

## *Research Progress on Anti-Epileptic Mechanism of Acorus Tatarinowii Schott*

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**Abstract:** Epilepsy is a disease that seriously affects human physical and mental health, causing a great burden on society and families. Acorus tatarinowii Schott has the effects of opening orifices and eliminating phlegm, awakening mind and benefiting intelligence, resolving dampness and appetizing. It is often used to treat various diseases in traditional medicine, and it has a good therapeutic effect on epilepsy. By sorting out the mechanism of Acorus tatarinowii Schott in the treatment of epilepsy, it provides a theoretical basis for clinical use of this traditional Chinese medicine. Therefore, this article reviews its mechanism of action as follows.

Epilepsy is a chronic brain disease caused by a variety of causes. It is characterized by recurrent, paroxysmal and transient central nervous system dysfunction caused by excessive discharge of brain neurons. Epilepsy is mainly manifested as recurrent seizures without warning, such as fainting, body convulsions or spasms, sensory abnormalities and so on. At present, it is believed that the main causes of epilepsy are genetic, congenital diseases, genetic metabolic diseases, central nervous system infections, cerebrovascular diseases, etc. The pathogenesis of epilepsy is complex and not completely clear. According to the current research, its pathogenesis is mainly related to ion channel dysfunction, neurotransmitter imbalance, immune response, gene mutation and so on [1].

At present, the treatment of the disease is still mainly based on Western medicine, but traditional Chinese medicine also has a deep understanding of epilepsy and a variety of treatment methods, which can be used for adjuvant treatment. Among them, there is a traditional Chinese medicine-Acorus tatarinowii Schott, which plays an important role in the treatment of epilepsy in traditional Chinese medicine. Acorus tatarinowii Schott belongs to the heart and stomach meridian, and its medicinal properties are pungent, bitter, dry and warm. It has the effects of inducing resuscitation and eliminating phlegm, awakening mind and benefiting intelligence, resolving dampness and appetizing. It can treat coma, epilepsy, forgetfulness, insomnia, tinnitus and deafness [2]. Traditional Chinese medicine has rich experience in the treatment of epilepsy. Exploring the mechanism of Acorus tatarinowii Schott in the treatment of epilepsy is of great significance for finding ideal therapeutic drugs. Therefore, this paper reviews the mechanism of Acorus tatarinowii Schott in the treatment of epilepsy.

## 1. Effective components

The chemical composition of *Acorus tatarinowii* Schott is complex, which can be divided into volatile oil, organic acid, terpenoids, flavonoids, etc. In addition to the above components, *Acorus tatarinowii* Schott also contains amino acids, lignin, sugars and other chemical components [3-4]. The volatile oil is the main effective component, of which  $\beta$ -asarone and  $\alpha$ -asarone are the two compounds with the highest content [5], and their metabolites are  $\beta$ -asarone and  $\alpha$ -asarone, respectively. The effective components of *Acorus tatarinowii* Schott have a variety of pharmacological activities, which are worthy of further research and development.

## 2. Mechanism

### 2.1 Regulating neurotransmitter levels

Epileptic seizures are considered to be the result of the imbalance between excitatory factors (glutamate, Glu) and inhibitory factors ( $\gamma$ -aminobutyric acid, GABA) in neurotransmission [6]. Studies have found that [7],  $\alpha$ -asarone can inhibit the activity of hippocampal neurons by enhancing GABA inhibition. At the same time, some studies have found that [8-9],  $\alpha$ -asarone can inhibit the excitatory neurotoxicity caused by excessive Glu by regulating the abnormal expression of glutamate-related receptor protein, thus affecting the Glu level in the hippocampus of mice and producing anti-epileptic effect. Therefore, it can be considered that  $\alpha$ -asarone can regulate the excitatory and inhibitory factors in neurotransmission, maintaining a balance between the two levels. Miao Jingkun [10] et al. found that the antiepileptic effect of  $\alpha$ -asarone was similar to that of sodium valproate, clonazepam, carbamazepine and other clinical first-line antiepileptic drugs. The  $\alpha$ -asarone in *Acorus tatarinowii* Schott has definite anti-epileptic effect, which can be combined with anti-epileptic western medicine to improve the control rate of epileptic seizures. It has great clinical practical value and broad research and development prospects.

### 2.2 Regulating protein kinase C (PKC) expression

After injecting kainic acid (KA) into the lateral ventricle of rats, Wu Yuan [11] et al. found that neuronal apoptosis occurred immediately after seizures. Recurrent seizures of epilepsy can cause apoptosis of nerve cells, and the decrease in the number of cells can cause reorganization of synapses between cells, forming abnormal synaptic loops, and promoting recurrent seizures of epilepsy [12]. Studies have found that PKC can promote apoptosis induced by various stimuli, and PKC is also an important target of pro-apoptotic protein Caspase3 in the process of apoptosis [13]. Wang Kunfang [14] et al. showed that the number of PKC positive cells in the hippocampus was significantly reduced by kainic acid test, which confirmed that PKC was involved in the apoptosis of brain neurons after seizures in KA rat model. At the same time, it was further confirmed that the antiepileptic effect of volatile oil of *Acorus tatarinowii* Schott was related to its regulation of PKC expression, thereby reducing neuronal apoptosis.

