

# Study on the Effect of *Phaseolus vulgaris* Methanol Extract on Haloperidol and Tacrine Induced Parkinsonism

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## ABSTRACT

**Background:** Parkinson's disease is neurodegenerative disease with no cure till now, there are treatments that can be explored to ease the symptoms of this disease, and using plant extract we explore the possibility of neutralizing the adverse symptoms and providing better quality of life to patients. **Purpose:** To demonstrate Anti-parkinson's activity of *Phaseolus vulgaris* methanol pod extract by using behavioural models in *Wister Albino* rats. **Materials and Methods:** Animals were given *Phaseolus vulgaris* methanol extract (PVME) prior Haloperidol and Tacrine induced Parkinsonism. **Results:** *Phaseolus vulgaris*, family (Leguminosae) is a plant, well known for its Traditional and Ayurvedic application for the treatment of various diseases. In the present studies, *Phaseolus vulgaris* pods were used to evaluate its Antiparkinson's activity in behavioral models in Albino rats. The models used here were Haloperidol-induced catalepsy and Tacrine-induced vacuous jaw movement. *Phaseolus vulgaris* methanol extract (PVME) of 200 and 400 mg/kg were given to rats prior to inducing Catalepsy. Haloperidol, an Antipsychotic drug that induces motor symptoms like Parkinson's disease, PVME administration for 5 days, and on last day Haloperidol (1mg/kg i.p) was given and catalepsy was observed, it was seen that PVME reduces catalepsy score in a dose-dependent manner. Behavioral parameters also observed using Tacrine, which is an Anticholinesterase drug induces chewing movements and orofacial bursts. The results were noted for a duration of 1 hr and found that PVME 400 mg/kg dose significantly reduces the movements and bursts as compared to 200 mg/kg dose. The given results were found close to the standard group (levodopa + carbidopa). **Conclusion:** The study conducted on *Phaseolus vulgaris* plant pod extract demonstrates the Neuroprotective activity of plant and its effectiveness to assess the symptoms of Parkinson's disease. Antiparkinson's effect of PVME shown to treat symptoms of motor dysfunction attributed to its tendency to reduce oxidative stress and having phenolic content.

**Keywords:** *Phaseolus vulgaris*, Haloperidol, Tacrine, Parkinson's disease, Levodopa, Neuroprotective, Carbidopa, Oxidative stress.

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## INTRODUCTION

Neurodegenerative diseases are defined by the lack of neurons in the brain causing cognitive and functional degradation over a period of time. Parkinson's disease (PD) is a neurological disease very actively found in elderly people over the age of 60 years, it's a disorder where dopaminergic neurons tend to decline in the substantia nigra region of the brain.<sup>1</sup> numerous factors affect the pathophysiology of this disease amongst which oxidative stress is one of

the dominant factor. Oxidative stress arises due to a lack of balance between internal antioxidant and free radical generation.<sup>2</sup> The characteristic feature of PD includes motor and non-motor symptoms, motor symptoms like tremor (predominantly observed in the distal part of the body including lips, jaw, legs and rarely head), bradykinesia, rigid body, instability in posture (freezing or abnormal posture), Lewy body. Non-motor symptoms may include depression,

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fatigue, apathy, co-genitive impairment, insomnia, etc.<sup>3</sup> Studies suggest that oxidative stress can initiate the chain reaction by free radical and damage various biomolecule and decreases various antioxidant enzymes like Glutathione, Superoxide dismutase, and Catalase that helps catalyzing reactive species.<sup>4</sup> Levodopa (a neurotransmitter) is a globally preferred drug to assess PD symptoms. *Mucuna pruriens* were the first species of plant to extract levodopa and later applied to treat PD symptoms. Legumes in general possess L-dopa naturally and have various nutraceutical properties.<sup>5</sup>

Plants possess secondary metabolites which provide a wide range of medicine to the chemist around the world. *Phaseolus vulgaris* belong to the family Leguminosae is also known as common bean, originated in the American continent, widely utilized around Mexico, America, and Africa as staple food having a high amount of protein content. *Phaseolus vulgaris* utilized as green pods or green-shelled beans, there are varieties of beans such as red beans or french bean, haricot bean, black bean, pinto bean, navy bean, etc depending on size, shape, and color.<sup>6-7</sup> The plant is rich in anthocyanin, flavonoids, phenolic acids, quercetin, terpenes, saponin, etc bioactive components responsible for various biological roles in cellular pathways. The studies show many pharmacological activities like anticancerous, antihyperglycemic, antioxidant, antimutagenic, anti-inflammatory, antibacterial, and helps in chronic degenerative diseases.

