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Neuroprotective Changes Induced in Substantia Nigra Of Rats by The Combination of Passiflora, Melatonin & Vitamin B6

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ABSTRACT

Background: Parkinson's is an age-related neurodegenerative disorder characterized by loss of dopaminergic neurons. The standard drug Levodopa has been used in the treatment of Parkinson's for decades, but long-term use leads to motor complications like dyskinesia and on-off phenomena. This study aimed to observe the neuroprotective effect of supplements (melatonin, vitamin B6, and Passiflora) in a rat model.

Method: This was an experimental animal study conducted on healthy male albino Wistar rats weighing between 150-200 g. The study was conducted at Baqai Medical University and Dow University of Health Sciences after getting approval from IREB of BMU (BMU-IREB/03-2023) for a period of 6 months. The Model was formed by MPTP (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine). 40 rats were selected by using the power analysis technique & were divided into groups: A: Control, 0.9% saline, B: MPTP, C: MPTP + Levodopa, D: MPTP + Levodopa + Supplement (melatonin 10mg/kg, Passiflora 25mg/kg & vitamin B6 100mg/kg). Weight of animals & behaviour tests (Pole and Plus Maze) were recorded for 5 weeks. Brains were isolated to observe histological changes & Alpha synuclein expression. Data was analysed by using SPSS version 27. One-way analysis of variance (ANOVA) was applied followed by an independent sample t-test.

Results: Behavioural analysis revealed a statistically significant difference between MPTP and treatment groups ($p<0.001$). Bradykinesia was reduced after the intake of the supplement in the pole test. The time spent in the open arm of the plus maze was significantly improved by approximately 80.28% ($p<0.001$) with supplement + L-Dopa. MPTP caused 50% reduction in the neuronal count, observed on H&E staining, while the supplement ameliorated this decrease. Degenerative changes like pyknosis, shrinkage, glial infiltration, and vacuolation were improved in the levodopa + supplement group($p<0.001$). IHC revealed, supplement reduced the accumulation of alpha synuclein aggregates, which were around 25-30-fold in the MPTP group.

Conclusion: The supplement has a neuroprotective role as observed by betterment in behavioural performance, improvement in neuronal degeneration, and reduction in the expression of alpha synuclein

Keywords: Alpha-Synuclein, Melatonin, Vitamin B6, Passiflora.

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INTRODUCTION

Over 6 million people worldwide suffer from Parkinson's disease (PD), second most prevalent age-related neurodegenerative illness[1]. PD cases globally would double from 7 million in 2015 to 13 million in 2040, raising the risk of a PD pandemic. PD is caused by a combination of environmental, genetic, and other unknown factors[2]. It affects the dopaminergic neurons of nigrostriatal pathway along with accumulation of misfolded proteins (Alpha-Synuclein/α-syn). PD has both motor (muscle stiffness, tremors, bradykinesia and instability of posture) and non- motor symptoms (depression, anxiety, and sleep disturbances)[3].

Primary line of treatment levodopa (L-Dopa) has been used for decades however various adverse effects like dyskinesia, “on” and “off” phenomena & psychosis are identified [4]. An important consideration is to use combination of drugs with different mechanisms of actions to cure symptoms of PD and to minimize side effects of L-Dopa. Various therapeutic agents can be combined to accomplish this goal. Conversion of levodopa to dopamine requires vitamin B6 as a co-factor. Deficiency of vitamin B6 has been found in patients with prolonged intake of L-Dopa[5]. Passiflora is a common herbal medicine, used for anxiety, sleep disturbances and pain relief[6]. Melatonin has neuroprotective effect due to its anti-apoptotic, antioxidant and anti-inflammatory activity[7].

Several supplements are in use to treat different conditions like sleeplessness, dizziness and migraine. While there is no study available on the neuroprotective effects produced by the combination of melatonin, vitamin B6 and Passiflora in PD. Thus, this study was designed to investigate the neurorestorative role of supplement on behavior and histomorphological changes in substantia nigra.

