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Promising Role of Natural Herbal Medications in Parkinson's Disease or as a Supplementation to Existing Therapy- A Systemic Review

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ABSTRACT:Parkinson'sDisease (PD) is a neurodegenerative disorder characterized by motor symptoms, including tremors, rigidity, and bradykinesia. It affects millions of people worldwide, with a prevalence of about 1% in the elderly population. Despite extensive research, there is no cure for PD, and current therapies aim to alleviate the symptoms rather than reverse the disease process. However, the long-term use of conventional medication can cause adverse effects and may not be sufficient to manage all the symptoms. Therefore, there has been growing interest in natural herbal medications as an alternative or complementary therapy for PD. Many plant-based compounds have shown potential neuroprotective and anti-inflammatory effects that could slow down or even prevent the progression of PD. In this review article, we will discuss the promising role of natural herbal medications in PD and their potential mechanisms of action.Curcumin is a polyphenolic compound found in turmeric, which has been shown to have anti-inflammatory and antioxidant properties. Studies have suggested that curcumin may be able to protect dopaminergic neurons and reduce the production of alpha-synuclein, a protein that accumulates in the brains of PD patients. Additionally, curcumin has been found to improve motor function and reduce oxidative stress in animal models of PD. Another promising natural compound is resveratrol, a polyphenolic compound found in grapes and red wine. Resveratrol has been shown to protect dopaminergic neurons from oxidative stress and reduce inflammation in the brain. Animal studies have demonstrated that resveratrol can improve motor function and prevent the loss of dopaminergic neurons in PD models. Ginkgo biloba is a popular herbal supplement that has been used for centuries in traditional Chinese medicine. It contains several bioactive compounds, including flavonoids and terpenoids, that have antioxidant and anti-inflammatory effects. Several studies have reported that Ginkgo biloba extract can improve motor function and reduce oxidative stress in animal models of PD. Ashwagandha, also known as Indian ginseng, is a medicinal herb that has been used in Ayurvedic medicine for centuries. It contains several bioactive compounds, including withanolides, that have been shown to have neuroprotective and anti-inflammatory effects. Animal studies have suggested that ashwagandha can improve motor function, reduce oxidative stress, and prevent the loss of dopaminergic neurons in PD models. Other natural compounds that have shown potential in PD include green tea, which contains catechins that have antioxidant and anti-inflammatory effects, and Bacopa monnieri, which contains bacosides that have neuroprotective properties. However, further studies are needed to confirm their efficacy and safety in PD.In addition to their potential neuroprotective and anti-inflammatory effects, natural herbal medications may also have fewer adverse effects than conventional medication. However, it is important to note that natural compounds can also interact with other medications and may not be safe for everyone. Therefore, it is essential to consult a healthcare professional before taking any herbal supplements, especially if you have a pre-existing medical condition or are taking prescription medication.
In conclusion, natural herbal medications have shown promise as a potential therapy for PD, with several compounds demonstrating neuroprotective and anti-inflammatory effects. However, further studies are needed to confirm their efficacy and safety in human subjects. Additionally, the optimal dosage, duration, and formulation of these natural compounds need to be determined to maximize their therapeutic potential. Nevertheless, the use of natural herbal medications in PD represents an exciting area of research and could provide new avenues for the management of this debilitating disease.

INTRODUCTION

James Parkinson initially identified Parkinson's disease (PD), a chronic neurodegenerative condition of the central nervous system (CNS) that primarily affects the motor system [1, 2]. According to epidemiology, the prevalence of PD in European countries is between 5 and 346/100,000 person-years, and it rises five- to ten-fold in populations between 60 and 90 years old [2, 3]. Tremor, rigidity, slowness of movement, trouble walking, autonomic dysfunction, pain, and cognitive deterioration in the latter stages are common clinical symptoms in PD patients [4-5]. Intraneuronal protein deposits known as Lewy bodies, aggregation of cytoplasmic inclusions containing insoluble -synuclein, and dopaminergic neuron loss in the substantia nigra pars compacta (SNpc) of the midbrain are the most common pathological findings in the brain tissues of PD patients [6]. It has long beenknown that the pathophysiology of PD is influenced by oxidative stress, decreased mitochondrial function, inflammation, apoptosis, dysfunctional

proteolysis, and loss of neurotrophic factors [7]. Levodopa and dopamine replacement, two common treatments for Parkinson's disease, only partially relieve symptoms but have numerous serious side effects, including hallucinations and uncontrollable movements [8, 9]. Hence, PD disease-modified treatment is not yet accessible.Due to their multilayer function properties and extraordinary performance (in some situations) with fewer side effects, herbal medicines—a key component of traditional medicine—have steadily gained acceptance for usage in the treatment of numerous diseases throughout the world [10]. Natural compounds derived from Chinese herbal medicines, such as curcumin, epigallocatechin gallate, ginsenosides, berberine, artemisinins, emodin, ursolic acid, silibinin, triptolide, cucurbitacins, oridonin, tanshinone, artesunate, shikonin, -elemene, gambogic acid, cepharanthine, and wogonin.

Several herbal remedies used in the treatment of PD in ancient China, such as Radix achyranthisbidentatae, Herbaasari, Fructus viticis, and Fructus xanthii, are being used today [13]. This is because Shennong's Classic of Materia Medica was the first comprehensive pharmacopoeia of China. Withaniasomnifera, Mucuna pruriens, and Tinospora cordifolia are a few examples of herbal treatments for neurological illnesses that have a long tradition in India. Several lines of research suggested that herbal remedies would make good candidates for disease-modifying medications for Parkinson's disease. The components or extracts of herbal remedies (such Acanthopanax, Alpinia, and Astragalus) have in fact been shown in contemporary pharmacological research to reveal continuous and significant effects on the models of PD [14, 15]. The identification of the bioactive substances of the pharmacodynamic mechanisms of these plants will be made easier by the vast discovery of the potential molecular targets of herbal medicine extracts during the past few decades [15]. We will cover the most recent developments in research that (1) enhance the effects of herbal medicine extracts on PD models and (2) investigate possible targets or mechanisms of action for herb extracts or other bioactive substances. We also used some popular Chinese herbal preparations with strong anti-Parkinsonian properties. We hope that this information will make it easier to create PD-treating medications.

