

REVIEW ON HERBAL'S USED FOR PARKINSON AND VARIOUS PROCEDURES FOR PARKINSON DISEASE

Patil Vishal Satish*, Manoj Alai and Mahesh Saralal

CK Pithawalla Institute of Pharmaceutical Science and Research, Surat-395007

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ABSTRACT

Parkinsonism is one of the commonest neurodegenerative diseases, which is characterized by a selective and progressive degeneration of dopaminergic neurons, causing a series of symptoms which might ultimately induce programmed cell death, Although the etiology of Parkinsonism remains unknown, recent studies have suggested that oxidative stress (OS), produces apoptosis which results in mitochondrial defects, neuroinflammation may also play important roles in its pathogenesis .Various agents as 6-Hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Rotenone a neurotoxin commonly and many more are used in models of PD, induces selective catecholaminergic cell death, mediated by reactive oxygen species (ROS) and mitochondrial defects. The present article puts focus on the possible use of various herbs used for parkinson The main purpose of this article is to have a closer look towards the herbal treatment for parkinsonism.

Keywords: Parkinson's disease, Neuroprotective, Antioxidant, Antiapoptotic, Herbal treatment

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative brain disorder that progresses slowly in most people. Most people's symptoms take years to develop, and they live for years with the disease [1,2]. In short, a person's brain slowly stops producing a neurotransmitter called dopamine. With less and less dopamine, a person has less and less ability to regulate their movements, body and emotions. Parkinson's disease itself is not fatal [3,4]. However, complications from the disease are serious; the Centers for Disease Control and Prevention (CDC) rated complications from PD as the 14th top cause of death in the United States. There is currently no cure for Parkinson's. Your doctor's goal will be to treat your symptoms to keep your quality of life as high as possible. That's why your gift to the National Parkinson Foundation goes directly to research that improves the daily lives of people with PD [5,6]. Normally, there are brain cells (neurons) in the human brain that produce dopamine. These neurons concentrate in a particular area of the brain, called the substantia nigra. Dopamine is a chemical that relays messages between the substantia nigra and other parts of the brain to control movements of the human body [6,7]. Dopamine helps humans to have smooth, coordinated muscle movements. When approximately 60 to 80% of the dopamine-producing cells are damaged, and do not produce enough dopamine, the motor symptoms of Parkinson's disease appear. This process

of impairment of brain cells is called neurodegeneration. The current theory (so-called Braak's hypothesis) is that the earliest signs of Parkinson's are found in the enteric nervous system, the medulla and in particular, the olfactory bulb, which controls your sense of smell. Under this theory, Parkinson's only progresses to the substantia nigra and cortex over the years [7,8]. This theory is increasingly borne out by evidence that non-motor symptoms, such as a loss of sense of smell, hyposmia, sleep disorders and constipation may precede the motor features of the disease by several years. For this reason, researchers are increasingly focused on these "non-motor" symptoms to both detect PD as early as possible and to look for ways to stop its progression [9,10]. Parkinson's disease impacts people in many different ways. Not everyone will experience all of the symptoms of Parkinson's, and if they do, they won't necessarily experience them in quite the same order, or at the same level of intensity. Even so, there are typical patterns of progression in Parkinson's disease that are defined in stages [11,12]. You might hear your doctor refer to your Hoehn and Yahr stage. This scale, first introduced in 1967, is a simple rating tool used by clinicians as a means to generally describe how motor symptoms progress in Parkinson's. Another more comprehensive tool is the Unified Parkinson's Disease Rating Scale (UPDRS) [13,14]. It takes into account factors other than motor symptoms, including mental functioning, mood and social interaction. While symptoms are unique to

each person, and the progression of symptoms varies from person to person, knowing the typical stages of Parkinson's can help you cope with changes as they occur. In some people, it could take 20 years to go through these stages. In others, the disease progresses more quickly.

