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Anti-Parkinson Drug from Chemical Medicines and Herbal Medicines: A Review

Yeni Yeni[1], Xia Wu[2], Budi Arman[1], Vivi Anggia[3*]
[1.]Department of Pharmacy, Universitas Muhammadiyah Prof. DR. HAMKA, Jl. Delima II/IV, Jakarta 13460, Indonesia
[2.]College of Traditional Chinese Medicine, Capital Medical University, Beijing City, China
[3] Department of Pharmacy, Faculty of Health Sciences, Universitas Islam Negeri Syarif Hidayatullah Jakarta. Cireundeu, Jl. Kertamukti No.4, Pisangan, Kota Tangerang Selatan, Banten 15419, Indonesia

**Corresponding author: vivi.anggia@uinjkt.ac.id*

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Abstract: Parkinson's disease (PD) is a disease of the central nervous system. It is a progressive disorder, meaning it gets worse over time. PD is usually characterized by tremor, rigidity, akinesia, and postural autonomic instability. In addition, it may also cause a series of non-motor symptoms (NMSs). The disease acts on substantia nigra (SNc), a tiny section of cells in the center of the brain. The ability of dopamine production is lost by degrees in the SNc. PD generally appears at the age of more than 60 years. Nowadays, a lot of anti-Parkinson drugs have been found either from that chemicals or herbs. In this essay, anti-Parkinson drugs from chemical medicine and herbal medicines especially from china will be discussed. Anti-Parkinson's drugs are derived from chemical medicines include levodopa (l-dopa), dopamine agonists, MAO-B inhibitors, catechol O-methyltransferase (COMT) inhibitors, anticholinergics and amantadine. Meanwhile, anti-Parkinson drugs derived from herbal medicine include *Scutellaria baicalensis* Georgi, *Polygonum cuspidatum* Sieb. et Zucc., green tea (*Camellia sinensis* L.), *Panax ginseng* C. A. Mey., *Cistanche deserticola* Y. C. Ma, *Panax Notoginseng* Wall. var notoginseng (Burkill.) F.H. Chen, *Gastrodia elata* Blume and *Polygala tenuifolia*Willd.. These drugs have the same effects to help ease symptoms of Parkinson's and can increase the amount of dopamine in substantia nigra pars compacta (SNc). However, some chemical drugs have more side effects although herbal medicines are less clear, more tests need to be planned.

Keywords: Chemical Medicines, Drugs, Herbal Medicines, Parkinson.

1. INTRODUCTION

James Parkinson is the initial British doctor who described Parkinson's Disease (PD) in his book "An Essay on the Shaking Palsy" which was published in 1817 (Baltuch and Stern, 2007). PD is a progressive neurodegenerative disease in which the definite cause is not known (idiopathic) (Kwon *et al.*, 2012). PD is usually characterized as tremors, rigidity, bradykinesia and postural and autonomic instability. In addition, there are also non-motor symptoms serial (NMSs) which may also frequently present in PD, including sensory symptoms, dyaustonomia, neurobehavioral disorders and sleep disturbances (Chen *et al.*, 2012).

There is a cluster of cells in the basal ganglia called the substantia nigra pars compacta (SNc) where dopamine is produced. Dopamine is a neurotransmitter in the brain that is responsible for sending signals for movement in the body. The SNc cells die in Parkinson's disease, resulting in less than normal production of dopamine (Nutan, 2008). When the death of SNc cells continues until the individual loses more than 80% of the supply of dopamine, at which point the individual tends to exhibit symptoms of PD (Silitonga, 2007). the cells in the basal ganglia play an important role whose function is to maintain muscle tone and smoothness and other directed activities.

The basal ganglia regulate activities carried out without the need for thought, e.g. walking (Nutan, 2008). The gain of age can increase the risk of PD. In general, PD patients are elderly. Patients who have an onset under the age of 40 years are 4%-10%. In a clinical study of 934 patients conducted for more than 22 years, only 6% of PD patients were under 40 years of age. The risk of developing PD is 2.0% for men and 1.3% for women (Factor and Weiner, 2008).

There are several types of PD treatments. They are speech, occupational, and physical therapy, as well as medical and surgical treatment. The speech remedy exercises the muscles involved in chewing, swallowing food and making speech clear so it can help PD patients. Occupational therapy is a treatment to help PD patients conserve their autonomy even though they have limitations. It discusses daily activities e.q. eating, bathing, dressing, applying makeup, writing and shaking. In physical therapy, motor function and strength can be enhanced and the range of shift in the joints is maintained.

The surgical treatment for PD patients includes restoration (cell transplantation), raising (use of growth factor), ablative (thalamotomy or Pallidotomy), gene cure, and electrophysiology (Deep brain stimulation [DBS]) which is used to startle the brain in these areas to assist the delivery process of messages to the body in order to reduce the symptoms of PD (Nutan, 2008). The medical treatment will be discussed in the section below.

