Modern-day naturopathic medicine and traditional Ayurveda in a combined attack against Parkinson's disease

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Abstract

In Parkinson's disease, the neuronal cells that produce the neurotransmitter dopamine deteriorate. As a consequence, dopamine levels decline and symptoms appear. Treatment has traditionally involved dopamine's chemical precursor, L-dopa. Although widely used, this treatment is accompanied by unpleasant toxic effects and causes only symptomatic relief while the disease progresses. The legume *Mucuna* pruriens (L) DC. (Fabaceae) has been used in Ayurveda as a naturopathic medicine for the treatment of Parkinson's disease (then known as Kampavata). The results from more recent clinical studies suggest that this nutraceutical may be more effective than L-dopa against the symptoms of Parkinson's disease, may possess neuroprotective properties, and may even cure patients suffering from this condition. This indicates a need for further *in vitro* as well as clinical research with *M. pruriens*.

Keywords: Ayurveda, Parkinson's disease, *Mucuna pruriens* (L) DC., naturopathic medicine, nutraceutical

Etiology of Parkinson's disease

Parkinson's disease was named after the English medical doctor, James Parkinson, who in 1817 was the first person to describe the symptoms as "the shaking palsy." These symptoms were supposedly caused by a deficiency in the neurotransmitter dopamine (Parkinson, 2002). A neurotransmitter is a chemical messenger between nerve cells (Van den Bosch, 1996; Parkinson, 2002). According to Wichmann and DeLong (1993), Parkinson's disease patients, as a result of dopamine deficiency (Figure 1), suffer from increased motor behavior impairment, usually at an older age. Based on the first symptoms, however, diagnosis can be difficult since at that point symptoms are often non-specific and can include weakness, tiredness, and fatigue. Consequently the disease may be unrecognized for some time. The primary symptoms of Parkinson's disease include: muscular rigidity, resting tremor, difficulty with movement initiation (bradykinesia), slowed voluntary movement, difficulty with balance, and difficulty with walking. Next to Parkinson's disease's primary symptoms mentioned above, a patient may also start to suffer from secondary symptoms which include: depression, senility, postural deformity, and difficulty in speaking. Regardless of these primary and secondary symptoms, Albert et al. (2010) found impairment of hand functions during daily activities to be the most disabling symptoms in Parkinson's disease. According to Dorsey et al. (2007), the number of Parkinson's patients over the age of 50

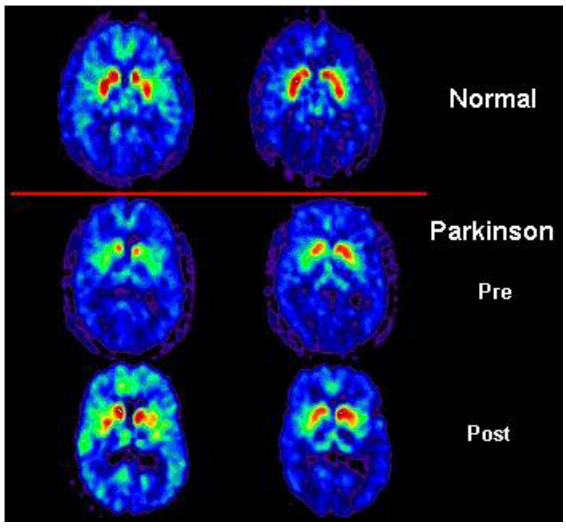

Figure 1. Positron Emission Tomography (PET) scans of the brain, showing dopamine production in red. From top to bottom: normal brain functioning, and before- and after-treatment of Parkinson's disease with L-dopa.