Stages of Parkinson's Disease

Stage One

During this initial stage, the person has mild symptoms that generally do not interfere with daily activities. Tremor and other movement symptoms occur on one side of the body only. Friends and family may notice changes in posture, walking and facial expressions.

Stage Two

In stage two of Parkinson's, the symptoms start getting worse. Tremor, rigidity and other movement symptoms affect both sides of the body. Walking problems and poor posture may become apparent. In this stage, the person is still able to live alone, but completing day-to-day tasks becomes more difficult and may take longer.

Stage Three

Stage three is considered mid-stage in the progression of the disease. Loss of balance and slowness of movements are hallmarks of this phase. Falls are more common. Though the person is still fully independent, symptoms significantly impair activities of daily living such as dressing and eating.

Stage Four

During this stage of Parkinson's, symptoms are severe and very limiting. It's possible to stand without assistance, but movement may require a walker. The person needs help with activities of daily living and is unable to live alone.

Stage Five

This is the most advanced and debilitating stage of Parkinson's disease. Stiffness in the legs may make it impossible to stand or walk. The person requires a wheelchair or is bedridden. Around-the-clock nursing care is required for all activities. The person may experience hallucinations and delusions. While stage five focuses on motor symptoms, the Parkinson's community acknowledges that there are many important non-motor symptoms as well.

Herbs Used as Anti- Parkinson

1. **Withania somnifera;** (Family: **Solanaceae**); Syn: **Physalis somnifera**

Sankar Surendran et al studied the effect of extract of withania somnifera root on parkinsonism. Animals are treated with root extract for 7 days and 28 days after 4 days after treating with MPTP. The extract at the dose of 100mg/kg shows significant improvement in motor neurons function, catecholamines, potential antioxidant levels and prevent lipid peroxidation ie. reduced elevated levels of TBARS28 .

Uncaria rhynchophylla; (family: **Rubiaceae**)

Myung Sook Oh et al provided the scientific basis to support the traditional use of the Uncaria rhynchophylla in Parkinson's disease. Uncaria rhynchophylla possess the

neuroprotective activity against 6-OHDA toxicity in PC12 cells. In invitro PC12 cells, URE significantly reduced neuronal cell death, increased GSH Levels ($74.55 \pm 1.57\%$), attenuated ROS and inhibited the activation of caspase-3 in dose dependant manner induced by 6-OHDA. In in-vivo low dose of extract decreased the number of APO induced rotations by attenuating super sensitivity mediated by a selective irreversible MAO-B Inhibitor of URE, in the striatum and protect DA neurons .

Gastrodia elata Blume; (Family: Orchidaceae)

Dong Kug Choi et al found that pre-treatment with ethanolic extract of *Gastrodia elata* Blume at various concentrations (10, 100, 200_g/mL) ameliorate the MPP⁺-induced Bax/Bcl-2 ratio elevation in SH-SY5Y cells, attenuated capase-3 activation and PARP cleavage in a dose-dependent manner, shows anti-oxidant effect with significant radical scavenging activity for DPPH, and alkyl radicals, suppressed the accumulation of ROS and inhibit the both intracellular ROS production and downstream apoptotic signaling pathways.

Anemopaegma mirandu; (family: Bignoniaceae); Syn: Catuaba

Lisandro Diego Giraldez et al investigated the neuroprotective activity of extract of *Anemopaegma mirandu* against Rotenone-induced apoptosis in human neuroblastomas SH-SY5Y cells using in-vitro parkinsonian models. At concentrations ranging from 0.0097 mg/mL to 1.250 mg/mL, extract shows the

effectiveness by increasing cell survival by $22.3 \pm 3.6\%$, $22.0 \pm 2.1\%$ and $15.8 \pm 0.7\%$, restoring cellular and nuclear morphology to undistinguishable levels from the survival cells under control and preserving cytoplasmatic membranes and mitochondria membrane in human neuroblastomas SHSY5Y cells

Hypericum perforatum; (Family: Hypericaceae)