2. CHEMICAL MEDICINE IN TREATING PD

In the treatment of PD, drug selection is the primary issue. The medical treatment is expected to control symptoms and may also reduce the risk of the late complications of the motor. The followings are chemical drugs used for the treatment of PD.

2.1 Levodopa (L-dopa)

Levodopa (L-dopa) is a chemical compound that can be obtained from plants or animals. L-dopa is converted to dopamine and other metabolites when it reaches the brain. The most effective symptomatic treatment option for PD patients is combining l-dopa with a dopa-decarboxylase inhibitor e.g. carbidopa or benserazide. Central dopa decarboxylase converts L-dopa into dopamine which is cached in dopamine neurons.

Dopamine is delivered to the synaptic space where it can bind to its receptors. Tachycardia, hypotension, nausea, and vomiting are side effects of l-dopa that can be alleviated by giving carbidopa and benserazide, peripheral inhibitors of dopa-decarboxylase. Their administration also maximizes the amount of l-dopa that can pass the blood-brain barrier (BBB). The changes of l-dopa have a different until it enters the brain due to the use of carbidopa. There are three types of dosage forms of l-dopa, the standard formulation with different doses, the slow-release preparations, and the fast-relief dispersible drugs (Starkstein and Merello, 2004).

L-dopa absorption occurs in the duodenum. Furthermore, l-dopa penetrates the BBB until it reaches a certain extent of the brain. The plasma half-life of l-dopa is short, 60-90 minutes. Dramatically, l-dopa can improve signs and symptoms of parkinsonism, dysfunctional body parts, and even survival (Playford, 2s04).

The dose of levodopa is 100 mg with carbidopa or benserazide 25 mg taken three times per day (Arlina and Evaria, 2011). The dose of l-dopa is adequate to make motor function in patients with mild to moderate PD better. Its side effects on cognitive function are also negligible.

There are no consistent reports of l-dopa-induced cognitive impairment in PD patients (Colosimo, Riley and Wenning, 2011). After many years, Parkinson's disease in patients will continue to evolve. It will lead to less stability of levodopa benefits. Levodopa administration in high doses can cause patients to experience involuntary movements (dyskinesia) (Atwood, Hunnewell and Saucier, 2005; Goldstein, 2008). The similar side effects associated with the use of l-dopa are likely to occur.

2.2 Dopamine Agonist

Dopamine agonists can bind the dopamine receptors directly by acting like endogenous neurotransmitters. However, neither of them can stimulate the full complement of dopamine receptors like l-dopa. Dopamine agonists have some benefits, they are long-acting drugs and bind dopamine receptors directly by passing through the degenerated nigrostriatal terminal. Dopamine agonists provide more stable physiological stimulation than l-dopa and can prevent or reduce motor complications. They were also thought to have neuroprotective properties (Playford, 2004).

Dopamine agonists may be used as monotherapy in early PD. Their valuable effects can last for more than three years on the average common patient. The half-life of various dopamine agonists is longer than that of levodopa which is about 6 to 12 hours. In addition, the undesirable effects of dopamine agonists on the body include nausea, vomiting, vomiting, postural hypotension and drowsiness anxiety and some of the psychiatric effects include confusion, hallucinations, and less commonly, delusional states. (Playford, 2004).

There are two types of dopamine agonists, namely ergot and non-ergot. Their differences are related to the chemical structure. Ergoline is a kind of ergot dopamine agonist with a characteristic chemical structure, which has been copied in a laboratory to make ergoline dopamine agonist drugs. Ergoline dopamine agonists (such as bromocriptine, cabergoline, pergolide and lisuride) act on dopamine receptors, which may also have beneficial effects on other chemical receptors in the brain. Non-ergoline dopamine agonists (apomorphine, pramipexole, ropinirole and rotigotine) are selective and have a specific effect on dopamine receptors. Now, these compounds will be discussed in detail (Ebersbach, 2008).

Bromocriptine is the D2 agonist and partial D1 antagonist in nanomolar concentrations, or partial D1 agonist in micromolar concentrations (Starkstein and Merello, 2004). Oral doses of bromocriptine should be given to PD patients gradually. The first week 1-1.25 mg at bedtime, the second week 2-2.5 mg before sleep, the third week 2.5 mg two times per day, fourth week 2.5 mg 3 times per day, after the fourth week, increase the dose by 2.5 mg every 3-14 days. The optimal dose will be given depending on the condition of the patient, usually continuously enhanced 10-40 mg per day (Tjay and Rahardja, 2007).