METHODS

An experimental animal study was conducted from January to May 2024 at Baqai Medical University and Dow University of Health science after getting approval from IREB of BMU (BMU-IREB/03-2023). 40 healthy male Albino wistar rats (150-200 grams) were included, while diseased animals were excluded. Animals were acclimatized for 2 weeks. Food and water were at libitum, adequate room temperature and 12 hr light/dark cycle was provided.

Animals were divided into 4 groups (n=10). A: Control received 0.9% saline B: MPTP (30mg/kg body weight) and Probenecid (250mg/kg b.w to decrease renal excretion of MPTP,1 hr before MPTP) for 3 weeks[8] C: Levodopa (12.5 mg/kg of b.w)[9] D: Supplement (melatonin 10mg/kg10, passiflora 25mg/kg9 and vitamin B6 100mg/kg b.w)[10] + Levodopa (8mg/kg b.w)[7]. Treatment drugs were started from day 14th and were given intraperitoneally for 3 weeks.

Behavior tests were performed every week to assess locomotor activity, anxiety, bradykinesia and exploratory behavior. Pole Test was performed to asses bradykinesia and motor co-ordination. The animals were placed with head facing upwards on a 50 cm metal pole. The time taken by the animals to reach the ground was recorded[11]. Elevated plus Maze (EPM) was used to assess motor performance and anxiety attitude. The maze consisted of two open & two closed arms (40 × 10 cm) and central area in which the animals were placed for 5 min to explore the apparatus. Time spent in open arm of EPM was recorded[12].

At day 35 of experiment euthanasia was done, whole brain was removed and fixed in neutral buffered formalin (10%). Brain slicer (Zivic, USA) was used to dissect and isolate substantia nigra by referring to George Paxinos atlas. 5-micron thick sections were prepared for H&E staining. For immunohistochemistry (IHC) sections were de- paraffinized. Heat induced epitope retrieval (HIER) method was used for retrieval of antigen. Primary antibody (Alpha synuclein) was applied for 1 hour. Horseradish peroxidase (HRP); secondary Antibody was applied for 30 minutes. After cleaning the sections with phosphate buffer solution (PBS), diaminobenzidine (DAB) was applied for 5 min. Counter staining was done with Hematoxylin.

Olympus microscope (CX23) was used to observe & capture images of different areas of brain at various magnifications. Image J software was used to count the neurons & aggregates of Alpha- synuclein. To ensure inter-rater reliability, histological slides were independently assessed by blind observer. Histomorphological features like shape, size & structure of neuron (shrunken, pyknotic), infiltration of glial cells, vacuolization was observed.

Statistical analysis was done by using SPSS version 27. Data was expressed as Mean ± Standard deviation. As the data was normally distributed, one-way analysis of variance (ANOVA) was applied followed by independent sample t-test. P-value of less than 0.05 was set as statistically significant with the confidence interval of 95%.

RESULTS

Table 1: Effects of Treatment on weight (gms), Pole test & Elevated plus Maze (sec)

