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REVIEW ARTICLE

Effects of *Mucuna pruriens* (L.) Supplementation on Experimental Models of Parkinson's Disease: A Systematic Review

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ABSTRACT

Introduction: *Mucuna pruriens* (L.)DC. (Mp) has been used in the treatment of numerous diseases in Indian Ayurvedic medicine, mainly for delaying the symptoms of Parkinson's disease (PD), and has as its main component levodopa (L-DOPA). The aim of this work is to systematically review the effects of Mp supplementation on experimental models of PD due to its neuroprotective and antioxidant properties. MATERIALS AND **Methods:** The search was conducted through PubMed, ScienceDirect, Cochrane Library, and Scientific Electronic Library Online databases, where a number of relevant articles were found. Results: Mp demonstrated significant positive responses in the experimental models of PD by improving motor deficits and by enhancing the activity of the antioxidant systems, reducing oxidative stress. In addition, it presented some advantages when compared to a conventional antiparkinsonian drug as it minimized the occurrence and severity of dyskinesias. **Conclusion:** Thus, considering that the use of herbal medicines decreases the likelihood of side effects associated with the pharmaceutical drugs, this work aims to summarize and evaluate the data available regarding the mechanism of action of Mp and the reported benefits of this plant as an alternative to improve the quality of life of individuals with PD.

Key words: Antioxidant, *Mucuna pruriens* (L.) DC, neuroprotection, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative condition, clinically characterized by different motor disorders, such as bradykinesia, stiffness, tremor, and postural instability,[1] which are associated with selective loss of dopaminergic cells in the nigrostriatal region.[2] In addition, nonmotor symptoms such as autonomic disorders and psychosis have also been reported in patients with PD.[1]

The classical *in vivo* models of PD result from the systemic or intracerebral administration of neuronal toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), and paraquat (PQ).[3] The MPTP model mimics the primary pathological and biochemical characteristics of PD such as oxidative stress, apoptosis, and induction of mitochondrial dysfunction, which makes this model more suitable to evaluate the neuroprotective effects of drugs.[4]

The autoxidation and inhibition of complexes I and IV of the mitochondrial electron transport chain are the main mechanisms of toxicity of 6-OHDA, which increases the production of reactive oxygen species (ROS) and causes neuroinflammation, microglial activation, and induction of apoptotic pathways, resulting in cell death.[5] The mechanisms of action of the PQ model are directly or indirectly related to the increasing production of ROS, which results in damage of the substantia nigra (SN) pars compacta.[6]

Mucuna pruriens (L.) DC. (Mp) comes from Hindi *Kiwach*, being called *Atmagupta* in Sanskrit.[7] It belongs to the *Fabaceae* family and *Papilionaceae* subfamily.[8] Mp has a wide variety of pharmacological properties including neuroprotective and antioxidant, which seem to be attributed to the presence of the dopamine (DA) precursor, levodopa (L-DOPA).[9] Mp has been used for a long time in traditional Ayurvedic (Indian) medicine for treating some diseases such as PD.[10,11]

Previous studies have reported that even after >40 years of clinical use, L-DOPA still remains the gold standard for treating PD.[12] This drug is considered the most effective agent for relieving a variety of symptoms related to PD, including tremor, stiffness, sluggishness, weak muscle control, and gait impairment.[13] However, its long-term use is associated with side effects such as motor fluctuations and dyskinesias.[14]

A double-blind clinical study demonstrated that the prolonged use of L-DOPA leads to the development of dyskinesia, whereas the use of Mp extract (MPE) during the same period of time did not demonstrate such effect.[15] In addition, nonhuman primates previously treated with MPTP demonstrated that Mp displayed antiparkinsonian activity without inducing dyskinesia and suggested that Mp acts through a mechanism that is different from that of L-DOPA.[16]

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Considering that the conventional treatment with L-DOPA induces dyskinesia and that this side effect was absent during the long-term use of Mp, it seems reasonable to assume that the use of the latter as an adjuvant treatment for PD might improve the quality of life of the individuals affected by this disease. Therefore, the aim of this work is to systematically review original articles that investigated the use of MPEs in animal models of PD.

MATERIALS AND METHODS

This study is a systematic review of the effects of Mp in animal models of PD that have been published between January 2000 and March 2017 through PubMed, ScienceDirect, Scientific Electronic Library Online (SciELO), and the Cochrane Library databases.

