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Research Progress on Non-motor Symptoms of Parkinson's Disease from the Perspective of the Kidney

FENG Zhenzhen [1#], WANG Yali[2*], DENG Hanfeng[1], WANG Fei[1]

1.The First Clinical Medical College of Shaanxi University of Chinese Medicine,Xianyang,Shaanxi,China;

2.Shaanxi University of Traditional Chinese Medicine,Xianyang ,Shaanxi,China

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Abstract

Parkinson's disease is a complex degenerative disease of the elderly nervous system, and its non-motor symptoms are important factors affecting the life and family of patients with Parkinson's disease. Clinically, constipation, anxiety and depression, sleep disorders and cognitive dysfunction are the main factors, which have a profound impact on patients' daily life and work. Moreover, non-motor symptoms sometimes appear earlier than motor symptoms, so early diagnosis and treatment are required. It has important implications for Parkinson's disease. However, the pathogenesis and pathological process of non-motor symptoms are still unclear. This article aims to provide ideas for the clinical diagnosis and treatment of non-motor symptoms of Parkinson's disease from the perspective of renal treatment.

Keywords: Parkinson；Non-motor symptoms；Dementia；Aypnia；Kidney.

Parkinson's disease (PD) is a common neurodegenerative disease that primarily affects middle-aged and elderly individuals, characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies as the main pathological changes. Currently, there is no clear cure for PD, and treatment mainly focuses on slowing the disease progression. In addition to the well-known motor symptoms, such as tremors, muscle rigidity, increased muscle tone, gait abnormalities, and difficulty turning over, PD patients also commonly experience non-motor symptoms (NMS) such as depression, anxiety, constipation, urinary difficulties, sleep disorders, olfactory dysfunction, autonomic nervous dysfunction, and cognitive and psychiatric disorders, which are also frequently encountered in clinical practice [1].

In recent years, the number of PD patients has gradually increased, and as the disease progresses, symptoms worsen, significantly affecting the patients' daily lives. NMS can appear at various stages of the disease, even before motor symptoms, and they can have a more serious impact on the physical and mental health of patients. Some studies suggest that NMS can substantially affect patients' daily life, work, and family [2]. The prevalence of depression in PD patients ranges from 22% to 91% [3], sleep disorders occur in 60% to 70% of patients [4], gastrointestinal dysfunction can affect up to 80% of patients [5], and about half of long-term PD patients experience consciousness disorders [6]. Yang Min et al. [7] conducted a clinical analysis of non-motor symptoms in 200 PD patients and concluded that kidney deficiency is present throughout the disease's progression and constitutes the majority of the findings.

Currently, traditional Parkinson's disease medications have no specific treatments for NMS and may even exacerbate these symptoms. For example, benztropine (Artane) can lead to insomnia as a side effect. Chinese medicine is gaining increasing importance in treatment due to its holistic approach and fewer side effects. In traditional Chinese medicine, the kidney is regarded as the foundation of innate health, with the function of various organs being closely linked to the kidneys. In NMS, cognitive dysfunction, insomnia, and constipation are all strongly associated with kidney deficiency. This article aims to explore the treatment of PD non-motor symptoms from the perspective of kidney deficiency in traditional Chinese medicine, in order to better serve clinical practice.

Traditional Chinese Medicine Understanding of Non-Motor Symptoms in Parkinson's Disease

Parkinson's disease is classified under the category of "tremor disease" in Traditional Chinese Medicine (TCM). There is a wealth of documentation in TCM literature regarding tremor diseases. Although the term "tremor disease" was not explicitly mentioned in the Huangdi Neijing (Yellow Emperor's Inner Canon) during the Qin and Han dynasties, similar descriptions can be found. In the Su Wen: Mai Yao Jing Wei Lun (The Essential Principles of Pulse), it states: "The bones are the storehouse of marrow; when unable to stand for long, they tremble and shake upon walking, and the bones will be exhausted." The Bian Que Xin Shu (The Heart of Bian Que) records a condition known as "hand tremor disease" and proposes that its pathogenesis is primarily due to "true essence deficiency." In the Tang Dynasty, Sun Simiao's Bei Ji Qian Jin Yao Fang (Emergency Prescriptions Worth a Thousand Gold) mentions: "Accumulated years of wind and spasm, the body trembling like a cicada's wings, unable to turn, with a stiff gait, unable to maintain control," which is similar to the bradykinesia and gait disturbances seen in Parkinson's disease. It was not until the Ming and Qing Dynasties that Wang Kentang, in his Zheng Zhi Zhun Sheng: Za Bing Zhen Zhen (The Essentials of Treating Miscellaneous Diseases), stated: "Tremor is shaking; vibration is movement," thereby clearly

defining the term "tremor syndrome," which had a profound influence on later generations of medical practitioners.