TheParkinson’s disease (PD), a chronic neurodegenerative disease which is characterized by the loss of dopaminergic neurons and the intracellular accretion of alpha-synuclein in the persisting neurons (Magistrelli et al.,2019). It is observed that the functions of the neurons like acetylcholine neu and dopamine located in the striatum are out of balance resulting in the Parkinson disease (Xu-Zhao Li et al, 2012). Also, it is now the second most ubiquitous neurodegenerative disease in the whole world which is portrayed by the motor symptoms (rigidity, tremorswhen at rest, hypokinesia, bradykinesia along with postural instability) and by the non-motor symptoms such as (autonomic, cognitive, and the psychiatric problems) (Zhang et al., 2005). To be more specific, there is reduction in the activity of mitochondria due to the complex I NADH dehydrogenase (ubiquinone) inhibition in PD brain, platelets, and muscle (Parker et al., 1989; Schapira et al., 1990; Cardellach et al., 1993;Haas et al., 1995). There are three majorpremeditated developments that have directed to the development in the medical supervision of Parkinson, also focused on the developments in dopaminergic therapies, the documentationafter finding the non-dopaminergic drugs for symptomatic development and the discovery of the compounds to amend the course of Parkinson disease (Schapira AH et al, 2006; Xu-Zhao Li et al, 2012). First detailed description of PD was given by James Parkinson in the year 1817 (Parkinson, 2002) but till now the pathogenesis and etiology of the disease remain not completely understood. It is observed that theolder people are mainly affected by Parkinson Disease which ultimately results in difficulty to perform motor tasks such as speaking, writing and walking. It is because of the fact that basal ganglia are dysfunctional in the Parkinson’s disease that leads to the imbalance between neurotransmitters such as Levodopa, GABA and acetylcholine. (Morris et al., 2001).The initialexplanation of Parkinson disease was outlined in the ‘Yellow Emperor's Internal Classic’, which is a book written almost 2000 years back. If we look into the traditional Chinese medicine we will find that theParkinson Disease has been described as “shaking palsy”, which can be called as asyndrome categorized by various observations in body like tremors, numbness or limpnessand weakness of the four limbs along with the pathologic hallmarks ofdisease which are termed as liver–kidney Yin and qi–blood deficiency(Li Q, Zhao D et al, 2006; Zhang L, et al, 2006).

Therefore, the development of an adjuvant that can allaviator, at least, mitigate these side effects will be very helpful inthe management of Parkinson’s disease. Historically, natural products and their derivatives usedin traditional medicine have been an invaluable sourceof therapeutic agents for drug development (Koehn FE et al, 2005; Breinbauer R et al, 2002; Park et al,2018).

SYMPTOMS

Each person will experience the signs and symptoms of Parkinson's disease differently. Early symptoms could be negligible and overlooked. Even after symptoms start to affect the limbs on both sides, symptoms frequently start on one side of the body and usually continue to be severe there.

Parkinson's symptoms and indicators include:

Tremor. The first limb to experience a tremor, or rhythmic shaking, is typically the hand or fingers. You could wiggle your thumb and forefinger. The term "pill-rolling tremor" describes this. Even when at rest, your hand could shake. While working on a task, the shaking might lessen.

Sluggish motion (bradykinesia). Parkinson's disease may cause movement slowdown over time, making routine actions challenging and time-consuming. While you walk, your steps can get smaller. It could be challenging to get up from a chair. If you attempt to walk, you can shuffle or drag your feet.

Stiff muscles. You can have muscle tightness in any area of your body. Your range of motion may be restricted and made painful by the stiff muscles.

Poor balance and posture. You might start to slouch. Perhaps Parkinson's disease may cause you to trip or have balance issues.

Reduction in automatic movement. It's possible that you'll be less able to make unconscious gestures like smiling, blinking, or swinging your arms when you walk.

Causes. Some brain nerve cells (neurons) eventually deteriorate or die in Parkinson's disease. A decrease of neurons that produce the chemical messenger dopamine in your brain is the cause of many symptoms. Dopamine deficiency results in abnormal brain activity, which worsens movement impairment and other Parkinson's disease symptoms.

Genes. Certain genetic alterations that can cause Parkinson's disease have been identified by researchers. These, however, are unusual unless there are several members of the family who also have Parkinson's disease. A relatively low risk of Parkinson's disease exists for each of these genetic markers, although some gene changes do appear to raise the risk of the disorder.

Triggers in the environment. Parkinson's disease may develop later if you are exposed to specific poisons or environmental factors, although the risk is quite low.

Lewy bodies present. Microscopical indicators of Parkinson's disease include clumps of particular chemicals within brain cells. Lewy bodies are what they are, and scientists think they offer a crucial insight to what causes Parkinson's disease. Lewy body alpha-synuclein was discovered. Lewy bodies include a variety of chemicals, but scientists think that the naturally occurring protein known as alpha-synuclein plays a significant role (a-synuclein).

Risk Factor

Parkinson's disease risk factors include:

Age. Parkinson's disease is a rare occurrence among young adults. It usually starts in middle or late life, and the risk gets higher as you get older. The disease typically strikes people at 60 or older. Making family planning decisions may be aided by genetic counselling if a young person is diagnosed with Parkinson's disease. Also distinct from those of an older individual with Parkinson's disease and requiring special consideration are work, social circumstances, and drug side effects.

Heredity. The likelihood that you'll develop Parkinson's disease increases if you have close family members who have the condition. Unless you have a large number of family members who suffer from Parkinson's disease, your risks are still minimal.

Sex. Parkinson's disease affects men more frequently than it does women.

Exposure to toxins. The risk of developing Parkinson's disease may somewhat rise if you are constantly exposed to pesticides and herbicides.

Complications

Parkinson's disease is often accompanied by these additional problems, which may be treatable:

Thinking difficulties. You may experience cognitive problems (dementia) and thinking difficulties. These usually occur in the later stages of Parkinson's disease. Such cognitive problems aren't usually helped by medications.

Depression and emotional changes. You may experience depression, sometimes in the very early stages. Receiving treatment for depression can make it easier to handle the other challenges of Parkinson's disease.

You may also experience other emotional changes, such as fear, anxiety or loss of motivation. Health care providers may give you medication to treat these symptoms.

Herbal Plants and There Role in Parkinson Disease

MUCUNA PRURIENS

About plant

The powder form of the seed of the leguminous plant Mucuna pruriens has been used for a long time in traditional Ayurvedic Indian medicine for various diseases including Parkinson. It is also known as the cowage and velvet bean. In India it is known as atmagupta. It is found as a climbing legume in India and tropics of Central and South America (RKatzenschlager et al, 2004). Levodopa which is a well-established drug for Parkinson disease was first extracted from the seeds of M. Pruriens. It was first isolated in 1973 (Manyam B. et al, 1999, Damodaran M et al(1937). According to some studies M. pruriens has been found to be more effective than levodopa and shows prominent effects on motor symptoms of Parkinson disease (Kasture et al,2008).Among all the mechanisms for Parkinson the major toxic mechanism is oxidative stress for the damage of dopaminergic neurons located in the substantia nigra of mid brain which ultimately causes neurodegeneration resulting in Parkinson’s disease (Dexter et al., 1989; Yoshikawa, 1993).

