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Chapter

Parkinsonism and Potential of Mucuna Beans

Suresh S. Suryawanshi, Prajakta P. Kamble, Vishwas A. Bapat and Jyoti P. Jadhav

Abstract

Parkinson's is a neurodegenerative disease, which is common all over the world. Various aspect like damages of reactive oxygen species, excitotoxicity, mitochondrial dysfunction, and inflammation-facilitated cell damages are included in the etiology of disease. Good-balanced nutrition is an important part involved in the body health maintenance and reduction in the risk of chronic diseases. Genus *Mucuna* falls under family Fabaceae, containing high contents of L-DOPA (commonly used as an anti-Parkinson drug). Plant-based medicines are the superfluous source of polyphenols, flavonoids, carotenoids, antioxidants (ROS and RNS), terpenoids, isoflavonoids, and other biologically active phytochemicals. All these molecules have health beneficial effects with superlative pharmaceutical values. The existing chapter summaries to determine the influence of different nutritional, anti-nutritional, and medicinal potential of the *Mucuna* species present in India and its significance in the management of Parkinson's disease (Shaking Palsy) as well as other medicinal values. It also covers various treatment models used in studying the Parkinson's disease like *Drosophila melanogaster*, zebrafish, mice, rat, and humans. This chapter also focuses light on the neurosurgical treatments used in the treatment of Parkinson's disease. This study concluded that the use of *Mucuna* seeds for the treatment of Parkinson's disease is the best choice besides chemical drugs and other therapies.

Keywords: Kampavata, L-DOPA, *Mucuna*, neuroprotective, experimental models, neurosurgical remedy

1. Introduction

Research in plant-based medicine is gaining much more attention due to its lack of side effects, its large availability, and its multiple medicinal applications. In the past few years, this has also increased people's awareness toward functional food, thus enhancing the consumption rate of legumes enormously [1]. The attention toward *Mucuna* improved colossally after 1937 when it was initially revealed that a huge quantity of levodopa is present in it. Genus *Mucuna,* which is familiar by different names (like: velvet beans, sea beans, cowitch, buffalo beans, cowhage, atmagupta, kapikachu, and dopa bean), is one of the conventional medicine performing crucial roles in both health and disease management. *Mucuna* is an excellent source of proteins, starch, micronutrients, dietary fiber, and bioactive compounds (L-DOPA), which play a great role in the traditional as well as modern medicine all

over the world against Parkinson's disease. The genus *Mucuna* belongs to the family *Leguminosae* distributed throughout the tropical and subtropical regions of various countries of the world comprising hundreds of species [2]. Recently, Pulikkalpura et al. [3] and Patil et al. [4, 5] studied the occurrence and biochemical activities of various *Mucuna* species in India.

Plant-based remedies are most beneficial remedies, having a cumulative effect of phytochemical and other bioactive components obtained from plants. *Mucuna* has various actions like antioxidant activity, anti-inflammatory activity, wound-healing activity, and activity against snake bite. Along with all this, *Mucuna* is also rich in nutritional and anti-nutritional compounds (rich in minerals) [6]. *Mucuna* is also well known for nematicidic effects and also possesses notable allelopathic activity, which was reported by Gliessman et al. [7]. In countries like Guatemala and Mexico, it is used as a coffee substitute. Along with that, in some countries (lower hills of the eastern country and Himalayas), it is commonly consumed as vegetable beans after frying and boiling. *Mucuna* seed powder has been used in active management of Parkinson's disease in several countries due to its L-DOPA content.