On monotherapy, bromocriptine produces significantly fewer dyskinesia and motor fluctuations in later disease than l-dopa. On the other hand, bromocriptine produces less improvement in symptoms and has poor tolerability compared with l-dopa therapy. The drug combination of l-dopa and bromocriptine can improve the adequate symptom, while the dyskinesias will be induced due to the lack of l-dopa compared with the treatment with l-dopa itself. The drug combination may reduce the need of l-dopa by approximately 10-40% and the dose of bromocriptine usually ranges from 15 mg to 25 mg (Starkstein and Merello, 2004).

Cabergoline is a dopamine D2 receptor agonist. Cabergoline monotherapy is the right choice for PD patients who were previously untreated (Starkstein and Merello, 2004). The dose of carbegoline that can be used for PD is 1 mg and increased to 2-6 mg once per day gradually (Tjay and Rahardja, 2007). The effect of carbegoline on treatment can improve motor symptoms, delay the presentation of motor complications caused by levodopa and reduce the amount of levodopa needed to control symptoms. This substance is usually given as adjunctive therapy in Parkinson's disease and is useful in improving sleep disturbances in progressive Parkinson's disease. But the side effects may occur, especially in the digestive and nervous systems (central and peripheral). The resorption of cabergoline of the gastrointestinal (GI) tract varies greatly. Cabergoline can be rapidly and extensively metabolized in the liver and excreted in the bile, and to a lesser extent in the urine. The elimination half-life is estimated to be 63-68 hours in Parkinson's disease patients.

Pergolide is a derivative of ergoline which is a kind of strong dopamine agonist. Pergolide activates several types of nerves in the brain. Pergolide acts as an agonists of dopamine D2, D1 and serotonin 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B and 5-HT2C receptors. Pergolide is used to treat the stiffness, tremors, spasms, and poor muscle control caused by Parkinson's disease. Patients need to take pergolide when their previous treatments for Parkinson's disease have not been successful or if side effects have been caused. Side effects may occur including nausea, vomiting, orthostatic hypotension, cognitive dysfunction, elevated liver enzymes, erythromelalgia, and peripheral edema.

The pergolide dose used in the initial treatment of PD was 0.05 mg once per day then gradually increased up to 0.5 mg three times per day (Tjay and Rahardja, 2007). Pergolide can also be combined with levodopa. Pergolide, with or without levodopa, did not achieve significant improvement for dysarthria but the perceptual assessment of dysarthria showed an improved trend during the drug combination of bromocriptine and levodopa (Halliday, Barker and Rowe, 2011).

Lisuride hydrogen maleate is a semisynthetic ergot alkaloid that activates the non-cyclase-linked receptor striatal dopamine and it is effective for Parkinson's therapy. Lisuride is a dopamine and serotonin receptor, partial agonist. It has a high affinity for dopamine D2, D3 and D4 receptors, and serotonin 5-HT1A and 5-HT2A/C receptors. The efficacy of lisuride is ten times as bromocriptine. Lisuride provides beneficial efficacy in patients with extensive degeneration of presynaptic nigrostriatal neurons with reduced response to levodopa and bromocriptine. Consumption of lisuride may delay the need for levodopa until lisuride is insufficient to control Parkinsonian disability. The lisuride dose used for PD in the first week is 0.1 mg at night, then every week the dose is increased by 0.1 mg to achieve an optimal dose of 0.6-2 mg per day (Tjay and Rahardja, 2007).

Apomorphine was the first dopamine receptor agonist used in Parkinson's disease. This active substance acts as a short-term dopamine agonist that acts directly on D1 and D2 receptors with a strong effect and is equivalent to qualitative or quantitative LD. Its rapid absorption (20 min cmx and a half-life of 43 min results in rapid onset of action and effects after 15-20 min of subcutaneous administration (Rana, 2011).

Apomorphine can be used in combination with l-dopa, to reduce the dose of l-dopa. It is given subcutaneously (IV) in doses of 25-40 mg per day or 1-7 mg six times per day, followed by a nasal spray administration 1-10 mg (HCl) 2-4 times per day (Tjay and Rahardja, 2007). The risk of psychiatric side effects from apomorphine is lower than that of other dopaminergic. Thus, patients experiencing psychiatric side effects who are dependent on dopaminergic agents may be treated with apomorphine infusion. Apomorphine has been reported to have several effects on humans including increased erotic visual stimulation, and penile erection a few minutes after injection.