Haloperidol is an antipsychotic drug known for its extrapyramidal symptoms by blocking the dopamine D2 receptor in striatum.<sup>8</sup> It gives rise to movement disorder like dyskinesias and dystonias and disruption of locomotor activity resembling symptoms of PD.<sup>9</sup> Tacrine is an anticholinesterase inhibitor that produces motor dysfunction and slowness in movement hallmark features of PD.<sup>10</sup> Tacrine is known to retard the uptake of serotonin, noradrenaline, and dopamine, the process occurs at monoaminergic storage granules level rather than axonal membrane.<sup>11</sup> In our present study, we are analyzing Anti-parkinson's activity of *Phaseolus vulgaris* methanol pod extract using haloperidol and tacrine induced rat models.

## MATERIALS AND METHODS

### Plant Selection and Extraction

The plant was collected from the local market of Bhopal (M.P) in November. The plant was authenticated and verified by Dr. Zia-ul-Hasan HOD (Botany), Safia College, Bhopal. The Voucher Specimen number of the plant was 448/bot/Saifia/17. Extraction was done by

using the maceration technique where the phytochemical constituents were separated based on solvent polarity from lower to higher. *Phaseolus vulgaris* Methanol extract (PVME) was collected for further studies.

### Drugs and Chemicals

Haloperidol + Carbidopa, Tacrine (Pinnacle Biomedical Research Institute) all chemicals used were of analytical grade.

### Animals

*Wister Albino* rats selected for the experiment were issued by Pinnacle Biomedical Research Institute, permission to conduct the experiment was taken from the Institutional Animal Ethical Committee (IAEC) of PBRI, Bhopal (M.P) (Reg No.1283/PO/c/09/CPCSEA). All the standard conditions were followed as per norms of CPCSEA (Committee for Purpose of Control and Supervision of Experimentation on Animals). Animals were taken irrespective of their sex having an average weight of 110-150 gm and kept at a maintained temperature of 22±2°C. Protocol Approval Reference No. PBRI/IAEC/PN-17110.

### Acute Oral Toxicity

Acute oral toxicity of *Phaseolus vulgaris* methanol extract (PVME) was tested against rats by following (OECD) guidelines. Female rats of 100-150 gm weight were taken and administered with PVME doses of 5, 50, 300, and 2000 mg/kg and check for mortality for various intervals. Finally, after checking for 24 hr, 48 hr, and 14 days the LD<sub>50</sub> was found below 2000 mg/kg. The dose level selected for PVME was 200 mg/kg and 400 mg/kg.

### Experimental Protocol

Animals were given *Phaseolus vulgaris* methanol (PVME) extract for 5 days except control or vehicle group. Parkinsonism was induced on last day by giving Haloperidol 1 mg/kg i.p or Tacrine 2.5 mg/kg i.p.

### Haloperidol Induced Catalepsy and *in-vivo* antioxidant assay (4 groups)

**Group I:** Control group (Haloperidol) 1mg/kg i.p

**Group II:** Standard drug (Levodopa + Carbidopa) 125 mg/kg

**Group III:** 200 mg/kg of PVME

**Group IV:** 400 mg/kg of PVME

### Tacrine Induced Vacuous Jaw Movements (5 Groups)

**Group I:** Vehicle group without any drug/extract

**Group II:** Control group (Tacrine drug) 2.5 mg/kg i.p.

**Group III:** Standard drug (Levodopa + Carbidopa)  
125 mg/kg

**Group IV:** 200 mg/kg of PVME

**Group V:** 400 mg/kg of PVME

### Behavioral models

#### Haloperidol-induced Catalepsy in Rats

In this analysis Albino rats (100-200 g) were used. The animals were divided into 4 groups each having 6 animals. Animals were pretreated with Control group (Haloperidol), *Phaseolus vulgaris* methanol extract (PVME) (200 mg/kg and 400 mg/kg) and Levodopa + Carbidopa (125 mg/kg) prior 30 min before giving Haloperidol (1mg/kg i.p). The albino rats were examined for catalepsy at 0, 30, 60, 90, and 120 min after giving haloperidol by placing their forepaw on a bar raised at the height of 6 cm. The retention time of the forepaw of an animal on a wooden bar was noted. The cut-off time was taken at 300 min.<sup>12</sup>

