

Progress in the Pharmacological Mechanism of *Gastrodia Elata* in Parkinson's Disease

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Abstract

Parkinson's disease's disease (PD) is a common neurodegenerative disease in clinical practice, with pathological manifestations of dysfunction or loss of dopamine neurons in the brain. PD patients are mainly manifested as bradykinesia, myotonic, static tremor, postural instability, etc. *Gastrodia elata* is one of the commonly used Chinese medicines in the treatment of Parkinson's disease. It has a long history, and has the effects of relieving wind and stopping spasmodic, calming liver Yang, dispelling wind and dredging collaterals. It is widely used in the treatment of neurological diseases. By summarizing the literature, it is found that *Gastrodia elata* contains various effective chemical components, such as gastrodin, 4-hydroxybenzyl alcohol, polysaccharide and organic acid, which can have a therapeutic effect on Parkinson's disease through anti-oxidative stress, inhibition of apoptosis and anti-inflammatory response. This paper summarizes the pharmacological mechanism of PD, expounds the effective components of *Gastrodia elata* and its influence on related signaling pathways and receptor proteins, and provides a new idea for the research direction of the treatment of Parkinson's disease.

Keywords

***Gastrodia elata*; Parkinson's disease; Pharmacological mechanism.**

1. INTRODUCTION

Parkinson's disease besides Alzheimer's disease is the second most common neurodegenerative lesions, its motor symptoms characterized by motor delay, muscle rigidity, resting tremor, slow gait, etc., non-motor symptoms include mild autonomic dysfunction (constipation, erectile dysfunction, urinary urgency), RBD (dream), smell of smell, and common psychological characteristics of Parkinson's disease, such as depression and anxiety [1]. PD is reported for 1.6 of nearly 1,000 people worldwide, and the number of PD patients is expected to increase to 9 million [2] by 2030. The pathogenesis of Parkinson's disease is extremely complex, with dysregulation of α -synuclein, mitochondrial dysfunction, oxidative stress, immune and neuroinflammation, NM overaccumulation, gastrointestinal dysfunction, central nervous axonal loss, and excitatory neurotoxicity, which are the main causes of its pathogenesis [3]. At present, the preferred method for the treatment of PD is drug treatment. The commonly used drugs include compound levodopa, dopamine receptor agonists, monoamine oxidase type B inhibitors (monoamine oxidase type B inhibitor, MAO-BI), catechol-O-methyltransferase inhibitors (catechol-O-methyltransferase inhibitor, COMTI), anticholinergic drugs, amantadine and other [4]. Although western medicine treatment plays a dominant role in the treatment of Parkinson's disease, it still cannot prevent the development of the disease and can only relieve

the symptoms. Long-term use of western medicine not only reduces the efficacy, but also gradually reveals the adverse reactions and toxic side effects of drugs. TCM has unique advantages in the treatment and prevention of PD, which can significantly delay the development of the disease, improve patients' symptoms, and reduce the occurrence of complications.

PD belongs to the category of "fibrillation disease" in Chinese medicine, also known as "vibration", "flutter" and "tremor". Modern doctors think that this false label is actually its pathogenesis, this deficiency is mainly deficiency of liver and kidney, and the standard is mainly mixed with wind, phlegm and blood stasis. After thousands of years, TCM theory has laid a solid foundation for the treatment of fibrillation syndrome. At present, there are a large number of modern clinical and experimental data showing that TCM has significantly improved the motor and non-motor symptoms of Parkinson's disease, without no obvious adverse reactions. In addition, when combined with western medicine to treat PD, TCM therapy can reduce the dosage of western medicine and its adverse reactions. *Gastrodia elata* has the effect of suppressing liver Yang, relieving wind and spasmodi, dredging collaterals and relieving pain, and has remarkable effect in the treatment of PD. Chinese medicine masters Duan Fujin [5], Xiong Jibai [6] and Zhang Xuewen [7] were treated with Parkinson's disease to relieve wind and stop spasmodic, calm liver Yang, dispel wind and smooth collaterals. Professor Duan Fujin, a master of traditional Chinese medicine, believes that the treatment of fibrillation should be regulating and tonifying the liver and kidney, pay attention to nourishing Yin and enriching blood, filling the lean marrow and relieving the wind, so the treatment with *Gastrodia elata* to enter the liver to calm the liver Yang, relieving wind and stop spasmodic [5]. According to modern literature data mining, 108 PD prescriptions were selected, among which the three drugs with the highest drug frequency were white peony root, *Gastrodia elata* and [8]. By exploring the pathogenesis of PD and the pharmacological effect of *Gastrodia elata*, we reviewed the pharmacological mechanism of *Gastrodia elata* for PD, and discussed the best varieties and processing methods of *Gastrodia elata* for PD, in order to provide reference for the clinical treatment of PD.

