) 2019;98:e18238.
45. Liu WG. Effect of Compound Danshen Dropping Pills Combined with antiepileptic drugs in the treatment of traumatic epilepsy. Chinese Journal of Convalescent Medicine 2019;28:1205-7.
46. Jia C, Han S, Wei L, et al. Protective effect of compound Danshen (Salvia miltiorrhiza) dripping pills alone and in combination with carbamazepine on kainic acid-induced temporal lobe epilepsy and cognitive impairment in rats. Pharm Biol 2018;56:217-24.
47. Xie W, Meng CX, Shi GJ, et al. Effect of saikosaponin-a on epileptic seizures in refractory epilepsy rats. Journal of Tropical Medicine 2012;12:381-5.
48. Gao W, Bi Y, Ding L, et al. SSa ameliorates the Glu uptaking capacity of astrocytes in epilepsy via AP-1/miR-155/GLAST. Biochem Biophys Res Commun 2017;493:1329-35.
49. Ye M, Bi YF, Ding L, et al. Saikosaponin a functions as anti-epileptic effect in pentylenetetrazol induced rats through inhibiting mTOR signaling pathway. Biomed Pharmacother 2016;81:281-7.
50. Yu YH, Xie W, Bao Y, et al. Saikosaponin a mediates the anticonvulsant properties in the HNC models of AE and SE by inhibiting NMDA receptor current and persistent sodium current. PLoS One 2012;7:e50694.
51. Hong Y, Deng N, Jin HN, et al. Saikosaponin A modulates remodeling of Kv4.2-mediated A-type voltage-gated potassium currents in rat chronic temporal lobe epilepsy. Drug Des Devel Ther 2018;12:2945-58.
52. Hsu HC, Tang NY, Liu CH, et al. Antiepileptic Effect of Uncaria rhynchophylla and Rhynchophylline Involved in the Initiation of c-Jun N-Terminal Kinase Phosphorylation of MAPK Signal Pathways in Acute Seizures of Kainic Acid-Treated Rats. Evid Based Complement Alternat Med 2013;2013:961289.
53. Shao H, Yang Y, Mi Z, et al. 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 2016;337:355-69.
54. Ho TY, Tang NY, Hsiang CY, et al. Uncaria rhynchophylla and rhynchophylline improved kainic acid-induced epileptic seizures via IL-1β and brain-derived neurotrophic factor. Phytomedicine 2014;21:893-900.
55. Geng H, Chen X, Wang C. Systematic elucidation of the pharmacological mechanisms of Rhynchophylline for treating epilepsy via network pharmacology. BMC Complement Med Ther 2021;21:9.
56. Huang T, Zhang ZQ, Han F, et al. Effect of Tetramethylpyrazine Assisting Antiepileptic Drugs for Traumatic Epilepsy: An Observation of 28 Cases. Journal of Guangzhou University of Traditional Chinese Medicine 2008;25:292-4.
57. Jin Y, Cai S, Jiang Y, et al. Tetramethylpyrazine Reduces Epileptogenesis Progression in Electrical Kindling Models by Modulating Hippocampal Excitatory Neurotransmission. ACS Chem Neurosci 2019;10:4854-63.
58. Li SY, Jia YH, Sun WG, et al. Stabilization of mitochondrial function by tetramethylpyrazine protects against kainate-induced oxidative lesions in the rat hippocampus. Free Radic Biol Med 2010;48:597-608.
59. Jiang YP, Jin Y, Bao J, et al. Inconsistent Time-Dependent Effects of Tetramethylpyrazine on Primary Neurological Disorders and Psychiatric Comorbidities. Front Pharmacol 2021;12:708517.
60. Meng Z, Chen H, Meng S. The Roles of Tetramethylpyrazine During Neurodegenerative Disease. Neurotox Res 2021;39:1665-77.

61. Liu Y, Gao J, Peng M, et al. A Review on Central Nervous System Effects of Gastrodin. Front Pharmacol 2018;9:24.
62. Yang CS, Chiu SC, Liu PY, et al. Gastrodin alleviates seizure severity and neuronal excitotoxicities in the rat lithium-pilocarpine model of temporal lobe epilepsy via enhancing GABAergic transmission. J Ethnopharmacol 2021;269:113751.
63. Yang Y, Li Y, Han J, et al. Gastrodin attenuates lithium-pilocarpine-induced epilepsy by activating AMPK-mediated PPARα in a juvenile rat model. Biosci Biotechnol Biochem 2021;85:798-804.