J. Benedi et al reported that pretreatment with 4mg/kg standardized extract of *Hypericum perforatum* for 45days in rotenone-exposed rats, exerts an antioxidant action which was related with a decreased of MnSOD activity, mRNA level, increased SOD and CAT activity and modified redox index thus protecting the cell from the damaging effect of hydrogen peroxide and shows neuroprotective activity 34 . M. Sabesan et al reported that combination of bromocriptine and *Hypericum perforatum* ethanolic extract prevented the behavioral deficits and biochemical alterations such as significant improvement in Dopamine, DOPAC levels, antioxidant status and significant reduction in lipid peroxidation

Plumbago scandens (Family: Plumbaginaceae); Syn: Jasmim azulQ

L.C.S.L. Morais et al found that Crude ethanolic extract (CEE) and total acetate fraction (TAF) of *Plumbago scandens* (1000 mg/kg, i.p.) Decrease locomotor activity, the presence of catalepsy and palpebral ptosis, thus acts against parkinsonism .

Bacopa monniera; (Family: Scrophulariaceae) ; Syn: Brahmi

Deepak Sharma et al found that Ethanolic extract of whole plant of Bacopa monniera shows the therapeutic effect in treatment of parkinsonism induced by aluminium neurotoxicity. It acts by reducing SOD activity significantly, prevents the increase in TBARS, lipofuscin accumulation and ultrastructural changes .

Muralidharan et al examined the neuroprotective properties of standardize extract of Bacopa monniera against rotenone induced oxidative damage and neurotoxicity. At concentrations of 0.05 and 0.1% for 7 days in the diet it exhibited significant diminution in the levels of endogenous oxidative markers viz., malondialdehyde, hydroperoxide and protein carbonyl content. Further, BM offered complete protection against rotenone (500 mM) induced oxidative stress and markedly inhibited dopamine depletion (head region, 33%; body region, 44%) and also conferred significant resistance (43–54% protection) in a paraquat oxidative stress bioassay in *Drosophila melanogaster* .

8.Pueraria thomsonii ;(Family:Fabaceae)

Mei-Hsien Lee et al investigated the Neurocytoprotective effects of Pueraria thomsonii bioactive constituents ie daidzein and genistein in 6-OHDA induced aptosis in differentiated PC12 cells. daidzein and genistein at concentrations of 50 µM and 100µM inhibited caspase-8 and partially inhibited caspase-3 activation, providing a protective mechanism against 6-OHDA-

induced cytotoxicity in NGF-differentiated PC12 cells.

CHINESE MEDICINES

In the literature studies, it was found that many Chinese medicines and formulation have been used in the treatment of parkinsonism. This includes:- Zhen-Wu-Tang consists of the Radix Paeoniae Alba (30 g), Rhizoma Atractylodis Macrocephalae (10 g), Rhizoma Typhonii Preparata (10 g), Poria (10 g), Rhizome Zingiberis Recens (10 g), at dose of 8 and 16mg/kg/day for 2 weeks⁴⁵ .

Bak Foong Pills consists of Panax ginseng, Renshen; Angelica sinensis, Danggui; Glycyrrhiza uralensis, Gancao; and Ligusticum chuanxiong

Medications

Medications may help you manage problems with walking, movement and tremor. These medications increase or substitute for dopamine, a specific signaling chemical (neurotransmitter) in your brain. People with Parkinson's disease have low brain dopamine concentrations. However, dopamine can't be given directly, as it can't enter your brain. You may have significant improvement of your symptoms after beginning Parkinson's disease treatment [15,16]. Over time, however, the benefits of drugs frequently diminish or become less consistent, although symptoms usually can continue to be fairly well-controlled .

Medications your doctor may prescribe include:

Carbidopa-levodopa. Levodopa, the most effective Parkinson's disease

medication, is a natural chemical that passes into your brain and is converted to dopamine.

