

Synergistic herb pairings of traditional Chinese medicine: applications and advances in the treatment of Parkinson's disease

Roujia Xie

Zhejiang Pharmaceutical University, Ningbo, China

xierouj@outlook.com

Abstract. Purpose: This study aims to discuss the application value of the synergistic herb pairing concept of traditional Chinese medicine in treating Parkinson's disease and analyses its differences from and potential advantages over conventional Western therapies. From the perspective of synergistic herb pairings, this study takes three classic herb pairings, including the Tianma-and-Gouteng (Gastrodia-and-Uncaria) pairing, the Shudi-and-Yurou (Rehmannia-and-Cornus) pairing, as well as the Shaoyao-and-Gancao (Paeonia-Glycyrrhiza) pairing, as examples to examine and summarize the pairing rules, chemical pharmacology, and clinical efficacy. Results: Through different formula combinations, it is found that mutually reinforcing herb pairings can enhance clinical efficacy. Meanwhile, new active compounds formed during the decoction process, such as 4-Hydroxybenzyl alcohol extracted from *Gastrodia elata* and *Rehmannia glutinosa* polysaccharide produced during the processing of prepared *Rehmannia* root, exhibit stronger anti-neuronal apoptosis and neuroprotective effects. Conclusion: The concept of synergistic herb pairings in traditional Chinese medicine exerts therapeutic effects through multi-target mechanisms, showing unique advantages in the treatment of Parkinson's disease. In particular, it demonstrates clinical value in slowing disease progression and alleviating non-motor symptoms such as sleep disturbances and constipation. By integrating modern extraction technologies with optimized herb pairings, it can further enhance clinical efficacy and improve patients' quality of life.

Keywords: Parkinson's disease, synergistic herb pairing, integrated traditional Chinese and Western medicine, clinical experience of renowned physicians

1. Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, predominantly affecting middle-aged and elderly populations. According to the *China Parkinson's Disease Report*, PD's incidence and prevalence are on the rise against the backdrop of population aging in China. According to data from community-based epidemiological surveys in China, PD prevalence in the population aged 60 years and above is 1.37% [1], imposing a significant burden on society due to the progress course of the disease.

The core pathological features of PD mainly include degeneration and loss of dopaminergic neurons in the substantia nigra of the midbrain, as well as the formation of eosinophilic cytoplasmic inclusions (Lewy bodies) within neurons. These markers are of significant importance for early diagnosis. The typical motor symptoms of PD include resting tremor, muscle rigidity, bradykinesia, and postural and gait disturbances. Dyskinesia, being the most common complication, is characterized by involuntary and uncontrolled abnormal movements. Current Western medical treatments mostly rely on pharmacological interventions. For example, levodopa-based medications (such as carbidopa/levodopa) alleviate motor dysfunction by supplementing dopamine, but their long-term use shows significant limitations. Approximately 25% of patients develop dyskinesia after five years of medication, with the incidence rising to 80% within ten years [2]. Moreover, prolonged treatment often leads to complications such as end-of-dose deterioration and on-off fluctuations, reflecting a decline in therapeutic efficacy. Although amantadine can inhibit dopamine reuptake and antagonize acetylcholine, it cannot halt disease progression [3]. In general, current Western therapies, including pharmacological, surgical, and rehabilitative interventions, can only provide symptomatic relief and cannot reverse the neurodegenerative process, and long-term use is associated with significant adverse effects.

In contrast, synergistic herb pairing in Traditional Chinese Medicine (TCM) demonstrates significant potential in alleviating non-motor symptoms and slowing disease progression. This can be attributed to TCM's advantages of a holistic approach and multiple targets, and the combination with TCM syndrome differentiation and treatment. This study selects three classic herb

pairings for analysis, namely the Tianma-and-Gouteng (Gastrodia-and-Uncaria) pairing, the Shudi-and-Yurou (Rehmannia-and-Cornus) pairing, and the Shaoyao-and-Gancao (Paeonia-Glycyrrhiza) pairing, all included in the top 15 most frequently used Chinese herbs with support from modern pharmacological research [4]. The Tianma-and-Gouteng pairing can be used to treat motor symptoms, relieving tremors and inhibiting internal movement of liver wind. The Shaoyao-and-Gancao pairing can also address motor symptoms by soothing the liver, relieving tension, tonifying the spleen, and alleviating muscle spasms. The Shudi-and-Yurou pairing can be used for non-motor symptoms, primarily to nourish the kidneys and marrow, support yin, and improve sleep. Different herb pairings can address different symptoms of PD, allowing for more individualized treatment, in line with the basic TCM principle of syndrome differentiation and treatment.

