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Research Article

SYNERGISTIC EFFECT OF MACUNA PRURIENS AND *CURCUMA LONGA* IN ROTENONE INDUCED PARKINSON DISEASED ANIMAL MODEL

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ABSTRACT

Objectives: Parkinson's disease (PD) is a brain disorder that causes unintended or uncontrollable movements, such as shaking, stiffness, and difficulty with balance and coordination. Symptoms usually begin gradually and worsen over time. As the disease progresses, people may have difficulty walking and talking. Recently, several herbal medicines have been tried for the treatment of such neurogenerative disorders. Studies on the extract of Macuna pruriens (MP) seeds and *Curcuma longa* (CL) rhizome have been done for better management of Parkinson's disease.

Methods: The combine effect of extracts of these herbs is studied on rotenone-induced PD on animal model. Both the plants were authenticated. Extracts of MP seeds and CL rhizome were prepared. These extracts were administered into rats to evaluate anti Parkinson's activity. It was included with the catalepsy test, rota rod test, open field test, and estimation of dopamine in the brain.

Results: The number of crossings was increased to 91.43±8.3 after the 28th of administration of both the extracts together. It is much higher than disease control and individual administration of extracts. After 28 days of animal study, attenuation of catalepsy behavior to 6.67±0.7 s was found with co-administration of both the extracts. The degree of prevention of fall-off time was much higher and significant on the 28th day of treatment, with 185.3±12.9 s in the groups treated with intranasal administration of the combination of both the extracts. The intranasal treatment with both the extracts elicited significantly higher elevation of brain dopamine content compared to the disease control group.

Conclusion: This result showed that the Mp and Cl combination may be useful for better management of PD.

Keywords: Macuna pruriens, *Curcuma longa*, Parkinson's disease.

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INTRODUCTION

Parkinson's disease (PD) is a chronic and progressive neurological condition that affects a small group of nerve cells (neurons) in a part of the brain. While this condition is best known for affecting muscular control, balance, and mobility, it can also impact the senses, thinking ability, mental health, and other aspects of life. The cause for this condition is still a puzzle. Although there is no defined cure so far, many treatment options are available to improve the symptoms and quality of life, which include medications and surgery. Though it is not fatal, it can cause serious complications.

Treatment

PD has no known cure; however, medicines can help individuals manage their symptoms [1].

Medicines can help treat the symptoms of Parkinson's by:

- Increasing the level of dopamine in the brain
- Influencing other brain chemicals, such as neurotransmitters, which transfer information between brain cells
- Helping controls non-movement symptoms.

The following are the treatment options for PD:

Medications

PD is treated with various medications [2].

- Carbidopa and levodopa are tremor-controlling drugs used in combination with other drugs to reduce tremors
- Benzodiazepines, sometimes known as tranquillizers, can temporarily relieve tremors
- Beta-blockers might also be used to ease out some symptoms of the disease, such as high blood pressure.

Macuna pruriens (MP), also referred to as the velvet bean, is a legume that grows in tropical and subtropical areas across the world, including Africa, Asia, the Caribbean, and the Pacific Islands [3]. Although the beans can be used as a source of food after they are boiled, MP is also a medicinal plant, used for millennia in traditional Ayurvedic Indian medicine, for a variety of conditions [4]. MP has been investigated for its anti-diabetic, anti-microbial, anti-oxidant, anti-epileptic, and anti-depressant properties, to name a few. In 1937, levodopa (L-dihydroxyphenylalanine or L-DOPA), which is used effectively to manage the motor symptoms of PD, was first isolated from seeds of MP and has been found in other *Mucuna* species: *Mucuna bracteata*, *Mucuna imbricata*, *Mucuna macrocarpa*, and *Mucuna mutisiana* [5].