2. RESEARCH OVERVIEW OF GASTRODIA ELATA

Gastrodia elata is a dry tuber of orchid family, also known as red arrow, solitary cheese, mother and sage. Its clinical efficacy is remarkable and it is often recorded in ancient books. Song "Kaibao herb" [9] divided red arrow and *Gastrodia elata* into two categories, "Materia Medica Classic" [10] called the stem red arrow zhi, the root meat is called *Gastrodia elata*; after "Compendium of Materia Medica" [11] divided red arrow and *Gastrodia elata* as the same drugs, unified using the name of *Gastrodia elata* until now. In the Eastern Han Dynasty, "Shennong Materia Medica Classic" [12] cloud: "*Gastrodia elata* taste spicy, warm". "element ask" [13] cloud: "all the wind fall dazzle, all belong to wood. Therefore, *gastrodia elata* enters the jue Yin meridian and treats various diseases".

Modern pharmacological studies have found that *Gastrodia elata* contains many chemical components, such as gastrodin (gastrodin, GAS), 4-hydroxybenzyl alcohol (p-hydroxybenzyl alcohol, HBA), vanilloalcohol, vanillin, 2- [4-hydroxy3- (4-hydroxybenzyl) benzyl] 4- (4-hydroxybenzyl) phenol (20C), polysaccharide, sterol and organic acid, antiepileptic, anti-convulsant, anti-anxiety, anti-depression, anti-aging, cardiovascular disease, memory improvement, sedative and hypnosis and other pharmacological effects [14]. Among them, gastrodin, vanilla alcohol, vanillin and 20C are the main active ingredients of *gastrodia elata* [15]. However, there are few studies on the treatment of PD with *Gastrodia elata*, so the pathogenesis of PD and the pharmacological effects of *Gastrodia elata* in the study of PD.

3. TREATMENT MECHANISM OF GASTRODIA ELATA IN PD

3.1. Anti-oxidative stress response

Numerous studies have shown that, PD is closely related to the oxidative stress response, In an oxidative stress environment, Cells produce large clusters of reactive oxygen species (reactive oxygen species, ROS), Intracellular mitochondrial damage; And to activate the microglia, The release of the abundant cyclooxygenase-2 (cyclooxygenase-2, COX-2) and ROS, Released tumor necrosis factor (tumor necrosis factor, TNF) also activates the reduced coenzyme oxidase, produce ROS, Increasing the oxidative stress, Causes irreversible damage of dopaminergic neurons [16].

Vanillol has a protective effect on MN 9 D dopaminergic cells to reduce ROS generation and inhibit oxidative stress [17]. Vanilloalcohol effectively improved motor dysfunction [18] in PD rats by reducing TBARS level, increasing SOD, CAT and GPx activity and increasing GSH level. The lipid-soluble component of *Gastrodia elata*, namely *Gastrodia* alcohol extract, can improve the levels of SOD and GSH-Px, reduce the levels of LPO and MDA, and remove the lipid peroxides in the brain to achieve the effect of antioxidant and protection of neuronal cells [19].

20C, a bibenzyl compound in *Gastrodia elata*, reduced the loss of TH-positive neurons in the nigral region, increased the TH protein expression level, ameliorated 6-OHDA-induced oxidative stress damage in PC12 cells, and improved pathological damage [20] in the nigra and striatum of PD model mice.