Due to the lack of protocols for systematic reviews of preclinical studies, the guidelines of the Ministry of Health[17] were used in this study, whose protocol was adapted to meet the proposal of this review. The scientific question that guided this study corresponded to "What are the effects of supplementation with MP on experimental models of PD?"

The initial screening included all the studies that met the following criteria: (a) studies that presented primary data; (b) experimental studies using MPE; (c) studies that presented tissue and/or behavioral analysis; (d) articles written in English; (e) being published within the last 17 years. The studies that were not performed *in vivo* and those that used animal models other than rats were excluded.

To maximize the number of articles related to this subject, no specific descriptors were used for the initial searching. Instead, a more general descriptor was used through which all the publications that dealt with this specific descriptor were identified, and each article was carefully analyzed whether it matched with our main subject. The terms used for the search were previously selected considering the regular vocabulary used for indexing articles in the Health Sciences Descriptors, through which the descriptor "*Mucuna pruriens*" was found.

The initial screening found 207 articles in PubMed, 735 in ScienceDirect, 10 in Cochrane Library, and 32 in SciELO, totaling 980 publications. After using the year of publication (from 2000 to 2017) as exclusion criteria, the articles found in PubMed reduced to 174, and after applying the "English language" as filter, the number went down to 64, maintaining this amount after the filter "animal research" was adopted. In ScienceDirect database, the use of year of publication as exclusion criteria limited the publications to 582. However, when the "original articles" filter was used on the 32 papers initially found at Cochrane Library, the quantitative remained the same. When the year of publication was used to filter the articles found in SciELO, the number was restricted to nine articles, which remained the same after the "English language" filter was used. Finally, a total of 665 articles were selected after the initial inclusion and exclusion criteria were adopted during the search in the four databases.

These 665 articles were stored in the reference management software called Endnote Web (Thomson Reuteurs Patente dos EUA); where after identifying the duplicate publications, it ended up with 642 articles. During the identification of potential eligible studies, the selected articles were analyzed by two evaluators: a nurse and a pharmacist, both with Ph.D in Psychobiology. The evaluation occurred independently and the disagreements regarding exclusion were resolved by consensus. After using the inclusion and exclusion criteria toward each manuscript's tittle, a total of seven articles were selected [Figure 1].

The process of extracting data from the selected articles was performed independently by the two evaluators using a standard analysis form, which was used throughout the aforementioned research strategies. There were disagreements in the collected data, where the inclusion of these in the study was conditioned to the consensus between the two evaluators.

Data analysis

The studies analyzed in this systematic review present high levels of heterogeneity in important aspects such as the PD-inducing agent, duration of treatment with the MPE, and the behavioral tests used. The studies used different compounds to simulate neuronal damage due to PD, and they all work through different mechanisms of