64. Jin M, He Q, Zhang S, et al. Gastrodin Suppresses Pentylenetetrazole-Induced Seizures Progression by Modulating Oxidative Stress in Zebrafish. Neurochem Res 2018;43:904-17.
65. Chen L, Liu X, Wang H, et al. Gastrodin Attenuates Pentylenetetrazole-Induced Seizures by Modulating the Mitogen-Activated Protein Kinase-Associated Inflammatory Responses in Mice. Neurosci Bull 2017;33:264-72.
66. Shin EJ, Bach JH, Nguyen TT, et al. Gastrodia elata bl attenuates methamphetamine-induced dopaminergic toxicity via inhibiting oxidative burdens. Curr Neuropharmacol 2011;9:118-21.
67. Liu YF, Gao F, Li XW, et al. The anticonvulsant and neuroprotective effects of baicalin on pilocarpine-induced epileptic model in rats. Neurochem Res 2012;37:1670-80.
68. Qian X, Wang ZR, Zheng JJ, et al. Baicalein improves cognitive deficits and hippocampus impairments in temporal lobe epilepsy rats. Brain Res 2019;1714:111-8.
69. Yang J, Jia Z, Xiao Z, et al. Baicalin Rescues Cognitive Dysfunction, Mitigates Neurodegeneration, and Exerts Anti-Epileptic Effects Through Activating TLR4/MYD88/Caspase-3 Pathway in Rats. Drug Des Devel Ther 2021;15:3163-80.
70. Li G, Zhang S, Cheng Y, et al. Baicalin suppresses neuron autophagy and apoptosis by regulating astrocyte polarization in pentylenetetrazol-induced epileptic rats and PC12 cells. Brain Res 2022;1774:147723.
71. Fu P, Yuan Q, Sun Y, et al. Baicalein Ameliorates Epilepsy Symptoms in a Pilocarpine-Induced Rat Model by Regulation of IGF1R. Neurochem Res 2020;45:3021-33.
72. Li Q, Li QQ, Jia JN, et al. Baicalein Exerts Neuroprotective Effects in FeCl3-Induced Posttraumatic Epileptic Seizures via Suppressing Ferroptosis. Front Pharmacol 2019;10:638.
73. Chen QX, Miao JK, Li C, et al. Anticonvulsant activity of acute and chronic treatment with a-asarone from Acorus gramineus in seizure models. Biol Pharm Bull 2013;36:23-30.
74. Huang C, Li WG, Zhang XB, et al. α-asarone from Acorus gramineus alleviates epilepsy by modulating A-type GABA receptors. Neuropharmacology 2013;65:1-11.
75. Wang ZJ, Levinson SR, Sun L, Heinbockel T. Identification of both GABAA receptors and voltage-activated Na(+) channels as molecular targets of anticonvulsant α-asarone. Front Pharmacol 2014;5:40.
76. Ding J, Huang C, Peng Z, et al. Electrophysiological characterization of methyleugenol: a novel agonist of GABA(A) receptors. ACS Chem Neurosci 2014;5:803-11.
77. Bahr TA, Rodriguez D, Beaumont C, et al. The Effects of Various Essential Oils on Epilepsy and Acute Seizure: A Systematic Review. Evid Based Complement Alternat Med 2019;2019:6216745.
78. Lam KYC, Wu QY, Hu WH, et al. Asarones from Acori Tatarinowii Rhizoma stimulate expression and secretion of neurotrophic factors in cultured astrocytes. Neurosci Lett 2019;707:134308.
79. Liu HJ, Lai X, Xu Y, et al. α-Asarone Attenuates Cognitive Deficit in a Pilocarpine-Induced Status Epilepticus Rat Model via a Decrease in the Nuclear Factor-κB Activation and Reduction in Microglia Neuroinflammation. Front Neurol 2017;8:661.
80. Liu H, Song Z, Liao DG, et al. Anticonvulsant and Sedative Effects of Eudesmin isolated from Acorus tatarinowii on mice and rats. Phytother Res 2015;29:996-1003.
81. Zhang J, Mu K, Yang P, et al. Synthesis, antiepileptic effects, and structure-activity relationships of α-asarone derivatives: In vitro and in vivo neuroprotective effect of selected derivatives. Bioorg Chem 2021;115:105179.