Non-motor symptoms (NMS) in TCM do not have a precise corresponding disease name. Based on the symptoms, they are mainly categorized under "dementia," "insomnia," "constipation," and other related conditions.

The Relationship Between the Kidney and Non-Motor Symptoms of Parkinson's Disease

Tremor syndrome is a condition characterized by both deficiency of the root and excess of the branch. Although different practitioners have varying interpretations of the root deficiency, there is a consensus regarding the liver and kidney deficiency as the root cause. Many renowned classical texts provide detailed records of this concept. In the Su Wen: Wu Yun Xing Da Lun (The Great Treatise on the Five Movements and Six Qi), it is stated: "The kidney generates marrow, and the marrow nourishes the liver," which presents the preliminary understanding that the liver and kidney share a common origin. Although the disease is located in the body's meridians, it is closely linked to the kidneys. The liver and kidney share an origin, with kidney essence nourishing liver yin. The liver stores blood, and the body uses yang to support yin. When the yin and blood are abundant, the tendons and meridians are nourished, and the body's motor functions are healthy. If water fails to nourish wood, the liver and kidney are not in harmony, and the marrow is depleted, it is easy for deficiency to manifest as tremors [8].

Zheng Zhi Zhun Sheng: Za Bing (The Essentials of Treating Miscellaneous Diseases) also mentions that tremor syndrome is rare in young adults but common in the elderly. The underlying reason is that older individuals experience kidney essence deficiency, insufficient yin blood, and a lack of kidney water to nourish the liver wood. The liver meridians lose nourishment, and internal wind begins to manifest. Therefore, the root cause of tremor syndrome is kidney essence deficiency.

1 The Kidney and Dementia

Kidney deficiency and marrow depletion are the primary pathogenesis for tremor syndrome and dementia. The kidney stores essence, which is the root of the five organs and shares an origin with the liver. When kidney water is deficient and fails to nourish wood, it leads to disharmony between the liver and kidney, causing deficiency in the lower body and shaking in the upper body, manifesting as tremors. In tremor syndrome, especially in the elderly, the root cause is the lack of water to control fire, leading to the emergence of liver wind, with the fundamental issue being kidney essence deficiency. Xu Chunfu, in the Gu Jin Yi Tong Da Quan (Complete Compendium of Ancient and Modern Medicine) [9], pointed out that kidney deficiency can lead to soreness and weakness in the lower back and knees, and tremors when walking. If kidney essence is

depleted, it is easy for essence to fail to transform into blood, resulting in insufficient blood to nourish the liver, which leads to the excessive rise of liver yang, creating internal wind that disrupts the meridians and causes tremors.

The Su Wen: Ping Ren Qi Xiang Lun (The Treatise on Healthy Qi and Vitality) states: "The kidney stores the qi of the bones and marrow." The Su Wen: Wu Zang Sheng Cheng Pian (The Treatise on the Formation of the Five Organs) mentions, "All marrow belongs to the brain." The Ling Shu: Hai Lun (The Spiritual Pivot: The Sea of Marrow) further states, "The brain is the sea of marrow." Later medical practitioners distilled the concept that kidney essence transforms into qi, which then ascends to nourish the brain. The kidney governs the bones and marrow, and the marrow ascends to the brain, which is the sea of marrow. If the sea of marrow is insufficient, the spirit is not nourished, and the body loses its regulation, leading to symptoms like dullness and cognitive impairment.

Some researchers have proposed the "kidney-brain axis" theory, suggesting that the kidney and brain are interconnected. The kidney generates marrow, which ascends to nourish the brain. When the brain is nourished, it is clear and bright, and when the brain marrow is full, thinking becomes sharp and clear [10]. Han Cheng [11] studied the decline of learning and memory function in aging through kidney-tonifying and brain-nourishing methods, providing a theoretical basis for the kidney-brain integration theory. The Ling Shu: Jing Mai (The Spiritual Pivot: The Meridians) states: "At birth, essence is formed first; when essence is formed, marrow is produced, and the brain is nourished." In the process of cognitive decline, kidney deficiency and marrow depletion are present throughout the disease's progression. The onset is rooted in prolonged illness or aging, where kidney essence gradually declines, and the sea of marrow becomes increasingly depleted, leading to a loss of nourishment for the spirit and a decline in brain function [12].