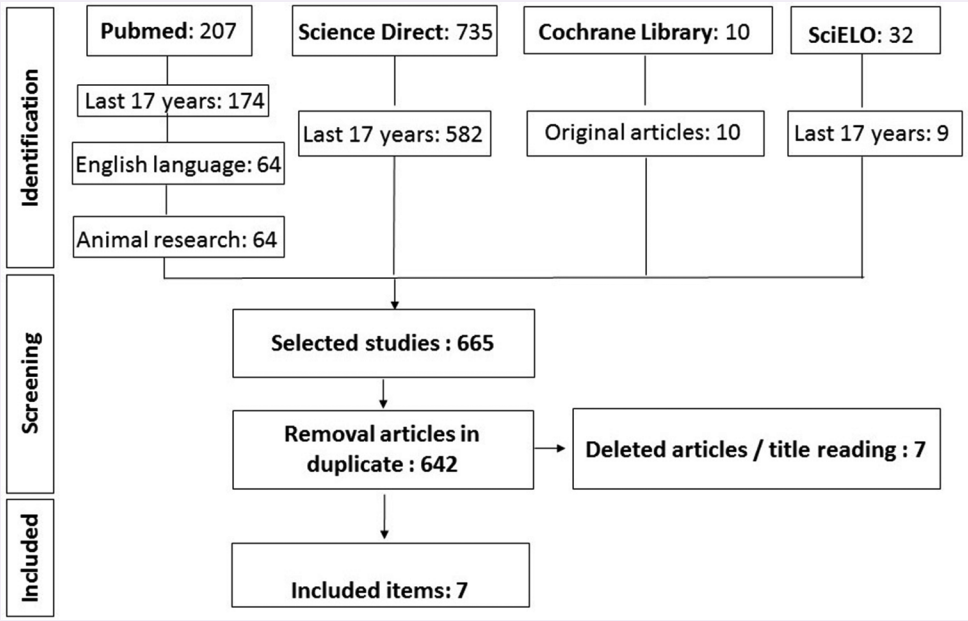

Figure 1: Flowchart representing the process of selecting the articles used in this review. The number of articles shown in this flowchart relates to studies that investigated the effects of *Mucuna pruriens* (L.) DC. supplementation in animal models of Parkinson's disease found in PubMed, ScienceDirect, Cochrane Library, and Scientific Electronic Library Online databases

action. Just like the MPEs, these compounds were administered at different doses and through different routes. For instance, MPTP is administered intraperitoneally as it is a lipophilic compound that crosses the blood–brain barrier and produces mitochondrial damage, inhibiting complex I, while 6-OHDA is administered intracerebral, which allows it to penetrate the neurons through the DA transporter, inducing neuronal death through the production of ROS. Therefore, their effects are largely intracellular. While PQ is also administered intraperitoneally, it exerts its deleterious effects through oxidative stress, inducing the subsequent production of ROS. In addition, the studies reported in this systematic review used different behavioral tests and neurochemical analyzes, which also reinforce the heterogeneity of the studies.

According to Brazil,[17] both clinical and methodological heterogeneities are the sources of statistical heterogeneity. When heterogeneity is significant and cannot be explained by any sensitivity analysis, meta-analysis is not recommended, and the effects of the study interventions should only be presented individually. Therefore, clustering statistics were not considered due to methodological heterogeneities among the studies, which justify the impossibility of performing a systematic review with meta-analysis.

RESULTS

The studies differed in some aspects. Regarding the sex of the animals used in the studies, most of them were males (6) and just one study used female rats. The agents used to induce PD symptoms also varied: MPTP (2), 6-OHDA (2), and PQ (2). The duration of Mp supplementation varied between 1 day and 9 weeks. For the behavioral analysis, the studies used the rotarod test (3), narrow beam test (2), stepping test (2), hanging test (2), footprint test (2), and vibrissae-evoked forelimb and other tests (4). Analysis of the cellular defense system was performed through glutathione (1), lipid peroxidation (3), nitrite (3), catalase (1) and immunohistochemistry for tyrosine hydroxylase (5), glial fibrillary acidic protein (2), CD11b (1), and inducible nitric oxide synthase (2). In addition, the amount of DA (1), dihydroxyphenylacetic acid (DOPAC) (1), and homovanillic acid (HVA) (1) were evaluated.

The seven articles were carefully analyzed and summarized in terms of authorship, year of publication, type of lesion, experimental groups, dose regimen, and main findings [Table 1].

DISCUSSION

Phenolic compounds are known for their antioxidant activity, which has been attributed to their ability to reduce oxides, and therefore, they have played an important role in neutralizing free radicals.[18] The antioxidant activity of an acidic MPE has been demonstrated, where the authors attributed this activity to its high phenolic content.[19] In addition, Singh *et al*.[20] performed an *in vivo* stress-induced lipid peroxidation study that demonstrated the antioxidant activity of an alcoholic MPE seeds [Figure 2].

In a recently published systematic review, the action of phytotherapics with multiple compounds and phytochemicals was demonstrated, especially phenolic compounds that presented neuroprotective effect in PD; among them, the action of Mp extract was evidenced, attributing its antioxidant and neuroprotective activity to its phenolic compounds, especially L-DOPA.[21]

Oxidative stress has been associated with degeneration of dopaminergic neurons in the SN of patients with PD.[22] Manyam *et al*.[23] studied the effect of a formulation containing Mp endocarp administered for 52 weeks at doses of 2.5, 5, and 10 g/kg/day, where they showed significant effect on DA content in the cortex. However, no change was observed in the levels of L-DOPA, noradrenaline, serotonin, or DA and its metabolites HVA, DOPAC, and 5-hydroxyindole acetic acid in the nigrostriatal pathway. In a subsequent study, Manyam *et al*.[24] evaluated the neuroprotective effect of an extract prepared with cotyledons of Mp in parkinsonian rats, showing a significant increase in the concentrations of L-DOPA, DA, noradrenaline, and serotonin in SN. In addition, Mp also increased mitochondrial complex I activity in the brain, which is usually reduced in this PD model. However, it did not affect the *in vitro* activity of monoamine oxidase. Thus, it seems reasonable to assume that the chemical constituents of the extracts might be different and that the source of Mp can influence its neuroprotective activity.