### 2.3 Inhibition of glial cell activation

Glial cells are another major type of cells in nerve tissue besides neurons. They are distributed between neurons and participate in the activities of neurons. They have the functions of supporting, pinching chemical substances, secreting and repairing. Among them, astrocytes account for 50 % ~ 60 % in various glial cells. When the function of membrane proteins on the surface of astrocytes is impaired, a large amount of glutamate accumulation leads to abnormal neuronal excitability and

induces epilepsy [15]. Other studies have found that there are a large number of abnormal activated and dysfunctional astrocytes in the brain of patients with epilepsy [16]. These abnormal activated astrocytes accumulate a large amount of glutamate, resulting in increased neuronal excitability and epilepsy. Zhao Mingming [17] et al. showed that  $\alpha$ -asarone, as a metabolite of  $\alpha$ -asarone, could inhibit the morphological changes of hippocampal neurons and the activation of astrocytes in epileptic young rats, thus inhibiting the occurrence and development of epilepsy.

## 2.4 Inhibition of c-fos gene expression

The c-fos gene is an immediate early gene. When the cells are stimulated by external stimuli, the c-fos gene will be activated, and the abnormal expression of the c-fos gene is related to a variety of diseases. At present, experiments have confirmed that the expression of c-fos gene has a significant correlation with the release of amino acid neurotransmitters in the brain [18-19]. When the balance between excitatory amino acids and inhibitory amino acids in the brain is broken, excitatory neurotransmitters are more than inhibitory neurotransmitters, it will lead to abnormal discharge of epileptic foci and enhanced c-fos expression. Many studies have found that [20-21], the volatile oil of *Acorus tatarinowii* Schott can significantly inhibit the expression of c-fos gene in rat brain, and effectively alleviate the seizures caused by different models. It is speculated that its mechanism may be related to inhibiting the release of excitatory neurotransmitter glutamate in the brain, increasing the content of inhibitory neurotransmitter GABA, and then affecting the expression of c-fos gene in the brain.

## 2.5 Regulating ion channels

At present, it has been found that the ion channels associated with epilepsy are sodium, potassium and calcium ion channels. The onset of epilepsy may be caused by multiple ion channels, but the final pathway is the same, which is the abnormal change of electrolyte distribution and transport, resulting in the disorder of ion channel function, further making the neurons hyperexcitable and causing seizures [1]. Calmodulin (CaM) and calmodulin-dependent kinase (CaMK) system play an important role in regulating neuronal excitability [22]. Miao Jingkun [23] et al. found that  $\alpha$ -asarone can reduce the concentration of free  $Ca^{2+}$  in hippocampal neurons and bind to CaM expression and up-regulate the expression of CaMKIIa-mRNA, so as to alleviate the neuronal damage caused by  $Ca^{2+}$  overload in hippocampal neurons after status epilepticus. Therefore,  $\alpha$ -asarone can inhibit seizures by regulating ion channels.

## 2.6 Protecting brain tissue

### 2.6.1 Elevating calcitonin gene-related peptide (CGRP), reducing neuron-specific enolase (NSE).

Calcitonin gene related peptide (CGRP) is a vasodilator substance, which is mainly distributed in the central nervous system and cardiovascular system. CGRP can participate in the regulation of the hypothalamus-pituitary-adrenal axis during acute hypoxia, exert its vasodilating activity, and reduce the hypoxic-ischemic damage of tissues [24]. In the early stage of epilepsy, the decrease of CGRP level may be involved in the brain injury caused by epilepsy [25].

Neuron-specific enolase (NSE) is an acidic protease unique to neurons and neuroendocrine cells. When brain injury occurs, the nerve cell membrane and blood-brain barrier are destroyed, and NSE leaks out of the cell and enters the cerebrospinal fluid and blood, resulting in a significant increase in its content [26]. NSE can be used as a biochemical index to judge the degree of neuronal damage

in the brain.

Gong Lei [26] et al. found in the experiment that the volatile oil of *Acorus tatarinowii* Schott increased the concentration of CGRP in serum and cerebrospinal fluid of rats, and decreased the number of NSE leakage, which indicated that the volatile oil of *Acorus tatarinowii* Schott could increase the content of CGRP and reduce the susceptibility of hippocampal neurons to ischemia and hypoxia. At the same time, it reduced the damage of nerve cells and the outflow of NSE, and played a protective role in brain tissue.

### 2.6.2 Inhibition of nitric oxide (NO) release

Nitric oxide (NO) is an important biological mediator. It has the function of information transmission in the central nervous system and participates in the occurrence and development of various central nervous system diseases. Excessive NO synthesis and release may damage neurons and induce epilepsy. At the same time, high concentration of NO has direct toxic effects on cells [27]. Yang Zhixian [28] et al. found that the endogenous nitric oxide synthase (NOS) / nitric oxide (NO) system is involved in the regulation of neuronal apoptosis. The mechanism of NO involved in apoptosis is mainly induced by the role of glutamate and NMDA receptors in convulsions. Yang Haigan [29] et al. found through research that *Acorus tatarinowii* Schott can significantly inhibit the concentration of NO in human brain glial cells (HEB) induced by lipopolysaccharide (LPS), thereby achieving a protective effect on brain cells.

## 3. Conclusion

The survey results show that the prevalence rate of epilepsy in China is 7.0 ‰, and the annual incidence rate is 28.8 / 100,000 population [30]. The disease seriously affects the physical and mental health of patients. Early, systematic and effective treatment can reduce the number of seizures, improve the quality of life and reduce the risk. At present, various studies have shown that *Acorus tatarinowii* Schott has a good therapeutic effect on epilepsy. Based on data mining, the medication rules of 157 drugs contained in 118 prescriptions for epilepsy were analyzed, and it was found that *Acorus tatarinowii* Schott had the highest frequency of use [31]. At present, *Acorus tatarinowii* Schott is mostly used in traditional Chinese medicine decoction, which can be developed into a more convenient medicine by modern pharmaceutical technology. *Acorus tatarinowii* Schott has great development potential, and its mechanism of action in the treatment of epilepsy can be further studied.

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