Advances in Research of Chinese Medicine Tianma in the Treatment of Parkinson's Disease

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Abstract In this study, a systematic review was conducted on the experimental study as well as the clinical application of Tianma (*Gastrodia elata* Blume), a traditional Chinese medicine, in the prevention and treatment of Parkinson's disease (PD). On this basis, a summary and outlook were made, so as to provide ideas and theoretical basis for the study, development and utilization of Tianma PD field.

Key words Tianma (*Gastrodia elata* Blume), Parkinson's disease (PD), Clinical application

1 Introduction

Tianma is an orchid fungus nutritive perennial herb *Gastrodia elata* Blume dried tubers into medicine, for the Yunnan Taoist medicinal herbs, sweet and flat in nature, belonging to the liver meridian, has the effects of calming the liver yang, resting the wind and stopping spasms, dispelling the wind and opening up the channels, is a kind of medicinal and edible Chinese herbs[1]. Modern medical research has shown that Tianma has the effects of increasing intelligence and strengthening brain[2], anti-aging[3], anti-cardiovascular disease[4], anti-convulsion, analgesia and sedation[5]. Chemical components include phenols and their glycosides, polysaccharides, organic acids and sterols, among which gastrodin and Gastrodia polysaccharide are the main active components of *G. elata*[6-7], which have therapeutic effects on Parkinson's disease (PD).

PD is a common progressive degenerative disease, second only to Alzheimer's disease (AD) in prevalence[8]. The main pathological changes are depigmentation of substantia nigra and locus cyanulus, accompanied by loss of neurons in the dense part of substantia nigra. In addition, neuron loss could also be observed in the basal nucleus of Meynert and the dorsal motor nucleus of vagus nerve, and a-synuclein (a-Syn) aggregation was widespread in the cells[9]. There are many pathogenic factors of PD, among which age is an important factor, environment, lifestyle, genetics are also the causes of PD. For the treatment of PD, Western medicine is generally used in the world, but the drugs on the market can only temporarily improve the symptoms of patients, and can not inhibit the process of PD, and long-term medication will appear a series of serious side effects[10]. Finding solutions from traditional Chinese medicine has become an urgent need for clinical practice. By summarizing the intervention effect of Tianma on PD model and the clinical application of Tianma formula in PD, we comprehensively analyzed the advantages of Tianma in the treatment of PD, so as to provide a theoretical basis for the clinical treatment of PD with traditional Chinese medicine.

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2 Intervention effect of Tianma on Parkinson's model

2.1 Anti-inflammatory effects It has been found that the development of PD is closely linked to inflammation, and neuroinflammation is involved in the progressive degeneration of DAergic neurons in PD. The Toll-like receptor 4/nuclear transcription factor-κB (TLR4/NF-κB) signaling pathway is a classical inflammatory pathway, and changes in its expression play an important role in the development of the body's inflammatory response[11]. It has been shown that after intervention with Tianma active component gastrodin, the expression of TLR4 and NF-κB in the brain tissues of Parkinson's rats decreased compared with the previous one, and the possible mechanism is that gastrodin can inhibit the activation of microglial cells by suppressing the expression or the function of these signaling pathways, which in turn attenuates the neuroinflammation[12]. In addition, Wu *et al.* [13] also found that gastrodin has the ability to inhibit the secretion of NO, IL-1β and TNF-α inflammation-related factors in BV2 cells induced by lipopolysaccharide, and can also reduce the mRNA expression levels of TNF-α and IL-1β, and inhibit the nucleation of NF-κBp65. The expression levels of LPS-induced BV inflammation-related proteins iNOS, TLR4, p-IKBa, NLRP3, cleavedcas pase-1 and Cleavestr-β were decreased, thus playing an anti-inflammatory role and delaying the occurrence and development of PD.

2.2 Anti-oxidative stress effect Tianma protects the structural and functional integrity of cells by regulating the intracellular antioxidant system, further enhancing cellular resistance to oxidative stress[14]. PC12 cells induced by rotenone produce oxidative stress damage, and 20C, the active component in Tianma, can effectively alleviate this damage, inhibit the apoptotic process, and also at-

tenuate clostridium-induced stress damage to the endoplasmic reticulum of PC12 cells[15-16]. Gastrodin can significantly up-regulate the ERK1/2-Nrf2 signaling pathway[17]. Activation of this pathway plays a crucial role in elevating the levels of Glutathione peroxidase (GSH-Px) and Superoxide dismutase (SOD) in striatum. As key antioxidant enzymes in cells, GSH-Px and SOD can efficiently remove free radicals, thus effectively reducing oxidative stress and protecting cells from damage[18]. Some studies have also shown that *G. elata* alcohol extract can increase SOD and GSH-Px values, which indicates that *G. elata* and its effective substances can up-regulate the content of antioxidant enzymes to play a significant antioxidant role, reduce the oxidative damage to neurons, and achieve the role of nerve protection[19].