In early health care system of India, Parkinson's disease (PD) is known as "Kampavata", which is a common neurological disorder related to neuromelanin containing nigrostriatal dopaminergic neuronal loss. Kampa means tremor and vata means lack of muscular movement. It was found via door-to-door survey in Bangalore (Karnataka, India) that 76 per 100, 000 (age adjusted) and 33 per 100,000 (crude prevalence) people suffered from Parkinsonism [8]. Out of that, 5–10% of individuals having PD belong to families with history of genetic disorders [9, 10]. The disease commonly occurs in the age group of 60–80. A survey on Parsi community in Mumbai shows that they were diminutively stable to PD [8]. Diagnosis of disease is sometimes difficult by clinical method, which involves analysis by considering large number of motor and non-motor symptoms in PD patients. PD is caused due to decrease in dopaminergic neurons in the substantia nigra pars compacta (SNpc) part of the brain, which leads to motor symptoms including rigidity, bradykinesia, tremor, and development of some non-motor symptoms in later stages of the disease. Although there is significant number of improvements in the medicinal and surgical actions against PD, scientists have not yet identified definite targets for disease management. According to research by Ramanan and Saykin, neurodegeneration is divided in to four main levels out of which aggregation and accumulation of abnormal or misfolded mutated proteins is crucial [11]. Some reports examine that oxidative stress (OS) and neuroinflammation (NIF) are the main reasons of neurodegenerative disease. Thus, to tackle these neurodegenerative disorders, researchers have diverted their attention toward finding oxidative stress enzymes and pathogenesis of PD. Abraham et al. studied 115 cases of PD and concluded that catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (G-Px), and glucose-6-phosphate dehydrogenase (G6PD) levels are present in greater quantities in PD patients as compared to the control patients [11]. Various oxidative stress enzymes, pro-inflammatory cytokines, proteinase, reactive oxygen intermediates, and complement proteins are secreted by the immune cells against the neuronal cell damage response, which leads to inflammation. Along with mitochondrial dysfunction, altered proteolysis, oxidative damage of cells and Lewy bodies' formation are some of the symptoms of Parkinson's disease.

There are various strategies for the management for PD but there is no complete cure for this disease. The only management of the lowered dopamine levels is to control various metabolic inhibitions and enhancement pathways, preventing degeneration of neurons and other non-dopaminergic (surgelogical) treatment. L-DOPA (L-3,4 dihydroxy phenylalanine) is a non-protein amino acid used in the

treatment of Parkinson's disease. It acts as precursor of dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline). It is synthesized by plants, animals, and microbes (bacterial and fungus) and has a different role in each source. Chemical synthesis of L-DOPA is easy but the purification of L and D forms is slightly complicated and expensive. Synthetic L-DOPA is considered as anti-nutritional factor and its consumption causes abdominal distention, vomiting, dyskinesia, nausea, etc. This happens when L-DOPA is converted to dopamine in the peripheral nervous system by enzyme dopa decarboxylase. Whereas, L-dopa is also used as the treatment against infertility recovering the spermatogenic harm to some extent. Numerous other secondary metabolites produced by plants like flavonoids and phenolics illustrate strong anti-inflammatory and antioxidant potentials, which have a significant role in the management of health and disease of human beings.

The current book chapter is focused on the use of plant source of L-DOPA and neuroprotective potential of magical dopa beans and their special prominence in Parkinson's disease treatment. Along with this we have also focused on the models and other treatments used in treating Parkinson's disease.

2. Treatment strategies of Parkinson's disease

2.1 Neuroprotective potential of *Mucuna*

Parkinson's disease (PD) was initially discovered by Dr. James Parkinson in 1817; it is a chronic neurological disorder triggered by a progressive loss of dopaminergic neurons present in the nigrostriatal part of the brain and found to be common in U.S [12]. In 1970, only few effective drugs were available for treatment of the PD but there is no such therapy yet that completely treats PD. Only thing we can do is to stop the progression of Parkinson's disease or delay the of PD by replacement of dopaminergic neuron or by mimicking the neuron by using substituent. Management of PD is mainly divided into two categories: first involves improving symptomatic treatment of motor and non-motor types of symptoms and second will be addressing potential causes of PD. Firstly in 1978 Vaidya et al., published the report that PD can be treated by *Mucuna* extract, a natural source of levodopa having better activity than the synthetic version of levodopa drug [13]. Similar studies were reported in 1990 and 1994 by Kempster et al. and Rabey et al. [14, 15]. L-DOPA is a precursor of dopamine (**Figure 1**), norepinephrine (noradrenaline),

