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Review

Potential use of neuroprotective and L-DOPA-rich plants in Parkinsonian therapy

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ABSTRACT

Parkinson's Disease (PD) is a prevalent movement disorder among the population with more than 10 million living with PD worldwide. L-DOPA has been a drug of choice in the treatment of PD for a long time due to its potential to cross the blood-brain barrier. However, prolonged use of synthetic L-DOPA also exerted toxicities in the patients. A significant number of research studies have been documented for a promising future of using natural L-DOPA resources for the management of PD or perhaps delaying the onset of PD. This review will highlight the potential of some of the natural L-DOPA sources and neuroprotective agents used in PD management.

Keywords: Parkinson's Disease; L-DOPA; *Mucuna pruriens*; *Solanum lycopersicum*, *Ginkgo biloba*.

INTRODUCTION

Parkinson's disease (PD) was formally recognized for the first time by British physician James Parkinson in 1817 and was referred to as "The Shaking Palsy". PD has been a major headache for public health around the world.[1] Globally, more than 10 million people are living with PD with the highest estimated patients in China (2.7M) followed by the US (930K), Japan (344K), Germany (266K), and Brazil (229K).[2] However, Australia (54K), Taiwan (56K), and South Korea (71K) showed a lower number of estimated PD in 2020.[2]

PD was long considered incurable and terminal. Yet in the 1940s and '50s, neurosurgeons had already started to operate on patients' basal ganglia, which proved as effective as rubbing salt into wounds. After the biochemical discovery that levels of the neurotransmitter dopamine are greatly diminished in PD patients' caudate nucleus and putamen, 3,4-dihydroxy phenyl-L-alanine (L-DOPA) became a core antiparkinsonian treatment within a couple of years.[3,4]

METHODS

This systematic review includes a selective search for relevant original articles and reviews, case reports, randomized and non-randomized controlled trials, and cohort studies from 1996-2023 using PubMed and Google Scholar. We used the following keywords: L-DOPA, Parkinson's Disease, *Mucuna pruriens*, natural sources of L-DOPA, treatment of PD, and neuroprotective effects of plants. Articles were restricted to English.

RESULTS

Our search resulted in a total of 506 relevant publications, and after the removal of duplicate studies by browsing the titles, subsequently reduced the numbers to 130. After assessing the abstracts for duplicate and irrelevant data to our review scope, an additional 57 were excluded. Out of 73 full-length articles, 16 were further excluded due to overlapping and inconclusive data. Finally, 57 relevant studies were included in the final review out of which 10 original pre-1996 studies were used and cited in this review.

Clinical Manifestations of Parkinson's Disease

PD is a prevalent movement disorder, ranking as the top disorder in its category and second only to Alzheimer's Disease (AD) among neurodegenerative diseases. The main signs of PD are the loss of dopaminergic neurons in the nigrostriatal area, which makes the striatum lack dopamine, and the buildup of α-synuclein in nerve cells. Different mechanisms can cause PD, but some of them are oxidative stress, mitochondrial dysfunction, unbalanced calcium levels in cells, and neuroinflammation problems involving other neurotransmitter systems.[5]

PD is characterized by three primary motor symptoms: bradykinesia, rigidity, and resting tremor. Aside from the fundamental characteristics, PD also presents a diverse array of non-motor symptoms that greatly affect an individual's overall well-being. One of the most critical of these manifestations is cognitive impairment, which plays a crucial role in the progression of the disease. It is estimated to occur six times more frequently in patients with PD than in healthy individuals, making it a crucial area for investigation.[6] Cognitive impairment can greatly affect a person's functioning and quality of life, and even in the early stages of the disease, it has been linked to significant economic consequences beyond the motor symptoms alone. Therefore, it is a crucial subject of concern for both individuals with PD and their caregivers.[7-9]