Pramipexole is a full agonist in a non-ergoline D2 subfamily of dopamine receptors Pramipexole is a full agonist in the non-ergoline D2 dopamine receptor subfamily with a higher affinity for D3 dopamine receptors than D2 and D4. Pramipexole is used to treat early stages of PD and able to stimulate direct striatopallidal pathway (by stimulation D3) at the same time and to inhibit the indirect striatopallidal pathway (by stimulation of D2). It can reduce PD symptoms by mimicking the effects of dopamine in the striatum. However, D3 receptors have the greatest dominance in the limbic system so theoretically pramipexole also has an impact on the psyche of PD patients. The dose used in early therapeutic is 0.375 mg per day in 3 divided doses. The dose may be increased every 5-7 days to a maximum of 4.5 mg per day (Arlina and Evaria, 2011). Pramipexole can be used before or in conjunction with levodopa. The study showed that patients' rest periods were reduced with the use of lower doses of pramipexole than levodopa. Side effects of pramipexole like other dopamine agonists include drowsiness, nausea, constipation, insomnia, and hallucinations (Atwood, Hunnewell and Saucier, 2005).

Ropinirole is a non-ergoline dopamine agonist with preferential affinity for D2-like receptors (D2, 3, 4) with a high affinity for D3 receptors concentrated in the limbic region of the brain thus explaining its neuropsychiatric effects. The affinity for D2 receptors in the striatum confer significant benefits in the motor state of PD. Meanwhile, ropinirole does not attach to D1-like receptors, GABA receptors or benzodiazepines. Specific unusual side effects to D3 agonists include hypersexuality and compulsive gambling, even in patients without this history of behaviours. Ropinirole can be used as monotherapy for PD or can be used as an additional therapy with l-dopa therapy. Gradual dose of ropinirol can be given, on the first week the dose is 0.25 mg, the second week 0.5 mg, the third week 0.75 mg, and fourth week 1 mg three times per day. It should be increased up to a maximum of 3 mg gradually (Tjay and Rahardja, 2007).

Rotigotine is a another new non-ergot dopamine agonist that attach on D1, D2 and D3 receptors (Rana, 2011). Rotigotine works by activating several types of nerves in the brain and is used in the treatment of patients with Parkinson's and Restless Legs Syndrome (RLS) used in monotherapy or in combination with levodopa. The application is in the form of skin patches or once-daily dosage forms (Factor and Weiner, 2008). Approximately 45% of rotigotine in the patch is released within 24 hours and the concentrations reach a steady state in 1-2 days. After it is extensively metabolized, rotigotine is excreted mainly as metabolites in the urine. Plasma concentrations decrease with a terminal half-life of 5-7 hours after patch removal.

2.3 MAO-B Inhibitors

MAO-B is one of the enzymes that present an essential role in the metabolism of dopamine. So MAO-B inhibitors may be defined as a compound that inhibits the metabolism of dopamine so that can be used in the treatment of Parkinson's disease. The metabolic processes that occur in the body are arranged in several steps and involve the breakdown of the body's natural chemicals or exogenous drugs given. Thus, dopamine metabolism inhibitory substance agents will manage dopamine in an active state for a long duration (Nutan, 2008).

Selegiline and rasagiline are inhibitors of monoamine oxidase-B, the other enzyme also responsible for degradation of dopamine in the brain (Baltuch and Stern, 2007). Selegiline is one of dopamine metabolism inhibitor. It inhibits the enzyme MAO-B, which acts in the central nervous system by breaking down dopamine to dihydroxyphenylacetic acid (DOPAC) and hydrogen peroxide. The latter has been implicated in oxidative damage to dopaminergic neurons in the substantia nigra. Selegiline was first introduced as a supporting therapy in the treatment of PD and was later combined with l-dopa to reduce motor fluctuations (Playford, 2004). Selegiline for PD as monotherapy is treated with 5 mg 1-2 times per day and can be given 5-10 mg 1-2 times per day after meal if it is combined with l-dopa (Tjay and Rahardja, 2007). Generally, the side effects caused are dryness in the mouth and dizziness. A new drug rasagiline has a similar action but the significant difference between these two drugs is still unclear, although it is sure that the drug inhibiting MAO-B is helpful in the treatment of Parkinson's disease (Nutan, 2008).

MAO-B inhibitors are studied in a model of neurotoxin MPTP-induced PD in both monkeys and mice. MPTP is a lipophilic compound that can penetrate the blood-brain barrier and is then oxidized by monoamine oxidase B (MAO-B) to 1-methyl-4-phenyl-2,3-dihydropyridinium (MPDP+) and 1-methyl-4-phenylpyridinium (MPP+) then carried into the cell by the transporters of dopamine, serotonin, and norepinephrine (DAT, SERT, NET). The presence of absorption by DAT explains the selectivity of MPTP-induced nigrostriatal damage. Studies show that neuromelanin contained in dopaminergic neurons can induce neural repair in PD and MPTP-treated monkeys by catalyzing ROS formation through their interaction with iron (Fisher *et al.*, 2008).