Variable	Weeks	Control	MPTP	MPTP + Levodopa	MPTP + Supplement + Levodopa
Weight of animals	0	158.3±6.9	160.4±6.5	164.7±7.9	162.5±8.6
	1	164.0±7.5	*156.5±6.2	161.0±7.5	158.1±7.9
	2	170.2±7.3	**151.1±5.8	**156.8±7.6	**152.9±7.7
	3	178.9±9.7	**147.3±5.2	**▪159.2±6.6	**▪155.6±7.6
	4	184.2±10.1	**144.3±5.5	**▪▪163.7±6.3	**▪▪159.5±7.9
	5	189.0±10	**141.6±5.3	**▪▪167.6±6.6	**▪▪164.0±8.3
Time to reach the base in seconds	0	3.8±1.2	3.8±1.3	3.6±1.4	3.8±0.7
	1	3.9±1.2	**6.1±1.3	**6.5±1.3	*#5.3±1.1
	2	3.6±1.2	**8.5±1.0	**▪6.6±1.7	**▪▪6.6±1.0
	3	3.5±1.3	**8.6±1.6	**▪6.4±1.2	**▪6.5±1.3
	4	3.6±1.4	**8.5±1.7	*▪▪5.1±1.2	*▪▪4.9±0.7
	5	3.7±1.3	**8.7±1.8	▪▪4.3±1.1	▪▪3.8±0.7
Time spent in open arm (s)	0	129.6±10.5	126.5±10.9	129.5±15.3	130.1±10.5
	1	124.5±12.1	**98.3±7.7	**93.8±14.5	*105.5±13.7
	2	130.1±10.5	**75.9±5.0	**79.2±8.5	**#71.5±5.3
	3	129.5±15.3	**54±8.1	**▪▪94.6±8.9	** ▪ ▪100.6±11.0
	4	147.6±10.1	**41.9±3.6	** ▪ ▪115±9.8	** ▪ ▪111.9±13.8
	5	157.9±9.7	**30.7±4.6	** ▪ ▪124.7±6.0	** ▪ ▪128.5±5.0

P<0.05, **P<0.001 when compared to Control

▪P<0.05, ▪▪P<0.001 when compared to MPTP. # P<0.05, ##P<0.001 when compared to Levodopa

Throughout 5 weeks experiment steady weight gain of control animals from 158.3-189gm (19.4%) was observed, this indicated normal growth pattern. MPTP group showed significant drop of weight from 160.4-141.57gm (-11.7%), indicating the effect of neurotoxin on weight. In Group C (Levodopa) & Group D (Supplement + Levodopa), loss of weight was observed in the initial 2 weeks of the experiment, but later there was a recovery with a minimal gain of weight **(Table 1).**

In the Pole test, motor performance was significantly impaired in the MPTP group due to bradykinesia (3.8s to 8.7s). In groups C & D, worsening of motor activity was seen in the initial 2 weeks, but later there was improvement, indicating partial recovery. Control group animals spent adequate time in the open and closed arms of the EPM. MPTP group animals preferred to remain in the closed arm due to increased anxiety. Group C & D animals preferred to stay in a closed arm with reduced exploratory activity in the initial 2 weeks, after administration of treatment drugs, animals of both groups showed recovery. A better overall outcome was observed among the supplement + levodopa-treated group **(Fig. 1).**