2.3 Inhibition of apoptosis Studies have shown that some neurodegenerative diseases are closely related to apoptosis disorders[20]. Abnormally activated apoptosis leads to impaired neuronal function, which is typical of neurodegenerative diseases such as PD and AD[21]. The active component of Tianma can effectively regulate the expression of related proteins and genes, specifically up-regulate the expression of Bcl-2 protein in PD model rats and cerebral hemorrhage rats, and down-regulate the expression of Bax gene[22]. In addition, it also reduced the expression of NMDA2B receptor protein and the activity of Caspase-3 and Caspase-9, which effectively inhibited the process of cell apoptosis[23]. Some studies suggest that the inhibitory effect of Tianma injection on apoptosis may be related to regulating the activity of Bcl-2 family members, inhibiting the anti-apoptotic effect of apoptotic protein Bcl-2, and promoting the phosphorylation and inactivation of apoptotic protein Bax[24]. He *et al.*[25] found that the expression of both Bcl-2 and Bax in the substantia nigra of PD model rats increased, with Bax mainly increasing. However, after Tianma treatment, the expression of Bax in the brain tissue of rats decreased significantly, while the expression of Bcl-2 increased significantly. These results indicated that Tianma could inhibit the apoptosis of Daergic neurons in PD model rats by increasing the expression of Bcl-2 and decreasing the expression of Bax protein. Gao *et al.*[22] found that Tianma treatment can reduce the expression level of Bax protein and increase the expression level of Bcl-2, thus alleviating the neurological impairment in rats. Liu *et al.*[26] also found that Tianma could maintain the expression level of Bcl-2 and reduce the expression of apoptosis marker Caspase-3, thus inhibiting rotenone-induced apoptosis in D Aergic neuronal cells.

3 Clinical application of Tianma formula in the treatment of PD

The clinical manifestations of PD mainly include early motor symptoms, early non-motor symptoms and late symptoms. Motor symptoms mainly include static tremor, muscle rigidity and slow movement, and slow movement is a necessary clinical manifestation in PD diagnosis. The non-motor symptoms mainly include anosmia, fatigue, depression, REM sleep disorder and constipation, while the late symptoms of PD mainly include some treatment-related symptoms, such as frozen gait, postural instability, swallowing disorders, postural dizziness, salivation, urgency of urination, nocturia and sexual dysfunction[27]. Current clinical studies support the applicability of Tianma in the treatment of PD.

In a study of 91 PD patients, the treatment group was treated with the traditional Chinese medicine Tianma formula combined with Levodopaand Benserazide tablets for PD, 1 dose daily for 3 months. The control group took Levodopaand Benserazide Tablet orally, 3 times a day, the course of treatment was the same as that of the treatment group. After treatment, MMSE score was used to find that the effective rate of the treatment group was higher than that of the control group, indicating that the traditional Chinese medicine Tianma formula given on the basis of Levodopaand Benserazide Tablet therapy can significantly improve the therapeutic effect, alleviate clinical symptoms and promote the improvement of cognitive function[28].

The above studies provide a basis for the clinical application of Tianma, and Tianma is indeed effective in the treatment of PD. However, there are still deficiencies in current clinical studies. There is considerable heterogeneity in existing study designs, and there are relatively few clinical studies on Tianma in the treatment of PD. Therefore, further high-quality randomized controlled trials are needed to clarify the role of Gastrodia in PD.

4 Conclusions

As a neurodegenerative disease, PD has a high disability rate, and it seriously reduces the quality of life of patients, and its prevalence rate increases year by year with the change of aging society. Tianma is a high-frequency Chinese medicine for the treatment of PD, and it has extensive pharmacological effects, and gastrodia does have therapeutic effects on PD. Through analysis, it is concluded that Tianma exerts anti-PD effects mainly through anti-oxidative stress reaction, anti-inflammation and inhibition of apoptosis, and has the advantages of multi-component, multi-target, multi-link and multi-channel treatment of PD. It is expected to be a new drug against PD.

The regulatory molecules and signaling pathways involved in the treatment of PD by Tianma are relatively complex, and each pathway has cross-influence with each other, but the key regulatory targets are still unclear, and systematic mechanism analysis is lacking. In addition, in the process of literature review, it was found that most of the relevant studies were animal and cell studies, and the results of many cell and animal experiments differed from the actual clinical observation results, which may be due to certain differences between the modeling process of cell and animal experiments and the occurrence and development of human diseases. Therefore, it is important to conduct extensive random-

ized clinical trials in the future to further verify the effectiveness of Tianma on PD patients, and to study the modeling method that is closer to human disease. Future studies can also combine Tianma with modern pharmaceutical technology to explore how to extract and utilize its effective components efficiently, as well as the effects of various extraction methods on the precipitation rates of different effective components of Tianma, providing new research ideas for the comprehensive development and utilization of Tianma and its efficacy in the treatment of PD.

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