In the Qing Dynasty, Wang Qingren, in his Yi Lin Gai Cuo: Nao Sui Shuo (Correction of Medical Errors: The Theory of Brain Marrow), stated: "The spiritual faculty and memory are not located in the heart, but in the brain... Children who have no memory have insufficient brain marrow; the elderly with memory loss have gradually depleted brain marrow." This emphasizes the role of the brain in cognition and questions the traditional notion that the heart is the center of spirit and mental activities, highlighting the brain's role in memory and cognition. The Yi Xue Ru Men (Introduction to Medicine) states: "The brain is the sea of marrow, and all marrow belongs to the brain... Marrow is governed by the kidney," pointing out that the brain's marrow is generated by the kidney. The Yi Jing Jing Yi (Essence of Medical Canon) says: "The reason we do not forget things is because of this memory, which is stored in kidney essence. By tonifying the kidney, essence is generated and transformed into marrow, which is stored in the brain," clearly stating that human memory and cognition originate from kidney essence.

2 The Kidney and Insomnia

Parkinson's disease (PD) is a prolonged condition that gradually depletes the kidneys. The kidney is the residence of water and fire, and the foundation of the yin and yang of the organs. Kidney yang is the root of all yang, and when kidney yang is deficient, its warming function declines, preventing it from nourishing the heart fire. As a result, the heart spirit is deprived of nourishment, water and fire are not balanced, and the heart and kidneys fail to communicate, leading to insomnia. The Ling Shu: Ying Wei Sheng Hui Pian (The Spiritual Pivot: The Discussion of Nutritive and Defensive Qi) states: "In the young, the qi and blood are abundant... hence, they are alert during the day and sleep soundly at night. In the elderly, the qi and blood are weakened... hence, they are not alert during the day and have poor sleep at night." Kidney yang is the fire of the life gate, the root of the body's yang energy. The Ling Shu also states: "When yang enters yin, sleep occurs; when yang exits yin, wakefulness occurs," highlighting the close relationship between sleep quality and yang energy.

The Ling Shu: Da Huo Lun (The Spiritual Pivot: Great Questions) states: "When the defensive qi does not enter yin and stays in yang, yang becomes abundant; if it does not enter yin, then yin becomes deficient, and the eyes cannot close." Those who can sleep do so because the yang energy is hidden, while those who cannot sleep suffer from the excessive rising of yang energy. With the changes in modern life, irregular eating and lifestyle habits, and a preference for cold environments, kidney depletion becomes inevitable over time. This leads to a gradual decline in kidney yang, and eventually to insomnia or even total lack of sleep.

The Su Wen: Sheng Qi Tong Tian Lun (The Treatise on the Transmission of Vital Qi) states: "Yang qi, when sufficient, nourishes the spirit." Insufficient yang qi leads to a condition where the person feels neither fully asleep nor fully awake, with symptoms of mental fatigue, which is characteristic of a typical lesser yin condition. The kidney stores essence, which is the root of life, the foundation of the five organs. The sufficiency of kidney essence directly impacts the vitality of the human body. Most patients with tremor syndrome are elderly and physically weak, with insufficient kidney essence, deficient qi and blood, and a gradual decline in essence. As blood fails to nourish the heart, the source of qi and blood becomes insufficient, leading to insomnia.

3 The Kidney and Constipation

During the aging process, kidney qi deficiency is one of the earliest manifestations. In PD patients, due to aging or prolonged illness, kidney deficiency and true yin depletion occur, which can affect the liver yin and result in liver meridian malnourishment, thus triggering the disease. Kidney yang deficiency leads to the spleen's inability to warm, causing a lack of qi and blood transformation, which results in the loss of nourishment for the tendons and meridians, manifesting as tremors and rigidity. Zhang Jingyue stated: "The kidney governs the lower jiao and opens to the yin... When kidney qi transforms, both urination and defecation are smooth; when kidney qi does not transform, both are blocked." He also said, "The two yin govern the two

excretions, and the master is the kidney," clearly outlining the kidney's role in controlling excretion. The kidney governs the bones and generates marrow. If the kidney is deficient and the marrow is depleted, with insufficient fluids, defecation becomes difficult. In PD, when constipation occurs, its origin lies in the kidney, and its manifestation is in the large intestine [13].