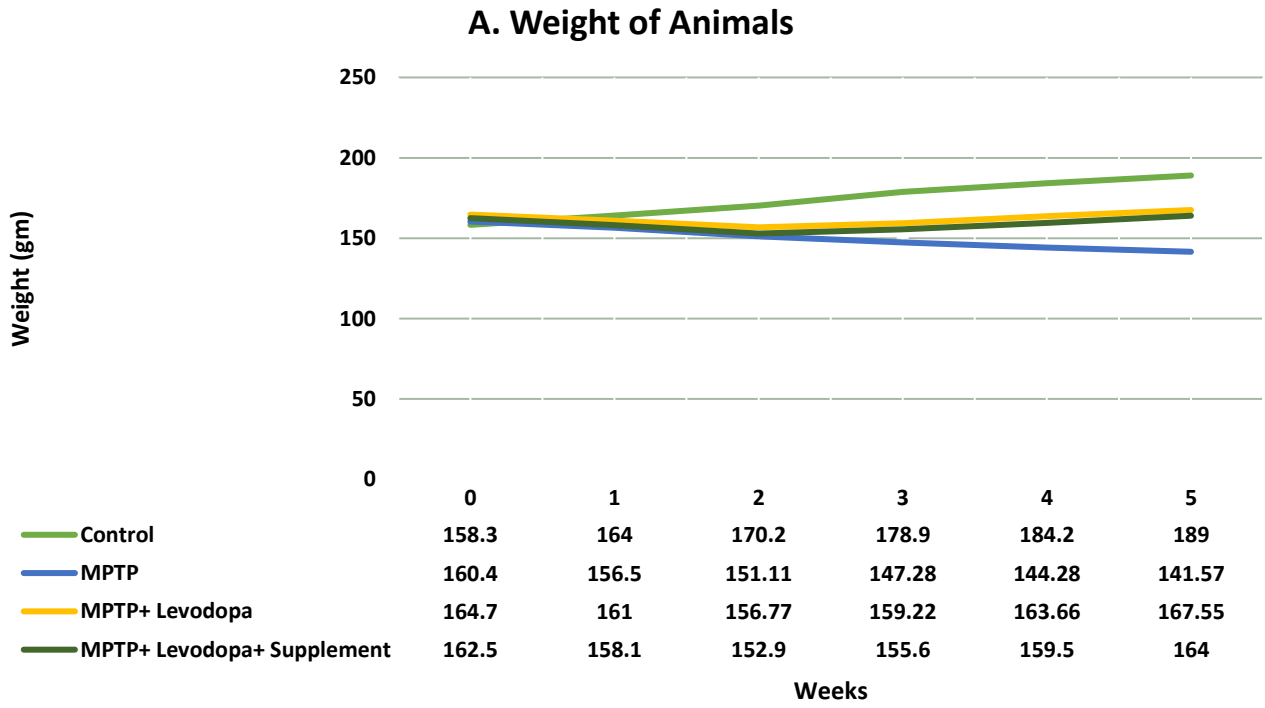

Figure 1: Linear diagrams showing week-wise changes (week 0 to 05) of experimental groups

(A) Weight of Animals

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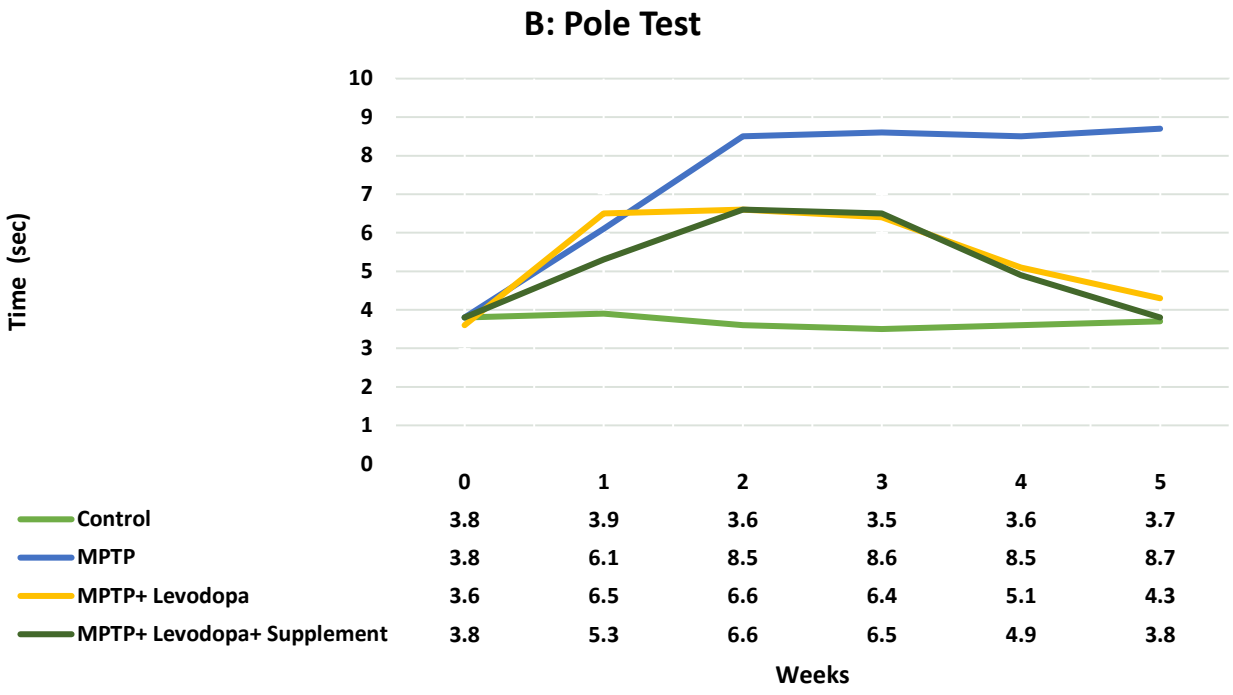