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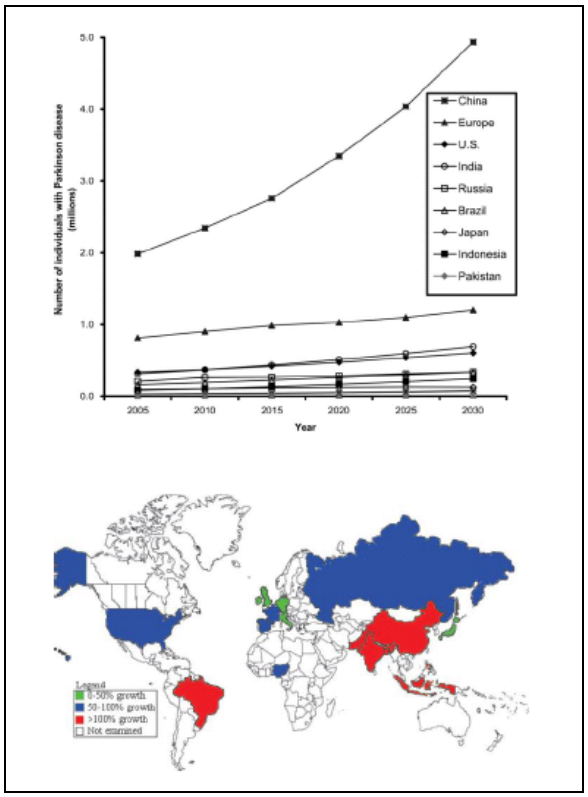

Figure 2. From: *Neurology*, 2007. 68:384-386. Projected number and growth rates of individuals over age 50 with Parkinson disease by country, 2005 through 2030. The values for Europe are for the five most populous nations in Western Europe (Germany, France, the United Kingdom, Italy, and Spain).

calculation leads to a total of up to 9.3 million patients by 2030 in Western Europe's 5 and the rest of the world's 10 most populous nations, with 4.94 million patients in China alone (Figure 2). The exact onset of Parkinson's disease is debatable (Caig and Tolosa, 2009). More than a century after the shaking palsy description, the main cause of its symptoms is still believed to be a dopamine deficiency in the basal ganglia of the brain. In Parkinson's disease, the neural cells, producing dopamine, deteriorate. When these neurons start to disappear, the normal rate of dopamine production decreases. It is noted that when dopamine supply is abnormally low, Parkinson's symptoms start to appear. However, according to Caig and Tolosa (2009), patients with Parkinson's disease often present non-motor symptoms years before the classical neurological signs develop; this is possibly related to an early pathological process of the non-dopaminergic lower brain stem or the autonomic plexuses.

A first diagnosis for Parkinson's disease is often the primary symptoms. If this test is significant, a trial test of anti-parkinsonian drugs may be used to further diagnose the presence of Parkinson's disease. This test is often performed with L-dopa, the precursor in the biosynthesis of dopamine in nerve cells. An excess of L-dopa causes the remaining dopaminergic cells to increase the production of dopamine. If the patient fails to benefit from L-dopa therapy, the diagnosis of Parkinson's disease is questioned. Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the brain may be helpful in ruling out other diseases with symptoms resembling Parkinson's disease. These diseases may include other neurological disorders such as: brain tumors, repeated head trauma, or prolonged use of certain drugs; such conditions need not be confused with Parkinson's disease. Lorenzl (2009) describes these atypical symptoms as Parkinson's syndrome, or Atypical Parkinson's.

Physiology of Parkinson's disease

A variety of small molecules can serve as neurotransmitters; some examples are glutamate, gamma-aminobutyric acid (GABA), and dopamine. These chemicals do not serve only one function, but the same chemical messengers can be released in the bloodstream to serve as hormones. In order for a substance to be considered a neurotransmitter, it needs to meet certain criteria such as: being synthesized in the neuron present in the presynaptic terminals and released in the synaptic gap; having a short distance signaling effect on the postsynaptic neuron, and there is a mechanism to remove it from the synaptic cleft. An extra criterion is that when the chemical is administered as a drug in comparable concentrations, it exerts the same effect (Schwartz, 1991). This is a key in finding treatment options for Parkinson's disease.

Neuronal signaling can occur electronically, by directly inducing a potential difference in the cell membrane of the connecting neurons; or chemically, by releasing a neurotransmitter that influences ion pumps in the cell membrane (Kandel, Siegelbaum, & Schwartz, 1991; Schwartz, 1991). An electrical signal is fast and of short duration while chemical transmissions are typically relatively slow and longer lasting. The manner of signal transmission depends on the type of synapse; for the purpose of L-dopa applications in Parkinson's disease the chemical synapses are most relevant.