According to Manyam *et al*.,[24] NADH and coenzyme Q10, which have beneficial effects on PD, are both present in the seeds of Mp. The presence of these compounds might have contributed to the neuroprotective effects of Mp. In fact, previous report has shown that the oral administration of coenzyme Q10 to animals that had been previously treated with MPTP demonstrated antioxidant and neuroprotective activities, which have been attributed to coenzyme Q10's ability to protect the nigrostriatal dopaminergic system.[25] In addition, Phase II studies of systemic high doses of coenzyme Q10 suggested a delay in the progression of PD, possibly due to an increased activity of mitochondrial complex I.[26] Thus, the mechanism of neuroprotection induced by the cotyledons of Mp seems to be mediated by an increase in the mitochondrial complex I activity as well as through the neutralization of the free radicals.[24]

Phytoestrogens and L-DOPA are both related to motor benefits. Phytoestrogens are nonsteroidal plant-derived compounds with similar effects as endogenous estrogen but without the undesirable adverse reactions.[27] The study conducted by Hussian and Manyam[28] indicated that MPE showed twice the antiparkinsonian activity of the synthetic L-DOPA in the induction of contralateral rotation in the parkinsonian animals. In addition, phytoestrogens have the ability to neutralize oxidative stress, which is crucial in reducing nerve damage and neuronal loss.[29,30]

It has been reported that L-DOPA induces the activation of caspases and the increase of brain oxygen, which lead to lipid peroxidation, DNA damage, and neuronal death.[31] In addition, the chronic use of antiparkinsonian drugs has been associated with the emergence of drug-induced dyskinesias.[32]

Other studies have shown the role of serotonin in the physiology of basal nuclei and in the long-term complications related to L-DOPA treatment.[33,34] Sathiyanarayanan and Arulmozhi[11] reported the presence of serotonin in the MPE. Based on this evidence, it is likely that the presence of both L-DOPA and serotonin in MPE may result in antidyskinetic effects.[12-35] A double-blind and randomized clinical study, performed with eight patients with PD, demonstrated that doses of 15 and 30 g of dry MPE seeds showed no incidence of dyskinesias as compared to conventional preparations of L-DOPA, supporting the results found in experimental studies.[15] Pathan *et al*.[36] also showed that Mp attenuates haloperidol-induced orofacial dyskinesia in rats, possibly due to its free radical scavenging ability.

Another study reported no neuroprotective activity for MPE (48 mg/kg), whose absence of activity might be due to the low dose used as another study showed that the most effective dose required for neuroprotective purposes is 100 mg/kg.[37] Thus, it is likely to assumed that higher doses of MPE would have shown an effective neuroprotective response. Figure 3 illustrates two proposed mechanisms of action of Mp.

Table 1: A summary of the studies about the effects of *Mucuna pruriens* supplementation on experimental models of Parkinson's disease found in PubMed, ScienceDirect, Cochrane Library, and Scientific Electronic Library Online databases, displaying the authorship, year of publication, type of lesion, experimental groups, dose regimen, and main findings