Figure 1: Linear diagrams showing week-wise changes (week 0 to 05) of experimental groups

(B) Pole test

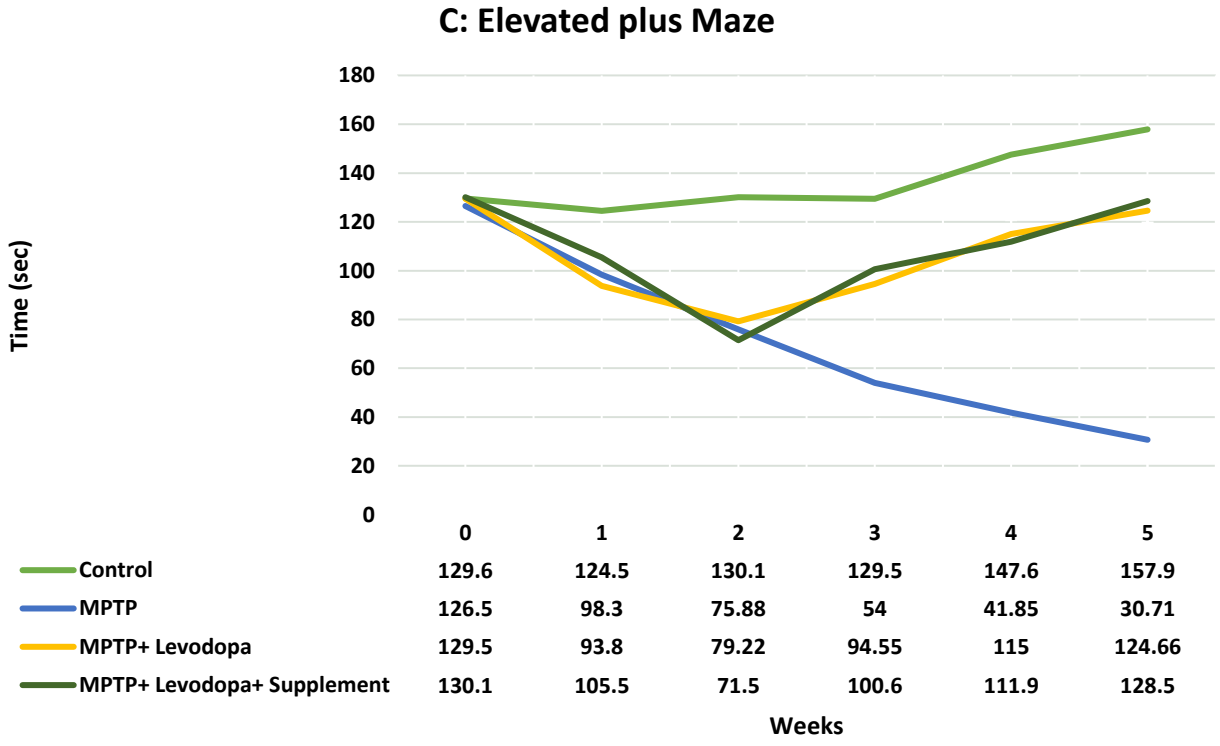

Figure : Linear diagrams showing week-wise changes (week 0 to 05) of experimental groups

(C) Elevated Plus Maze

Table 2: Effects of Treatment on count of neuron & Alpha-synuclein expression

Group	Count of neurons on H&E	Aggregates of Alpha-Synuclein on IHC
Control	64.1	0.6
MPTP	30.6 **	18**
MPTP + L-Dopa	40.3**▪	12.1**▪
MPTP + Supplement + L-Dopa	52.3**▪▪##	6.7**▪▪##