2. PD and the holistic treatment concept of synergistic herb pairings

TCM has a long history of understanding PD, which has generally been classified under categories such as tremor disease, tremor syndrome, or trembling. These terms typically refer to involuntary or rhythmic tremors in certain parts of the body. TCM emphasizes syndrome differentiation and treatment according to different pattern types and clinical manifestations. Based on patterns such as qi and blood deficiency, liver and kidney insufficiency, or phlegm-heat with wind agitation, tailored herbal formulas are applied to improve both motor symptoms, including tremor and muscle rigidity, and non-motor symptoms, including constipation, sleep disturbances, and reduced bodily fluids with excessive sweating.

Various decoction combinations have been proposed, with adjustments to prescriptions to slow disease progression in patients with PD and thereby improve their quality of life. Introducing the concept of synergistic herb pairing represents a feasible clinical strategy. Particularly, it is effective in alleviating non-motor symptoms that can further enhance patients' quality of life.

Non-motor symptoms often emerge progressively over time, such as constipation, urinary disturbances, sleep disorders, and reduced bodily fluids with excessive sweating, which can be effectively alleviated by TCM treatment with a holistic perspective. Different decoctions employ different combinations of Chinese herbs, which are often presented in paired forms. These pairings can improve both motor and non-motor symptoms in patients with PD, reflecting the basic TCM principles of mutual enhancement and guiding synergy, constituting the concept of synergistic herb pairing.

3. Classic cases and function mechanism of synergistic herb pairings

3.1. The Tianma-and-Gouteng pairing: targeting motor symptoms by calming internal wind and alleviating tremor

The syndrome differentiation and treatment approach of TCM involves the four comprehensive examinations (inspecting, listening and smelling, questioning, and palpating), and the framework of principle, method, formula, and medicinals. Applying these principles, Academician Wang Yongyan categorized PD into three major syndrome patterns based on clinical case collection. The first is qi and blood deficiency with wind stirring due to blood stasis, which are characterized by a sallow complexion, shortness of breath with reluctance to speak, joint stiffness, hand and foot tremors, a swollen tongue with teeth marks, dark tongue with stasis spots, and a thready, weak pulse. The therapeutic principle is to tonify qi and nourish blood, activate collaterals, and extinguish wind. The second is liver and kidney insufficiency with wind stirring due to blood stasis, which is characterized by insomnia with excessive dreaming, spontaneous sweating and night sweats, dizziness and headache, a dark tongue with little coating, and a wiry, thready pulse. Treatment should focus on extinguishing wind, activating collaterals, and tonifying the liver and kidney. The third is phlegm-heat with wind stirring and phlegm-heat obstructing the lung, which are characterized by dullness and rigidity in movement, fatigue with reluctance to move, chronic cough and dyspnea, expectoration of yellow sputum, a red tongue with yellow greasy coating, and a thready, rapid pulse. The therapeutic principle is to clear and transform phlegm-heat, extinguish wind, and activate collaterals. Three distinct formulas are proposed to address the three syndrome patterns, all using the same medicinal materials, namely Tianma and Gouteng, also known as Gastrodia and Uncaria. To prevent disease exacerbation caused by abrupt withdrawal, all patients discontinued Western medications two weeks after admission. Subsequent treatment was carried out exclusively with TCM, resulting in notable improvement in both motor and non-motor PD symptoms [5].

The Tianma-and-Gouteng Decoction, first recorded in *Zhongyi Neike Zabing Zhengzhi Xinyi* (New Meaning Of Miscellaneous Disease Of Chinese Internal Medicine), is composed of 11 herbs, including Gastrodia and Uncaria. It produces therapeutic effects of calming the liver, extinguishing wind, and unblocking the channels, with the two herbs acting in mutual enhancement for better efficacy. Gastrodia specifically targets liver wind, while Uncaria focuses on clearing liver heat. Used in combination, they address both root and manifestation. Gastrodia, with its neutral and steady nature, anchors internal wind, whereas Uncaria, being cool and dispersing, alleviates constrained heat. When used complementarily, they yield the effects of calming the liver, clearing heat, and extinguishing wind.