PD causes patients to experience a range of cognitive dysfunctions, ranging from Subjective Cognitive Decline (SCD), PD-Mild Cognitive Impairment (PD-MCI), and PD Dementia (PDD). SCD refers to a supposed decline in cognitive function without any identifiable cause or event. The decline must be greater than would have occurred given the person's age, sex, and education level on tests of standardized intelligence.[10] Second, PD-MCI is a gradual linear deterioration in cognitive function, either reported by patients with PD themselves or their informant; the cause of this can even be witnessed directly and confirmed by the clinician. Patients also demonstrate signs of impairment on neuropsychological testing as well as global scales designed to test overall levels of impairment.[11]

PD-affected people have a neuropathology that is defined by the premature loss of dopaminergic neurons in the substantia nigra and an unusual accumulation of α-synuclein, giving rise to early symptoms. This protein initially affects cholinergic and monoaminergic neurons in the brainstem and eventually spreads to normal synapses.[12] Commonly seen in PD patients with co-existing AD pathology along with cognitive impairment, α-synuclein deposition, and synaptic dysfunction are not within the brainstem but rather in limbic regions however, it remains unclear if the mechanisms of neurotoxicity or aberrant amplification exist.[13]

Overview of L-DOPA in the Management of Parkinson's Disease

The first-line treatment for PD is L-DOPA. A constant obstacle in its reinvention is new formulations that equal or exceed dose-by-dose motor fluctuations and all the other shortcomings of therapeutics. L-DOPA's entry into the therapeutic scene came after several years of blind alleys, and this continued to have a huge impact on raising people's view of PD as a disease in which suffering is inevitable.[14-16]

L-DOPA's effectiveness in treating Parkinsonism became known by the rapid-fire reversal of hypokinesia it fulfilled in the reserpine rabbit.[16] With this information, a strategy for enhancing striatal dopaminergic neurotransmission came with an egregious precedence.[17] This thing couldn't be achieved by dopamine, because this patch's electrical charge prevented its movement across the blood–brain barrier. Still, an indispensable approach was to use L-DOPA as dopamine's immediate precursor[18,19] because it could transfer into the brain via a medium of eased amino acid transport.

Even though only a small portion of L-DOPA administered systemically can reach the brain, studies have shown that it is still enough to repair striatal dopaminergic neurotransmission. The treatment for parkinsonism using L-DOPA was soon joined by peripherally acting decarboxylase inhibitors as a significant pharmaceutical advancement. Co-administering Benserazide and Carbidopa with L-DOPA prevents dopamine conversion in the body, allowing more of it to be available in the central nervous system, consequently enhancing tolerance and therapeutic efficiency.[20]

Treatment with tiny doses that are titrated up over intervals of 3-4 days to reach a recommended dosage range between 300-1200 mg daily administered orally divided into multiple boluses throughout each day.[21] Different formulations available include: typical oral formulations usually taken alongside Benserazide and Carbidopa; Immediate Release tablets; disintegrating tablets; and extended-release capsules/tablets.[22,23] In terms of gastrointestinal irritation, taking one hour before protein-rich meals is recommended to maximize absorption efficiency.

In 2018, the U.S. Food and Drug Administration (FDA) greenlit an L-DOPA inhaler as an alternative treatment for PD. This inhaled form of L-DOPA bypasses the usual processes of absorption and metabolism in the intestines and liver and is presented in a dry, grease-like formulation.[24]

Infusion therapy, involving a 16-hour infusion through a nasojejunal tube, is also a viable option for administering L-DOPA. Recent studies have demonstrated that this method can lead to low plasma trough levels, similar to those seen with oral ingestion.[25] Moreover, these infusions have been found to effectively reduce the negative effects of motor complications. On the other hand, there is evidence indicating that pulsatile administration of L-DOPA may cause more frequent motor complications compared to continuous drug treatment. It is worth noting that research on the use of L-DOPA infusion in the pediatric population is scarce and, therefore, should not be recommended for patients under the age of 18.[25]