Vermeulen (1994) gives a detailed description of the functioning of a chemical synapse that is much wider and that does not consist of direct connections. The presynaptic terminals have active zones that contain collections of synaptic vesicles, which in turn consist of thousands of neurotransmitter particles usually synthesized in the synaptic terminal. The neurotransmitter relevant to Parkinson's disease, dopamine, is synthesized in the presynaptic terminal by several metabolic pathways (Figure 3); a general coupling mechanism between neurotransmitter synthesis and packaging of transmitter into synaptic vesicles takes place using the GABA synthesizing enzyme, GAD (Chen et al. 2003). First tyrosine in the cell is converted to L-dopa with the help of the enzyme tyrosine hydroxilase (TH). L-dopa is in turn converted into dopamine by the enzyme aromatic amino acid decarboxylase (AADC). The synthesized dopamine molecules in the presynaptic terminal are then taken up by synaptic vesicles. After the dopamine is released from the vesicles into the synaptic cleft, the remaining

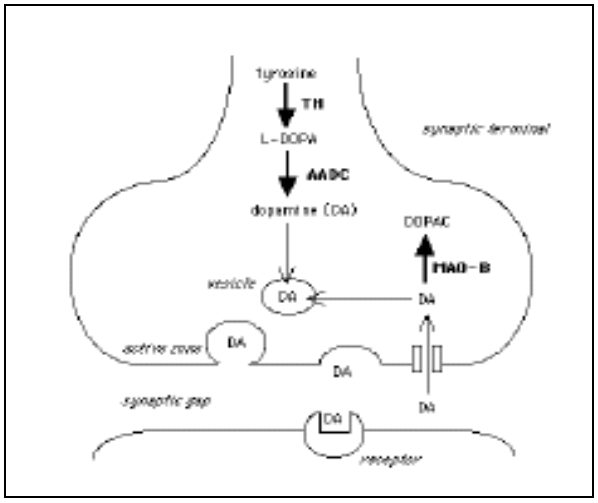

Figure 3. Prototype dopaminergic terminal with cycle of synthesis, storage, release, and removal of dopamine (Cooper et al, 1996).

molecules are taken back into the synaptic terminal by transporters in the membrane. There they are transported back into vesicles or broken down to DOPAC by the enzyme monoamine amine oxidase type B (Vermeulen, 1994).

Pathophysiology of Parkinson's disease

The *substantia nigra*, a midbrain structure, is part of the basal ganglia complex due to its close ties with the striatum. It has been divided into two components: the *pars compacta*, and the *pars reticulata*. The *pars compacta* is a cell-rich region is composed of large pigmented neurons in humans. These neurons exhibit a characteristic black pigmentation; hence the origin of the structure's name ("black substance").

In postmortem studies of Parkinson patients it was discovered that the *substantia nigra* had lost its pigment (Werner et al, 2008). Subsequent studies have shown that dopamine levels in the striatum of these patients' brains were drastically reduced. Because the basal ganglia contains most of the dopaminergic neurons of the brain, these observations suggested that the dopaminergic pathway between the striatum and *substantia nigra* are degenerated in Parkinson's disease patients. The depletion of dopamine unbalances the direct and indirect pathways from the striatum, causing overstimulation of the thalamus. As a result the frontal cortex is less activated, which would account for most of the Parkinsonian symptoms. Parkinson's disease has become the first example of a disorder related to a deficiency of a neurotransmitter, and can now be called a molecular disease with a growing research-interest in genetic underlying factors (Xiromerisiou et al., 2010).

Conventional treatment of Parkinson's disease

The objective for management of Parkinson's disease is often to attempt to keep the individual functionally active and independent as long as possible (Singhal et al., 2003). The role of exercise and relaxation (e.g. yoga) at all stages of the disease is emphasized, and patient and caregiver are educated about the conditions and options. When the need for pharmacologic therapy arises, the appropriate drug is selected, starting with a low dose and increasing it very slowly. L-dopa is the best available remedy currently known to ease the lives of Parkinson's patients (Pezzoli and Zini, 2010). However , it is not a cure, because this treatment aims to increase dopamine levels and not stop the further deterioration of dopaminergic cells, and hence it does not work well in the long term. Long-term use of L-dopa frequently results in fading of the therapeutic effect and the development of serious side effects such as further motor impairment and psychiatric complications. Furthermore, while the lack of dopamine causes most of the Parkinson's symptoms, Parkinson's disease patients also suffer a loss of noradrenergic and serotonergic neurons, which contribute to the disease as well.