Authorship/year of publication	Type of lesion	Experimental group and dose regimen	Main findings
Arulkumar and Sabesan, 2012	Intraperitoneal injection of MPTP	6 groups: Control group, groups treated with Mp extract (MPE) (400 mg/kg), Mp nanoparticles ($MPGNP_s$) (20 mg/kg), MPTP alone (40 mg/kg), MPTP with MPE (200 mg/kg) and MPTP with $MPGNP_s$ (500 μg/kg, 5 mg/kg, 10 mg/kg and 20 mg/kg).	The treatment with MPE and MPGNPs improved motor coordination in the rotarod test, however, animals treated with MPGNPs showed better retention time than those treated with MPE. The groups treated with 10 and 20 mg of MPGNPs showed better retention time when compared to the groups treated with 500 μg and 5 mg. In addition, treatment with MPE and MPGNPs improved the crossing and hanging time in the narrow beam and hanging tests, respectively, even though the group treated with MPGNPs showed better results in both tests than the one treated with MPE.
Yadav *et al*., 2014	Intraperitoneal injection of MPTP	4 groups: Control group, group treated with MPTP alone, with MPTP plus MPE (100 mg/kg) and with MPTP plus estrogen.	Animals treated with Mp demonstrated better results in the hanging time test in addition to a decreased walking time in the narrow beam test when compared with the group treated with estrogen. However, the results were similar in the footprint test for both groups. Treatment with Mp allowed recovering the number of TH-positive cells in the substantia nigra (SN) and striatum as it reduced the expression of iNOS and GFAP in SN. In addition, Mp treatment significantly increased the levels of dopamine, DOPAC and HVA, regulating NO production, neuroinflammation and microglial activation.
Manyam *et al*., 2004[b]	Unilateral lesion in the right hemisphere with 6-OHDA.	5 groups: Control group and groups treated with 6-OHDA plus Mp at 2,5 g/kg, with 6-OHDA plus Mp at 5 g/kg, with 6-OHDA plus L-DOPA at 125 mg/kg and with 6-OHDA plus L-DOPA at 250 mg/kg.	Administration of Mp (5 g/kg) improved the endogenous contents of L-DOPA in SN and striatum. It also restored dopamine content in SN, but not on striatum. Treatment with Mp (2.5 and 5 g/kg) restored serotonin content in the dopaminergic cells of the nigrostriatal pathway and increased mitochondrial I complex activity.
Lieu *et al*., 2010	Unilateral lesion of the medial forebrain bundle and the substantia nigra with 6-OHDA.	EXPERIMENT 1: 3 groups with L-DOPA: L-DOPA (2mg/kg) + benserazide (BZ) (15 mg/kg), L-DOPA (4 mg/kg) + BZ (15 mg/kg), L-DOPA (6 mg/kg) + BZ (15 mg/kg); 3 groups with Mp: Mp (40 mg/kg) + BZ (15 mg/kg), Mp (80 mg/kg) + BZ (15 mg/kg) and Mp (120 mg/kg) + BZ (15 mg/kg). The stepping test and drug-induced dyskinesias (DID) rating were performed 30 minutes after treatment. EXPERIMENT 2: Mp at two doses: 240 and 400 mg/kg. Stepping test and DID rating were performed 30 minutes after treatment. EXPERIMENT 3: Mp 400 mg/kg. Stepping test, vibrissae-evoked forelimb placement test, body axis bias test and cylinder test were performed 30, 60 and 90 min after treatment, and DID rating was analyzed 5, 15, 30, 60 and 90 minutes after treatment. EXPERIMENT 4: LD alone (24 mg/kg), MPE alone (480 mg/kg) and L-DOPA + BZ (6 mg + 15 mg). Stepping test and vibrissae-evoked forelimb placement test were performed 30, 60 and 90 min after treatment, while DID rating was analyzed 60 minutes after treatment. EXPERIMENT 5: L-DOPA + BZ (6mg+15 mg) followed by treatment with MPE alone (480 mg) as well as associated with L-DOPA and BZ (6mg+15mg).	The results of experiment 1 showed that L-DOPA + BZ and MPE+BZ at high and medium doses provide significant antiparkinsonian effects, however, they all induced DID. Only the lowest dose of MPE+BZ was able to significantly ameliorate PD symptoms, while the equivalent dose of LD+BZ did not provide significant behavioral benefits. In experiment 2, MPE without any dopa decarboxylase inhibitor (DDCI) provided behavioral benefits with the reduction of DID severity. In experiment 3, the findings suggest that MPE alone can provide a significant long-term behavioral benefit while reducing the severity of DID. The results of experiment 4 demonstrated that MPE alone provides a significant behavioral benefit and that when the dose of equivalent synthetic L-DOPA was administered without DDCI (BZ) it was not able to provide significant equivalent antiparkinsonian effects. In experiment 5, the group L-DOPA+BZ immediately treated with MPE showed that this extract alone decreased the occurrence of DID in animals that had previously exhibited DID, whereas the group pre-treated with MPE and immediately administered L-DOPA+BZ showed that pre-treatment with MPE alone did not appear to improve the intensity of LD + BZ-induced dyskinesias. Thus, it was found that the activity of Mp alone in the parkinsonism symptomatology was more effective than in combination with L-DOPA and BZ, for both the behavioral benefits and for the prevention and minimization of the severity and frequency of dyskinesias.

Contd...

Table 1: Contd...