Levodopa is combined with carbidopa (Rytary, Sinemet), which protects levodopa from premature conversion to dopamine outside your brain, which prevents or lessens side effects such as nausea.

Side effects may include nausea or lightheadedness (orthostatic hypotension).

After years, as your disease progresses, the benefit from levodopa may become less stable, with a tendency to wax and wane ("wearing off").

Also, you may experience involuntary movements (dyskinesia) after taking higher doses of levodopa. Your doctor may lessen your dose or adjust the times of your doses to control these effects.

Carbidopa-levodopa infusion. The U.S. Food and Drug Administration approved a drug called Duopa in 2015. This medication is made up of carbidopa and levodopa. However, it's administered through a feeding tube that delivers the medication in a gel form directly to the small intestine.

Duopa is for patients with more advanced Parkinson's who still respond to carbidopa-levodopa, but who have a lot of fluctuations in their response. Because Duopa is continually infused, blood levels of the two drugs remain constant.

Placement of the tube requires a small surgical procedure. Risks associated with

having the tube include the tube falling out or infections at the infusion site.

Dopamine agonists. Unlike levodopa, dopamine agonists don't change into dopamine. Instead, they mimic dopamine effects in your brain.

They aren't as effective as levodopa in treating your symptoms. However, they last longer and may be used with levodopa to smooth the sometimes off-and-on effect of levodopa.

Dopamine agonists include pramipexole (Mirapex), ropinirole (Requip) and rotigotine (given as a patch, Neupro). A short-acting injectable dopamine agonist, apomorphine (Apokyn), is used for quick relief.

Some of the side effects of dopamine agonists are similar to the side effects of carbidopa-levodopa, but also include hallucinations, sleepiness and compulsive behaviors such as hypersexuality, gambling and eating. If you're taking these medications and you behave in a way that's out of character for you, talk to your doctor.

MAO-B inhibitors. These medications include selegiline (Eldepryl, Zelapar) and rasagiline (Azilect). They help prevent the breakdown of brain dopamine by inhibiting the brain enzyme monoamine oxidase B (MAO-B). This enzyme metabolizes brain dopamine. Side effects may include nausea or insomnia.

When added to carbidopa-levodopa, these medications increase the risk of hallucinations.

These medications are not often used in combination with most antidepressants or certain narcotics due to potentially serious but rare reactions. Check with your doctor before taking any additional medications with a MAO-B inhibitor.

Catechol-O-methyltransferase (COMT) inhibitors. Entacapone (Comtan) is the primary medication from this class. This medication mildly prolongs the effect of levodopa therapy by blocking an enzyme that breaks down dopamine.

Side effects, including an increased risk of involuntary movements (dyskinesias), mainly result from an enhanced levodopa effect. Other side effects include diarrhea or other enhanced levodopa side effects.

Tolcapone (Tasmar) is another COMT inhibitor that is rarely prescribed due to a risk of serious liver damage and liver failure.

Anticholinergics. These medications were used for many years to help control the tremor associated with Parkinson's disease. Several anticholinergic medications are available, including bethanechol (Cogentin) or trihexyphenidyl.

However, their modest benefits are often offset by side effects such as impaired memory, confusion, hallucinations, constipation, dry mouth and impaired urination.

Amantadine. Doctors may prescribe amantadine alone to provide short-term relief of symptoms of mild, early-stage Parkinson's disease. It may also be given with carbidopa-levodopa therapy during

the later stages of Parkinson's disease to control involuntary movements (dyskinesias) induced by carbidopa-levodopa.

Side effects may include a purple mottling of the skin, ankle swelling or hallucinations.