Curcumin

The imbalance between reactive oxygen species (ROS) generation and cellular antioxidant activity leading to oxidative stress is known to be a major cause of neurodegenerative diseases such as Alzheimer's disease and PD. Therefore, antioxidants are regarded as a potential treatment for neurodegenerative disorders, including PD [7]. Antioxidants, natural sources, have recently gained popularity in combating the effects of ROS. The *Zingiberaceae* family contains the rhizome turmeric *Curcuma longa* (CL). For centuries, it has been used in India, China, and Southeast Asia for flavoring, food processing, coloring, and as traditional medicine. Turmeric has long been used to treat rheumatism, eye infections, and liver problems. Curcumin, turmeric's active ingredient, has antioxidant, anti-apoptotic, and anti-inflammatory properties

that protect tissues from the harmful effects of ROS [6]. The phenol moiety, which donates a proton to ROS, is thought to be responsible for curcumin's antioxidant properties. Curcumin also protects against A53T α-synuclein aggregation and monoamine oxidase B, becoming a compound of interest in treating neurodegenerative disorders such as PD. Curcumin has been found to protect nigrostriatal dopaminergic neurons from damage in animal models. Curcumin had protective effects on alpha7-nicotinic acetylcholine receptors after administration of 6-hydroxydopamine in rats with a curcumin dose of 200 mg/kg. Curcumin restored nigrostriatal dopamine neurons to 87.3% and 84.8% after low-dose 11-methyl-4-phenyl-1, 2, 3,6-tetrahydropyridine (MPTP) administration, compared to 49.1% in the MPTP group [7]. The use of tyrosine hydroxylase (TH) immunohistochemistry to determine dopamine denervation in the coronal parts of the brain further confirmed these findings.

METHODS

Authentication of plant

The plant specimen used for the research work was collected from the forest of Kusgaon BK. Lonavala, Pune, Maharashtra, India. The plant specimen was authenticated by the Botany Department at Agharkar Research Institute, Pune, India.

Preparation of the extract

MP

A significant amount of seed powder was mixed with the stipulated volume of acidified water and followed by ultrasonication with 250 rpm at room temperature. The extract was passed through a suitable filter medium [9]. The yield obtained was around 5–6% w/v.

CL

Accurately weighed turmeric powder is extracted with n-Hexane using Soxhlet extractor for 2 h, then with acetone for 2 h, at 600C temperature, and then recrystallized with ethanol [9,10]. The yield obtained was around 2–3% w/v.

Animal experiment

Healthy either sex, Wistar rats (14–18 weeks old) of 350–400 g, were divided into various groups (n=6). They were housed 3 animals per cage (polycarbonate cages) with normal animal house conditions as temperature 22–25°C, 40–60 relative humidity and a 12:12 light and dark cycle. Animals were fed with a standard animal diet (Krishna Aggrotech Ltd., India) with water ad libitum.

Experimental design

The antiparkinsonian activity of the test formulation was conducted as per the procedure described in the documented report [10,11]. Briefly, 7 days acclimatized animals were divided into various groups.

Group-I served as the normal control group and was administered with 0.5% CMC (5 mL/kg p.o.) and sunflower oil (1 mL/kg s.c.) as a vehicle.

Group II-disease control animals received rotenone (2 mg/kg s.c. emulsified in sunflower oil at 2 mg/mL).

Group III-animals received Intranasal levodopa gel (INL)+rotenone (2 mg/kg s.c. emulsified in sunflower oil at 2 mg/mL).

Group IV-animals received Intranasal curcumin gel (INC)+rotenone (2 mg/kg s.c. emulsified in sunflower oil at 2 mg/mL).

Group V-animals received an Intranasal combination of levodopa and curcumin gel (IN-L+C)+rotenone (2 mg/kg s.c. emulsified in sunflower oil at 2 mg/mL).

All the drugs were administered once daily for 30 days, and after 30 days post-treatment, various behavioral changes were studied.

Behavioral evaluations

All the behavioral evaluation was performed on a weekly basis during the treatment regimen. Catalepsy. Number of crossing behavior by open field test (OFT) [11], Muscle grip, and postural instability (inclined test).

Catalepsy test

Catalepsy is a symptom of PD characterized by rigid body, rigid limbs, limbs staying in the same position when moved, no response, loss of muscle control, and slowing down of bodily functions, such as breathing [12,15]. Thus, in the present study, we evaluated the catalepsy condition induced by repeated rotenone administration.

Catalepsy can be studied by placing an animal into an unusual posture and recording the time taken to correct this posture. In this test, catalepsy was studied as the duration of catalepsy behavior showed by the respective animal with treatment.