According to Szabo and Tebbett (2002), L-dopa itself has very little pharmacological effect, since it is rapidly converted to dopamine; thus, ingestion of L-dopa results in significantly elevated levels of systemic dopamine. It is not possible to administer dopamine itself as a drug because it will not pass the blood-brain barrier between the blood vessels and neurons, wherasL-dopa-the precursor in the synthesis of dopamine- will. Boosting the dopamine production to higher levels by providing the few remaining healthy dopaminergic neurons with large amounts of extra L-dopa could solve thisproblem (Côté & Crutcher, 1991; Vermeulen, 1994).

Positive effects are, however, potentially countered by serious signs of L-dopa toxicity such as nausea, vomiting, diarrhea, weight loss, anorexia, skin lesions, orthostatic hypotension resulting in dizziness and in some cases staggering, and increased heart rate (Huisden et al., 2008 a, b). The undesirable effects narrow the therapeutic window with the natural progression of Parkinson's disease (Pezzoli and Zini, 2010). Most side effects could be explained by the presence of the enzyme AADC, which converts L-dopa to dopamine, in the liver, kidney and many other places in the body. Thus, while the dopamine levels in the striatum become more normal, the extra dopamine production disturbs chemical balances elsewhere in the body.

To bypass the problem of the side effects of L-dopa treatment, researchers started to synthesize compounds that would directly act on dopamine receptors. These compounds, called receptor agonists, would take over the role of dopamine, so that no administration of L-dopa would be needed. This would counter side effects induced by large amounts of L-dopa. In reality, however, the dynamics are more complicated (Brodsky et al., 2010) and require further investigation.

There are controversies surrounding side effects of the current pharmaceutical supplementation of L-dopa. Over the long term, supplemented L-dopa appears to lose its effectiveness (Pezzoli and Zini, 2010). Another area of controversy questions whether

L-dopa is toxic to dopamine neurons; more evidence is, however, required to support this concern.

While long-term treatment with the available dopamine receptor agonists results in fewer dyskinesias, the effect is inferior to that of L-dopa and increasing the dose only leads to other serious side effects such as psychotic reactions. Better effects result from a combination of low doses of L-dopa with an agonist (Szabo and Tebbett, 2002). Synthetic agonists have the advantage that they can be made highly selective for a particular receptor, but often the interaction of the drugs requires extensive research and proper balancing (Brodsky et al., 2010). There are currently multiple types of dopamine receptors identified; detailed knowledge on their mechanism of action is required to develop better tailored agonists with fewer side-effects.

Szabo and Tebbett (2002) describe the bioavailability of L-dopa with regard to its prescription in a drug regimen with a peripheral decarboxylase inhibitor (usually carbidopa or benserazide) to prevent loss of L-dopa by the L-aromatic amino acid decarboxylase (LAAD) metabolism that begins in the intestinal mucosa. The presence of an inhibitor increases the amount of L-dopa available to the brain by 75-80%, thereby decreasing the dosage necessary to achieve a therapeutic effect. This, in turn, results in a corresponding decrease in dose-dependent peripheral side effects.

Because its transport across the intestinal membrane is facilitated, the bioavailability of L-dopa is highly dependent on competitive factors such as the presence of amino acids (especially phenylalanine and leucine) utilizing the same carrier and the gastric emptying rate (longer stay, lower availability due to metabolism in the mucosal lining), which is affected by pH and the presence of protein (Cereda et al., 2010). Thus, nutritional status and metabolic characteristics of the individual influence the absorption and conversion rates for L-dopa, which assists in explaining the wide disparities observed in peak plasma levels (up to tenfold). Dietary vitamin B6 (pyridoxine) also plays a role in L-dopa metabolism and in cases of overdose, administration of vitamin B6 is used as a means of increasing peripheral decarboxylation to quickly lower the drug level and resolve the overdose (Szabo and Tebbett, 2002). Consequently, treatment is not as effective when vitamin B6 is given in the presence of an LAAD inhibitor. Patients taking L-dopa for Parkinson's are counseled against eating large quantities of protein and against taking vitamins or consuming foods prepared with vitamin B6, as the protein will limit absorption and a single vitamin B6 dose of 10-25 mg can effectively cancel the therapeutic L-dopa effect (Cereda et al., 2010; Szabo and Tebbett, 2002).

Figure 4. *Mucuna pruriens* (L) DC. (Fabaceae).