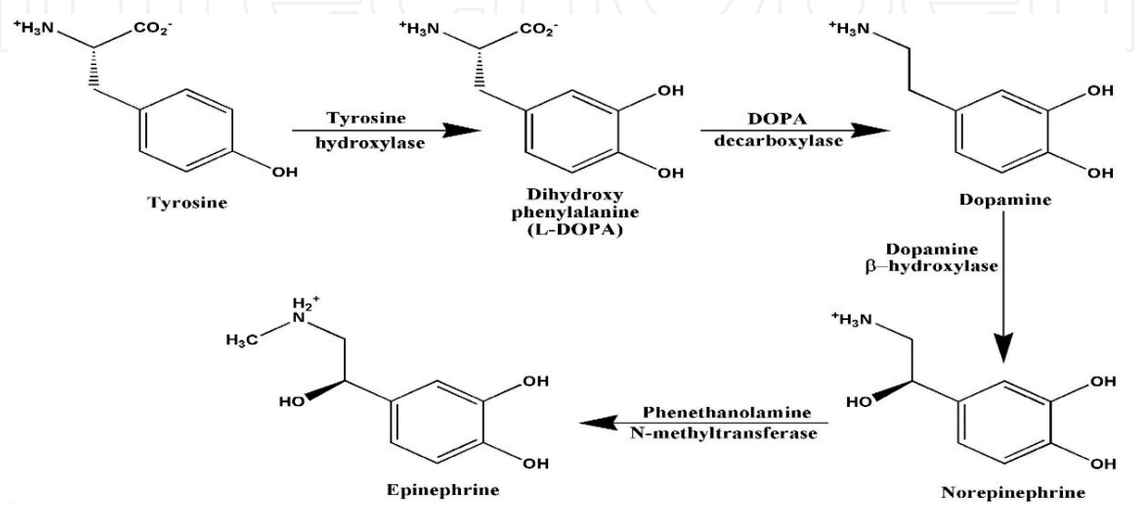

Figure 1.
Synthesis pathway of L-DOPA, dopamine and further metabolites.

and epinephrine (adrenaline), together known as catecholamines. The dopamine produced cannot cross the blood–brain barrier but L-DOPA can. Outside the brain, L-DOPA can directly be converted to 3-O-methyldopa (3-OMD) by catechol-O-methyl transferase (COM T) and then further to vanillactic acid (VLA), which leads to primary same side effect. To avoid this conversion, standard clinical practices use DOPA decarboxylase inhibitor such as carbidopa or benserazide and often a catechol-O-methyl transferase (COMT) inhibitor [16–18]. L-DOPA present in *Mucuna* plant (anti-Parkinson's drug) [19–21] helps to produce dopamine. Along with L-DOPA, the reactive oxygen species (ROS) and reactive nitrogen species (RNS) produced by *Mucuna* are stress-producing free radicals playing a great role in the physiological functioning of the body [21–30]. The content of antioxidant compounds using different solvents in different species of *Mucuna,* the concentration of antioxidants and other phytochemicals are extremely different. Ethanolic extract of *Mucuna* seed shows good antioxidant activity due to high phenolic content as compared to methanol, water, and acetone [31]. Some reports also conclude that water is as universal solvent, which shows the significant quantity of phenolic, flavonoids, and strong antioxidants which have the ability to scavenge free radicals using different assays. LCMS (liquid chromatography mass spectrophotometry) report of four different species (**Table 1**) shows that there are various components like phenolic flavonoids and bioactive compounds present in the *Mucuna* that are responsible for the production of reactive species [32]. Along with L-DOPA and antioxidants, other secondary metabolites like phenolics, flavonoids, vitamins, enzymes, and protein also have a cumulative effect in the management of PD. Few reports on *Mucuna* show correlation between L-DOPA, protein, and carbohydrates. The use of plants for the treatment of PD is more beneficial than chemically manufactured L-dopa due to its high potential required in the levo and dextro form purification. It is also studied that various compounds present in *Mucuna* are responsible for the antimicrobial action, which can be utilized in dealing with various infectious diseases and ulcers [31, 32, 44]. Experiments on various plant pathogens suggest that methanolic extract of *Mucuna pruriens* seeds showed the highest antimicrobial activity [45]. A similar type of study done by Pujari et al. also determined that methanol extracts of *Mucuna pruriens* seeds were found to have the best inhibiting activity among all scrutinized pathogens as compared to ethanol and acetone solvents. But alcoholic extract of *Mucuna pruriens* (L.) leaves has significant antioxidant and antibacterial

Sr.no	*Mucuna* species	Reference
1	*Mucuna imbricata*	[32]
2	*Mucuna macrocarpa*	[33]
3	*Mucuna monosperma*	[34]
4	*Mucuna Bactetia*	[35]
5	*Mucuna sanjepee*	[36]
6	*Mucuna Autripuria*	[37]
7	*Mucuna Latiparica*	[5]
8	*Mucuna prurience*	[3, 6, 20, 21, 24, 38–43]
9	*M. nigricans*	[5]
10	*M. gigentea*	[5]
11	*Dhanwantari*	[5]