The catalepsy was studied during various weeks of rotenone administration during 30 days' time period and the duration of catalepsy (time during which the mice maintained the fixed rearing posture) was measured, and behaviors were recorded. The cut-off time was 5 min.

OFT

The OFT was performed on animals as per the method described. An individual rat was placed in the open field and the number of squares crossed with all paws (crossings) was counted in a 6-min session. The apparatus was cleaned with a solution of 10% ethanol between tests to hide animal clues. Reduction in the crossing behavior by the individual rat is the reduction in the motor coordination action. Impairment in motor coordination was observed in the PD.

Rota rod test

The Rota rod test was used to study the muscle grip strength of the rats by using the Rota rod apparatus [13]. The latency to fall off time was determined as per the procedure described in the findings of Sharma *et al*. (2021). Briefly, rats were placed on the rotating rod for 2 min, and the latency to fall off time (time from placement of rat on the rod to falling off the rod in seconds) was recorded. The cut-off for the animals was kept at a maximum score of 120 s.

Biochemical estimation on 31st day, after the behavioral evaluation, all the animals were sacrificed by CO_2 euthanasia, brain was immediately removed and homogenized (10% w/v) in phosphate buffer solution (pH 7.0), Homogenates were poured in 15 mL centrifuge tubes and rotated at (Neaution, India) at 3,000 RPM at 4°C for 30. The Supernatant was removed in Eppendorf tubes and labeled, respectively. The supernatant was separated and stored at −80°C until used.

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Estimation of dopamine contents in brain homogenate [14].

The stored supernatant was allowed to be kept at normal temperature for 30 min before dopamine estimation. The dopamine contents were estimated by using a ready-made enzyme-linked immunosorbent assay (ELISA) kit and procedure described in the leaflet provided in the ki

Table 1: Effects of intranasal administration of gel of levodopa or curcumin or their combination on number of crossing behavior in rotenone-induced Parkinsons disease in rats

Treatment and dose	Number of crossings at various days (numbers, mean±SEM)				
	0th day	7th day	14th day	21st day	28th day
Normal control	96.33±9.2	94.01±9.1	95.92±7.9	99.67±9.3	94.12±8.2
Disease control	97.2±8.7	96.33±9.2	66.67±8.3#	45.33±5.3##	37.12±6.3##
Intranasal levodopa gel	94.33±8.4	91.67±8.2	94.33±8.9*	72.67±6.3*	81.23±8.4*
Intranasal curcumin gel	97.67±9.8	96.67±9.9	72.33±6.7	80.33±8.4*	78.72±7.4**
Intranasal combination of levodopa and curcumin gel	93.33±7.9	94.67±9.0	83.67±8.3*	90.33±8.4*	91.43±8.3***

##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to Disease control of respective day, one-way ANOVA followed by Bonferroni *post hoc* test. ANOVA: Analysis of variance, SEM: Standard error of mean

Table 2: Effects of intranasal administration of gel of levodopa or curcumin or their combination in on catalepsy in rotenone-induced Parkinson's disease in rats

Treatment and dose	Catalepsy (second) (Mean±SEM)				
	0 day	7th day	14th day	21st day	28th day
Normal control	1.33±0.2	1.67±0.2	2.33±0.3	2.67±0.4	1.67±0.3
Disease control	1.33±0.2	3.67±0.2	5.67±0.5#	15.67±2.3###	43.67±4.6###
Intranasal levodopa gel	1.33±0.2	2.0±0.2	5.33±0.6	9.67±0.8**	18.67±1.8**
Intranasal curcumin gel	1.33±0.2	2.01±0.2	7.02±0.7	14.67±1.7	28.33±2.8**
Intranasal combination of levodopa and curcumin gel	1.33±0.2	2.01±0.3	4.33±0.2	10.67±1.0*	6.67±0.7***

##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to disease control of respective day, one-way ANOVA followed by Bonferroni *post hoc* test. ANOVA: Analysis of variance, SEM: Standard error of mean