The Su Wen: Wu Zang Bie Lun (The Treatise on the Five Organs) states: "The gate of the soul also acts as a governor for the five organs," indicating that the opening and closing of the gate is closely related to the kidney. If kidney qi is abundant, the organs and their functions are in harmony, and the gate opens and closes in an orderly manner. However, when kidney qi is deficient, the gate's function is impaired, and waste is unable to be eliminated. Gu Jin Yi Che points out: "In people with kidney deficiency, urination is often dribbling, and defecation becomes dry and difficult... more severe than constipation, the difficulty in defecation is caused by a lack of essence and blood, resulting in hard stools; urination becomes bloated and uncomfortable, with qi not transforming and the body deteriorating." Kidney essence deficiency leads to insufficient qi and blood transformation, causing the intestines to lose moisture and making defecation difficult.

When the kidney is deficient, the marrow sea loses nourishment, leading to brain malnourishment, disordered organ functions, and irregular intestinal activity, which leads to constipation. At the same time, the nourishment and warming functions of kidney yin and kidney yang significantly determine the physiological function of the five organs. If kidney yang is insufficient, the life gate fire weakens, cold accumulates internally, and its warming and driving functions are impaired, resulting in weakened gastrointestinal motility and difficult defecation. If kidney yin is insufficient, there is no water to nourish the intestines, leading to dryness and constipation [14]. From this, it is clear that kidney essence, kidney yin, and kidney yang all have a close relationship with constipation.

Modern Application of Kidney-based Treatment for Non-Motor Symptoms of Parkinson's Disease

1 Improving Dementia

Kidney deficiency and marrow depletion—tonifying the kidney, replenishing essence, and nourishing marrow. Fan Xiaoge [15] used a modified version of Liuwei Dihuang Decoction combined with Pramipexole to treat Parkinson's disease with mild cognitive impairment due to kidney deficiency and marrow insufficiency. After treatment, the experimental group's Webster Drug Treatment Assessment Score was lower than the control group's, indicating that the method of tonifying the kidney and replenishing essence can effectively improve the patients' cognitive function. Zhu Bin [16] and others used Dihuang Yinzi combined with rehabilitation therapy to improve cognitive impairment in PD patients. The results showed that the cognitive

function, assessed using the Mini-Mental State Examination (MMSE) and Activities of Daily Living (ADL) scale, both improved, with a total effective rate of 82.93%, higher than the 58.54% of the control group. The formula mainly includes Shu Di Huang, Jiu Yu Rou, Rou Cong Rong, and Ba Ji Tian, which together play a role in both nourishing Yin and Yang. Wang Yali [17] proposed through years of research that kidney deficiency and toxic damage is the final result of tremor syndrome. The brain, as the repository of essence, is invaded by turbidity and toxins, causing dysfunction in the brain and leading to symptoms like dementia and memory loss. Wang recommended a detoxification formula to treat this condition, which involves tonifying the kidney, replenishing marrow, activating blood circulation, and detoxifying. The formula includes Shu Di Huang to tonify the kidney and nourish the marrow. Since Yin and Wei (nourishment and toxin clearing) are mutually related, the formula also includes Bai Shao to nourish Yin and blood, and clinical treatment has shown that this method can improve symptoms such as dementia and memory loss to a certain extent. Deckwerth [18] and others found that anti-apoptotic protein Bcl-2 and pro-apoptotic protein Bax play important roles in neuronal apoptosis. Li Yu [19] and others demonstrated that Shu Di Huang can inhibit cell apoptosis, thereby protecting the activity of dopaminergic neurons, which may be related to the regulation of Bcl-2, Bax/Bcl-2, and Caspase-3 protein expression levels. Bai Shao total glycosides can improve dementia in rats by elevating hippocampal Bcl-2 levels and reducing Bax and Caspase-3 protein expression [20].