Nuclear factor red cell 2-related factor 2 (Nrf 2) is a key protein that regulates the cellular redox state in response to oxidative stress. *Gastrodin* can stimulate phosphorylation of ERK 1 / 2, a protein kinase upstream of Nrf 2, to promote Nrf 2 nuclear translocation of Nrf 2, which then activates Nrf 2, increase gene expression controlled by Nrf 2, increase striatal heme oxygenase-1 (HO-1), SOD and GSH levels, reduce LPO levels, prevent oxidative stress and prevent oxygen free radical damage, and then prevent movement disorders in Parkinson's disease [21,22].

Iron death is a necrotic form of death caused by iron-induced accumulation of lipid hydrogen peroxide that involves multiple molecular events and is implicated in Parkinson's disease. *Gastrodin*, a component with strong antioxidant activity, reduces β -secretase expression, alleviates oxidative stress in the hippocampus, reduces ROS generation, downregulates MDA levels, and enhances SOD and CAT activities, and its molecular mechanism links to the inhibition of the PKR / eIF 2 α pathway [23].

3.2. Inhibition of cell apoptosis

Although the pathogenesis of PD is not complete, many theories believe that the factors causing the pathogenesis of PD are diverse and complex, which eventually lead to the degeneration and death of DA neurons in the substantia nigra. The nerve damage in PD patients is mainly apoptosis, and the results of many animal models of PD also confirm that apoptosis is involved in the pathogenesis of PD.

The neuroprotective mechanism of *Gastrodia elata* can be regulated by (A2A-R) / cAMP / PKA / CREB signaling pathway, and adenosine A2A receptor (A2A-R) as a target for therapeutic intervention of neurodegeneration can promote cAMP formation, increase PKA activity, and induce CREB phosphorylation. *Gastrodia* alcohol extract targets A2A-R to prevent serum deprivation-induced apoptosis [24].

Gastrodin has protective effects on SH-SY 5 Y cells, increasing Bcl-2 mRNA expression, reducing Bax mRNA expression, inhibiting caspase-3 activation and PARP splicing, and its mechanism of action is closely related to the inhibition of cell apoptosis [25].

Vanillin ameliorated rotenone-induced motor dysfunction in PD rats, elevated Bcl-2, expression, decreased Bax expression, upregulated Cyt-C expression, and increased Caspase-3, Caspase-8 and Caspase-9 expression [26].

3.3. Anti-inflammatory response

Studies have shown that the onset of PD is closely related to the inflammatory response, and improving the inflammatory response of brain tissue can reduce the body nerve damage, is conducive to neuroprotection, and achieve the intervention effect. Experimental studies have shown that gastrodin can downregulate the IL- β level, upregulate the number of tyrosine hydroxylase-positive cells, inhibit the activation of microglia and dopamine dysfunction, and improve the motor symptoms [27] in rats. Zhang Chengchen experiment, with LPS Wistar rat Parkinson mold, 3 days before the intraperitoneal injection of low, medium and high doses of vanillin, after 24 days, observe rat activity and movement, vanillin can effectively inhibit LPS induced dopaminergic neurons degeneration and microglia excessive activation, indirectly inhibit the occurrence of inflammatory reaction, improve PD rat motor dysfunction [28]. Li Yang's study showed that in [29], Parkinson rats, the expression of TLR 4, NF- κ B p65, p38MAPK decreased in brain tissue, and the levels of downstream inflammatory factors TNF- α , IL-1 β , IL-6 also decreased, and the degree of decline was positively correlated with the dose of gastrodin.

4. SUMMARY

According to our current research and analysis, the effective chemical components of *Gastrodia elata* have good effects in the treatment of Parkinson's disease, which mainly participates in regulating the pathogenesis of PD through anti-oxidative stress, inhibition of cell apoptosis, and anti-inflammatory response, so as to play the role of preventing and controlling PD. In addition, the current research is mainly animal experimental research, and the lack of corresponding clinical research, so further research on *Gastrodia elata* needs to carry out more clinical research to verify the pharmacological mechanism of PD treatment.

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