82. Zheng M, Xin Y, Li Y, et al. Ginsenosides: A Potential Neuroprotective Agent. Biomed Res Int 2018;2018:8174345.
83. Shi Y, Miao W, Teng J, et al. Ginsenoside Rb1 Protects the Brain from Damage Induced by Epileptic Seizure via Nrf2/ARE Signaling. Cell Physiol Biochem 2018;45:212-25.
84. Lee BH, Kim HJ, Chung L, et al. Ginsenoside Rg_3 regulates GABAA receptor channel activity: involvement of interaction with the γ_2 subunit. Eur J Pharmacol 2013;705:119-25.
85. Zeng X, Hu K, Chen L, et al. The Effects of Ginsenoside Compound K Against Epilepsy by Enhancing the γ-Aminobutyric Acid Signaling Pathway. Front Pharmacol 2018;9:1020.

86. Zhou L, Chen L, Zeng X, et al. Ginsenoside compound K alleviates sodium valproate-induced hepatotoxicity in rats via antioxidant effect, regulation of peroxisome pathway and iron homeostasis. Toxicol Appl Pharmacol 2020;386:114829.
87. Yuan X, Li Z, Wang XT, et al. Roles and mechanisms of traditional Chinese medicine and its active ingredients in treating epilepsy. Zhongguo Zhong Yao Za Zhi 2019;44:9-18.
88. Lin TY, Lu CW, Huang SK, et al. Tanshinone IIA, a constituent of Danshen, inhibits the release of glutamate in rat cerebrocortical nerve terminals. J Ethnopharmacol 2013;147:488-96.
89. Buenafe OE, Orellana-Paucar A, Maes J, et al. Tanshinone IIA exhibits anticonvulsant activity in zebrafish and mouse seizure models. ACS Chem Neurosci 2013;4:1479-87.
90. Tan XQ, Cheng XL, Yang Y, et al. Tanshinone II-A sodium sulfonate (DS-201) enhances human BKCa channel activity by selectively targeting the pore-forming α subunit. Acta Pharmacol Sin 2014;35:1351-63.
91. Du W, Liang X, Wang S, et al. The Underlying Mechanism of Paeonia lactiflora Pall. in Parkinson's Disease Based on a Network Pharmacology Approach. Front Pharmacol 2020;11:581984.
92. Wang L, An H, Yu F, et al. The neuroprotective effects of paeoniflorin against MPP+-induced damage to dopaminergic neurons via the Akt/Nrf2/GPX4 pathway. J Chem Neuroanat 2022;122:102103.
93. Sugaya E, Sugaya A, Kajiwara K, et al. Nervous diseases and Kampo (Japanese herbal) medicine: a new paradigm of therapy against intractable nervous diseases. Brain Dev 1997;19:93-103.
94. Hino H, Takahashi H, Suzuki Y, et al. Anticonvulsive effect of paeoniflorin on experimental febrile seizures in immature rats: possible application for febrile seizures in children. PLoS One 2012;7:e42920.
95. Chen YF, Lee MM, Fang HL, et al. Paeoniflorin inhibits excitatory amino acid agonist-and high-dose morphine-induced nociceptive behavior in mice via modulation of N-methyl-D-aspartate receptors. BMC Complement Altern Med 2016;16:240.
96. Pearl PL, Drillings IM, Conry JA. Herbs in epilepsy: evidence for efficacy, toxicity, and interactions. Semin Pediatr Neurol 2011;18:203-8.
97. Che CT, Wang ZJ, Chow MS, et al. Herb-herb combination for therapeutic enhancement and advancement: theory, practice and future perspectives. Molecules 2013;18:5125-41.
98. Yip KL, Zhou X, Chook P, et al. Herb-drug interaction of gastrodiae rhizoma on carbamazepine: A pharmacokinetic study in rats. Epilepsy Res 2020;165:106376.
99. Yip KL, Koon CM, Chen ZY, et al. The antiepileptic effect of Gastrodiae Rhizoma through modulating overexpression of mTOR and attenuating astrogliosis in pilocarpine mice model. Epilepsia Open 2020;5:50-60.
100. Abushammala IM, El-Shaikh Ali FK, Abu Shammaleh KF, et al. Effect of Panax ginseng on Carbamazepine Pharmacokinetics in Rabbits. Turk J Pharm Sci 2021;18:17-20.

Cite this article as: Tao F, Cai Y, Deng C, Chen Z, Shen Y, Sun H. A narrative review on traditional Chinese medicine prescriptions and bioactive components in epilepsy treatment. Ann Transl Med 2023;11(2):129. doi: 10.21037/atm-22-3306