2 Improving Insomnia

The treatment of Parkinson's disease (PD) non-motor symptoms from a kidney perspective mainly involves tonifying the kidney, replenishing marrow, and harmonizing the heart and kidney. The treatment can be adjusted according to the patient's clinical condition, and may also include methods for activating blood circulation and removing blood stasis. Song Jie [21] and others developed a formula called Yishen Ningxin Decoction to treat PD patients with kidney essence deficiency and heart-kidney disharmony. They found that the treatment group showed a significant reduction in the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) scores, with notable improvement in sleep quality. The formula includes Gui Ban (Tortoise Shell) and Lu Jiao Jiao (Deer Antler Gel) as the chief herbs, aiming to warm and tonify the liver and kidney, nourish essence, and enrich the blood. It is also combined with Long Gu (Dragon Bone) and Mu Li (Oyster Shell) to anchor Yin and calm the spirit. Chen Songsheng [22] and others used a method of tonifying the kidney and activating blood circulation to treat 70 PD patients and found that the treatment not only improved the motor symptoms of PD, but also significantly reduced the incidence of non-motor symptoms such as insomnia and fatigue compared to the control group. The formula includes He Shou Wu (Polygonum multiflorum) to nourish the kidney, Shu Di Huang (Rehmannia) to replenish essence, and Yi Zhi Ren (Alpinia) to calm the spirit, with all three herbs entering the kidney meridian as the chief herbs. It is combined with Dan Shen (Salvia), Chuan Xiong (Chuanxiong), Shan Zha (Hawthorn), and Yin Xing Ye (Ginkgo Leaf) as assistant herbs to move Qi, break blood stasis, and activate blood circulation, assisting the chief herbs in benefiting the kidney and clearing the mind. Modern

pharmacological research [23] has shown that the essential oils of Yi Zhi Ren can decrease glutamate (Glu) content in the brain cortex and hypothalamus of rats, while significantly increasing gamma-aminobutyric acid (GABA) content, thus exerting calming and brain-boosting effects. Ye Qing [24] and others found that using Zishen Pingzhen Decoction not only improved the life and motor functions of PD patients, but also significantly alleviated sleep disturbances and depressive symptoms.

3 Improving Constipation

Constipation is one of the most common non-motor symptoms of Parkinson's disease (PD), often appearing even before motor symptoms. Jichuan Decoction, from the Jingyue Quanshu, uses Rou Cong Rong (Cistanche) as the chief herb. Rou Cong Rong is sweet, salty, and warm in nature, entering the kidney meridian. It warms the kidney, replenishes essence, and moistens the intestines. Together with Dang Gui (Angelica) and Niu Xi (Achyranthes), it supplements the kidney, invigorates blood, moistens dryness, and promotes bowel movement, making it an effective formula for treating this condition. Chen Dachao [25] treated PD patients with constipation using Jichuan Decoction and found a total effective rate of 98%, with significant reduction in constipation scores. Xu Chaohui [26] and others discovered that Rou Cong Rong contains six active components: β-sitosterol, arachidonic acid, dehydrated lactone, methyl eugenol, quercetin, and maplinoid. These components may treat Parkinson's disease by protecting mitochondrial function, regulating autophagy, and inhibiting neuroinflammatory responses. The chief herb Niu Xi has been confirmed in modern pharmacological studies to exert neuroprotective effects by inhibiting hippocampal neuronal damage caused by N-methyl-D-aspartate (NMDA) in injury models [27]. Wang Kaijun [28] and others used a combined method of tonifying the kidney and nourishing Yin with lactulose to treat PD-related constipation. The clinical symptoms and constipation scores improved significantly, with an effective rate of 83.64%, higher than the control group at 63.64%. The degree of constipation is closely related to the prevalence of PD.

4 Improving Other Symptoms

Wu Tianchen [29] and others found that using a method of warming the kidney and nourishing the liver significantly improved drooling symptoms in PD patients compared to the control group. This method also addressed urinary, sleep, and gastrointestinal symptoms. Chen Lu [30] and others observed the effects of tonifying the kidney and replenishing marrow in treating non-motor symptoms of PD in kidney essence deficiency patients. They found that the treatment group had lower scores on the Parkinson's Social Disability Scale, Fatigue Scale, and Epworth Sleepiness Scale, with a total effective rate of 90%, significantly higher than the control group at 66.67%. This suggests that the method of tonifying the kidney and replenishing marrow can effectively improve fatigue, daytime sleepiness, and sleep disorders in PD patients with kidney deficiency. The Expert Consensus on Clinical Diagnosis and Treatment of Parkinson's Disease in Traditional Chinese Medicine [31] proposed that the primary formula for treating PD

with kidney Yin deficiency is Zhi Yin Xi Feng Decoction, which mainly consists of Shu Di Huang (Rehmannia), He Shou Wu (Polygonum multiflorum), Tian Ma (Gastrodia), and Gui Jia (Tortoise Shell). The formula nourishes Yin and anchors Yang, while He Shou Wu and Shu Di Huang replenish kidney essence and generate blood. This formula has observed therapeutic effects on the emotional, cognitive, and memory aspects of PD patients with kidney Yin deficiency and blood deficiency [32].