Table 1.
Different species of Mucuna *studied till date.*

activity [45]. Dopaminergic agonists or dopamine replacement therapy is a common and most effective way to cure PD. It decreases the signs of disease by sustaining the level of dopamine; however, it cannot regenerate or halt the degeneration. It only replaces or mimics dopamine by inhibiting its breakdown. Apomorphine, bromocriptine, pergolide, piribedil, pramipexole, and ropinirole are some dopaminergic agonists mainly used to heal the PD. All these bioactive compounds present in the *Mucuna* species have cumulative effect in the treatment of PD. *Mucuna pruriens* is a species from the Fabaceae family and Faboideae subfamily. *M. pruriens* is an annual twinning plant in bushes, hedges, and one of the popular medicinal plants indigenous to tropical countries like India [42]. It is useful in relieving inflammation, delirium, neuropathy, cephalalgia, and general debility, nephropathy, dysmenorrhea, amenorrhea, ulcers, constipation, elephantiasis, consumption, helminthiasis, fever, and dropsy. The trichomes of pods contain serotonin and mucunain. The trichomes are used as anthelmintic. Seeds contain glutathione, gallic acid, levodopa (4-3, 4-dihydroxy phenylalanine), lecithin, prurenine, prurenidine, glycosides, nicotine, minerals, and dark brown viscous oil [42].

2.2 Experimental models studied for PD

Natural products are valuable sources of bioactive compounds that can be exploited for novel therapeutic potential in PD pathogenesis. There are number of publications reported till now dealing with experiments on hundreds of compounds from various plant species for their different activity in curing the Parkinson's disease [46]. However, rapid screening of plant-derived natural products and characterization of bioactive compounds is a challenging job. This problem was combated by using *Drosophila melanogaster* and zebrafish as experimental models at initial stages then followed by studies on various experimental models like, *C. elegans,* mice/rat, and also cell lines (e.g., murine BV-2 microglia and human SH-SY5Y neuroblastoma cells). Few verdicts using different models are listed underneath.

2.2.1 Drosophila melanogaster

Drosophila melanogaster, universally familiar as the fruit fly, have turned up as an outstanding model for human neurodegenerative diseases, comprising PD. Due to their high degree of conserved molecular pathways with mammalian models, Drosophila PD models serve to be an inexpensive solution to pilot stages of target validation in the drug discovery pipeline. Fruit fly acts as a screening platform to evaluate the therapeutic potential of phytochemicals from natural extracts against PD [47]. *Drosophila melanogaster* is a persuasive tool to explore molecular facets and physiopathology of Parkinson's disease (PD) [48]. There are studies that compare the effects of L-DOPA vs. MP extract using a Drosophila model of autosomal recessive PD in which flies carried a mutation in the PTEN-induced putative kinase 1 (PINK-1) gene [49]. Their observations illustrates that *Drosophila* fed on MP had a significantly extended lifespan, showed a restored olfactory response and improved climbing behavior compared to flies that consumed L-DOPA.

*2.2.2 Zebra fish (*Danio rerio*)*

Owing to its large number of favorable properties, Zebra fish has been used widely as experimental animal for various diseases. Zebra fish are inexpensive, easy to conserve, develop rapidly, and breed in large quantities. Larval zebra fish are also extensively used in toxicity screens since they have a permeable skin through which substances added in the rearing medium are effortlessly taken up. This permits for

greater control over dosage and ease of administering substances to large numbers of animals. Furthermore, larval behaviors can be exploited in assays to test the effects of the treatment. Being a vertebrate, the central nervous system of larval zebra fish expressions an extremely homologous to humans. Therefore, toxicology studies performed on larval zebra fish can be very helpful in deciding the putative targets in humans [50]. Thus *Danio rerio* commonly known as zebrafish is a charming popular animal model for treatments in neuropharmacology and pharmacogenetics. Both the adult and larval zebrafish are presently studied to increase the understanding of central nervous system's function and dysfunction [51]. There are various studied reports by Gerlai et al. on the latent learning, behavior, and memory alteration of adult zebrafish [51–55]. Apart from fish, there are several other experimental models.