#### Tacrine Induced Vacuous Jaw Movements

Albino rats of weight 100-150 g were taken and divided into 5 groups, 6 animals each ( $n=6$ ). The animals were treated with Vehicle, Control, *Phaseolus vulgaris* methanol extract PVME (200 mg/kg and 400 mg/kg) and Standard Levodopa + Carbidopa (125 mg/kg) 1 hr before treating with tacrine (2.5 mg/kg i.p.). After the administration of tacrine, animals were placed in a Plexiglas observation box (22×22×22 cm<sup>3</sup>) and hebitualized for 10 min. The observer blind to treatment was made to note the tremulous jaw movements and orofacial bursts for 1 hr.<sup>13</sup>

#### Statistical analysis

The result data were shown as Mean  $\pm$  SEM. Significance of data was observed using one-way analysis of variance (ANOVA) along with Multiple Comparison Procedures (Bonferroni *t*-test). The results were found to be significant at ( $p<0.001$ ).

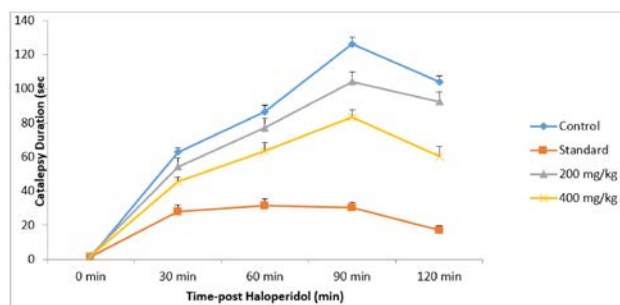
## RESULTS

#### Haloperidol-induced Catalepsy in Rats

The results were expressed in Figures (1 and 2). Animals were taken in 5 different groups  $n=6$  and dosing took place for 5 days and on the last day, haloperidol was given prior to 1 hr of dosing. Haloperidol group, where it administered with 1mg/kg i.p produced noteworthy catalepsy, whereas the standard group having levodopa + carbidopa showed the lesser amount of catalepsy. The duration of catalepsy varied over a time duration of 0 to 120 min. In almost all groups maximum catalepsy was seen at 90 min time after haloperidol administration, the



**Figure 1: Haloperidol induced Parkinsonism in albino rat.**



**Figure 2: Effect of PVME on haloperidol induced catalepsy in rat.**

Control group: Haloperidol, 1mg/kg i.p, Standard: Standard drug (Levodopa + Carbidopa) 125 mg/kg, 200 mg/kg and 400 mg/kg; PVME (*Phaseolus vulgaris* Methanol Extract), \* $p<0.001$  shows Statistical significance as Compared to Control group.

lowest amount of catalepsy should be seen at 120 min for effective drug action. The animals were given 200 and 400 mg/kg of PVME and found that 200 mg/kg has shown significant ( $p<0.001$ ) reduction in the amount of catalepsy when compared to control group and 400 mg/kg was effective in catalepsy reduction than its 200 mg/kg equivalent in (Table 1). Both the concentrations of plant extract have shown a gradual increase in catalepsy till 90 min and after that, they appear to lessen the catalepsy significantly ( $p<0.001$ ).

#### Tacrine Induced Vacuous Jaw Movements

Animals were tested for another Parkinson-related motor dysfunction induced by anticholinesterase

**Table 1: Effect of Haloperidol, Levodopa + Carbidopa and *Phaseolus vulgaris* Methanol Extract on Catalepsy Score at Various Time Intervals.**

Groups	Doses mg/kg	Catalepsy score (0 min)	Catalepsy score (30 min)	Catalepsy score (60 min)	Catalepsy score (90 min)	Catalepsy score (120 min)
Hal	1 mg/kg	1.16±0.75	62.83±2.71	86.33±4.13	126.16±4.07	103.83±3.65
Hal + L-Dopa + C-dopa)	1 mg/kg + 125 mg/kg	1.33±0.51*	28±3.84*	31.5±3.98*	30.16±3.37*	16.83±2.99*
Hal +200 mg/kg methanol extract	1 mg/kg + 200 mg/kg	2±0.63*	54.16±5.56*	77±5.47*	104.16±5.85*	92.5±5.82*
Hal +400 mg/kg methanol extract	1 mg/kg + 400 mg/kg	1.66±0.51*	45.33±2.8	63.33±5.31*	83.16±4.53*	60.33±5.78*

