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Experimental Research Progress on the Intervention of Epilepsy with Traditional Chinese Medicine in the Past Five Years

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Abstract: Epilepsy is a common chronic and recurrent neurological disorder characterized by abnormal neurological dysfunction, severely impacting quality of life and endangering human health. In recent years, the role and advantages of Traditional Chinese Medicine (TCM) in treating epilepsy have become increasingly prominent. This article aims to review experimental research progress on TCM-based treatments for epilepsy over the past five years, with the goal of providing stronger data support for future clinical practice and research. Epilepsy primarily refers to a group of clinical syndromes caused by highly synchronized abnormal discharges of neurons in the brain, characterized by episodic, transient, stereotyped, and recurrent features. It severely impacts patients' quality of life and psychological well-being. Consequently, effectively controlling epileptic seizures and clarifying the pathogenesis have long been critical concerns. However, the underlying mechanisms of epilepsy remain incompletely elucidated, with current hypotheses focusing on neuroinflammation, oxidative stress, microglial activation, and imbalances in neurotransmitter metabolism [1]. Research on the prevention and treatment of epilepsy using Traditional Chinese Medicine (TCM) has spanned decades. This article reviews recent experimental advances in the intervention of epilepsy using active ingredients derived from Chinese herbal medicine.

1. Introduction

Oxidative stress plays a significant role in the occurrence and development of epilepsy. By influencing the expression of inflammatory factors and related proteins, it leads to lipid peroxidation, free radical damage to nerve cells, inflammatory cascade reactions, and cell apoptosis, ultimately causing hippocampal neuron damage and inducing epilepsy [2]. Jiang Ranran et al. administered crocin to rats with epilepsy induced by intraperitoneal injection of lithium chloride and subcutaneous injection of pilocarpine. The MDA content in the rats decreased, while the activities of SOD and CAT increased. The pathological changes in the hippocampal tissue of the rats' brains were significantly improved, indicating that crocin may reduce hippocampal tissue damage in epileptic rats by inhibiting oxidative stress and inflammatory responses [3]. Song Xiaona et al. administered Cornus officinalis polysaccharides to rats with epilepsy induced by intraperitoneal injection of lithium chloride and pilocarpine. The contents of SOD and GSH-PX in

the hippocampal tissue of the rats significantly increased, while the MDA content significantly decreased ($P < 0.05$), suggesting that Cornus officinalis polysaccharides have antioxidant effects on epileptic rats [4]. Wang Zi et al. found that anthocyanins could significantly reduce the expression of oxidative stress products 15-LOX and 4-HNE in the hippocampus of epileptic rats and inhibit the excitability of hippocampal neurons, thereby exerting antioxidant effects and alleviating the severity of epilepsy [5]. Li Jing et al. [6] administered verbascoside to rats with epilepsy induced by pentylenetetrazol. They found that the SOD level increased and the MDA level decreased in the verbascoside group, indicating that verbascoside can improve oxidative stress and reduce nerve cell damage, thereby exerting a neuroprotective effect. Xie Tao et al. discovered that parthenolide could significantly reduce the MDA content in the brain tissue of epileptic model rats ($P < 0.05$) and increase the GSH content, inhibiting oxidative stress reactions and exerting an antiepileptic effect. Deng Chujun et al. [7] administered the Chinese herbal formula Qingqing V to mice with epilepsy induced by kainic acid. They found that it could reduce the MDA content and increase the activities of SOD, CAT, and T-AOC in the hippocampal tissue of the mice, exerting an antiepileptic effect through antioxidant stress. In the experimental research of traditional Chinese patent medicines, Qi Yue et al. found that Epilepsy Clear Granules could increase the contents of GSH and GPX and decrease the content of GSSG, thereby inhibiting oxidative stress and scavenging oxygen free radicals [8].

2. Improving Mitochondrial Dysfunction

Mitochondria are the main sites for oxidative phosphorylation and ATP formation within cells, playing a crucial role in maintaining cellular energy metabolism and life activities. Studies have shown that epilepsy can cause damage to mitochondrial function and structure. At the same time, mitochondrial damage can lead to recurrent epileptic seizures through a series of reactions, increasing the susceptibility to epilepsy[9]-[10]. Wu Qiongying et al. administered quercetin to rats with epilepsy induced by intraperitoneal injection of lithium chloride, scopolamine, and pilocarpine hydrochloride. The levels of IL-1β, TNF-α, and IL-6 in the rats were significantly reduced, the hippocampal tissue structure was relatively intact, the number of surviving neurons increased significantly, the apoptosis index decreased significantly, and the Racine grade decreased significantly. This indicates that quercetin contained in various traditional Chinese medicines can effectively alleviate epileptic seizures by reducing inflammatory damage to neural tissues.

