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Neuroprotective Effects of VEM-PD Nasal drops against MPTP- Induced Parkinson's Disease in Mice

Muralidhar S Talkad [1]*, Aamir Javed[2], Niranjan Koirala[3], Vijay Satish[4] and Anil Kumar HV[5]

[1,2,3,4]R&D Centre, VEM Biotech Pvt. Ltd. #468, 39th cross, 9th main, 5th block Jayanagar, Bangalore 560041, Bengaluru, Karnataka, India

[5]Professor of Sericulture, Laboratory for Applied Biological Science, DVS College of arts and Science, Shimoga, Karnataka, India

***Corresponding author:** Dr. Muralidhar S Talkad, R&D Centre, VEM Biotech Pvt. Ltd. #468, 39th cross, 9th main, 5th block Jayanagar, Bangalore 560041, Bengaluru, Karnataka, India, **E-mail**: drtsm49@gmail.com*

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ABSTRACT

Objective: *VEM-PD nasal drops are made of a proprietary herbal blend with micro-emulsions and CNS & PD-beneficial Bio-Actives. Which looked into the potential protective mechanisms of VEM- PD Nasal drops on a mouse model of Parkinson's disease (PD) caused by 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP).*

Methods: *PD Nasal Drops dose levels that are specific on the levels of glutathione and malondialdehyde in the brain, as well as the activities of antioxidant enzymes in the striatum, extracts of 2 drops twice and 2 drops three times each were administered orally for 15 days in a row until behavioral observations were made.*

Results: *MPTP (20 mg/kg, ip) was administered twice daily for five days prior to behavioral observation. When combined with MPTP + VEM-PD 2 drops /3 times, the striatum's glutathione (GSH) levels and antioxidant enzyme activity returned to nearly normal levels in the MPTP-induced group (1.33 0.06). In the MPTP-induced group 8.11 0.05, treatment group 2.63 0.143 reduced the increased levels of malondialdehyde (MDA) in mice to close to normal in the MPTP + VEM-PD 2 drops /3 times, striatum. 4.45 0.169 for the treated group. In the High Dose 2 drops (extracts) /3 times treated mice, histopathological analysis of the hippocampus region of the brain demonstrated a considerable reduction in MPTP-induced severity and a return of the brain's histological architecture to nearly normal morphology.*

Conclusion: *Overall, our research indicated that VEM-PD Nasal drops have neuroprotective qualities and may be a useful treatment for Parkinson's disease.*

Keywords: VEM-PD nasal drops; MPTP; Parkinson's disease; oxidative stress; Free radical; Scavenging capacity; Brain histopathology

INTRODUCTION

Parkinson's disease (PD), a neurodegenerative condition that is chronic and progresses over time, causes a number of motor and non-motor dysfunctions, such as the death of dopaminergic neurons, oxidative stress, and neuroinflammation [1].

To examine PD in vivo, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) is frequently utilized. In addition to harming dopaminergic neurons, MPTP also causes the striatum and substantia nigra to develop –synuclein [2]. Within the remaining dopaminergic neurons, Lewy bodies are a hallmark of Parkinson's disease (PD).

Animal models of Parkinson's disease allow researchers to gain insight into the mechanisms underlying a number of symptoms, making them invaluable resources for both basic and practical research. When 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) is administered to rodents or monkeys, biochemical and cellular alterations that ensue are strikingly similar to those seen in idiopathic Parkinson's disease [3]. Oxidative stress, apoptosis, and neuroinflammation are thought to have a role in these negative effects even if the molecular processes are unclear [4].

The imbalance between the amounts of intracellular free radicals and the actions of the intracellular antioxidant defense system is known as oxidative stress, a major biochemical pathogenic component of Parkinson's disease (PD) [5]. According to [6] administration of Catalpol isolated from Rehmannia glutinosa herb reduces MPTP-induced oxidative stress to stop chronic inflammation and neuro degeneration. In order to restore the nigrostriatal dopaminergic function, Sophora tomentosa L, an herbal extract, demonstrated neuroprotective mechanisms against MPTP-induced Parkinsonism.

These mechanisms may be related to the reduction of GSK-3 phosphorylation and -synuclein accumulation as well as the restoration of the striatal antioxidant defenses mechanisms [7] By penetrating the blood-brain barrier, embelin demonstrated a protective impact on the central nervous system [8] Embelin was found to have a positive effect on rotenone-induced Parkinson's disease (PD) models [9]

The restoration of striatal antioxidant defenses, restoration of nigrostriatal dopaminergic function, and reduction of -synuclein buildup may all play a role in the neuroprotective mechanism of VEM-PD nasal drops against MPTP-induced Parkinsonism.