Toxicities

According to the studies, L-DOPA toxicity can kill neuronal cells. After the body oxidizes L-DOPA, free radical formation helps induce degeneration of nerve cells and death by stimulating apoptosis. Furthermore, L-DOPA undergoes decarboxylation in the periphery to raise levels of dopamine, norepinephrine, and epinephrine. The rise in catecholamines engages alpha and beta-adrenergic receptors, with toxic results. L-DOPA does cross the placenta in pregnant women and can be metabolized by the fetus. However, there is insufficient data to determine the proper use of L-DOPA for pregnant women. Moreover, nursing women should use the medication with caution as it appears in the breast milk. After treatment for toxicity, such as gastric lavage and clearing the airways, IV fluids are used to fully recover.[24]

Contraindications

Specific circumstances or conditions that make a particular treatment or medication unsuitable or potentially harmful for an individual. The use of L-DOPA and monoamine oxidase inhibitors (MAOIs) together is not recommended due to the risk of a dangerous spike in blood pressure. When switching between L-DOPA and MAOIs, a minimum of 14 days should pass. Additionally, individuals taking D2 antagonists may experience reduced efficacy of L-DOPA, leading to a decrease in its beneficial effects. It's important to use caution when giving L-DOPA to patients with narrow-angle glaucoma, as it may elevate eye pressure. Extra care must be taken when treating patients with atrial, nodal, or ventricular arrhythmias. To ensure safety, it is strongly advised that these patients receive L-DOPA while under the careful observation of a cardiac intensive care unit. If patients have pre-existing neuropathy, it is crucial to avoid the use of L-DOPA as it may worsen symptoms. Additionally, those with a history of peptic ulcer disease have a higher risk of experiencing gastrointestinal bleeding when taking L-DOPA. Furthermore, individuals with a pre-existing serious psychotic condition should be cautious, as L-DOPA can potentially exacerbate psychosis symptoms. As per the FDA label, individuals with a history of malignant melanoma should steer clear of taking L-DOPA, as it may promote the growth of this cancer. However, research shows that the drug exposure itself does not necessarily lead to a heightened risk of melanoma. Rather, there seems to be a link between PD and this type of cancer. Additional research is needed to fully understand the relationship between L-DOPA and its potential effects on the skin.[26]

Complications of prolonged L-DOPA Therapy

In the 1960s, after L-DOPA had been in clinical use for several years, reports emerged of potential complications with its therapy. However, in 1969 a few years after the introduction of L-DOPA, doctors noticed that despite improvement in the symptoms of a series of patients, there were some unwanted side effects such as movement and gait impairment.[18] Furthermore, in 1976, Marsden and Parks noticed that morning akinesia, chills, and number completion may be due to disease progression, and that peak levels of dyskinesia and yo-yo-ing due to excessive doses of L-DOPA may be due to all these problems.[27] About 15% to 40% of subjects showed on-off conversion after 1 to 3 years of treatment, although Barbeau et al reported that this occurs in more than 50% of patients after 5 to 10 years of treatment.[28] According to a notable article by Obeso et al. in 2017[29], as well as other experts in the field of PD, dyskinesias can be manifested in different forms, such as on-period dyskinesias, off-dystonia, and phasic dystonia. Another distinctive type, peak-dose dyskinesia, is characterized by involuntary head-bobbing and repetitive movements in the head, trunk, or limbs. Diphasic dyskinesias typically involve phases of movement and rest in a cyclical pattern.

More evidence suggests that tetrahydroisopapaveroline, a byproduct of dopamine, may partially activate dopamine receptors and interfere with the effects of L-DOPA.[29] After a few hours had passed, the dyskinesias resurfaced because of a drop in L-DOPA levels in the bloodstream, leading to the reappearance of PD symptoms. This is especially noticeable in off-period dystonia, which typically manifests in the early morning due to low L-DOPA levels. This type of dyskinesia is characterized by muscle spasms, foot inversion, and toe flexion, causing significant discomfort. A less common type of dyskinesia is paroxysmal, which can occur regardless of the individual being in an "on" or "off" period and is commonly known as the "yo-yo" response.[29] In addition to physical symptoms, non-motor features such as anxiety, depression, and sweating may also arise during off-periods.[30] Furthermore, an individual's diet, particularly the intake of protein, can impede the absorption of L-DOPA from the stomach. These complications are often seen in those with advanced stages of PD, as well as those with an early onset of the illness.