Authorship/year of publication	Type of lesion	Experimental group and dose regimen	Main findings
Kasture *et al.*, 2009	Unilateral lesion made into the medial forebrain bundle with 6-OHDA and intraperitoneal injection of tacrine and MPTP.	Groups lesioned with 6-OHDA: Control, 6-OHDA, 6-OHDA+L-DOPA (2 mg/kg), 6-OHDA + L-DOPA (6 mg/kg), 6-OHDA + Mp (16 mg/kg), 6-OHDA+ Mp (48 mg/kg). Groups lesioned with tacrine: Control, tacrine (2,5 mg/kg) + Mp (48 mg/kg). Groups lesioned with MPTP: Control, MPTP alone, MPTP + Mp (48 mg/kg).	The results show that Mp extract (16 mg/kg containing 2 mg/kg of L-DOPA) was able to antagonize the deficiency in the initiation step and adjustment step induced by 6-OHDA. At the same dosage, Mp significantly improved both leg and anterior limb placement. Mp (48 mg/kg) administered with L-DOPA (6 mg/kg) induced a significantly higher contralateral turning behavior than that of L-DOPA alone (6 mg/kg). Treatment with Mp (48 mg/kg) was also effective in antagonizing tacrine-induced tremulous jar movements. Mp was not able to prevent MPTP-induced decrease in TH, astroglial or microglial.
Yadav *et al.*, 2013	Intraperitoneal injection of PQ	3 groups: Control group and groups treated with PQ alone and with PQ and Mp (100 mg/kg). PQ was administered twice a week during the third, sixth and ninth weeks of treatment.	Treatment with Mp increased the TH-positive dopaminergic neurons and the activity of the catalase enzyme, decreasing the levels of malonaldehyde (MDA) and nitrite in the nigrostriatal region. In addition, Mp treatment improved behavioral abnormalities according to the results of the behavioral tests (hanging time, narrow beam walk time and footprint test).
Yadav *et al.*, 2017	Intraperitoneal injection of PQ	3 groups: Control group, group treated with PQ alone and group treated with PQ and Mp (100 mg/kg).	Treatment with Mp resulted in a significant attenuation of iNOS expression, nitrite content and lipid peroxidation, demonstrating that Mp can reduce nitric oxide levels in PD induced by PQ. Simultaneously, Mp recovered the number of TH-positive cells in the nigrostriatal region.