MATERIALS AND METHODS

VEM-PD Nasal Drops (extracts formulations) were prepared by Soxhlet extraction process. Selective herbs present the formulations as follows: (dosage 100mg /ml).

Table 1: Materials Used

Botanical Name	Part Used	Form of ingredient	Qty in ml
Mucuna pruriens	Seed	Extract	2.0
Vitis vinifera	Seed	Oil	1.5
Sida cordifolia	Root	Extract	1.0
Curcuma longa	Rhizome	Extract	0.05
Prunus amigdalus	Seed	Oil	0.05

Acute toxicity LD 50 evaluation subjected in an ideal laboratory environment as per OCED guidelines (OECD 2001) (5). The maximum therapeutic dose is 1/10th of the maximum tolerated dose, hence the therapeutic dose selected for the extract formulations were 250 mg/kg and 750 mg/kg body weight respectively.

The experimentation was carried out as per Research and Ethics (CPSEA/154/106/2022) approved experimental protocols. The methodology includes 6 rats which were divided in to 3 groups. Group 1- normal (drinking water – 10ml/kg b. wt.), Group 2 -VEM-PD Nasal Drops (extracts formulations): low dosage-250mg/kg b. wt. (PO), Group 3 VEM-PD Nasal Drops (extracts formulations) - high dosage-750mg/kg b. wt. (PO). The rats were fed for 21 days. On 21st day - blood collection for Reduced Glutathione (GSH) Levels. The body weight was measured before and after feeding process. And the weight of Liver, Kidney, brain organs was also taken after the necropsy and subjected for histopathological analysis.

Experimental design for PD induced model with therapeutic response: as 6 mice were divided in to 5 groups. Group 1- Normal Control, Group 2- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced, Group 3- standard Levodopa (7.5mg/kg of body weight -PO), Group 4 - MPTP +

VEM-PD 2 drops (extracts) /2 times (low dosage) Group 5-MPTP + VEM-PD 2 drops (extracts formulations) /3 times (high dosage). VEM-PD: Nasal Drops (extracts formulations) was administered for 15 consecutive days on nasal route until the behavioral observation. MPTP (20 mg/kg, Ip) were given two times at 4-h interval daily for 5 days until behavioral observation. The activities of antioxidant enzymes in the Brain striatum like, glutathione peroxidase, glutathione reductase, glutathione, malondialdehyde and all the groups Brain tissue were subjected for histopathological evaluation

RESULTS

Table 2: Effects of VEM-PD: PD Nasal Drops (2 drops /2 times, and 2 drops /3 times, nasal drops) extract on the levels of glutathione and malondialdehyde, and the activities of antioxidant enzymes in the striatum of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) - induced Parkinson disease (PD) mouse model.

Sl.no	Groups	GSH (nmoL/mg of Protein)	GR (mU/mg of Protein)	GPx (mU/mg of Protein)	SOD (U/mg of Protein)	Catalase (U/mg of Protein)	MDA (nmoL/mg of Protein)
1	**Normal Control**	2.55 ± 0.13	204.23 ± 3.60	4.45 ± 0.16	21.46 ± 0.49	11.91 ± 0.30	4.4 ± 0.15
2	**MPTP**	1.33 ± 0.06	144.5 ± 2.39	3.11 ± 0.05	12.08 ± 0.05	4.68 ± 0.09	8.11 ± 0.05
3	**MPTP + Std Levodopa: 7.5 mg/kg (P.O)**	1.91 ** ±0.10	149.83 ± 1.58	3.67 ± 0.04	14.99 ± 0.08	5.5 ± 0.06	7.30** ± 0.17
4	**MPTP + VEM-PD 2 drops /2 times**	2.06 ** ± 0.05	179.5 ± 2.28	4.21 ** ± 0.07	17.11 ± 0.12	8.06** ± 0.09	4.77** ± 0.07
5	**MPTP + VEM-PD 2 drops /3 times**	2.63 * ± 0.143	248* ± 3.307	5.63 ± 0.161	26.18 * ± 0.290	12.1* ± 0.127	4.45* ± 0.169

Data are expressed as mean SEM (n = 6). * $p < 0.004$, ** $p < 0.001$, compared with MPTP group. VEM-PD: PD Nasal Drops was administered for 15 consecutive days on nasal route until the behavioral observation. MPTP (20 mg/kg, ip) were given two times at 4-h interval daily for 5 days until behavioral observation. GPx: glutathione peroxidase, GR: glutathione reductase, GSH: glutathione, MDA: malondialdehyde, MPTP: 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine, PD: Parkinson disease, SOD: superoxide dismutase, VEM-PD: PD Nasal Drops **(Figure 1) (Figure 1) (Figure 2)**.