2.4 Catechol O-methyltransferase Inhibitors

COMT (catechol-O-methyltransferase) inhibitors are commonly used in the treatment of advanced PD (Playford, 2004). This enzyme is responsible for decomposing levodopa in the blood before it is transported into the brain (Nutan, 2008). Administration of levodopa with a COMT inhibitor has the advantage of increasing its elimination half-life (from 90 minutes to about 3 hours) as well as increasing the interdose, trench, and mean levodopa concentrations. Tolcapone and entacapone are COMT inhibitors approved for use with levodopa in the treatment of PD. Tolcapone acts by inhibiting COMT at the peripheral level and to a lesser extent at the central level, whereas entacapone acts only at the periphery.

Administration of levodopa with COMT inhibitors increases plasma levels more subtly and has the potential to deliver levodopa into the brain at more stable levels and decreased fluctuations in levodopa concentrations can be seen when standard levodopa is administered intermittently (Dushanova, 2012).

Entacapone inhibits the activity of the enzyme COMT and increases the amount of levodopa in the brain. The dose of entacapone for PD is 200 mg and can be combined with levodopa or dopa-decarboxylase inhibitor, the maximum dose is 200 mg ten times per day (Arlina and Evaria, 2011). The most common side effects of entacapone are abdominal pain and fatigue. The benefits of entacapone treatment include reducing total daily dose of levodopa, improving mobility within the optimum, and reducting the number of times when a patient has to take medication (Nutan, 2008).

The use of tolcapone has the same effect as entacapone in increasing levodopa levels in the brain. A rare but fatal side effect is acute liver failure, so its use is usually limited to patients who do not get satisfactory effects from other Parkinson's drugs (Nutan, 2008). However, every drug has side effects, it is important for neuroscience will prepare the most optimal treatment plan. even though no therapy can slow the progression of Parkinson's disease.

2.5 Anticholinergics

Anticholinergic agents are the oldest class of drugs used for the treatment of Parkinson's disease. Two of them are trihexyphenidyl (Artane) and benztropine (Cogentin) which are the most widely available (Nutan, 2008). Trihexyphenidyl is used orally with a dose of 1 mg and if necessary increased to 6-12 mg gradually to a maximum dose of 15 mg once per day (Tjay and Rahardja, 2007). Trihexylpenidyl exerts a similar effect as the neurotransmitter acetylcholine and is most effective at reducing resting temperature and stiffness from anti parkinsonism so it can be used as initial therapy in mild disease, especially if the tremor is the main symptom. This substance exerts a peripheral parasympathomimetic effect resulting in side effects such as dry mouth, blurred vision, urinary retention (especially in patients with prostatic hypertrophy), deposition of closed-angle glaucoma and constipation. Therefore, its use should be careful in geriatric patients. Anticholinergics may also be associated with withdrawal effects (Playford, 2004).

2.6 Amantadine

Amantadine is an antiviral agent that has been used in Parkinson's disease (Nutan, 2008). Several mechanisms have been proposed for its antiparkinson effects which include the release of dopamine from dopaminergic neurons, dopamine reuptake inhibition, anticholinergic action and NMDA glutamate receptor antagonism (Playford, 2004). Amantadine might be acted by increasing the release of dopamine from dopamine neurons that are still healthy and producing (Nutan, 2008). The dose of amantadine for PD is 100 mg once per day (HCl or sulfuric) after breakfast, then after a week it can be increased to 100 mg twice per day and the maximum dose is 400 mg per day (Tjay and Rahardja, 2007).

Amantadine provides a limited improvement in bradykinesia (slow movement), stiffness, and tremor at rest. However, the effect of amantadine on the control of dyskinesia may develop later in Parkinson's disease. Side effects that may occur with the consumption of this drug are lower extremity edema (swelling due to fluid accumulation), confusion, and hallucinations. This confusional effect causes its use to be limited in patients (Nutan, 2008).

Poor response to l-dopa consumption as well as hallucinatory effects due to dopaminergic medication

can lead to dementia. This cognitive failure is caused by l-dopa-induced hyperhomocysteinaemia. Consumption of amantadine can delay and overcome these effects of dementia (Burn, 2007).

3. HERBAL MEDICINE IN TREATING PD

The development of PD pharmacological treatment was progressing greatly with the discovery of various new therapies and strategies for their therapy. However, existing treatments only improve symptoms but do not improve disease progression. Therefore, it is still necessary to identify compounds that can reduce the effects of oxidative stress that cause PD and function as neuroprotective substances in PD. Based on the literature search, these compounds can be found in the following herbs.

3.1 *Scutellaria baicalensis* Georgi

Scutellaria baicalensis Georgi is a Chinese herb known as Huangqin commonly used as an anti-Parkinson's drug. *Scutellaria* baicalensis is a herbal medicine that is widely used to treat various infectious and inflammatory diseases. Herbal ingredients of this plant are used in medicine as antipyretic, antibacterial, antihypertensive and stroke. The root part of this plant contains various flavone derivative compounds including baicalin, baicalein and wogonin.(Li *et al.*, 2005).