5 Non-Pharmacological Treatment of PD Non-Motor Symptoms

Traditional Chinese medicine (TCM) non-pharmacological treatments, with their unique advantage of minimal side effects, have been widely applied in clinical practice. Among them, acupuncture has become the focus of recent TCM non-pharmacological therapies. Acupuncture has the effects of harmonizing Qi and blood, unblocking meridians, and regulating the body. Studies have proven that acupuncture can effectively inhibit neuroinflammatory responses and oxidative stress, thus protecting dopaminergic neurons [33-34]. In animal studies, acupuncture has been shown to improve sleep by increasing GABA levels and enhancing the expression of GABA (A) receptors [35]. In addition to acupuncture, Xu Yiban [36] used a modified Liu Wei Di Huang Wan to treat PD patients with liver and kidney Yin deficiency, and found that the treatment group had significant improvement in the Parkinson's Disease Rating Scale, Sleep Quality Scale, and Autonomic Nervous Function Scale scores compared to the control group. This suggests that this method can effectively alleviate both motor and non-motor symptoms of PD and improve clinical efficacy.

Conclusion

Traditional Chinese medicine (TCM) has distinct advantages in treating non-motor symptoms of Parkinson's disease (PD). Kidney deficiency and marrow depletion play a key role throughout the progression of the disease. By integrating TCM diagnostic and therapeutic theories with modern medical research advancements, this approach not only deepens our understanding of TCM classical theories but also offers more evidence-based treatment strategies for PD non-motor symptoms. TCM formulas have multi-mechanism and multi-target advantages. Among non-pharmacological TCM therapies, acupuncture has the most significant effects, stimulating the nervous system. A combination of pharmacological and non-pharmacological treatments can promote more comprehensive and rapid improvement in PD non-motor symptoms. However, due to a limited number of case studies and insufficient research, further exploration of the mechanisms underlying the treatment of PD non-motor symptoms from a kidney perspective is necessary, requiring more experimental studies to reveal the finer details of related mechanisms.

References

[1] Neurology Branch of the Chinese Medical Association, Parkinson's Disease and Movement Di

sorder Group, Neurology Branch of the Chinese Medical Doctor Association, Parkinson's Disease and Movement Disorder Group. Chinese Parkinson's Disease Treatment Guidelines (4th Edition) [J]. Chinese Journal of Neurology, 2020, 53(12): 14. DOI: 10.3760/cma.j.cn113694-20200331-00233.

[2] Verónica Cabreira, Massano J .[Parkinson's Disease: Clinical Review and Update][J].Acta medica portuguesa, 2019(10).DOI:10.20344/AMP.11978.

[3] Smeltere L , Kuz?Ecovs V ,Erts, Renārs.Depression and social phobia in essential tremor and Parkinson's disease[J].Brain and Behavior, 2017, 7(9):e00781.DOI:10.1002/brb3.781.

[4] Falup-Pecurariu C , Diaconu T .Sleep Dysfunction in Parkinson's Disease - ScienceDirect[J].International Review of Neurobiology, 2017, 133(1):719-742.DOI:10.4997/JRCPE.2017.108.

[5] Kunshan,Zhaoqin,Wang,et al.Efficacy of electroacupuncture for the treatment of constipation in Parkinson's disease: study protocol for a multicentre randomised controlled trial.[J].BMJ open, 2019, 9(11):e029841.DOI:10.1136/bmjopen-2019-029841.

[6] Kumar N .The Sydney Multicenter Study of Parkinson's Disease: The Inevitability of Dementia at 20 years[J].Yearbook of Neurology and Neurosurgery, 2009, 2009:94-95.DOI:10.1016/S0513-5117(09)79027-1.

[7] Yang Min. Study on the TCM Syndrome Characteristics of Non-Motor Symptoms in Parkinson's Disease Patients [D]. Guangzhou University of Chinese Medicine, 2024-04-10.

[8] Liu Zhan, Wang Yali, Zhu Sijia, et al. Wang Yali's Staging Treatment of Parkinson's Disease [J]. Journal of Changchun University of Chinese Medicine, 2020, 36(3): 3.