Marketed Formulation available in india

BR-16A (Mentat, The Himalaya Drug Co., Bangalore, India) is a herbal medication derived from principles laid down in Ayurveda, a traditional system of medicine in India. BR-16A (Mentat) contains over 20 different ingredients, the exact formulation differing between paediatric and adult presentations of the composite. Important ingredients of BR-16A (Mentat) suggested to improve memory functions include the following: Brahmi (Bacopa monnieri), Mandukaparni (Centella asiatica), Ashvagandha (Withania somnifera), Vishnukrantha (Evolvulus alsinoides), Jatamansi (Nardostachys jatamansi), Vacha (Acorus calamus), Jyotishmati (Celastus paniculatus) and Sunthi (Zingiber officinale). The other ingredients of BR-16A (Mentat) claimed to be nerve tonics include Tagara (Valeriana wallichii), Vatadha (Prunus amygdalus), Salabmisri (Orchis mascula), Lavanga (Syzygium aromaticum) and Mukta pishti. The remaining ingredients are putative, general tonics and vitalizers¹⁻³. Each ingredient is a plant extract which contains a variety of psychotropic and other compounds. The formulation of BR-16A (Mentat) is in accordance with Ayurvedic principles - different components of the formulation mutually complement each others' properties.

Surgical procedures

Deep brain stimulation. In deep brain stimulation (DBS), surgeons implant electrodes into a specific part of your brain. The electrodes are connected to a generator implanted in your chest near your collarbone that sends electrical pulses to your brain and may reduce your Parkinson's disease symptoms.

Your doctor may adjust your settings as necessary to treat your condition. Surgery involves risks, including infections, stroke or brain hemorrhage. Some people experience problems with the DBS system or have complications due to stimulation, and your doctor may need to adjust or replace some parts of the system.

Deep brain stimulation is most often offered to people with advanced Parkinson's disease who have unstable medication (levodopa) responses. DBS can stabilize medication fluctuations, reduce or halt involuntary movements (dyskinesias), reduce tremor, reduce rigidity, and improve slowing of movement.

DBS is effective in controlling erratic and fluctuating responses to levodopa or for controlling dyskinesias that don't improve with medication adjustments.

However, DBS isn't helpful for problems that don't respond to levodopa therapy apart from tremor. A tremor may be controlled by DBS even if the tremor isn't very responsive to levodopa [17,18].

Neuroprotective Therapy

So far no drug or surgical approach has been shown unequivocally to slow the

rate of progression of PD, but if any drug should be proved to delay the progression of the disease process, it should be incorporated in treatment early in the course of the There are some controlled clinical trials that were sufficiently positive to have raised the possibility that the propargylamine agents selegiline and rasagiline and the mitochondrial enhancing agent coenzyme Q10 could have some neuroprotective qualities.^{36–38} Larger clinical trials with neuroimaging of striatal dopamine nerve terminals would be necessary to provide adequate documentation of neuroprotection.

Symptomatic Therapy Dopamine replacement therapy is the major medical approach to treating PD, and a variety of dopaminergic agents are available .The most powerful drug is levodopa. It is usually administered with a peripheral decarboxylase inhibitor to prevent formation of dopamine in the peripheral tissues. In addition to being metabolized by aromatic amino acid decarboxylase, levodopa is also metabolized by catechol-O-methyltransferase (COMT) to form 3-O-methyldopa. The use of a COMT inhibitor with levodopa can extend the plasma half-life of levodopa without increasing its peak plasma concentration and can thereby prolong the duration of action of each dose of levodopa. Although levodopa is the most effective drug to treat the symptoms of PD, about 60% of patients develop troublesome complications of disabling response fluctuations (the "wearing-off" effect) and dyskinesias after five years of levodopa therapy; younger patients (less