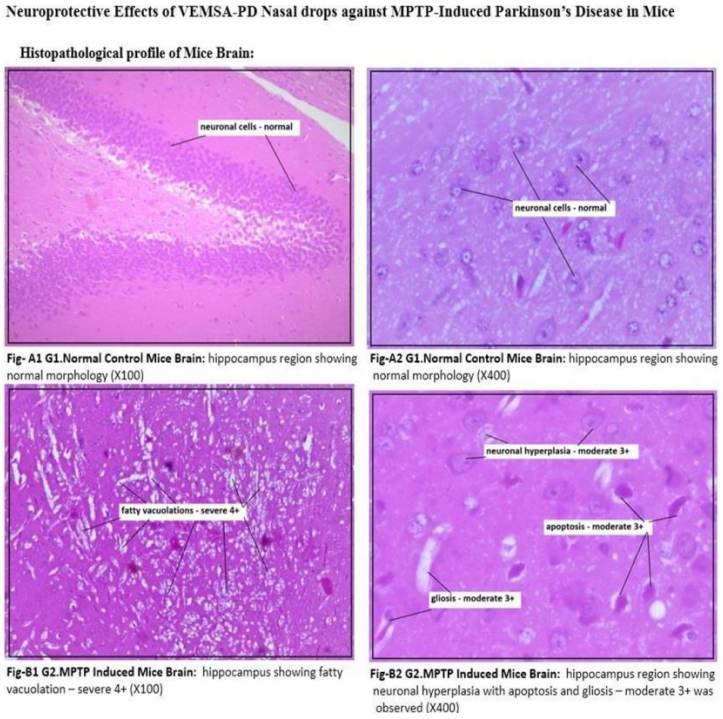

Figure 1: MPTP induced Mice Brain

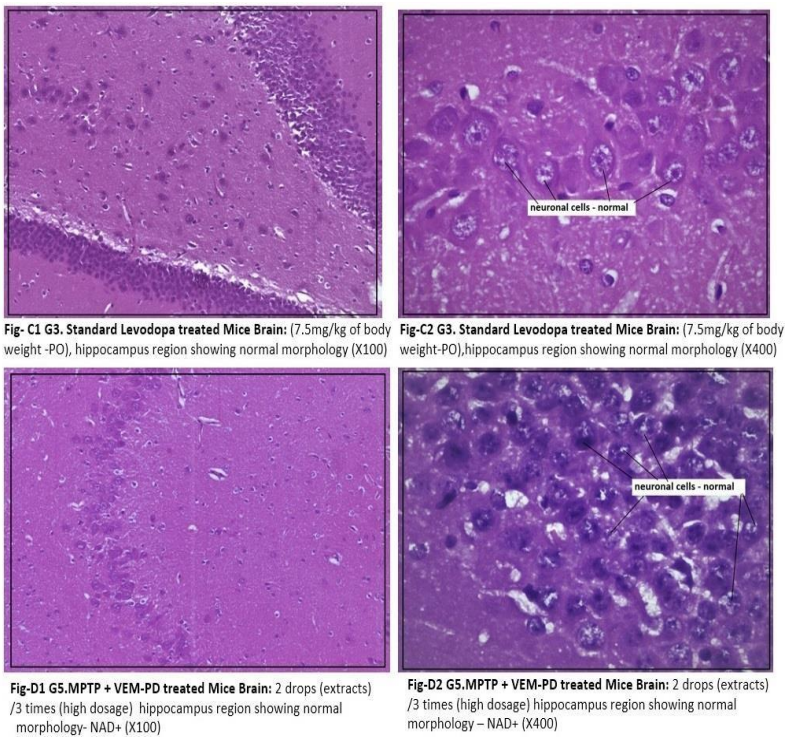

Fig- C1 G3. Standard Levodopa treated Mice Brain: (7.5mg/kg of body weight -PO), hippocampus region showing normal morphology (X100)

Fig-C2 G3. Standard Levodopa treated Mice Brain: (7.5mg/kg of body weight-PO),hippocampus region showing normal morphology (X400)