3. Inhibiting Neuroinflammatory Responses

WU Qiongying et al. administered quercetin to epileptic model rats induced by intraperitoneal injection of lithium chloride, scopolamine, and pilocarpine hydrochloride. The results showed significant reductions in IL-1β, TNF-α, and IL-6 levels, improved hippocampal structural integrity, increased survival of neurons, decreased apoptosis index, and reduced Racine seizure scores. These findings indicate that quercetin, present in various traditional Chinese medicines, can alleviate epileptic seizures by mitigating neuroinflammatory damage [11]. SHI Yu treated pentylenetetrazol (PTZ)-induced epileptic model rats with Arisaema cum Bile, observing marked decreases in hippocampal TNF-α, IL-1β, and IL-6 expression levels. This further suggests that Arisaema cum Bile may suppress the synthesis and release of inflammatory factors, thereby ameliorating epileptic pathogenesis[12].YANG Weilong injected gentiopicroside into lithium chloride-pilocarpine-induced epileptic juvenile rats, demonstrating a significant alleviation of neuroinflammation in the hippocampal region, with notable declines in IL-1β, IL-18, and TNF-α levels. This indicates that gentiopicroside may inhibit neuroinflammatory responses, reduce seizure severity, and exert neuroprotective effects [13]. YUAN Peng [14]administered Qingmengshi

powder to PTZ-induced epileptic model rats and found decreased serum levels of inflammatory cytokines such as IL-1β, IL-2, IL-6, and TNF-α, suggesting that Qingmengshi mitigates epilepsy by reducing inflammation and protecting neuronal cells. In studies on Chinese herbal formulas, FENG Jiaojiao et al. [15] treated pilocarpine-induced epileptic model mice with Poria cocos polysaccharides. They observed reduced hippocampal IL-1β, IL-6, and TNF-α levels, as well as decreased p38 MAPK and NF-κB protein expression. These results imply that Poria cocos polysaccharides suppress the p38 MAPK/NF-κB signaling pathway, thereby lowering seizure frequency and intensity while alleviating hippocampal neuronal damage and inflammation. ZHAO Yu et al. [16]reported that Compound Danshen Dripping Pills (composed of Salvia miltiorrhiza, Panax notoginseng, and borneol) reduced serum TNF-α and IL-6 levels in PTZ-induced epileptic rats, indicating that the formula inhibits pro-inflammatory factor synthesis and secretion, suppresses inflammatory responses, and prevents epileptic seizures.

4. Inhibiting the activation of glial cells

Neural stem cells have two tendencies: differentiation towards glial cells and neural cells. The initial stage of neurogenesis determines the fate of stem cell differentiation. Epilepsy leads to the differentiation of neural stem cells towards glial cells and causes post-epileptic stem cell ectopia, gliosis, and abnormal circuit formation. Gliosis is a significant feature after epileptic seizures, especially the activation of astrocytes and microglia, which may promote the progression of epilepsy. Zhang Ninnan administered curcumin to mice with epilepsy induced by intraperitoneal injection of scopolamine and pilocarpine and found that the number of 5-bromodeoxyuridine-labeled cells in the mice was significantly reduced, indicating that curcumin treatment could reduce glial cell activation, thereby reducing the activation of astrocytes. At the same time, curcumin could reduce post-epileptic ectopic neurogenesis and the frequency of epileptic seizures [17]. Yan Yaoyao prepared a traumatic brain injury model in mice by the Feeney free-fall method, causing closed brain injury on the left side of the mice. She administered rhynchophylline to the mice and found that rhynchophylline could shorten the latency of epileptic seizures; reduce the fluorescence density of GFAP in the DG and CA1 regions of the hippocampus and the number of BDNF-positive cells in the CA3 region. It inhibits the activation and proliferation of astrocytes and participates in the regulation of multiple signaling pathways, exerting neuroprotective effects and ultimately achieving antiepileptic effects [18].