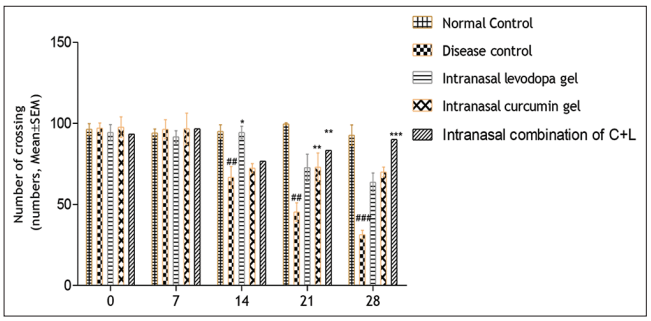

Fig. 1: Effects of intranasal administration of gel of levodopa or curcumin or their combination in on number of crossing behavior in rotenone-induced Parkinson's disease in rats ##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to Disease control of respective day, one-way ANOVA followed by Bonferroni *post hoc* test. ANOVA: Analysis of variance

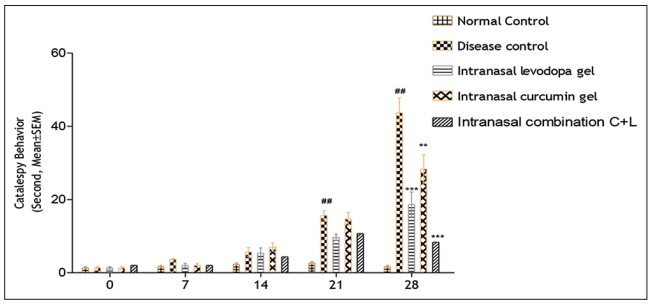

Fig. 2: Effects of intranasal administration of gel with of levodopa or curcumin or their combinations on catalepsy behavior in rotenone-induced Parkinsons disease in rats ##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to disease control of respective day, one-way ANOVA followed by Bonferroni *post hoc* test. ANOVA: Analysis of variance

Statistical analysis

Results are expressed as the mean±standard error of the mean. Statistical analysis was performed by one-way analysis of variance followed by Bonferroni *post hoc* test by using the GraphPad Prism version 5 software (GraphPad Software, Inc., La Jolla, CA, USA). A value p<0.05 was statistically significant.

RESULTS AND DISCUSSION

OFT

The present study demonstrated that, intranasal administration of standard levodopa alone and curcumin and their combination in rotenone induced Parkinson like symptoms in Wistar rats (Table 1 and Fig. 1). The findings revealed that, the after repeated administration of rotenone for 30 days exhibited significant decrement in number of crossings in open field test from 14th day and remarkable (p<0.001) declined on 28th day when it is compared to normal control group on the respective week. Further, pre-treatment with a novel formulation of levodopa gel and curcumin gel elicited amelioration of crossing behavior significantly (p<0.01, p<0.001) compared to the disease control group. Nevertheless, the improvement was found to be much significant (p<0.0001) on day 28th with the repeated administration of a combination formulation of curcumin with levodopa by the intranasal route the present findings thus, suggested that combination treatment exhibited improvement in Parkinson symptom of motor coordination by reversing the crossing movement in the rats.

Catalepsy

In the present study, evaluation of the catalepsy condition induced by repeated rotenone administration was done (Table 2 and Fig. 2). The present experimental findings showed that the disease control group rats exhibited a remarkable (p<0.0001) increase in cataleptic behavior compared normal control group. Pre-treatment with intranasal gel of levodopa and curcumin elicited significant (p<0.0001) attenuation of cataleptic behavior compared to disease control. Furthermore, the combination of levodopa and curcumin gel treatment exhibited better attenuation in cataleptic behavior compared to vehicle-treated disease control.

Fall off latency by rota rod test

In the present study, determination of the rigidity and muscle coordination and grip strength is done, which are the major

Table 3: Effects of intranasal administration of gel with of levodopa or curcumin or their combinations on fall-off latency in rotenone-induced Parkinson's disease in rats

Treatment and dose	Fall off time (second) (mean±SEM)				
	0 day	7th day	14th day	21st day	28th day
Normal control	196.2±20.3	184.3±18.2	200.5±19.2	195.5±17.7	205.5±22.3
Disease control	202.67±21.8	169.67±12.3	141.2±12.9#	109.67±9.4###	68.33±4.5###
Intranasal levodopa gel	196.7±17.6	180.33±12.4	171.2±12.4	164.33±15.2*	127.33±11.2*
Intranasal curcumin gel	196.2±16.3	171.33±18.2	162.33±17.9	144.2±13.6*	131.67±12.6**
Intranasal combination of levodopa and curcumin gel	196.5±18.4	156.33±13.3	162.67±14.2	183.9±12.3**	185.3±12.9***