Baicalein is one of the major flavonoid compounds isolated from the roots of *S. baicalensis*. Several studies have shown that this compound has potent antioxidant activity, scavenger radicals and has been considered a 12/15-lipoxygenase and xanthine oxidase inhibitor. Anti-inflammatory activity study of baicalein was shown to oppose the expression of adhesion molecules induced by interleukin-β1 (IL-β1) and tumor necrosis factor (TNF-α). Recent studies have shown that baicalein protects nerve tissue against amnesia induced by -amyloid peptide-(25–35) and nerve injury secondary to ischemia. This study shows that baicalein can be an active compound that is useful in the prevention and treatment of neurodegenerative diseases such as Parkinson's disease. (Mu *et al.*, 2009).

In another study, baicalein was shown to improve the abnormal behavior of mice treated with MPTP. The protective effect may be due to increased levels of DA and 5-HT in the striatum, increased number of dopaminergic neurons, inhibition of oxidative stress and astroglial response. This confirms the activity of baicalein on neural activity and its potential as a Parkinson's drug. The neuroprotective effect of baicalein is thought to be related to its ability to inhibit the production of neurotoxic factors such as NO, and in particular superoxide, by activated microlgia (Cheng *et al.*, 2008).

3.2 *Polygonum cuspidatum* Sieb. et Zucc.

Polygonum cuspidatum Sieb. et Zucc. is a medicinal plant used historically in Asia as a traditional medicine in the treatment of neuropsychiatric disorders, such as Parkinson's disease. Resveratrol is a compound that is efficacious in the treatment of Parkinson's. In addition, these compounds have an important role in the prevention of cancer, cardiovascular and neurodegenerative diseases (Liu *et al.*, 2011).

Polygoni cuspidati Rhizoma Et Radix is the dried root and rhizoma of *Polygonum cuspidatum* Sieb. et Zucc. (Polygonaceae). In vitro, resveratrol was shown to induce autophagy to prevent neurotoxicity, thereby protecting against rotenone-induced apoptosis in SH-SY5Y cells, and increasing synuclein-degradation in the PC12 cell line and providing a protective effect against MPP+-induced oxidative stress. by

modulating markers of apoptotic death in dopaminergic neurons (Li *et al.*, 2013).

Progressive neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's diseases are generally caused by nerve dysfunction and metabolic imbalance and resveratrol have been shown to overcome this via the SIRT1 pathway. Resveratrol can penetrate the brain barrier and exert a strong neuroprotective effect even at low doses. Prevention of Parkinson's disease is based on the scavenging mechanism performed by resveratrol. The efficacy of resveratrol against a variety of different mechanisms has been proved recently and is potentially useful in protecting against brain destruction following cerebral ischemia (Fernández-Mar *et al.*, 2012).

3.3 Green Tea (*Camellia sinensis* L.)

Green tea is a product derived from the leaves *Camellia sinensis* L. (Theaceae). A recent study shown that the Chinese and Japanese tea intake can reduces the risk of PD. Green tea extract can attenuate 6-OHDA-induced nuclear Factor-kB (NF-kB) activation and cell death in SH-SY5Y cells. Catechin polyphenols are derived from green tea have protective effect on SH-SY5Y cells. The four main components of polyphenols catechin are (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin gallate, (-)-epigallocatechin, and (-)-epicatechin (Mandel *et al.*, 2004; Li *et al.*, 2013). In one study, (-)-Epigallocatechin-3-gallate may regulate dopamine transporter internalization through a protein kinase C-dependent in MPP^+-induced PC12 cells, reducing dichlorodiphenyltrichloroethane-dopaminergic cell death in SHSY-5Y cells. In vitro, (-)-epigallocatechin-3-gallate can inhibit expression (inducible nitric oxide synthase) iNOS and cell death in mouse MPTP PD (Levites *et al.*, 2001; Li *et al.*, 2013).

Green tea is currently widely regarded as a food source filled with various biological and pharmacological activities that are beneficial to human health. In recent human and animal epidemiological data, it has been suggested that tea consumption may protect the brain from aging and recently proved that tea consumption is inversely correlated with the incidence of dementia and Alzheimer's and Parkinson's diseases. The main polyphenolic component, EGCG, demonstrated a protective and repairing effect on neural networks in tests in different cellular and animal models of heurological disorders. More consumption of green tea is related to decreased cognitive impairment. Besides that, sufficient experimental and animal evidence suggests that green tea may have potent neuroprotective, neuro-salvage, and amyloid precursor protein processing activities that may induce cognitive enhancement, no human data available (Sharangi, 2009).

3.4 *Panax ginseng* C. A. Mey.