The severity of the illness and the extended duration of therapy are essential aspects to consider when examining the emergence of potential complications. However, the gradual increase in L-DOPA dosage and its non-physiological and non-pulsatile administration should not be overlooked as contributing factors.[29] Fortunately, newer methods of administering L-DOPA have been experimentally utilized and have displayed positive outcomes. These methods include sustained-release formulations, intraduodenal infusions, nasal and subcutaneous administrations, micro tablets, electronic dose dispensers, DM-1992, and accordion pills.[25,31-34]

Natural Sources of L-DOPA

Complications due to prolonged therapy of L-DOPA lead to a question existed for a while and has been in research, the introduction of natural sources of L-DOPA to extract the compound or possibly include them in the diet as a regular food consumption item. Nature has provided us with many natural sources of L-DOPA in the form of edible plants. However, there is a lot of uncertainty about whether the amount of L-DOPA found in natural sources is sufficient to lower the dosage of L-DOPA medications in people who are already suffering from PD or to delay the onset in people who are more likely to get PD as they age. Nevertheless, a significant number of research studies have been documented for a promising future of using natural L-DOPA resources for the management of PD. Before the 1950s, the primary understanding of L-DOPA was its role in the production of melanin and epinephrine within living organisms. However, groundbreaking research in the early 1960s revealed that this same amino acid had the potential to be a precursor for essential neurotransmitters, leading to a wide range of therapeutic uses.[35] Since then, scientists have been exploring alternative sources for L-DOPA, with particular interest in plants. Following an extensive screening process of over 1000 species from 135 different plant families, the genus Mucuna, from the Leguminosae family, was found to contain the highest levels of L-DOPA. This discovery has since been successfully applied in various commercial ventures.[36-41] Of the many types of Mucuna, *M. holtonii*, *M. pruriens*, and *M. monosperma* have demonstrated significant levels of L-DOPA with potential benefits, as evidenced by studies.[42-46]

Mucuna pruriens

Mucuna pruriens (MP) or velvet beans, have long been used as a natural remedy for spasms associated with conditions like Parkinsonism and Bell's palsy.[47] These beans are a rich source of L-DOPA, with a reported yield of 1.9%. However, a more efficient method- a simple hot water extraction has shown an improved yield of 3.1-6.1% for L-DOPA from nine different species of Mucuna.[48] Surprisingly, the MP endocarp (MPE) has been found to exhibit twice the antiparkinsonian activity of synthetic L-DOPA in Parkinsonian animal models in inducing contralateral rotation (CLR).[49] This could be due to unidentified compounds in the extract that work alongside L-DOPA to enhance its effectiveness.[48] Further, when evaluating its effectiveness, it was found that MP acted quickly and was stronger than L-DOPA.[50]

In addition, the MP has also been shown in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model to provide neuroprotection by down-regulating nitric oxide production, neuroinflammation, and microglial activation.[50]

Researchers[51] utilized an innovative experimental model to explore the potential neuroprotective properties of MP, which is an anti-inflammatory Ayurveda drug. The extract improved the motor function of these Parkinson-induced mice, showcasing its promising potential in treating this neurodegenerative disorder.