Mechanism

Mucuna pruriens is well known for its antioxidant effects that confirms its therapeutic use as a neuroprotective and neurorestorative herb. It is reported that mucuna pruriens have naturally occurring antioxidants havewhichpossess a broad range of various biological and pharmacological activities (Shahidi, 2000, Dhanasekaran et al,2008)

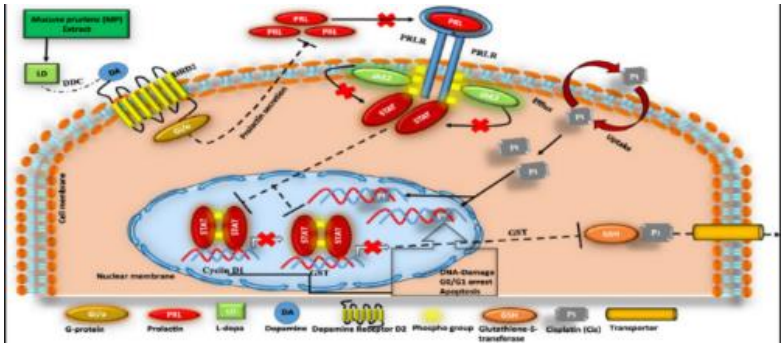


Figure: Mechanism of Mucuna Pruriene

Withania *Somnifera*

About plant-

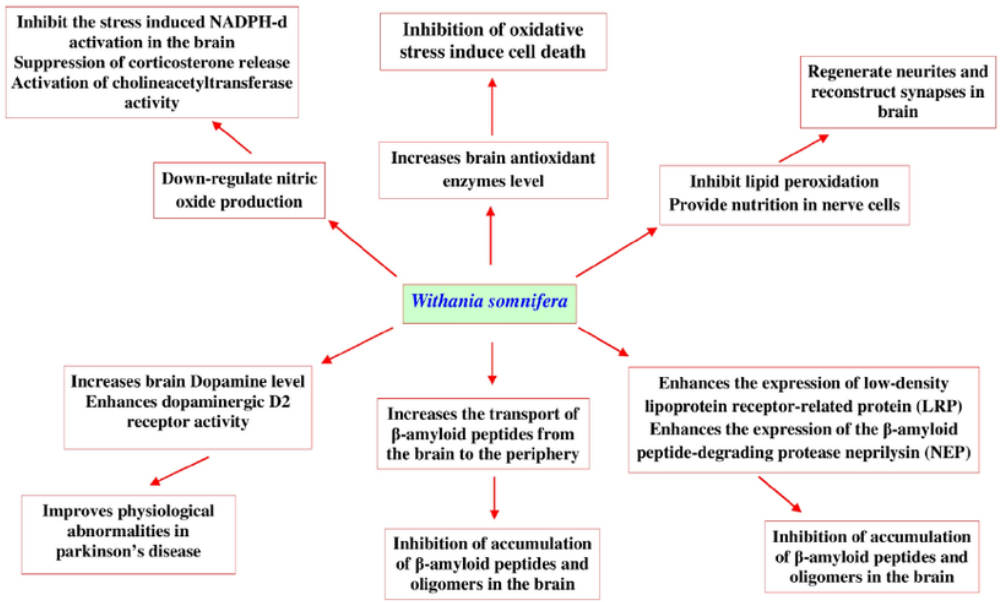
WithaniaSomnifera also known as Ashwagandha is very reverd herb in our Indian ayurvedic medicine system (singh et al,2016).*It is very*popularly known as “Indian Ginseng” or “Indian Winter cherry” in india (Andallu et al,2000). India’s native medicinal plant revealing a very crucial role in the diseases like stress and anxiety (Bhattacharya et al,2001). It also works for the treatment of central nervous system disorders like Parkinson and Alzheimer(Guota et al,2014, Prakash et al,2014). Levodopa is also found to be present in withaniasomnifera (singh et at,2016).

Pharmacological activities-

It is a potent drug for the treatment of various diseases like epilepsy, cancer and also a very potent source as a diuretic, hypoglycemic , neuroprotective and hypocholestremic agent (singh et al,2016, Prakash J. et al,2013, gupta et al2014, Andallu et al,2014).