Ginseng has long been known in traditional Chinese medicine to treat various health disorders for thousands of years, but only recently has it been recognized for its pharmacological effects on the central nervous system. Among them is its effect in modulating several biochemical markers thought to be important in the initiation and progression of PD (Van Kampen *et al.*, 2003). The roots of *Panax ginseng* C.A. Meyer (Araliaceae) is popular in the world as traditional medicine. Its main constituents are saponins, polysaccharides, alkaloids, and polyacetylenes (Park *et al.*, 2009). The molecular components responsible for the actions of ginseng are ginsenosides, also known as ginseng saponin (Radad *et al.*, 2004). The ginsenosides are contained in the root of Panax ginseng CA Meyer are ginsenoside Rg1, ginsenoside Rb1, ginsenoside Rh1, and

ginsenoside Rg2. The four compounds play a role in the treatment of PD (Rausch *et al.*, 2006).

Ginsenosides Rb1 and Rg1 can increase the secretion of acetylcholine especially in the hippocampus which results in improved performance in behavioral memory tests. Ginsenosides increase the concentrations of dopamine and norepinephrine in the cerebral cortex tested in rodents, which exert beneficial effects on attention, cognitive processing, integrated sensory-motor function and auditory reaction time in healthy human subjects. In addition, the effect of giving ginseng extract has been shown to prevent neuronal death in the forebrain and protect hippocampal neurons from ischemia. In in vitro studies, it was reported that ginsenosides could increase the viability of cultured cells and increase their neurite growth. For example, ginsenosides Rb1 can increase the growth of neurites from chicken dorsal root ganglia and cerebral cortex neurons in cultured cells. Against toxic insults, ginsenosides Rb1 and Rg1 protect neurons in spinal cord culture from excitotoxicity induced by glutamate and kainic acid, as well as oxidative stress induced by hydrogen peroxide (H2O2) and promote neurite length and neurite number of dopaminergic cells after exposure to MPP+ (Radad *et al.*, 2004).

3.5 *Cistanche deserticola* Y. C. Ma

Cistanche Herba, stem species Cistanche (Orobanchaceae), is a traditional Chinese medicine known as “Desert Ginseng” and has been used since 2000 years ago and among other Cistanche species, only this plant is documented in the Chinese Pharmacopoeia. In a recent study, it was reported that the main compounds of this plant, phenylethanoids and polysaccharides provide antioxidant, anti-inflammatory and immunomodulatory activities as well as anti-apoptotic effects. The glycoside compound of phenylethanoids such as verbascoside and echinacoside affects the central nervous system. Correspondingly, echincoside compounds have been shown to protect against a behavioral decline in a mouse model of Parkinson's disease (Stefanova *et al.*, 2011).

In a study on PC12 cells, verbacoside was shown to have an effect on MPP+ and glutamate-induced neurotoxicity and in vivo increased scopolamine-induced memory deficits. In addition, Echincoside exhibited an antiapoptotic effect on SH-SY5Y neurons after induction with TNF and exerted a behavioral storage effect in a mouse model of Parkinson's disease. In another test, raisin herb extract (CHE) increased the induction of nerve growth in C6 cells at a concentration of 250 g/ml and caused neurite growth in PC12 cells. Not only that, CHE also significantly stimulated the release of NGF in the rat cortex and hippocampal brain at a test dose of 5-20 mg/kg per day for 3 days. Furthermore, CHE increased nerve cell differentiation, neurite length, and synapse formation in the rat hippocampus and significantly improved learning and memory (Choi, Moon, *et al.*, 2011).

Nerve growth factor (NGF) is a signaling molecule in the nervous system that was discovered initially and is required for the survival, differentiation and maintenance of synaptic plasticity in cholinergic neurons and thus is required in cholinergic neuronal dysfunction. In one study it was found that NGF can prevent the neuronal loss, promote cholinergic growth, improve memory impairment and stimulate neurite growth through regulation of the cytoskeletal system and cell adhesion.
(Choi, Moon, *et al.*, 2011). However, due to the high molecular weight of NGF, it requires neurosurgical procedures for its treatment. Therefore, it is hoped that the synthesis of low molecular weight compounds, one of which is from the herb Cistanche

deserticola Y. C. Ma, is expected to be a solution so that it can maintain nerve function.

3.6 *Panax notoginseng* (Burk.) F. H. Chen

Panax notoginseng (Burk) F.H. Chen root is commonly known as Sanqi or Tianqi in China. It belongs to the Araliaceae family. This herbal medicine has been used in China for 600 years for the treatment of cardiovascular and cerebrovascular diseases. From the study shows that p. notoginseg can increase the expression of nestin and brain-derived neurotrophic factor (BDNF). In addition, this herb can improve nerve plasticity and functional recovery after focal cerebral ischemia. The active compound, Panax notoginseng saponin (PNS) is suspected to be the main bioactive compound available commercially and widely used in clinical medicine in China. This component consists of the saponins panaxadiol and panaxatriol. (PTS) (Luo *et al.*, 2010).