5. Regulating autophagy levels and inhibiting apoptosis

Autophagy is an important quality control pathway in neurons and plays a crucial role in maintaining neuronal function. Under normal physiological conditions, it is at a low level and maintains the stability of the intracellular environment by degrading damaged and senescent proteins and organelles. However, excessive autophagy can lead to neuronal apoptosis, brain tissue damage, and epileptic seizures, especially in the complex and diverse mechanisms of hippocampal neuronal damage caused by epileptic status. Autophagy regulatory factors, including microtubule-associated protein 1 light chain 3 (LC3) and Beclin1, can promote the occurrence of spontaneous epilepsy in rat brain neurons [19]-[20]. Han Weinan [21] et al. administered tanshinone IIA to a rat epilepsy model induced by kainic acid (KA) and found that the number of NeuN(+) positive cells in the CA3 region of the hippocampus significantly increased, and the levels of LC3I/II and Beclin1 proteins were significantly reduced. TA reduces the excessive activation of autophagy and has a neuroprotective effect on epilepsy-induced neuronal damage. Hu Yu et al. [22] studied the administration of Ganoderma lucidum spore powder by gavage to rats with pentylenetetrazol-induced epilepsy and found that Ganoderma lucidum spore powder could improve

epilepsy by increasing the expression of autophagy-related proteins (LC3B and Beclin-1) and reducing the expression of IL-1β. Weng Ning et al. [23] administered ginsenoside to rats with pentylenetetrazol-induced epilepsy and found that ginsenoside could regulate the expression of autophagy-related factors LC3, Bax, Caspase3, Beclin1, etc., inhibit excessive autophagy and apoptosis, and thereby suppress the occurrence of epilepsy. In the study of traditional Chinese medicine formulas, Lu Ling et al.[24] administered Dingxian Decoction (Gastrodia elata, Poria cocos, Pinellia ternata, Bile Bupleurum, Fritillaria thunbergii, Poria cocos, Acorus tatarinowii, Bombyx batryticatus, Scorpion, Cinnabar, Citrus reticulata, Polygala tenuifolia, Salvia miltiorrhiza, Ophiopogon japonicus, Cinnabar) to mice with epilepsy induced by pilocarpine hydrochloride and found that Dingxian Decoction could down-regulate the excessive expression of ATG7 and LC3 II in the model mice, inhibit autophagy in mouse hippocampal neurons, and exert therapeutic effects on epilepsy. LC3 II and ATG7 are important marker proteins of autophagy.

6. Maintaining the stability of the blood-brain barrier

The blood-brain barrier is composed of the endothelial cells of the brain's capillaries, the basal lamina surrounding the outer layer of the brain, and the end feet of astrocytes. The endothelial cells are connected through junctional complexes (such as tight junctions and adherens junctions), forming a complete ring. Tight junctions also ensure the high resistance of endothelial cells and the low permeability of the paracellular pathway, thereby maintaining the normal function of the blood-brain barrier. When the blood-brain barrier is damaged, a large amount of albumin and inflammatory factors can infiltrate the brain parenchyma, disrupting the homeostasis of the central nervous system and inducing epilepsy [25]. Xu Pei et al. [26]perfused saikosaponin a into mice with epilepsy induced by kainic acid. The expression levels of PECAM-1 and ZO-1 in the hippocampus of the mice decreased significantly. PECAM-1 is a cell adhesion factor of the blood-brain barrier, which plays an important role in maintaining the integrity of endothelial cell connections and regulating the stability of connections. It can also inhibit the activation of circulating platelets and maintain the integrity of endothelial cell (EC) connections [27].

7. Conclusions

In conclusion, traditional Chinese medicine has a definite therapeutic effect on epilepsy, with advantages such as high clinical effectiveness, significant improvement of symptoms, few adverse reactions, and high safety. At the same time, the mechanism of action has been preliminarily explored, mainly including promoting the expression of neurotrophic factors, regulating the toxicity of excitatory amino acids, anti-inflammation, anti-oxidative stress, regulating autophagy, and anti-apoptosis. Currently, there are still some deficiencies in clinical and experimental research that need to be improved: ① Some clinical studies have insufficient sample sizes, single outcome indicators, and lack of high-quality randomized controlled trials with multi-center, large samples, and random double-blind designs. In the future, laboratory mechanism research can be fully combined with clinical treatment to maximize the therapeutic effect of traditional Chinese medicine on epilepsy. ② Research on the anti-inflammatory, anti-oxidative stress, and anti-apoptotic mechanisms of traditional Chinese medicine has gradually deepened, but research on mechanisms such as reducing cerebral hematoma and regulating signaling pathways is still limited. If each mechanism and pathway, as well as their internal connections, can be fully studied, it is expected to improve the cure rate and recovery rate of epilepsy. ⑤ Syndrome differentiation and treatment is the basic principle of traditional Chinese medicine in treating diseases, but it is difficult to establish animal models of syndrome types. In the future, modern technology can be combined with traditional Chinese medicine research, such as using artificial intelligence to assist in the creation of

"epilepsy" experimental models.

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