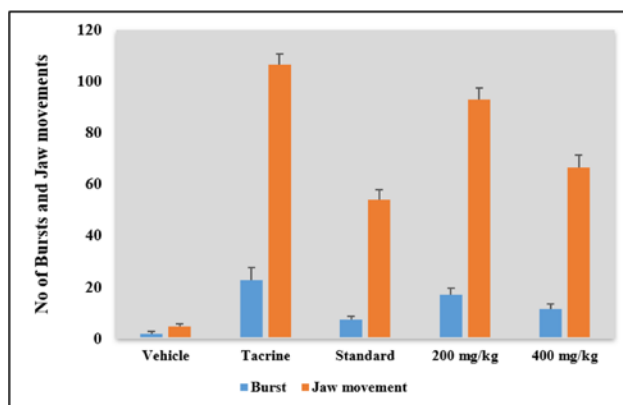
Results were expressed as mean± standard error of mean (SEM), analyzed by one way Anova (ANOVA)  $n=6$ , followed by bonferroni test. \* $p<0.001$  shows Statistical Significance as compared to Control group. Hal: Haloperidol, L-dopa + C-dopa: Levodopa and Carbidopa, PVME: *Phaseolus vulgaris* methanol extract

**Table 2: Effect of *Phaseolus vulgaris* on tacrine-induced orofacial dyskinesia and bursts.**

Groups	Treatment	Bursts (Mean±SD)	Jaw movements (Mean±SD)
I	Vehicle Group	1.66±0.81	4.5±1.04
II	Tacrine Group	22.66±4.76	106.33±4.36
III	Tacrine+L-Dopa+Carbidopa	7.16±1.16*	53.83±3.81*
IV	Tacrine + Methanol extract 200 mg/kg	16.66±2.58*	93±4.56*
V	Tacrine + Methanol extract 400 mg/kg	11.33±1.96*	66.5±4.80*

Expressed as mean± standard error of mean (SEM), analyzed by oneway Anova (ANOVA)  $n=6$ , followed by bonferroni test. \* $p<0.001$  compared to vehicle Treated group.

inhibitor drug i.e Tacrine. The animals were divided into 5 groups and dosing took place for 5 days. The vehicle group has not given any drug or extract shows no effect. Animals in all groups were given tacrine prior to 1 hr of dosing and results were noted. Maximum movements are supposed to be observed in 30-50 min of given 1 hr time duration. The control group (Haloperidol) reveal elevated jaw movements and orofacial bursts in rats and the standard group have a minimum value for both the movements (Table 2). Pretreatment with 200 and 400 mg/kg of PVME shows a significant ( $p<0.001$ ) decline in jaw movements and orofacial bursts. 400 mg/kg PVME dose showed lesser movements as compared to 200 mg/kg extract. Comparable data showing both the orofacial bursts and Vacuous jaw movements were represented using graphical representation in (Figure 3).



**Figure 3: Effects of *Phaseolus vulgaris* plant extract on tacrine induced Vacuous Jaw Movement and Burst Various group represents comparable values of Bursts and Vacuous Jaw movements in 60 min duration, each column represents as mean ± Standard error (SEM) of the mean ( $n=6$ ), \* $p<0.001$  compared to vehicle treated Group (One way ANOVA followed by bonferroni test Vehicle group without any Drug/extract, Control group (Tacrine drug) 2.5 mg/kg i.p, Standard drug (Levodopa + Carbidopa) 125 mg/kg, 200 mg/kg and 400 mg/kg PVME (*Phaseolus vulgaris* Methanol Extract).**

## DISCUSSION

In our present study Anti-parkinson's effect of *Phaseolus vulgaris* methanol pod extract was observed using two PD models namely Haloperidol induced catalepsy and Tacrine Induced Vacuous Jaw Movement and Burst in experimental Wister Albino rats.