PTS were applied to the clinic for cardio and cerebro-vascular diseases in China by suppress thrombosis and blood viscosity in the brain. A recent report showed that PTS could protect against focal cerebral ischemia in rat brain through alleviating cerebral edema, up-regulating heat shock protein HSP70 expression and down-regulating transferring (Luo *et al.*, 2011). Another study showed that the PTS were inducers thioredoxin-1 (Trx-1) and could have potential as a therapeutic agent for Parkinson's disease (PD).

Thioredoxin-1 (TRX-1) is a multifunctional protein that exhibits an enhancing effect on cell growth and an inhibitory effect on apoptosis. It was reported that this protein acts as a neurotrophic co-factor that can enhance the effects of differentiation and repair factors on nerves. Research has shown that thioredoxin transgenic mice show a longer life span and resistance to ischemic injury, diabetes, and toxicity caused by environmental factors (Luo *et al.*, 2010). The bioactive compound PTS acts as a neuroprotective against nerve loss and behavioral disturbances caused by MPTP. In addition, it suppresses MPTP-mediated neuronal death in the SNC by increasing Trx-1 protein expression, suppresses COX-2 overexpression and inhibits mitochondrial-mediated apoptotic pathways.

3.7 *Gastrodia elata* Blume

Gastrodia elata Blume (GE) belongs to the family Orchidaceae. GE is a traditional plant in the oriental country. It is known for its enormous benefits to treat headaches, dizziness, vertigo and fatigue. GE also has been reported to have anti-seizure, anti-oxidative, anti-fungal, antifatigue, anti-angiogenic, anti-inflammatory, anti-epileptic, anti-obesity, anxiolytic and memory improving activities (Kim *et al.*, 2003). Gastrodiae Rhizome is the dried tuber of *G. elata* Blume and has a protective effect on MPP^+-induced cytotoxicity in human dopaminergic SH-SY5Y cells (Li *et al.*, 2013).

GE extract inhibited lipopolysaccharide (LPS)-stimulated production of inflammatory cytokines. It inhibited NO and iNOS by 4-Hydroxybenzyl alcohol (4-HBA), which was one of the bioactive components of GE in LPS-stimulated BV-2 cells. GE extract and bioactive components 4-HBA could be used to reduce microglial activation and developed to new therapeutic drugs to treat a variety of neuroinflammatory diseases such as PD. Besides 4-HBA, other bioactive components of GE were also investigated their activity to inhibit NO and iNOS releasing in LPS-stimulated BV-2 cells to support antineuroinflammatory effect of GE.

The other bioactive components are gastrodin, vanillyl alcohol and 4-hydroxybenzaldyde. The important role of GE extract in reducing various CNS

disorders is mediated by neuroinflammation. In a study, Vanillyl alcohol was known to protect dopaminergic MN9D cells against MPP^+-induced apoptosis by liberating oxidative stress and modulation of apoptotic processes. Therefore GE could be potential to treat PD (Kim *et al.*, 2012).

3.8 *Polygala tenuifolia* Willd

Polygalae radix (PRE) is the root of *Polygala tenuifolia* Willd (Polygalaceae). It is commonly used in traditional medicine amnesia and anxiety. PRE is one of the most prescribed herbal medicines for the treatment of a variety of cognitive symptoms associated with aging, dementia, and PD. PRE consists of various xanthones, saponins, and oligosaccharide esters. Extracting water from the PRE could inhibit toxin-induced neuronal death in PC12 cells caused by MPP^+.

Oligosaccharides were derived from PRE to inhibit the effects of depression in the cell by binding to the norepinephrine transporter protein and 3, 4, 5-trimethoxycinnamic acid (TMCA), the active constituent PRE. It has anti-stress effects via the suppression of norepinephrine. *P. tenuifolia* also contains Tenuigenin which has neuroprotective effects against 6-OHDA-induced injury in SH-SY5Y cells and protected dopaminergic neurons from inflammation-mediated damage induced by LPS. PRE could significantly protect PC12 cells against 6-OHDA-induced neurotoxicity through inhibition of ROS and NO production and caspase-3 activation. It suggested that PRE could provide prospective nerve for treating or preventing PD (Choi, Kim, *et al.*, 2011).

4. CONCLUSION

Differents modern medicine has been used in the treatment of Parkinson's disease with their respective levels of effectiveness and side effects. The presence of traditional herbal plants can be an option for

Parkinson's patients and is expected to be a way out to overcome the disease. The use of this herbal medicine needs further research so that it can provide clear information about the dose given and how to use it in patients so that treatment becomes more effective.

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