*P<0.05, **P<0.001 when compared to Control

▪P<0.05, ▪▪P<0.001 when compared to MPTP, #P<0.05, ##P<0.001 when compared to Levodopa

On immunohistochemistry, the lowest Alpha-Synuclein aggregates were seen in control animals, indicating a healthy protein balance. In the MPTP group drastic increase in abnormal protein aggregates was seen, indicating oxidative stress & neurodegeneration. In the Levodopa group, reduced aggregates were seen. Antioxidative & neurorestorative potential of the supplement significantly reduced Alpha-Synuclein aggregates in group D **(Table 2).**

On H&E staining, good neuronal density, with normal shape & size of neurons was seen in control group animals. In the MPTP group, severe neuronal loss with altered morphology like degeneration, pyknosis, glial cells infiltration and vacuolization was observed. Moderate recovery was seen in Levodopa group. Animals that received supplement along with levodopa showed restoration of histological features with many intact neurons & minimal glial cell populations indicating the neuroprotective potential of the supplement **(Fig 2).**

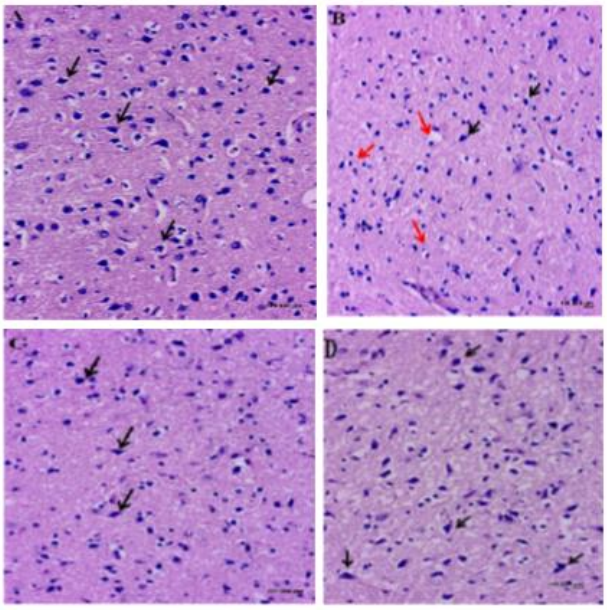

Figure 2A: H&E-stained sections of substantia nigra at 40x magnification. A. Control: normal neuronal shape B. MPTP: Degenerated neurons with shrunken, pyknotic nuclei (black arrows). Vacuolization and gliosis (red arrows). C. Levodopa and D. Supplement + Levodopa: Apparently normal shaped neurons (black arrow) & minimal glial cell infiltrates.

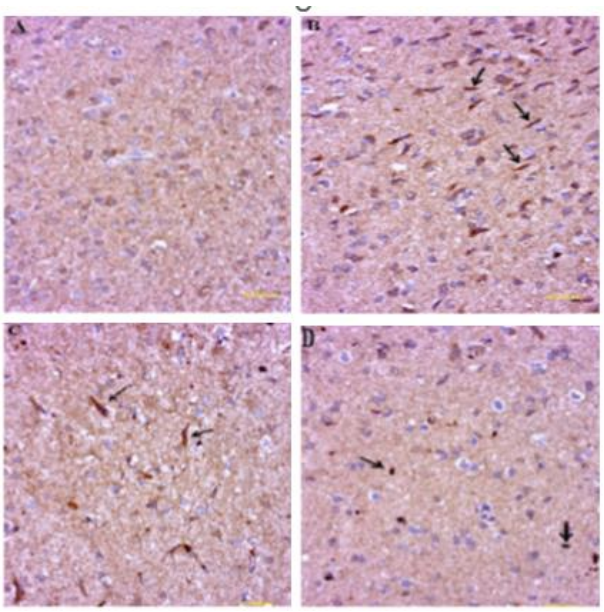

Figure 2B: Immunohistochemical Sections of Substantia nigra at 40x magnification. A. Control: no aggregates of α-syn B. MPTP: greater number of α-syn aggregates (black arrows). Group C. Levodopa & D. Supplement+ Levodopa: few aggregates of α- syn.