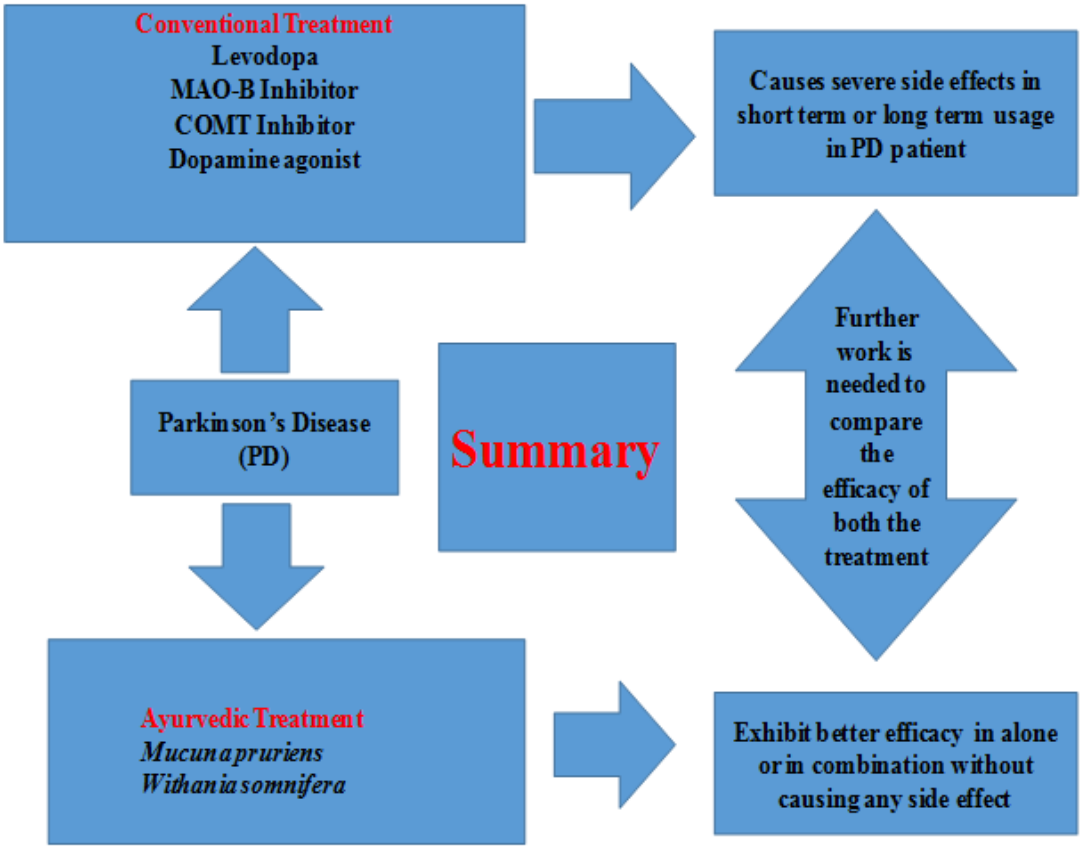
Mechnism-

This herb works through the mechanism of strong antioxidant potential . The ROS scavenging property plays an important role in the prevention of PD by defying neurodegeneration(SINGH ET AL,2014).



SUMMARY

Mucuna prueiensansWithaniasomnifera both the herbs are found with the presence of levodopa and somewhat work through a similar mechanism. Both the drugs could synergize the treatment effects of the potential already existing therapy of Parkinson disease through levodopa or could be individually potent enough to show a very good response in treating the Parkinson disease . A summarized flow chart shown below depicts the functions of both (Girdhari et al,2009).



Bacopa Monnieri

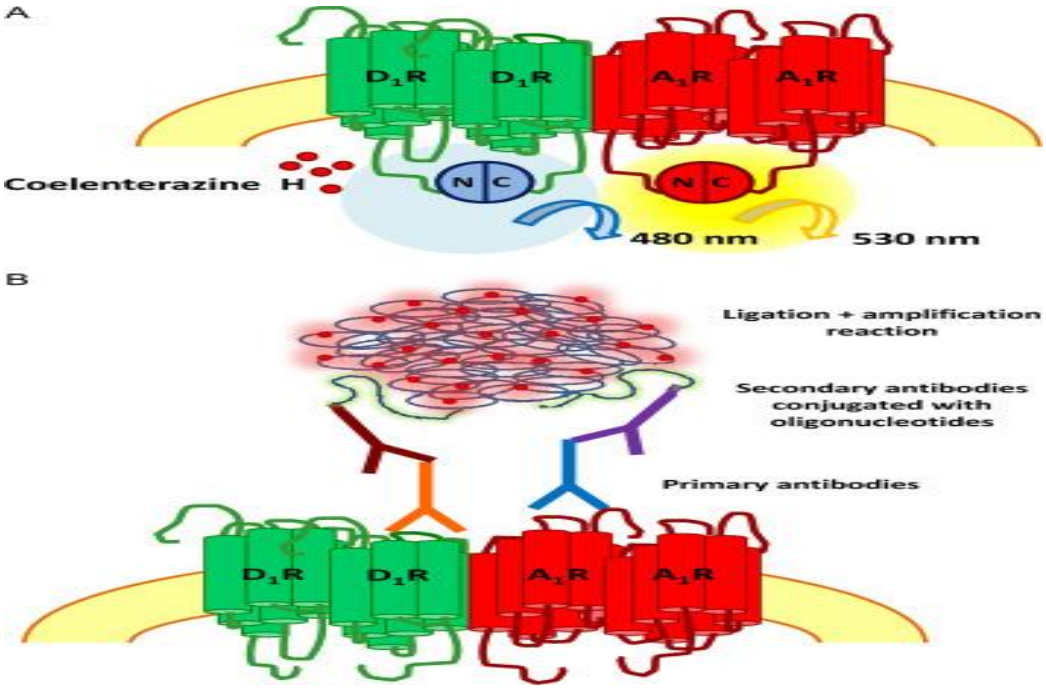
About plant-

An Indian herb widely used inIndian Ayurvedic medicine system found throughoutindia subcontinent area specially in wet damp and marshy areas (shinemol et al,2010).

The medicinal plant has been used extensively for centuries in treating various diseases like epilepsy, insomnia and anxiety. It ia also used as a mild sedative and memory enhancer (Tripathi et al. 1996; Kishore and Singh 2005; Ernst 2006).it is commonly known as bramhi and is evaluated to show beneficial effects in treating various other diseses apart from Parkinson like epilepsy, stress and anxiety (Jadiya et al,2011).

Mechanism-

It is reported that the herb is having an anti oxidant and anti inflammatory mechanism of action . these two pathways are the key mechanisms for Parkinson disease (jadiya et al,2011)



Unbalance of Metal Ion Homeostasis in the Brain

Ions (in particular calcium and iron) have been explicitly shown to be involved in a number of crucial biological processes in physiological conditions, including DNA biosynthesis, the production of neurotransmitters and the myelin sheath, mitochondrial respiration, and brain development and metabolism . Iron builds up in the SNpc and reticulate of PD patients, and this accumulation also rises with the severity of the disease. In Figure 1. By reducing brain tau levels, Lei et al. discovered in 2017 that lithium

administration in mice causes the elevation of nigral and cortical iron, which causes the animals to exhibit cognitive decline and parkinsonian characteristics [8] Moreover, dopaminergic neurons from PD patients were found to have single nucleotide polymorphisms or mutations in DMT1 (divalent metal transporter 1, which transports iron). Ferroptosis, an iron-dependent form of necrotic cell death characterised by oxidative damage to phospholipids, was found to contribute to the pathogenesis of Parkinson's disease in human iPSC-derived neurons in 2020, according to a report by Angelova et al. Typically, 15-hydroperoxy Hp-arachidonoyl phosphatidylethanolamine (15-HpETE-PE), which might trigger a death signal, builds up during ferroptosis. Sun et al. recently discovered. Specific elevation in 15-HpETE-PE level susceptibility to ferroptosis in fibroblasts from a patient with a PD-associated mutation (fPDR747W) [9]. They also used CRISPR/Cas9 technology to create Pnpla9R748W/R748W (mutations relate to neurodegeneration in humans) mice, and they saw that the mice had accumulating 15-HpETE-PE and progressive parkinsonian motor impairments. In the meanwhile, they offered proof that the midbrains of rotenone-treated PD rats and -synuclein-mutant A53T mice have higher 15-HpETE-PE levels. These findings suggest that the physiological operations of the brain depend on iron ion homeostasis.