[9] Xu Chunfu (Ed.). Complete Works of Traditional Chinese Medicine from Ancient to Modern. Volume II [M]. People's Medical Publishing House, 1991.

[10] Zou Jianpeng, Bi Hongyan, Peng Wei, et al. Establishment of TCM Rehabilitation Model for Multiple System Atrophy Based on Brain-Kidney Axis Theory [J]. Shandong Journal of Traditional Chinese Medicine, 2019(1): 14-17.

[11] Han Cheng. Study on the Mechanism of Brain Dysfunction in Aging and Memory Decline from the "Kidney-Brain Connection" [D]. Shandong University of Traditional Chinese Medicine, 2019.

[12] Wang Jing, Yu Yueyi, Fu Dongting, et al. TCM Etiology, Pathogenesis, and Syndrome Differentiation Treatment of Lewy Body Dementia [J]. Journal of Jilin Traditional Chinese Medicine, 2021, 41(5): 4. DOI: 10.13463/j.cnki.jlzyy.2021.05.001.

[13] Liu Xinyu, Yue Lifeng, Ma Pei, et al. Treatment of Parkinson's Disease-Related Constipation Based on Kidney Theory [J]. Chinese Journal of Basic Medicine in Traditional Chinese Medicine, 2022, 28(10): 3.

[14] Long Feng, Luo Chunxiu, Lei Xiao, et al. Research Progress on Kidney Tonifying Methods for Treating Constipation [J]. Xinjiang Journal of Traditional Chinese Medicine, 2023(5): 110-114.

[15] Fan Xiaoge. Clinical Observation of 37 Cases of Parkinson's Disease with Mild Cognitive Impairment Treated with Integrated Traditional Chinese and Western Medicine [J]. Chinese Ethnic Folk Medicine, 2021.

[16] Zhu Bin, Wang Ce, Xu Qingqing. Clinical Study on the Combination of Dihuang Yinzi and Cognitive Rehabilitation Therapy for Mild Cognitive Impairment in Parkinson's Disease [J]. New Traditional Chinese Medicine, 2021, 53(17): 4. DOI: 10.13457/j.cnki.jncm.2021.17.009.

[17] Wang Qi, Zhu Sijia, Liu Zhan, et al. Clinical Experience of Wang Yali in Treating Parkinson'

s Disease from Kidney Deficiency and Toxic Damage [J]. World Journal of Integrated Traditi onal and Western Medicine, 2020, 15(6): 1038-1041.

[18] Deckwerth T L , Elliott J L , Knudson C M ,et al.BAX is required for neuronal death after t rophic factor deprivation and during development.[J].Neuron, 1996, 17(3):401-411.DOI:10.1016/S 0896-6273(00)80173-7.

[19] Li Yu, Wang Dou, Li Tao, et al. Research Progress on the Pharmacological Mechanism of Sh udihuang in Treating Parkinson's Disease [J]. Chinese Journal of Experimental Formulae, 202 2.

[20] Liao Xiangping, Zhang Ziliang, Liu Chenli, et al. Effect and Mechanism of Total Glycosides of Paeonia Lactiflora on Cognitive Function in Vascular Dementia Rats [J]. Science and Tech nology Vision, 2019, (13): 186-187. DOI: 10.19694/j.cnki.issn2095-2457.2019.13.088.

[21] Song Jie, Yang Yanfu. Clinical Study on the Treatment of Parkinson's Disease Combined wit h Sleep Disorders Using Yishen Ningxin Decoction with Adjustments [J]. Shaanxi Traditional Chinese Medicine, 2021, 042(006): 747-750. DOI: 10.3969/j.issn.1000-7369.2021.06.017.

[22] Chen Songsheng, Ma Qiaoya, Wang Ruili, et al. Clinical Study on the Treatment of Parkinso n's Disease with Kidney-Tonifying and Blood-Activating Formula [J]. Chinese Medical Herald, 2014, 11(22): 4. DOI: CNKI:SUN:YYCY.0.2014-22-030.

[23] Cui Kaiyu, Wang Ping, You Qiuyun. Effects of Yizhiren Volatile Oil on Amino Acid Neurotr ansmitter Content and Its Receptor Expression in Brain Tissue after REM Sleep Deprivation Recovery in Rats [J]. Chinese Journal of Experimental Formulae, 2013(4): 223-227.

[24] Ye Qing, Zhou Jie, Yuan Canxing. Effect of Zishen Pingzhan Decoction on Parkinson’s Disea se with Depression and Sleep Disorders [J]. Guangdong Medical Journal, 2014, 35(14): 4. DOI: 10.3969/j.issn.1001-9448.2014.14.052.