than 60 years of age) are particularly prone to developing these problems even sooner. The next most powerful drugs in treating PD symptoms are the dopamine agonists. Several of these are available [19,20]. Apomorphine may be the most powerful, but it needs to be injected or taken sublingually. The others agonists are effective orally. Pergolide, pramipexole, and ropinirole appear to be equally effective; and all are more powerful than bromocriptine. Cabergoline and lisuride are not available in the U.S. Cabergoline has the longest half-life and therefore may prove ultimately to be most useful. Compared to levodopa, dopamine agonists are more likely to cause hallucinations, confusion, and psychosis, especially in the elderly. Thus, it is safer to use levodopa in patients over the age of 70 years. They are also more likely to cause drowsiness and, after several years of use, can cause leg edema. On the other hand, controlled clinical trials have revealed that dopamine agonist therapy is less likely to produce dyskinesias and the wearing-off phenomenon than levodopa. But these trials also showed that levodopa provides greater symptomatic benefit than do dopamine agonists. The neuroimaging component of these studies reveals that striatal dopamine nerve terminals disappear at a faster rate with levodopa treatment than with the agonists [21,22]. There is uncertainty about how to apply the information gleaned from these studies to the patient; a frank discussion between physician and patient should lead to the appropriate treatment for that individual.

Although DBS may provide sustained benefit for Parkinson's symptoms, it doesn't keep Parkinson's disease from progressing.

Other treatment methods and side effects

The other methods of treating the Parkinson disease include the Repetitive Transcranial Magnetic Simulation or RTMS even though there is no evidence that it has improved the lifestyle of the person suffering from the Parkinson disease. Other treatments such as acupuncture, Tai Chi have any effect on the course of the disease or its symptoms [23,24]. Eating natural sources of food such as eating Fava beans and Velvet beans seem to make a difference, but their intake is not risk free as in some cases life threatening adverse reactions has been noticed in the form of Neuroleptic Malignant Syndrome or NMS.

Diet for Parkinson's disease treatment

Here are a few dietary tips for those who have Parkinson's and are undergoing medication to treat it. *It is vital for the patients to remember that they have to control their diet in order to get a better grasp on their weight. Being healthy and being the right weight can go a long way when it comes to keeping the body ready for the medication it takes in every day.*

It is vital for people with Parkinson's to include high fiber foods in their diet. Some of the most important foods with high fiber

include legumes like peas and beans, whole grain bread and food, vegetables, cereals, bran, pasta, rice, fresh fruits etc.

3.It is important for these people to also avoid food that has a lot of cholesterol or saturated fat.

4.It is best to reduce the amount of milk or yogurt a person consumes as well. Sugar intake should also be severely limited.

5.Salt intake should also be limited.

6.High water intake would be an important aspect of Parkinson's disease treatment. At least 8 glasses of water should be consumed per day. However, people have to make sure that they don't severely increase the intake of water for they might end up losing important minerals from their body.

7.It is better for people to avoid alcohol when they are on medication to treat Parkinson's for the alcohol might interfere with the medication.

DISCUSSION

A huge number of herbal medicine ie herbs, formulations have been reported for their effective action in prevention and treatment of parkinsonism. Most literatures have been focused on the antioxidant, neuroprotective, anti-inflammatory and anti-apoptosis herbs such as Thuja orientalis, Mucuna pruriens, Ginkgo biloba, Plumbago scandens and various other ayurvedic, Chinese plants [25,26]. The many constituents presents in these plants used against parkinsonism are Dopamine, flavonoids, alkaloids,

other polyphenols. One should have closer look towards pharmacological and phytochemical constituents of this herbs, which can be useful for preparation of formulation [27,28].

CONCLUSION

There are currently a few plant-derived drugs approved for clinical use. This is largely because most herbal medicines are complex mixtures of chemical components and have diverse biological and pharmacological actions [29]. The information collected in this review on a large number of herbal extracts and constituents that possess therapeutic effects on animal models of Parkinson is may be used in a search for novel pharmacotherapies from medicinal plants for these disorder [30]. The herbal constituents for whom behavioral effects and pharmacological properties have been well characterized may be good candidates for further investigations that may ultimately result in clinical use. Considering the limitations of the available conventional pharmacotherapeutic agents for parkinsonism, particularly the treatment refractoriness, high relapse rates and diverse adverse side effects that occur with long-term treatments, herbal remedies may provide an alternative for patients, especially for those with lingering conditions and intolerance to adverse effects

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