2.2.3 Mice/rat/rodents

Many clinical trials have been done on herbal extract and their isolated compound, which has opened a new scenario in the area of PD. The models of PD are induced by different chemical compounds like 6-OHDA, rotenone, and MPTP based on the aim of the experiment. Singh et al. investigated the effect of ethanolic extract of *Mucuna pruriens* (Mp) on the reduction of oxidative stress level, nitric oxide (NO), and subsequent influence on lipid peroxidation in paraquat (PQ)-induced Parkinsonian mouse model. MTTP-induced Parkinson mouse models were also studied by them for the reduction of estrogen by *Mucuna pruriens* [26, 55, 56]. Yadav et al. demonstrated that Mp seed extract reduces oxidative stress in nigrostriatal tissue and improves neurobehavioral activity and the expression of tyrosine hydroxylase (TH) in SN and striatum of the brain in PQ-intoxicated mice [56]. Apoptotic pathways of dopaminergic neurons in the PQ mouse model were also found to be inhibited by the neuroprotective activity of *Mucuna pruriens* [57]. Experiments also reveal that the *Mucuna pruriens* has a resilient anti-inflammatory property that diminishes the neuroinflammation by plummeting inducible nitric oxide synthase expression in Parkinsonian mice model. Symptomatic and neuroprotective efficacy in rodent model of Parkinson's disease using *Mucuna pruriens* seed extract were studied by Kasture and Pontis [58]. Significance of *M. pruriens* in sperm parameters and sexual behavior of streptozotocin-induced diabetic male rat were studied by Sekar Suresh et al. [59]. Earlier efforts exhibited the capability of *Mucuna pruriens* seeds extract to induce contralateral turning behavior in the 6-hydroxydopamine (6-OHDA)-lesion persuaded rat model of PD [60]. Likewise, the potential of *Mucuna* seed powder extract significantly improved activity of brain mitochondrial complex-I without disturbing total monoamine oxidase activity *in vitro* [61]. *Mucuna pruriens* also has the potential to amend immune components like tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interferon-λ (IFN-λ), interleukin-1β (IL-1β), inducible nitric oxide synthase (iNOS), and interleukin-2 (IL-2) in the central nervous system, thereby, averting the progression of dopaminergic neurons degeneration, in PD [62]. Moreover *M. pruriens* was also assessed for levodopa pharmacokinetics by Sarrafchi et al., in a double-blinded clinical and pharmacological study. They observed that administration of *M. pruriens* at doses of 2.5, 5.0, or 10.0 g/kg/day for 52 weeks significantly increased the dopamine content of the cortex in animal model of PD. Therefore, they concluded that *M. pruriens* seed powder with natural source of levodopa probably has benefits over conventional levodopa preparations in treatment of PD due to its longer action and speedy onset without increase in adverse effect [63]. Thus, *M. pruriens* would seem to be a remarkable commercially viable alternative to standard L-dopa [64]. Likewise, an improvement in motor

skills and dyskinesia analogous to those induced by equivalent doses of L-DOPA was also found to be induced by *M. pruriens* preparations in rat and macaque monkey models of PD [61]. Therefore, all these studies strongly advocate the use of *Mucuna pruriens*: a treasurable herbal plant for treatment of PD.

2.2.4 Human trials

Copious studies have scrutinized the effect of MP in PD patients. The bioavailability of L-DOPA in the central nervous system is about one-fifth when pooled with carbidopa or benserazide due to nonexistence of DOPA decarboxylase inhibitor (DDCI) in *Mucuna* [61–65]. Even then, the first report in 1978 revealed that 23 PD patients were treated with MP with similar effect and better tolerance than L-DOPA/benserazide. This study was followed by an open study where 60 PD patients in Hoehn and Yahr stage I–IV were treated with MP preparations for over 12 weeks, which led to momentous headways in both UPDRS score and the Hoehn and Yahr stage. This captivated the attention on the registration of *Mucuna* preparation (Zandopa™) as a treatment for PD in India [61]. Cilia et al. executed a crossover study (N = 14) on PD patients in an advanced stage with motor fluctuations and peak-of-dose dyskinesia. The observations indicated better motor improvement on *Mucuna* powder consumption in comparison to the effect imparted by intake of an equivalent dose of L-DOPA/benserazide [66]. Innumerable experiments are still under investigation by several assemblages of researchers from all over the world to understand the PD progression and come up with innovative strategies to treat Parkinson's disease [61, 62].