[25] Chen Dachao. Clinical Efficacy of Modified Jichuan Decoction in Treating Constipation in Par kinson's Disease Patients [J]. Systematic Medicine, 2019, 4(4): 3. DOI: CNKI:SUN:XTYX.0.2019-04-001.

[26] Xu Chaohui, Zou Yuan, Chen Ying, et al. Exploring the Mechanism of Rhemuria in Treating Parkinson's Disease Based on Network Pharmacology and Molecular Docking [J]. Food Indu stry Technology, 2022, 43(9): 10. DOI: 10.13386/j.issn1002-0306.2021100009.

[27] Tian Shuo, Miao Mingsan. Discussion on the Chemical, Pharmacological, and Application Ch aracteristics of Achyranthes Bidentata [J]. Journal of Traditional Chinese Medicine, 2014, 29(8): 3.

[28] Wang Kaijun. Clinical Study on the Combined Use of Kidney-Tonifying, Yin-Nourishing, and Laxative Formula with Lactulose in Treating Constipation in Parkinson’s Disease: A Rando mized Parallel Controlled Trial [J]. Practical Journal of Traditional Chinese Internal Medicine, 2019(1): 4. DOI: 10.13729/j.issn.1671-7813.Z20180017.

[29] Wu Tianchen, Liang Yan, Zou Liping. Clinical Observation on the Treatment of Salivation an d Other Non-Motor Symptoms in Parkinson's Disease Using Kidney-Warming and Liver-Nou rishing Formula [J]. Shanxi Journal of Traditional Chinese Medicine, 2023, 39(6): 30-33.

[30] Chen Lu, Wei Yifo, Liu Ming, et al. Effect of Kidney-Tonifying and Marrow-Nourishing Met hod on Non-Motor Symptoms in Parkinson’s Disease Patients with Kidney Deficiency and M arrow Deficiency Syndrome [J]. Journal of Traditional Chinese Medicine, 2019(3): 4. DOI: CN KI:SUN:ZZYZ.0.2019-03-012.

[31] Luo Xiaodong, Li Zhe, Zhu Meiling, et al. Expert Consensus on Clinical Diagnosis and Treat

ment of Parkinson’s Disease (Tremor-Parkinsonism) in Traditional Chinese Medicine [J]. Journ al of Traditional Chinese Medicine, 2021, 62(23): 8. DOI: 10.13288/j.11-2166/r.2021.23.017.

[32] Wen Xiaodong, Ren Ding, Wang Chunling, et al. Effect of Parkinson's Disease No. 2 Formul a on the Quality of Life in Early Parkinson's Disease Patients [J]. Chinese Journal of Traditio nal Chinese Medicine, 2013, 28(10): 5. DOI: CNKI:SUN:BXYY.0.2013-10-027.

[33] Feng Wandi, Wang Yuanyuan, Gai Cong, et al. Effects of Acupuncture Combined with Mad opar on Dopamine Neurons and Protein Kinase B Expression in Parkinson's Disease Mice [J]. Journal of Beijing University of Traditional Chinese Medicine, 2017(3). DOI: 10.3969/j.issn.100 6-2157.2017.03.012.

[34] Sun Xiaobei, Sun Zhongren, Yin Hongna, et al. Research Progress on the Mechanism of Acu puncture in Treating Parkinson's Disease [J]. Acupuncture Research, 2021, 46(11): 973-979. ME DLINE ISTIC PKU CSCD, 2021: National Key R&D Program Project. DOI: 10.13702/j.1000-060 7.201177.

[35] Zhou Yanli, Gao Xiyan, Wang Peiyu, et al. Effect of Acupuncture at Different Acupoints on Hypothalamic γ-Aminobutyric Acid and GABA-A Receptor Expression in Insomnia Rats [J]. Acupuncture Research, 2012, 37(4): 6. DOI: CNKI:SUN:XCYJ.0.2012-04-010.

[36] Xu Yiban. Effect of Modified Liuwei Dihuang Pills Combined with Topical Chinese Medicine Ointment on Liver-Kidney Yin Deficiency Type Parkinson’s Disease and Its Impact on Moto r and Non-Motor Symptoms [J]. China Medical Guide, 2019, 17(31): 2. DOI: CNKI:SUN:YYX K.0.2019-31-140.