PD is associated with several motor and non-motor dysfunctions in patients. The symptoms corresponding to motor dysfunctions were externally induced using a drug called Haloperidol. Haloperidol is widely known as an Antipsychotic drug, it initiates the blockade of transmission of dopamine causing symptoms like muscle rigidity, decline in locomotion causing catalepsy.<sup>14</sup> The rats were administered 200 and 400 mg/kg PVME and found they successfully reverse the catalepsy by

decreasing the catalepsy score found with the Haloperidol group. The standard group has the lowest catalepsy, in-plant extract the catalepsy was found to decrease in a dose-dependent manner. Amelioration of symptoms of haloperidol by PVME treatment demonstrates the Anti-parkinson's activity.

Tacrine an anticholinesterase is traditionally used for the treatment of Alzheimer's disease and found effective to cause PD-like symptoms like bradykinesia, tremors, and rigidity. In given studies, animals were treated with tacrine and in response to that motor, dysfunctions result causing Induced Vacuous Jaw Movement and Orofacial Bursts. The results were observed for a 1- hr duration in which the maximum movements were found in 30-40 min duration where the observer was kept blind to respective groups under study. The PVME 200 and 400 mg/kg shows a significant reduction in movements and bursts as compared to the vehicle and control group. The concentration value of 400 mg/kg extract was observed to be close to the Standard group. This corresponds to the anti-parkinson action of the plant.

In the present investigation, sufficient data was collected to prove the anti-parkinson's activity of PVME. Plant's natural neuroprotective action disease preventive properties were supposed to be responsible for the anti-parkinson's activity. The plant possesses antioxidant properties responsible for reducing oxidative stress, which was found as one of the main factors for the pathophysiology of PD.

## CONCLUSION

The above study concludes that *Phaseolus vulgaris* methanol extract (PVME) shows Anti-parkinson's activity in both PD models which represents through results. The Anti-parkinson's activity of plant was attributed due to presence of antioxidant nature and the presence of various phytochemicals observed in previous studies. Further studies need to be conducted to estimate the components responsible for Anti-parkinson's nature of plant. Isolation and characterization of active components responsible for the neuroprotective properties further need to be carried out.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

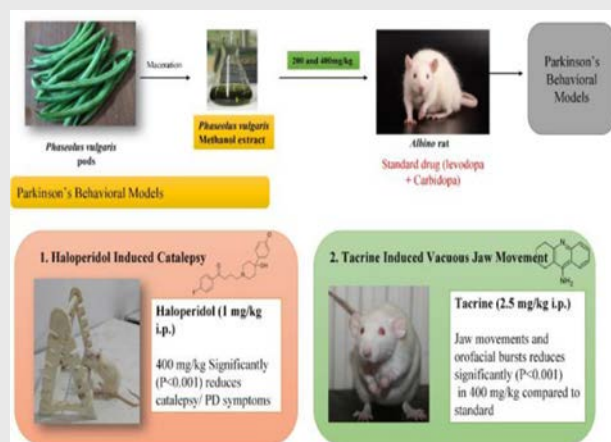
## ABBREVIATIONS

**PD:** Parkinson's disease; **PVME:** *Phaseolus vulgaris* methanol extract; **OECD:** Organisation for Economic Co-operation and Development; **LD<sub>50</sub>:** Lethal dose; **ANOVA:** Analysis of variance; **SEM:** Standard error of the mean; **CNS:** Central nervous system.

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## PICTORIAL ABSTRACT



## SUMMARY

In our study we are using behavioural models to determine Anti-parkinson's activity of *Phaseolus vulgaris* methanol extract (PVME). *Phaseolus vulgaris* is known for various medicinal applications, here we are trying to find out its neuroprotective properties. Haloperidol is an antipsychotic drug act by blocking the dopamine receptor in CNS of brain, while Tacrine which is Anti-cholinesterase drug function by suppressing the motor effects, both these drugs induces Parkinson's disease like symptoms. Albino rats were given *Phaseolus vulgaris* methanol extract (200-400 mg/kg) prior haloperidol and tacrine administration. The results showed that catalepsy induced by haloperidol was effectively reduced by higher dosage (400 mg/kg) of PVME and orofacial bursts and jaw movements induced by tacrine were reduced in dose dependent manner by PVME administration. *Phaseolus vulgaris* methanol extract produced significant  $*p < 0.001$  data in terms of Anti-parkinson's activity through behavioural models.

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