Another way to put it is that the cytosolic Ca2+ in SNpc DA neurons primarily performs three complementary tasks: (1) maintains the slow tonic spiking in these neurons, even though pace making is not dependent on it; (2) positively modulates the expression and activity of enzymes involved in DA synthesis, ensuring a balance between the supply and demand of the neurotransmitter; and (3) stimulates oxidative phosphorylation and ATP synthesis [10]. In the SNpc of adult (but not juvenile) mice, it was discovered that dopaminergic neurons susceptible to neurodegeneration employ CaV1.3, a subtype of Ca2+ channel, for their pacemaking function . In SNpc dopaminergic neurons of PD patients with mitochondrial dysfunction, several studies by separate groups found that CaV1.3 channels increase cell susceptibility to Ca2+-mediated excitotoxicity . Moreover, it was recently shown that the FDA-approved medication benidipine, a voltage-gated calcium channel antagonist, inhibits rotenone-induced apoptosis in DA neurons. These data suggest that PD aetiology may be significantly influenced by calcium homeostasis disruption.

Neuroinflammation

There is evidence that the pathophysiology of Parkinson's disease is involved in both innate and adaptive immune responses [16]. (Figure 1). For instance, dopaminergic neurons from PD patients were found to have higher levels of nuclear ally translocated NF-B (nuclear factor kappa-light-chain enhancer of activated B cells) expression [17]. The main characteristic of inflammation-induced processes is an increase in cytokine levels in the cerebrospinal fluid and striatum of PD patients, including T-cell activation-associated cytokine (IL-2), proinflammatory cytokines (TNF-, IL-1, and IL-6), anti-inflammatory cytokine (IL-4), and several growth factors (EGF and TGF-1). The enhanced astroglial response and microglia activation were also seen in the SNpc and striatum of MPTP-induced PD rats, mice, and monkeys.Perez et alrecant’s in vivo research using Tlr4-knockout mice demonstrated the importance of Tlr4-mediated inflammation in intestine and/or brain inflammation, which may be one of the main causes of neurodegeneration in Parkinson's disease (PD) [18]. Overall, these results are consistent with the idea that dopaminergic neurons play important roles in the development of Parkinson's disease and release inflammatory cytokines.

However, in the nigrostriatal system of mice that had received MPTP injections, Brochard et al. discovered elevated levels of CD8+ T-cytotoxic and CD4+ T-helper cell infiltration [19].The striatum and SNpc of MPTP-exposed PD patients exhibit increased levels of Fas ligand, a cell-surface ligand of the TNF-family that activates the Fas receptor and promotes apoptosis [20]. The increased expression of major histocompatibility complex (MHC), the molecules that bind to the pathogen-derived peptide fragments exposed on the cell surface, is another neuroinflammatory alteration in PD [21]. Firstly, McGeer et al. found that the SNpc of PD patients has a significantly higher proportion of HLA-DR-positive microglial cells (MHC-II) . In line with this, more light chain MHC-I was found in the striatum of PD patients than in healthy controls .Moreover, Bokor et al. discovered that the etiology of PD involves killer cells produced by an antibody-dependent cell-mediated cytotoxicity response . Recently, Sulzer et al. demonstrated that specific peptides generated from -synuclein function as antigenic epitopes presented by these alleles and activate helper and cytotoxic T-cell responses in people with Parkinson's disease (PD). Prior research has shown that circulating CD4+ and CD8+ T-cells from PD patients can release Th1/Th2 cytokines in the presence of -synuclein, indicating that PD may have a chronic memory T cell response. In order to determine if -synuclein aggregation in the midbrain of mice can stimulate memory T cells to result in PD, Williams et al. created a -synuclein overexpression and T cell-deficient mouse model in 2021 [21].In fact, they found that

overexpressing -synuclein increases the quantity of MHC-II protein in the CNS myeloid cells and causes IFN-producing CD4+ and CD8+ T cells to infiltrate the CNS. More significantly, the immunosuppressive medication fingolimod may cause loss of TCR or CD4 function, which could lessen the CNS myeloid MHC-II response to -synuclein. Many of the observations emphasize the pivotal roles that inflammation plays in the PD pathophysiology.

Oxidative Stress

Oxidative stress, which frequently results in the destruction of cellular components like lipids, proteins, and DNA, develops in human bodies when the creation of reactive oxygen species (ROS) cannot be neutralized by antioxidants.Many experimental studies on the metabolism of dopamine, lipid peroxidation (LPO), and glutathione depletion have shown that oxidative stress is a significant factor in the development of Parkinson's disease (PD).The plasma membrane's lipid peroxide (LPO) can create fatty acid radicals and H2O2 by eliminating hydrogen atoms from the methylene bridges (-C2H2-).Prior studies have shown that the level of basal malondialdehyde, an intermediary in the formation of LPO, is significantly higher in the substantia nigra of patients with Parkinson's disease when compared to other brain regions, indicating that LPO may play a role in the onset of PD.

Chinese Herbal Medicines and PD

Acanthopanax

The roots and stems of Acanthopanax senticosus, also known as Wujipi in Chinese, are frequently utilized in traditional Chinese medicine. The pole-climbing test revealed that Acanthopanax senticosus (Figure 2) root ethanol extracts (45.5 mg/kg daily) have neuroprotective effects on MPTP-induced PD mice. When the extract was administered, there were considerably fewer dopamine receptor D1/2-positive cells and lower amounts of caspase-3 protein in the substantia nigra in disease. By promoting tyrosine hydroxylase or glial cell line-derived neurotrophic factor- (GDNF-) positive neuron activity in the midbrain, sesamin, a component of Acanthopanax senticosus roots, pharmacologically offers protective effects against PD-related depressive behaviours in rotenone-administered rats.Sesamin also increases SOD activity and lowers catalase activity and nitric oxide (NO) synthase protein levels in MPP+-induced neuronal PC12 cells, according to Lahaie et al. (Figure 3). Another key ingredient in ASRS, eleutheroside B (Figure 4), has similar anti-fatigue, memory-improving, and cognitive-improving properties. Eleutheroside B significantly lowers the amount of c-Fos and c-Jun expression in MPP+-induced PC12 cells while increasing the phosphorylation of ERK1/2 (extracellular signal-regulated kinase 1/2) (Figure 3). Li et al. used lncRNA microarray analysis in 2016 to systematically examine the pathology and physiological consequences of ASRS on the Brain.These findings imply that the bioactivities of ASRS for both diseased and physiological CNS may be bidirectional under certain conditions.Acanthopanax is a plant commonly used in traditional Chinese medicine for its potential therapeutic effects. Recent studies have suggested that acanthopanax may have neuroprotective effects and could be useful in the treatment of Parkinson's disease. Parkinson's disease is a neurodegenerative disorder characterized by the loss of dopamine-producing neurons in the brain. Acanthopanax has been shown to increase dopamine levels in the brain, potentially helping to alleviate some of the symptoms of Parkinson's disease, such as tremors and difficulty with movement. In addition, acanthopanax contains compounds that have antioxidant and anti-inflammatory properties, which may help protect the brain from further damage and slow the progression of the disease. While research into acanthopanax as a treatment for Parkinson's disease is still in its early stages, these initial findings are promising and suggest that this plant may have potential as a complementary therapy for individuals with Parkinson's disease. As with any complementary therapy, it is important to discuss the use of acanthopanax with a healthcare professional before incorporating it into a treatment plan. Further research has indicated that acanthopanax may also have potential in improving cognitive function in individuals with Parkinson's disease. However, it is important to note that while these studies suggest that acanthopanax may have potential in the treatment of Parkinson's disease, more research is needed to fully understand its effects and potential risks. It is also important to note that herbal supplements like acanthopanax are not regulated in the same way as prescription medications, and the quality and potency of supplements can vary widely. Therefore, it is crucial to consult with a healthcare professional before taking acanthopanax or any other herbal supplement for the treatment of Parkinson's disease.