Fig-D1 G5.MPTP + VEM-PD treated Mice Brain: 2 drops (extracts) /3 times (high dosage) hippocampus region showing normal morphology- NAD+ (X100)

Fig-D2 G5.MPTP + VEM-PD treated Mice Brain: 2 drops (extracts) /3 times (high dosage) hippocampus region showing normal morphology – NAD+ (X400)

Figure 2: G5.MPTP + VEM-PD Treated Mice Brain

VEM- PD Nasal Drops (extracts) were established safe dosage regimes in LD50 studies for 21 days in rats, no toxicity effects either in body wt., organ wt. GSH biochemical marker were normal and even histopathological evaluation of target organs showed NAD+, No Abnormalities Detected, it is devoid of toxicity Selective 2 dose levels studied in present PD induce mice model, VEM-PD nasal drops restored the levels of glutathione (GSH) and the activities of antioxidant enzymes i.e., in MPTP induced group 1.33 ± 0.06to near normal in MPTP + VEM-PD 2 drops /3 times, striatum. Treated group 2.63 ± 0.143and decreased the elevated levels of malondialdehyde (MDA) in mouse i.e., in MPTP induced group 8.11 ±0.05to near normal in MPTP + VEM-PD 2 drops /3 times, striatum. Treated group 4.45 ± 0.169, in the present study Histopathological evaluation mice, the hippocampus region of brain revealed in the High Dose 2 drops (extract formulations) /3 times treated, marked reduction of MPTP induced severity as gliosis.

In the treatment of neurodegenerative illnesses, catalpol can pass the blood-brain barrier and act as a protective substance. In primary microglia cell culture studies, even Catalpol treatment decreased the levels of tumor necrosis factor (TNF) and nitric oxide synthase upregulated by the inflammatory primer, lipopolysaccharide (LPS), and it also shielded astrocytes from hydrogen peroxide-induced oxidative damage [10] A PD mouse model's midbrain was shown to have higher TNF- levels; in fact, the first oxidative insult that led to the development of PD resulted in the death of ventral midbrain DA neurons, which led to an inflammatory response TNF- stimulates the creation and release of ROS, which causes neurodegeneration. According to earlier research TNF- and IL-1 levels were higher in the brains of mice treated with MPTP than in controls in our investigation. The injection of catalpol significantly increased antioxidant defense capability and reversed the MPTP-induced effects, which led to reductions in the expression of the proteins SOD1, NLRX1, and GPX4. Additionally, it decreased the levels of NLRP3 inflammasome components and the proinflammatory cytokines TNF- and IL-1. In order to reduce the oxidative damage in C57BL/6 mice, Sophora tomentosa L, herbal extract (100 mg/kg), restored the level of GSH and the antioxidant enzymes that were lowered by subacute (five-day) MPTP treatment. Since Sophora tomentosa extract may be upregulated partially via the striatal antioxidant status to prevent motor impairments and dopaminergic dysfunction in an MPTP-induced PD mouse model Rotenone administration in Swiss Albino mice results in decreased TAC and SOD, suggesting a compromised anti-oxidant state associated with morphological alterations in the brain and liver in the PD disease condition.

To establish the therapeutic properties of embelin as well as embelin plus levodopa combination therapy, embelin treatment alone (40 mg/kg) and in combination with Levodopa 7.5 mg /kg restored brain and liver tissue damage in rotenone-induced PD mice.

It also improved peripheral oxidative stress, thyroid hormone changes, and brain alpha synuclein expression. In the MPTP-induced group 1.33± 0.06, for example, VEM-PD treatment reduced the increased levels of malondialdehyde (MDA) and restored glutathione (GSH) levels and antioxidant enzyme activity to levels that were close to normal. In the current study, a histological examination of the mouse brain's hippocampus

indicated mild 3+ abnormalities, including oxidative damage, gliosis, apoptosis, neuronal hyperplasia, and severe 4+ fatty vacuolar changes. However, the hippocampal region of the brain revealed a considerable reduction in MPTP-induced severity in mice that were given High Dose 2 drops (extract formulations) /3 times, and the brain's histological architecture had returned to nearly normal morphology. According to the MPTP animal model activates glial cells and increases pro-inflammatory factors in the striatum and SNpc of the brain.

CONCLUSIONS

The results of our study demonstrate convincingly that VEM-PD Nasal Drops can prevent oxidative stress, neuro-inflammation, and motor dysfunctions caused by -synuclein. Biochemical and histopathological evidence also support the effectiveness of VEM-PD Nasal Drops (extract formulations) in treating MPTP-accelerated neurotoxicity.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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