The plant extract was found to enhance the amount of catecholamines and boost antioxidant capability, specifically within the nigrostriatal area. Furthermore, it also showed improvements in tyrosine hydroxylase expression in both the substantia nigra and striatal regions. Additionally, it normalized the expression levels of inducible nitric oxide synthase and glial fibrillary acidic protein in animals treated with MPTP. These findings suggest that MP may be a promising treatment for the MPTP-induced Parkinsonian mouse model. However, there is currently no evidence to support its effectiveness in treating PD.[51]

Vicia faba

In 1913, Guggenheim extracted L-DOPA from *Vicia faba* beans which contained 0.2-0.6 % L-DOPA.[48] These beans have since been the subject of numerous studies, revealing the dose-response absorption qualities of the L-DOPA. Through single-dose studies, scientists have investigated the potential benefits of *Vicia faba* on patients with noticeable fluctuations in motor function, commonly known as "on-off" oscillations.[47]

Ginkgo biloba

A study was conducted to explore the neuroprotective properties of a standardized extract of this remarkable plant in rats with 6-hydroxy dopamine (6-OHDA) induced neurotoxicity. The findings demonstrated that rats given a larger daily dosage of 100mg/kg of *Ginkgo biloba* showed significant enhancements in comparison to those receiving lower doses (50mg/kg) or a control. This exciting finding suggests that the extract may hold promise in managing PD.[52]

Solanum lycopersicum

There have been some interesting studies related to tomatoes regarding unlocking potential new sources of L-DOPA. According to the extensive research and experimentation by Breitel et al[53], they used the BvCYP76AD6 gene found in beetroot and genetically engineered tomato to produce healthy amounts of L-DOPA and compared its benefits to the MP. In addition, they were able to enhance the L-DOPA levels even more by boosting the activity of the metabolic powerhouse, MYB12, in tomato fruit, in combination with BvCYP76AD6, providing a chance to expand the range of plants that can accumulate L-DOPA, thus offering the potential for new sources of this valuable pharmaceutical. These tomato fruits hold promise as a viable alternative for providing L-DOPA to PD patients which may slow down the clinical manifestations of PD.[53] This may also be investigated if given in the diet to the normal subjects might delay the onset of the PD.

Panax ginseng

Though L-DOPA has been used for PD management for several decades, however, the discovery of a multitargeted therapy provided a viable option for symptomatic treatment and neuroprotection of PD. The potential neuroprotective effects of ginseng extract were investigated in two animal models of PD. Recent studies have shown that ginseng has properties that can protect against neuronal cell loss, such as the degeneration of the nigrostriatal cells in PD.[47] This highlights the potential for ginseng to be used as a preventive treatment for various forms of neurodegeneration.[47]

Korean red ginseng (KRG) has been extensively used as a healthy supplement in Asia, especially in South Korea. There have been some studies in South Korea regarding the use of this herb and its potential benefits or toxicities.[54] In a study, it was found that the KRG extract protected dopaminergic neurons from MPTP-induced neurotoxicity, possibly through multifunctional mechanisms of

antineuronal apoptosis, antioxidation, anti-inflammation, and maintenance of the integrity of the blood-brain barrier.[55]

Recent statistics on PD in South Korea indicated the rise of PD occurrence in the Korean community, particularly in those 50 years and older, with a prevalence of around 0.4%, which is on the lower side of the spectrum when compared to many other countries.[55,56] A relatively lower incidence of PD in the Korean community may be correlated with the widespread use of this herb in South Korea.[57]

CONCLUSION

Advancement of research in PD and its management therapeutics is continuously improving PD symptoms in patients with relatively reduced associated risks. In addition, the natural sources of L-DOPA have greatly increased the interest in using them as potential supplements in the diet for the treatment of PD. However, more animal studies and clinical trials are required with the natural L-DOPA herbal extract or other natural neuroprotective agents to know the pharmacokinetics through the blood-brain barriers and associated toxicities, safety, and contradictions before making them a safe treatment option for PD patients or preventive option to the high-risk subjects in delaying the PD onset.

Abbreviations

AD: Alzheimer Disease; CLR: Contralateral Rotation; FDA: Food and Drug Administration ; L-DOPA: L-3,4-dihydroxy phenylalanine or Levodopa; MAOIs: Monoamine Oxidase Inhibitors; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD: Parkinson's Disease; PDD: PD Dementia; PD-MCI: PD-Mild Cognitive Impairment; SCD: Subjective Cognitive Decline

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Conflict of Interest

The authors declare no conflicts of interest relevant to this article.

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