2.3 Other drugs and their effects

Gargantuan improvement has been done to treat the PD for over half-century. Diverse individuals from different places have come up with different treatments. Miscellaneous categories of drugs are being used apart from levodopa. Yet to date there are no complete cure strategies for PD. But some symptomatic palliative treatments are being implemented to slow down the disease progression. There are various enzymes used in the management of PD. Enzymes monoamine oxidase-B (MAO-B) and catechol-o-methyl-transferase (COMT) are normally involved in metabolism of dopamine. Therefore, few inhibitors of the two enzymes (MAO-B and COMT) have been extensively studied. Inhibitors like selegiline, rasagiline, tolcapone, and entacapone are being used for the disease modification in PD from previous few years. N-propargyl-methamphetamine is known as selegiline, which is an irreversible inhibitor of MAO-B. Action of selegiline was studied in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinsonism in monkeys [67]. It was used at concentration of 10 mg/day, but they found that it loses its selectivity at higher concentrations of dosage [67]. Various other reports show the neuroprotective potential of selegiline but there is no such report proving that selegiline has "disease-modification" effects [68–70]. The *in vitro* and *in vivo* experimental Parkinsonian models indicate that rasagiline (N-propargyl-1-(R)-aminoindan) acted as irreversible MAOB inhibitor exhibiting anti-apoptotic effect [68–70].

There are various studies proving that the dopamine agonist or levodopa has stronger symptomatic benefits as the MAOB inhibitor; however, there was no evidence of direct comparison between them [71–74]. Older people provide more rapid onset improvement than younger patients. Dopamine agonist is more prominent in younger people with dyskinesia and older people with orthostatic hypotension and CNS effects (hallucinations). Pharmacokinetic studies revel that COMT inhibitors

prevent degradation of peripheral levodopa by extending half-life and also permit it to cross the blood–brain barrier in higher concentrations. There are large number of compounds used to treat motor symptoms and motor complications occurring due to dopaminergic mode of action as reported in review by Oertel et al. Whereas **carbidopa** (modified form of L-dopa soluble), **opicapone** (COMT-inhibitor), **safinamide** (MAO-B-inhibitor), **droxidopa** (NMDA-receptor antagonist), **stradefylline** (noradrenaline precursor), **tozadenant** (Adenosine 2A receptor antagonist), **pimavanserin** (5HT2A inverse agonist), **and donepezil** (Acetyl choline esterase inhibitor) are some of the most common compounds used in the treatment internationally [16]. Along with benzhexol and orphenadrine, anticholinergic drugs are also recommended as they reduce the effect of acetylcholine in the brain by antagonizing cholinergic receptors and restore the acetylcholine/dopamine balance within the brain. They also prevent hyperkinesia.

3. Neurosurgical treatments

Apart from chemical drugs, there are some physical therapies involved in the treatment of PD that have given special attenuation toward movement (motor) symptoms of patient. In this treatment, parts of the brain involved in the progression of disease are either removed, bombard with electric impulse, or subjected to neuroimaging [75]. In **pallidotomy and thalamotomy,** the globus pallidus part of the brain, which is overactive in the PD patients, resulting in slackening down the body movements, is surgically destroyed permanently. This destruction of globus pallidus significantly reduces tremor, bradykinesia, balance problems, and writing problems, and eliminates rigidity, while thalamus part is involved in the involuntary movement (like tremor) [76, 77]. **Deep brain stimulation** (DBS) is also one of the unconventional treatments used, in which brain pace markers (microelectrode) are applied where an electrical impulse passes over the electrodes to the specific part of the brain. DBS decreases the secondary difficulties elevated due to dopaminergic replacement therapy. There are survival disadvantages of pallidotomy and thalamotomy cases due to dysphagia, hypophonia, and dysarthria [78]. DBS is having significant results over thalamotomy because it does not need hardware and have very fewer side effects and relatively lowers the risk of complications. Besides all these pharmacological and surgical treatments, few other strategies like speech therapy, mediations are being currently explored along with it for the treatment of PD. Apart from singular therapy, doctors are now recommending a combination of treatments to impart cumulative effect in the treatment of PD.

4. Conclusion

Mucuna is a natural, rich source of precursor of dopamine that acts as gold standard for the treatment of Parkinson's disease to control body movements, hormonal balance, emotion, and memory. The *Mucuna* is a pharmaceutically and biochemically valuable plant used from the early days, having high market value due to its large amount of bioactive compounds. It also contains a maximum amount of phenolics, flavonoids, and antioxidants, which have a cumulative role in the release of oxidative stress produced by body systems. *Drosophila melanogaster*, zebrafish, mice/rat, and human models were used to check the potential of *Mucuna* seed powder on rotenone, MPTP-induced Parkinson's model, and it was concluded that *Mucuna* seeds have great values in the treatment of PD. The book chapter also covers various other drugs and neurosurgical treatments used in Parkinson's

disease. It also gives an introduction to various other species (apart from *Mucuna FSTA*) used in the PD treatment and lowers the burden on commonly used (Mucuna pruriens) species.

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