In experiments on PD model rats, the Tianma-and-Gouteng Decoction demonstrated a notable inhibitory effect on dopaminergic neuronal apoptosis. The mechanism is associated with upregulation of the B-cell lymphoma-2 (Bcl-2) gene and

suppression of activation of the pro-apoptotic regulator BCL2-Associated X (Bax), thereby inducing an anti-apoptotic effect [6]. Modern pharmacological studies have shown that gastrodin yields p-Hydroxybenzyl Alcohol (HBA) after processing, which possesses favorable lipophilicity and readily crosses the Blood-Brain Barrier (BBB). HBA promotes mitochondrial biogenesis, alleviates mitochondrial dysfunction, and facilitates neuronal repair by activating the SIRT1/PGC-1 α /TFAM signaling pathway [7]. The active constituent rhynchophylline, derived from *Uncaria*, has been shown to modulate the expression of superoxide dismutase, striatal dopamine, and malondialdehyde in the brains of PD model rats, suggesting its neuroprotective potential [8]. Gastrodin and rhynchophylline jointly protect substantia nigra neurons and slow the progression of PD. In the future, it is suggested to optimize active derivatives, such as gastrodin analogs and rhynchophylline oxides, and modify pharmacological properties, thereby achieving more precise regulation of the dopaminergic system, suppression of aberrant neuronal discharges, and anti-neuroinflammatory effects.

3.2. The Shaoyao-and-Gancao pairing: targeting motor symptoms by calming the liver and easing constriction, and relieving muscular spasms

The primary pathogenesis of PD is associated with the internal movement of liver wind. To alleviate muscle rigidity and spasms (often referred to as "tendon tension" in TCM) in PD, the classic herb pair of Shaoyao and Gancao is commonly used in clinical practice. Shaoyao and Gancao are combined in equal proportions, as first mentioned in the Shaoyao-and-Gancao Decoction from Shang Han Lun (Treatise on Febrile and Miscellaneous Disease). Shaoyao, also known as Paeonia, with its sour and cooling properties, enters the liver meridian to nourish the blood, preserve yin, and soften the liver to relieve spasms. Gancao, or Glycyrrhiza, with its sweet and neutral nature, strengthens the middle burner, alleviates tension, and relieves pain. In combination, the two herbs embody the principle of mutual enhancement, pairing sour and sweet flavors to generate yin. Therefore, the combination can nourish yin and blood while relaxing the tendons. Clinical observations suggest that Shaoyao-and-Gancao Decoction, used in conjunction with levodopa, can reduce the required dosage of the Western medication and mitigate its side effects, such as the aforementioned dyskinesia.

Modern pharmacological studies have demonstrated that paeoniflorin, an active component of Paeonia, produces anti-neuroinflammatory and antioxidant effects, thereby protecting dopaminergic neurons; while glycyrrhizin, derived from Glycyrrhiza, has anti-apoptotic properties and modulates neurotransmitter activity. In animal experiments, a rat model of PD was established using 6-hydroxydopamine (6-OHDA) induction. Rats in the TCM group exhibited reduced rotational behavior and shorter traversal times on the balance beam, indicating that the administration of Shaoyao-and-Gancao Decoction significantly improved motor performance in the model rats. Meanwhile, rats in the TCM group showed alleviation of morphological alterations in the substantia nigra and enhanced expression of Tyrosine Hydroxylase (TH), a marker of dopaminergic neurons. Collectively, these findings indicate that Shaoyao-and-Gancao Decoction confers neuroprotective effects on dopaminergic neurons in the substantia nigra of PD model rats [9].