Fig:1

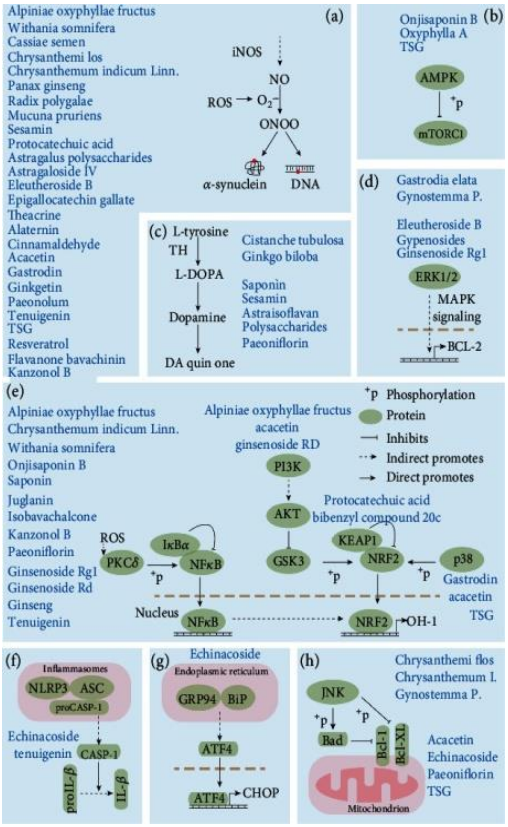


Fig:2

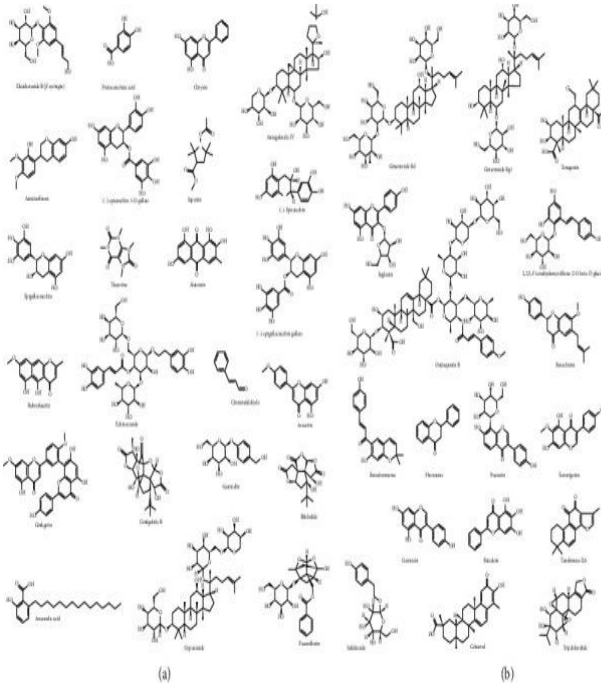


Fig :3

Alpinia

The dried, ripe seed of Alpinia oxyphyllaMiq. (Figure 2), known as AlpiniaeOxyphyllae Fructus (AOF, also known as YizhiRen in Chinese), is frequently used in clinics to strengthen the spleen, stomach, and kidney functions and treat vomiting, diarrhea, cold pain in the abdomen, excessive salivation, etc. In a zebrafish model of Parkinson's disease, ethanol extract of AOF was found to reduce locomotor deficits and recover 6-OHDA-induced dopaminergic neuron degeneration by reducing inflammation (downregulation of IL-1 and TNF- expression) and oxidative stress (inhibition of NO production). (Figure 3). Furthermore, the PI3K-AKT pathway plays a role in some of how AOF achieves its bioactivities in neuroprotection. (Figure 3).Protocatechuic acid and chrysin were two polyphenols from AOF that were discovered by Zhang et al. in 2015 and shown to synergistically improve cell survival in 6-OHDA-treated PC12 cells and dramatically reduce dopaminergic neuron loss in both zebrafish and mice PD models. They demonstrated in mechanisms that protocatechuic acid and chrysin (1) raise NRF2 protein level and transcriptional activity, (2) modify cellular redox

status, and (3) lower levels of malondialdehyde. (3 Figures). In vitro chemically induced primary neuron damage is reduced by Oxyphylla A, a bioactive molecule from AOF, and in vivo chemically induced dopaminergic neuron loss and behavioural impairment are reduced. (Figure 3).According to recent studies, Oxyphylla A greatly increases the breakdown of -synuclein in a cellular PD model by stimulating the PKA-AKT-mTOR pathway, which in turn causes PSMB8 expression and boosts UPS activity. (Figure 3). Moreover, in A53T -synuclein transgenic mice, it decreases the accumulation of both triton-soluble and -insoluble forms of -synuclein to shield neurons from -synuclein-induced neurotoxicity.