DISCUSSION

Even while synthetic medications have advanced significantly in the modern period, it is now clear that they are associated with major side effects. Multivitamins and herbal products are in light due to their minimal side effects. The results of this research indicated that the combination of melatonin, vitamin B6, and Passiflora plays a neuroprotective role by lowering the buildup of Alpha-synuclein, mitigating oxidative stress, and exhibiting anti-inflammatory effects, as evidenced by an increase in neuronal count and enhancement in motor performance. All these findings are in line with studies performed using these treatments.

Studies reveals decrease in the weight of animals with MPTP administration. In a study conducted in 2022, it was found that prolonged use of L-Dopa leads to dyskinesia and tremor that increases energy expenditure & causes a decrease in weight[13]. Melatonin ameliorated the weight loss caused by MPTP in a study conducted in 2021[14]. Vitamin B6 & Passiflora were found to have a protective effect on dopaminergic neurons, but no effect on weight was observed[15, 16].

In the pole test time taken by animals to reach the ground was longer in MPTP animals, as observed in studies conducted in 202[17]. In 2022, another research work concluded melatonin as a treatment option in PD due to its neuroprotective effect [18]. Decreased levels of Vitamin B6 were recorded in patients of PD[19]. Intake of Vitamin B6, B12, and folic acid has reported to have a decreased prevalence of PD[20].

Literature search revealed that animals that received MPTP spent less time in the open arm in the plus maze[12]. Melatonin administration was found to improve anxiety behavior as shown by an increase in the time spent in the open arm and more entries[21]. Vitamin B6 supplement also found to reduce depression & anxiety[22]. Anxiolytic effects of Passiflora in EPM were seen in a study conducted in 2023[23].

Neurodegenerative changes were observed by MPTP administration. Melatonin improved the neurohistological changes in the substantia nigra[24]. Vitamin B complex produces histological improvement in the cerebellum of rats with diabetes[25]. Improvement in neuronal degeneration and glial cell infiltration was also observed by Passion flower administration[26].

The death of dopaminergic neurons leads to overexpression of α-syn. Increased concentration of α-syn was observed in PD patients in a study conducted on postmortem brain [27]. Melatonin was found to lower the accumulation of α-syn by preventing apoptosis[28]. Decreased levels of α-syn were seen when pretreated with B-complex[29]. Flavonoids derived from passion flower have been found to exert

neuroprotection in rats by decreasing dopaminergic neuronal degeneration and aggregation of α-syn[30].

This study has provided substantial evidence that the compounds used in the supplement are active and cost-effective source of neuroprotection in experimental animals. They are also beneficial in lowering the dose and reducing the complications associated with L-Dopa. The limitations are that other regions of brain involved in PD were not studied, HPLC, TH & Anti-ubiquitin immunohistochemistry was also not performed due to limited budget

CONCLUSION

The current study concluded that herbal products along with multivitamins can improve the symptoms of PD and confers neuroprotection. Behavioral parameters, anxiety in the animals were improved by giving the supplement. Aggregates of Alpha-syn were found to decreased and neurohistological features were restored. The supplement helped to reduce the dose of levodopa and prevented the dose related side effects of levodopa. The novel combination of melatonin, Passiflora and vitamin B6 can be a treatment option for PD.

LIST OF ABBREVIATIONS

MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

PD: Parkinson's disease

α-syn: Alpha-Synuclein

L-Dopa: Levodopa

Ip: Intraperitoneally

EPM: Elevated plus Maze

HRP: Horseradish peroxidase

FUNDING

None.

CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

The experimental study was carried out in accordance with the regulations established by the Board of Advanced Studies and Research (BASR) and the institutional review and ethical board (IREB) of Baqai Medical University Karachi.

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE.

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