Traditional treatment of Parkinson's disease

The shaking palsy has existed in different parts of the world since ancient times (Manyam, 1990). The first clear description is found in the ancient Indian medical system of Ayurveda under the name Kampavata (Manyam & Sanchez-Ramos, 1999). Traditional therapies in the form of herbal preparations containing anticholinergics, L-dopa, and monoamine oxidase inhibitors were used in the treatment of Parkinson's disease in India, China, and the Amazon basin. According to Nagashayana et al. (2001), the ancient medical science being practiced in India from the *Vedic* times (1500–1000 BC), Ayurveda ("knowledge concerning longevity"), used plant tissues as medicine. Singhal et al. (2003) report that Parkinson's disease has a low prevalence in India except in the small Parsi community. Although early onset Parkinson's disease and familial cases have been described from India, no genetic mutations have as yet been identified. Parkinson's disease has been known in India since ancient days and the powder of *Mucuna pruriens* (L) DC. (Fabaceae) seeds was used for its treatment (Figure 4). *M. pruriens* is a climbing legume that originates in southern China and eastern India (Huisden, 2005). The genus thrives under warm, moist conditions, below 1500m above sea level, and in areas with plentiful rainfall. It is currently widely available in most tropical regions of Asia, South and Central America, and Africa. The holistic approach of Ayurveda takes advantage of the known and unknown active biochemical ingredients of the plant tissue. The disadvantages are the bulkiness of the preparation and difficulty in its administration. Thus, extracts of such medicinal preparations need to be made available in a user friendly form.

The clinical features and treatment of Kampavata ("kampa" = tremors) resembling Parkinson's disease are also mentioned in Ayurveda. The various signs and symptoms of Kampavata are found in Caraka Samhita (written by Atreya in 2500 BC) and Madhavanidhani (Singhal et al., 2003). These include rigidity, tremors of hands and feet, head tremor, drooling of saliva, love of solitude (depression), somnolence, reptilian stare, stammering, tremors of hands and feet, difficulty in body movements, disturbed sleep and dementia.

According to Singhal et al. (2003), Ayurveda described several formulations for the treatment of Kampavata. Nearly 18 of these contain *M. pruriens* (known as Atmagupta in Sanskrit).

Naturopathic treatment of Parkinson's disease

Although *M. pruriens* has been used by Ayurvedic physicians in the past for the treatment of Parkinson's disease, it was felt that it should be re-evaluated using modern methods of testing. There is a clear trend in favor of alternative medicine; according to Miller et al. (2000), the number of visits to alternative medical practitioners had risen from 427 million in 1990 to 629 million in 1997; in that same time frame the use of herbal and natural products increased by 380%.

With this heightened interest, the need for scientific validation of ethno-pharmacologic products increases. *M. pruriens*, with its many anecdotal claims (Taylor, 2004; Huisden, 2005), has been subject to naturopathic testing on various fronts (Huisden et al. 2008; Huisden et al., 2010). The safety of *M. pruriens* has been demonstrated in animal experiments in rats and rabbits; it is found to have a pharmacokinetic profile similar to the combination of L-dopa and carbidopa. Using a 6-hydroxydopamine rat model, researchers found *M. pruriens* to be more effective than L-dopa. The authors speculated that *M. pruriens* endocarp may contain more than one antiparkinsonian compound in addition to L-dopa or it may have adjuvants that enhance the efficacy of L-dopa.

Nagashayana et al. (2001) studied the importance of eliminative therapy followed by palliative therapy in Ayurveda treatment of Parkinson's disease. The study also emphasized the need for a complete biochemical characterization of medicinal plants as well as the need to assess whether Ayurveda treatment can be more beneficial or can improve upon L-dopa therapy in Parkinson's disease. Based on Ayurveda principles given in the classical text *"Charakasamhitha"*, a concoction of powdered *M. pruriens* in cow's milk is prescribed for treating Parkinson's disease. *M. pruriens* is reported to contain L-dopa as one of its constituents. The study by Nagashayana et al. (2001) compared the effects, if any, of cleansing and palliative therapy as prescribed in ancient textbooks compared to that of palliative therapy alone. Contents of L-dopa were analyzed in the seeds of the plants used as medicine. They also evaluated the efficacy of Ayurveda treatment in 18 clinically diagnosed (with a mean Hoen and Yahr value of 2.22) Parkinson's patients. Analyses of powdered samples in milk, as administered to patients, revealed about 200 mg of L-dopa per dose. The study established the necessity of cleansing therapy in Ayurveda medication prior to palliative therapy. It also revealed contribution of L-dopa in the recovery as observed in Parkinson's disease following Ayurveda medication.