Astragalus

A common and well-known medication in traditional Chinese medicine is Astragali Radix (Huangqi in Chinese), which is the dried root of Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao or Astragalus membranaceus (Fisch.) Bge. (Leguminosae). (Figure 2). Astragali Radix has at least three bioactive substances that have been found to have neuroprotective properties, including astragalus polysaccharides, astraisoflavan, and astragaloside IV. Although the cause of neuronal death in PD patients is unknown, oxidative stress, including free radicals, undoubtedly plays a role in the progression of this condition.It has been discovered that astragalus polysaccharides can reduce oxidative stress in dopaminergic neurons. (Figure 3). Astragaloside IV dramatically reverses the loss of cell viability, nuclear condensation, production of intracellular ROS, elevation of the Bax/Bcl-2 ratio, and caspase-3 activity in SH-SY5Y cells that have been exposed to MPP+ (Figure 3). Important cellular sources for transplantation therapy for PD patients include neural stem cells (NSCs). Additionally, Gao et al. systematically assessed the protective effects of astraisoflavan and astragalus polysaccharides on NSCs and discovered that these components significantly promote the expressions of tyrosine hydroxylase and dopamine transporter in dopamine neurons as well as the motivators of dopamine neurons like Shh (sonic hedgehog), Nurr1 (orphan nuclear hormone 1), and Ptx3 (pituitary homeobox 3).

Camellia

The product made from Camellia sinensis (L.) O. Kuntze (Theaceae) leaves is referred to as camellia (also known as green tea in Chinese) (Figure 2). Traditionally, stomach issues, headaches, and nervous tension were typically treated with camellia infusion as a relaxant or cleansing agent. The antioxidant, anti-inflammatory, and neuroprotective properties of green tea polyphenols (such as epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate) have been demonstrated in current pharmacology. (Figure 3). Standardized extracts from camellia seeds, epicatechin, and epigallocatechin gallate clearly reverse the behavioral damage, reduce depression, and enhance cognitive performance in 6-OHDA-induced PDrats.Moreover, treatment with epigallocatechin gallate protects against and prevents the neurotoxicant paraquat's (PQ) induction of a decrease in lifespan and locomotor activity as well as a rise in lipid peroxidation and neurodegeneration in Drosophila melanogaster flies. Another important chemical found in camellia seeds called saponin reduces inflammation and behavioural disturbance in MPTP-induced PD mice and boosts dopamine levels in the striatum and tyrosine hydroxylase-positive cells in the substantia nigra. (Figure 3). Theacrine, a purine alkaloid from the camellia plant that was recently studied for its protective properties in a number of animal models of Parkinson's disease, was found to reverse the loss of dopaminergic neurons and behavioural performance degradation.

Cassia

The dried, ripe seed of Cassia obtusifolia L. or Cassia tora L. (Leguminosae) is known as Cassiae Semen (Juemingzi in Chinese) (Figure 2). It was used to cure headaches and vertigo in ancient China. It also helped the eyes by nourishing and anchoring the liver. The complete ethanol extract of Cassiae Semen was observed to reduce the excessive production of ROS, glutathione depletion, mitochondrial membrane depolarization, and caspase-3 activation in PC12 cells treated with 6-OHDA. (Figure 3). Moreover, Cassiae Semen substantially reduced the degeneration of dopaminergic neurons in the substantia nigra and striatum of mice treated with MPTP. A crucial oxidant called peroxynitrite (ONOO), which reacts with a variety of cellular components such lipids, amino acids, sulfhydryls, and nucleotides, has been implicated in the etiology of Parkinson's disease (PD) [131].Alaternin (Table 1), a phenolic active ingredient of Cassia tora L., was found to be powerful ONOO scavengers that work by donating electrons to lessen the ONOO-mediated nitration of tyrosine. (Figure 3). Another important bioactive substance from Cassia tora L., cinnamonaldehyde (Table 1), was likewise discovered to dramatically improve the viability and reduce the ROS level of 6-OHDA-treated PC12 cells. (Figure 3).

Formulations	Herbal medicines and their contents
Bushen-Yanggan-Recipe	15 g *Rehmanniae Radix* Praeparata, 15 g *Rehmanniaglutinosa* Libosch., 15 g *UncariaeRamulus* Cum Uncis, 15 g *Paeonia lactiflora* Pall., 9 g *PolygoniMultiflori* Radix Praeparata
Bushen-Huoxue-Granule	20 g *Fructus Corni*, 20 g *RhizomaAcortatarinowii*, 20 g *Radix Polygonimultiflori*, 15 g *HerbaCistanches*, 10 g *RaixAngelicaesinensis*, 15 g *Radix Salviaemiltiorrhizae*
Bu-ShenJie-Du-Fang	*Rehmanniaglutinosa*, *Cistanchedeser* ticola, *Paeonia lactiflora* Pall, *Radix Angelica* Sinensis, *Puerariae Radix*, *CoptidisRhizoma*, *Scutellariae Radix*, *Antelope Horn* Powder, and *Glycyrrhiza uralensis* with a weight ratio of 5 : 5 : 4 : 4 : 5 : 4 : 4 : 1 : 2
Chuanxiong-Chatiao-Pulvis	12 g *Ligusticum chuanxiong* Hort., 12 g *Schizonepeta tenuifolia* Briq., 6 g *AngelicaeDahuricae* Radix, 6 g *NotopterygiiRhizoma* Et Radix, 6 g *Glycyrrhizae Radix* Et Rhizoma, 3 g *Asari Radix* Et Rhizoma, 4.5 g *Saposhnikoviadivaricata* (Turcz.) Schischk., 12 g *Mentha haplocalyx* Briq., 4.5 g green tea
Fangji-Dihuang-Decoction	*Rehmanniaglutinosa*, *Cistanchedeserticola*, *Paeonialactiflora Pall*, *Radix Angelica* sinensis, *Puerariae Radix*, *RhizomaCoptidis*, *Radix Scutellariae*, *Antelope Horn* powder, and *GlycyrrhizaeRadixina* with a weight ratio of 5 : 5 : 4 : 4 : 5 : 4 : 4 : 1 : 2
Huanglian-Jiedu-Decoction	9 g *Coptis chinensis* Franch, 6 g *Scutellariabaicalensis* Georgi, 6 g *Phellodendronamurense* Rupr, and 9 g *Gardenia jasminoides* Ellis
Modified formulation of *Huanglian-Jie-Du-Tang*	*Rhizomacoptidis*, *Radix scutellariae*, *Cortex phellodendri*, and *Fructus gardeniae* with a weight ratio of 3 : 2 : 2 : 3
Hua-Feng-Dan	10% cinnabar (96% as HgS) and 10% realgar (90% as As4S4), along with other components, such as Jingjie (*Nepeta cataria*), Tianma (*Gastrodiaelata*), Jiangchan (*Bombyx batryticatus*), Tiannanxing (*Arisaema erubescens*), Baifuzi (*Aconitum coreanum*), Cangshu (*Atractylodes japonica*), and Quanxie (*Buthusmartensii* Karsch)
Jia-Jian-Di-Huang-Yin-Zi-Decoction	*RehmanniaGlutinosa* Libosch, *CornusOfcinalis* Sieb. et Zucc, *MorindaOfcinalis* How, *CistancheDeserticola* Y.C. Ma, *Angelica Sinensis* (Oliv.) Diels, *Asparagus Cochinchinensis* Merr., *Paeonia Lactiflora* Pall. with weight ratio of 1 : 0.6 : 1 : 1 : 1 : 1 : 1