SEM: Standard error of mean

Table 4: Effects of levodopa gel or curcumin gel or levodopa and curcumin combination gel on dopamine contents in brain homogenate in rotenone induced Parkinson's disease in rats

S. no.	Particular	Dopamine concentration
1	Normal control	0.525±0.06
2	Disease control	0.129±0.01##
3	Intranasal levodopa gel	0.332±0.02*
4	Intranasal curcumin gel	0.272±0.04*
5	Intranasal combination of levodopa and curcumin gel	0.482±0.05**

##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to Disease control of respective day, one-way ANOVA followed by Bonferroni *post hoc* test. ANOVA: Analysis of variance

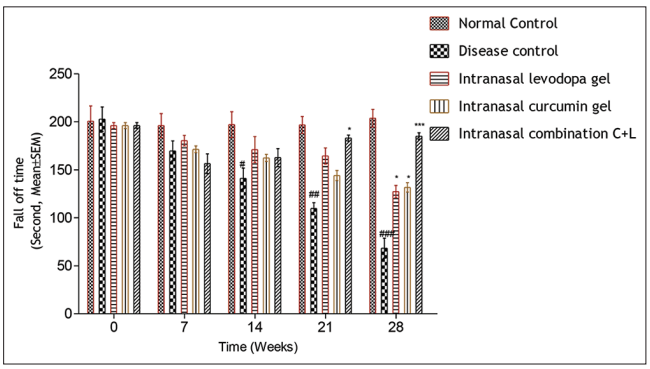

Fig. 3: Effects of intranasal administration of gel with of levodopa or curcumin or their combinations on fall off latency in rotenone-induced Parkinsons disease in rats; ##p<0.0001 when compared to normal control animals of respective day; ***p<0.0001, **p<0.001, *p<0.01, when compared to disease control of respective day, one-way ANOVA followed by Bonferroni post hoc test.

manifestations developed in PD (Table 3 and Fig. 3). Present experimental findings revealed that, the repeated administration of rotenone showed reduction in the fall off time from 14 days and continued thereafter until the last day of treatment. Further, treatment with levodopa gel and curcumin gel alone by intranasal administration elicited significant (p<0.01) prevention of fall-off time compared to disease control treated with vehicle at the respective week. However, the degree of prevention of fall off time was much higher and significant (p<0.001) on 21st and 28th day in the groups treated with intranasal administration of combination of levodopa and curcumin gel Thus, the treatment of levodopa and curcumin combination exhibited better effects on muscle coordination disturbance due to repeated rotenone administration observed in the present studies.

The dopamine contents were estimated using a ready-made ELISA kit

Present experimental findings demonstrated that the dopamine levels were found to be significantly (p<0.0001) attenuated in the disease control group treated with vehicle compared to the normal control group. Treatment with levodopa gel and curcumin gel per se by intranasal administration exhibited significant (p<0.01) amelioration of brain dopamine contents compared to vehicle-treated disease group. However, the intranasal treatment with levodopa and curcumin gel elicited significantly (p<0.0001) higher elevation of brain dopamine content compared to the disease control group, as mentioned in Table 4.

CONCLUSION

The animal study results also showed that there is a considerable enhancement of dopamine level in the brain after administration of gel of MP seed extract and Curcumin longa rhizome extract. The finding suggests that the formulation made with a combination of both extracts can be used to enhance the efficacy single herbal extract. Antiparkinsonian activity of the test nasal gel formulation showed improvement in behavioral pattern after administration of the combination MP seed extract and Curcumin longa rhizome extract.

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AUTHORS' CONTRIBUTIONS

Mr. Aniruddha S. Kulkarni: Experimental work Data collection, Data analysis and drafting the article.

Dr. Manoj Tare and Dr. Meera Singh: Conception or design of the work and interpretation of results.

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CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

All data generated or analyzed during this study are included in this published article (and its additional files).

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