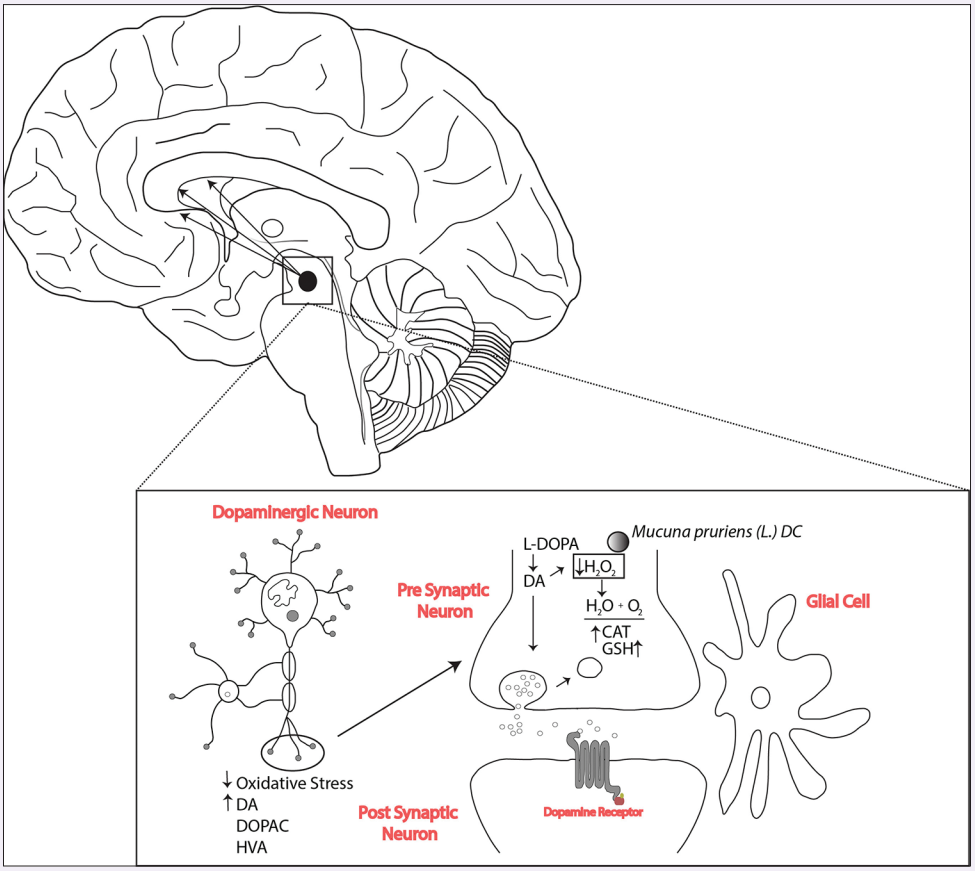

Figure 2: Schematic showing the antioxidant and neuroprotective effect of *Mucuna pruriens* (L.) DC. in experimental models of Parkinson's disease. Oxidative stress inhibits the synthesis of dopamine and free radicals act on the lipid membranes of the synaptic vesicles, decreasing the release of neurotransmitter in the synaptic cleft. The main results of the article indicate the action of *Mucuna pruriens* (L.) DC. acting on the reduction of free radicals and consequently, the increase of dopamine and its metabolites dihydroxyphenylacetic acid and homavanilic acid. Due to the improvement in the motor system in the reviewed articles, this action is suggested in dopaminergic neurons of the nigrostriatal pathway

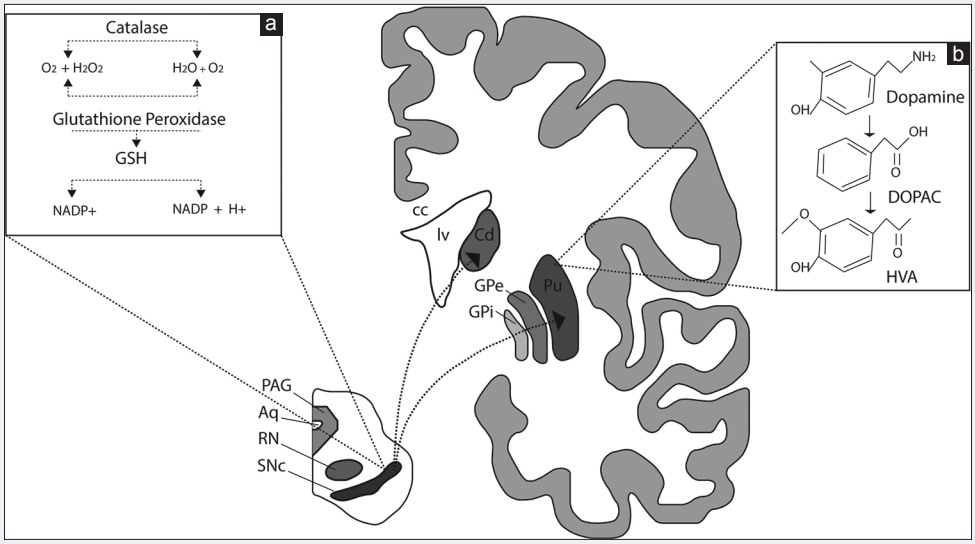

Figure 3: Schematic showing to proposed mechanisms of action of *Mucuna pruriens* (L.) DC. (a) The role of *Mucuna pruriens* (L.) DC. in increasing the activity of the enzymes involved in the antioxidant cellular defense system, avoiding lipid peroxidation and reducing the toxic action of oxygen free radical and hydrogen peroxide. (b) The areas highlighted in black: substantia nigra pars compacta and striatum (caudate nucleus and putamen), correspond to the areas that compose the nigrostriatal pathway, where *Mucuna pruriens* (L.) DC. has reversed the damage caused by Parkinson's disease, resulting in better responses in the behavioral tests, in addition to increased levels of dopamine and its metabolites dihydroxyphenylacetic acid and homovanilico acid

CONCLUSION

Although limitations were faced regarding the bibliography, with a limited number of studies about this subject, this systematic review revealed that the animals treated with Mp had their antioxidant systems improved, which resulted in reduced neuronal loss in the SN and striatum. The use of Mp improved the results of the behavioral tests in experimental models of PD. Therefore, in addition to its low incidence of side effects, it seems reasonable to assume that the use of Mp as an adjuvant treatment for PD might improve the quality of life of the individuals affected by this disease.

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Conflicts of interest

There are no conflicts of interest.

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