Commercial preparations of *M. pruriens* (HP-200; Zandu Pharmaceuticals, Bombay) are available in India. One study examined the efficacy and tolerability of HP-200, derived from *M. pruriens*, in patients with Parkinson's disease ("An Alternative Medicine Treatment for Parkinson's Disease," 1995). Sixty patients with Parkinson's disease were treated in an open study of 12 weeks; 26 patients took synthetic L-dopa/carbidopa formulations before treatment with HP-200, and the remaining 34 were L-dopa naive. HP-200, a powder (supplied as a 7.5 g sachet), was mixed with water and given orally. The Unified Parkinson's disease Rating Scale (UPDRS) was used at baseline and periodically during the 12-week evaluation. Statistically significant reductions in Hoehn and Yahr stage and UPDRS scores were seen from baseline to the end of the 12-week treatment. The group mean (+/- SD) dose for optimal control of symptoms was 6 +/- 3 sachets. Adverse effects were mild and were mainly gastrointestinal in nature. No adverse effects were seen in clinical laboratory reports; HP-200 was found to be an effective treatment for patients with Parkinson's disease. In addition to these findings, Manyam et al. (2004) found HP-200 to be more effective than synthetic L-dopa. Oral administration of *M. pruriens* endocarp in the form of HP-200 had a significant effect on dopamine content in the cortex with no significant effect on L-dopa, norepinephrine or dopamine, serotonin, and their metabolites in the nigrostriatal tract. Similar findings were reported, based on a double blind clinical trial with *M. pruriens* seed powder by Katzenschlager et al. (2004). Katzenschlager et al. conducted a randomized, controlled, double blind crossover trial with eight patients. Dyskinesias were assessed using modified AIMS and Goetz scales. *M. pruriens* seed powder was fast to act and showed prolonged activity without concomitant increase in dyskinesias over L-dopa.

In another study Manyam et al. (2004) also report the neurorestorative benefit of *M. pruriens* cotyledon powder on degenerating dopaminergic neurons in the 6-hydroxydopamine lesioned rat model of Parkinson's disease. Nicotine adenine dinucleotide (NADH) and coenzyme Q-10, known compounds with therapeutic benefits, are reportedly present in cotyledon powder of *M. pruriens* and at least partially responsible for the restorative effects on degenerated dopaminergic neurons in the *substantia nigra* (Manyam et al., 2004).

An *M. pruriens*-based coffee substitute also known as "Nescafé" (not to be mistaken for the Nescafé brand by Nestlé) has been used as a nerve tonic for nervous system disorders and possible use in treating Parkinson's disease (Taylor, 2004). The high concentration of L-dopa in *M. pruriens* seeds is advantageous in that L-dopa gains access to the brain where it is converted to the beneficial dopamine. However, the failure of *M. pruriens* endocarp to significantly affect dopamine metabolism in the striatonigral tract along with its ability to improve Parkinsonian symptoms in the 6-hydoxydopamine animal model and humans may suggest that its antiparkinson effect may be due to components other than L-dopa or that it has a L-dopa enhancing effect (Szabo & Tebbett, 2002).

The present day management of Parkinson's disease is unfortunately characterized by both a lack of awareness and lack of acceptance of available

naturopathic remedies. Limited human resources, cost factors, and a lack of scientific research and validation deny the benefits of therapy to many patients (Singhal et al., 2003). According to Guyatt (2003), the evidence based medicine (EBM) approach offers clinicians and patients an optimal use of the medical literature in solving health challenges. Although there is a steady increase in research trials, both *in vitro* and *in vivo*, a thorough EBM evaluation that could affect the worldwide acceptance of this promising naturopathic medicine, *M. pruriens*, remains premature and more clinical work is necessary. A combined effort to better validate and promote the use of *M. pruriens* in the treatment of today's Parkinson's disease patient should focus on multi-continent clinical trials that emphasize the exceptional neuroprotective and healing properties as well as patient comfort and wellbeing in a quest for acceptance and global recognition of *M. pruriens* in the treatment of Parkinson's disease.

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