Formulations	Herbal medicines and their contents
Kami-Shoyo-San	3 g *Bupleurum falcatum*, 3 g *Paeonia lactiflora* Pall., 3 g *Atractylodeslancea*, 3 g *Angelica acutiloba*, 3 g *Poriacocos* (Schw.) Wolf, 2 g *Gardenia jasminoides* Ellis, 2 g *Paeonia suffruticosa* Andr., 1.5 g *Glycyrrhiza uralensis* Fisch., 1 g *Zingiber officcinale* Roscoc, and 1 g *Menthae arvensis*
Liuwei-Dihuang-Pill	24 g *Rehmanniae Radix* Praeparata, 12 g *Corni Fructus* Praeparata, 9 g *Paeonia suffruticosa* Andr., 12 g Dio*scoreaopposita* Thunb., 9 g *Poriacocos* (Schw.) Wolf, and 9 g *Alisma orientalis* (Sam.) Juzep.
San-Huang-Xie-Xin-Tang	5 g *Coptis chinensis* Franch, 5 g *Scutellariabaicalensis* Georgi, and 10 g *Rheum officcinale* Baill.
Tianma-Gouteng-Yin	9 g *Gastrodiaelata* Bl., 12 g *UncariaeRamulus* cum Uncis, 18 g *Haliotidis Concha*, 9 g *Gardenia jasminoides* Ellis, 12 g *Cyathula officinalis* Kuan, 9 g *Eucommia ulmoides* Oliv., 9 g *Taxillus chinensis* (DC.), 9 g *PolygoniMultiflori* Caulis, 9 g *Fulingshe*, and 9 g *Leonurus japonicas* Houtt.
Yeoldahanso Tang	*Pueraria lobata* (Willd.) Ohwi, *Angelica tenuissima* Nakai, *Scutellariabaicalensis* Georgi, *Platycodon grandiflorum* (Jacq), *AngelicaeDahurica*, *Cimicifuga heracleifolia* Kom, *Raphanus sativa* L., *Polygala tenuifolia* (Willd.), *Acorus gramineus* Soland., and *Dimocarpus*

Ginkgo

In patients with senile dementia, ginkgo biloba (Figure 2) extract EGb761 improves memory loss and cognitive deficits, and it encourages NSC proliferation in the subventricular zone of PD mice.Ginkgetin (Table 1), a naturally occurring bioflavonoid derived from Ginkgo biloba leaves, was discovered by Wang et al. to reduce intracellular ROS levels and sustain MMP in MPP+-induced PD models both in vitro and in vivo. Also, they showed that ginkgetin significantly reduces MPP+-induced cell death by inhibiting caspase-3 and the Bcl-l2/Bax pathway, substantially chelates ferrous ion to decrease L-ferritin, and increases transferrin receptor 1 levels.In SY5Y cells containing recombinant monomeric or aggregated -synuclein, bilobalide and ginkgolide B (Table 1), two essential bioactive components of Ginkgo biloba, increase cell survival and decrease cell death in vitro. Ginkgo biloba extract consistently increases locomotor activity in A53T -synuclein transgenic PD mice, suppresses the production of methane dicarboxylic aldehyde, and restores the expression of tyrosine hydroxylase and dopamine transporters . The oral supplementation of Ginkgo biloba extract also lowers the enhanced oxidative and inflammatory stress in rotenone-induced Parkinson's disease (PD) animals. Ginkgolic acid, a naturally occurring substance isolated from Ginkgo biloba leaves, was found to greatly increase the number of autophagosomes while decreasing intracytoplasmic -synuclein aggregates and SUMO-1 levels .Most recently, Wu et al. discovered that protocatechuic acid (Table 1), a substance contained in Ginkgo biloba, boosts the effectiveness of ginkgolide B in the treatment of Parkinson's disease, offering a fresh notion for effectively utilising Ginkgo biloba leaves' constituents .

Herbal Formulation with Anti-Parkinsonian Activities

Several Chinese herbal formulations have been studied in the past decades for the treatment of PD in both human trials and animal research. Some examples are given in Table 1. Traditional Chinese medicine called Banxia-Houpo-Tang has been shown to lessen the risk of pneumonia in elderly dementia patients and to ease the swallowing reflex in people with Parkinson's disease (PD). Patients with psychosis-induced Parkinson's disease (PD) can benefit from Kami-Shoyo-San, a combination of numerous traditional Chinese

medicine-known medicinal herbs, for the treatment of tremors. Bushen-Yanggan-Xifeng-Decoction, according to Lu et al., enhances neuron functioning by raising the levels of striatal DA and 5-HT in PD mouse models. In MPTP-induced PD mice, Chuanxiong-Chatiao-Pulvis dramatically reduces the motor deficit and dopaminergic neurodegeneration. Huanglian-Jiedu-Decoction exhibits protective effects on cells in MPP+-treated PC12 cells, according to Jin et al2008 .'s research. Independent studies found that Liuwei-Dihuang-Pill shields dopaminergic neurons in PD mice from MPTP-induced damage. San-Huang-Xie-Xin-Tang significantly boosts tyrosine hydroxylase-positive neurons in the SNpc both in vitro and in vivo, and it enhances the motor function of MPTP-induced PD animals[22]. Independent studies indicated that Tianma-Gouteng-Yin might prevent the death of dopaminergic neurons brought on by oxidative stress in PD rats[24]. In rats treated with MPTP, Zhen-Wu-Tang was shown to have the ability to maintain DA concentration and DA transporter mRNA level. Intriguing evidence suggests that Zhichan-Soup encourages NSC differentiation in PD model rat models [25]. A specific Chinese herbal combination called Bu-ShenJie-Du-Fang has a long history of treating motor deficits like Parkinson's disease. Recently, Lie et al. showed that Bu-ShenJie-Du-Fang increases cell survival by promoting autophagy in the MPP+-induced cell model of PD [26]. In 2020, Hua-Feng-Dan, a traditional Chinese medicine used to treat neurological problems, was also shown to efficiently restore dopaminergic neuron loss in PD rats and ameliorate behavioral ability impairment caused by LPS and rotenone [27].

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