3.3. The Shudi-and-Yurou pairing: targeting non-motor symptoms by tonifying the kidney and marrow, nourishing yin, and promoting sleep

Academician Tong Xiaolin extended the traditional Triple Jiao (burner) theory from the *Huangdi Neijing* (The Yellow Emperor's Classic of Internal Medicine) and reformulated it into the "Four Jiao and Eight Systems." In this framework, the cranial cavity, encompassing vital organs such as the brain and medulla oblongata, and the spinal cavity, encompassing the spinal marrow, are designated as a separate functional domain termed the "Top Jiao." Within this model, the marrow system is considerably overlapped by the neurological system in modern medicine. PD, as a disorder primarily involving motor function, is classified under the marrow system, with its pathological locus understood in TCM as being situated in the top jiao–marrow system. The pathological manifestations are primarily categorized into two types: hyperactivity and deficiency, with hyperactivity corresponding to an excess condition and deficiency corresponding to a deficient state. Patients with PD generally present a deficient pattern. Therefore, treatment focuses on tonifying the kidney and replenishing essence to address this deficiency. In practice, therapy mainly aims to nourish the kidneys and replenish essence, while also transforming phlegm and unblocking the channels as needed. The prescription is typically based on *Dihuang Yinzi* (a traditional Chinese herbal prescription) with appropriate modifications [10].

In this formula, *Rehmannia glutinosa* (Shudi, or prepared Rehmannia root) and *Cornus officinalis* (Yurou, or Cornus fruit) work synergistically to nourish yin, tonify the kidneys, and replenish essence and marrow, exhibiting particularly strong therapeutic effects. The original *Dihuang Yinzi* formula, recorded in *Shengji Zonglu* (Collection of Holy Benevolence), consists of twelve Chinese medicinal herbs, including prepared Rehmannia root and Cornus fruit. *Dihuang Yinzi* has therapeutic effects on brain disorders. In experiments examining the expression of hippocampal Brain-derived Neurotrophic Factor (BDNF) and Stromal Cell-derived Factor 1 (SDF1) in rats, comparisons were made among the treatment group, ischemia group, and normal control group. The results indicated that *Dihuang Yinzi* can upregulate BDNF and SDF1 protein levels, thereby reducing free

radicals, inhibiting neuronal apoptosis, protecting neurons, and enhancing endogenous protective mechanisms, including the proliferation and migration of neural stem cells and neuronal protection [11].

Modern pharmacological studies have shown that processing *Rehmannia glutinosa* into prepared *Rehmannia* root produces polysaccharides that can modulate the Gut-Brain Axis (GBA). There are three main pathways that mediate bidirectional signaling to the brain, including the functional immune regulation pathway, the neuroendocrine pathway, and the vagus nerve pathway, which indirectly influence the sleep-wake cycle [12]. *Cornus officinalis* contains bioactive compounds such as iridoid glycosides and polysaccharides, among which loganin (Log) is one of the iridoid glycosides. In a mouse model of PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), loganin was able to restore the MPTP-induced reduction of striatal dopamine levels and inhibit the decline in TH expression, suggesting its neuroprotective effects [13]. Additionally, polysaccharides from prepared *Rehmannia* root and *Cornus officinalis* can help alleviate PD-related sleep disturbances by modulating the sleep-wake cycle or reducing neuroinflammation, thereby assisting in sleep regulation.

4. Conclusion

The above summary and analysis of three TCM pairings examine the principles of ancient formula compatibility from a holistic perspective and explore pharmacological pathways individually to validate the therapeutic efficacy of these herbal pairings in modern pharmacology. This study investigates individual motor and non-motor symptoms, providing evidence that the listed herbal pairings are effective in treating the disease. A wide range of clinical symptoms of PD has been observed. The appropriate treatment for each symptom should be individually verified, indicating that every symptom should receive a tailored therapeutic approach. This also reflects TCM's characteristic of personalized treatment.

Significant efforts are required for TCM to gain recognition worldwide, and employing modern pharmacological methods is merely one of the approaches, and the commonly used one. Under the guidance of TCM principles, it is imperative to preserve the original compatibility of herbal formulas while integrating advanced modern techniques for further development. This will facilitate the international promotion of TCM research in the future. Motor and non-motor symptoms in patients with PD can be alleviated through syndrome differentiation and treatment in TCM. This study presents three pairs of Chinese medicinal herbs, investigates their mechanisms through modern pharmacological pathways, and systematically addresses the discomforts associated with both motor and non-motor symptoms. The concept of synergistic herb pairing suggests that interactions between herbs can alter their constituents, thereby enhancing their therapeutic efficacy in treating PD. In the future, with further exploration of herbal pairs and optimization of modern formulations using advanced extraction techniques, motor symptoms can be alleviated and non-motor symptoms mitigated on a phase-by-phase basis, ultimately improving clinical outcomes and enhancing patients' quality of life.

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