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Research Article

NEUROPROTECTIVE AND ANTI- OXIDANT EFFECTS OF FARNESOL AGAINST IN-VIVO PARKINSON'S DISEASE MODEL

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A B S T R A C T

The purpose of this study is to evaluate Neuroprotective and anti- oxidant effects of Farnesol against *in-vivo* Parkinson's model. Haloperidol induced Parkinson's disease in Wistar rats was used to evaluate the neuroprotective effect of Farnesol. Haloperidol (1mg/kg) was used for the induction of disease, followed by treatment with 50 mg/kg and 100 mg/kg of farnesol for 14 days. The effect of motor symptoms was evaluated using actophotometer, rotarod apparatus and open field test. Animals showed significant improvement in locomotor activity, grip strength after the treatment of farnesol compared to disease control. Animals treated with farnesol significantly reduced Haloperidol induced alterations in the levels of neurotransmitter dopamine and anti-oxidant enzymes superoxide dismutase, catalase and lipid peroxidation. Based on the effect of farnesol on neurobehavioral and biochemical parameters in Haloperidol induced Parkinson's, we conclude that farnesol is effective against Haloperidol induced Parkinson's disease in Wistar rats.

INTRODUCTION

Majority of the Central nervous system diseases are life threatening. When there is a recognition of the sign and symptoms of this disease it will help the patient to acquire instant treatment and which will lead to recovery easily and faster. Many neurodegenerative diseases- including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease- occur as a result of neurodegenerative processes. Parkinson's disease is the second most common neurodegenerative disease and manifests as bradykinesia, rigidity, resting, tremor and posture instability. Parkinson's disease is a degenerative disorder of the central nervous system. It results from the death of dopamine-generating cells in the substantianigra, a region of the midbrain; the cause of cell death is unknown. Dopamine has a number of important functions in the brain. It plays a critical role in the reward system, but dysfunction of the dopamine system is also implicated in Parkinson's disease and Schizophrenia. There is no cure for Parkinson's disease, but medications, surgery, and physical treatment can provide relief and are much more effective than treatments available for other neurological disorders like Alzheimer's disease, motor neuron disease, and Parkinson plus syndromes.

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Farnesol is a acyclic sesquiterpene alcohol. Farnesol is produced from isoprene compounds in both plants and animals. Farnesol is found in a flower extract with a long use in perfumery. Farnesol has been suggested to function as a chemopreventive, anti-tumor, neuroprotective, anti-bacterial agent.

METHODS

Drugs and Chemicals Used

Pure Compound of Farnesol (Compound ID: F203) was purchased from Sigma Aldrich. Haloperidol, Levodopa + Carbidopa.

Ethical Consideration

Experimental protocols and procedures used in this study were approved by the Animal Ethics Committee of CPCSEA (Committee for the purpose of control and Supervision of Experiment on Animals) and was approved by the Institutional Animal Ethical Committee (Proposal number: NCP/IAEC/No:2019-20/04).

Experimental Animals

Wistar rats of both sexes weighing between 250-300 g were obtained from the animal house of Nandha College of Pharmacy and Research Institute, Erode, Tamilnadu, India. The animals were grouped into five groups each containing six

animals are marked for their identification by using Indian ink. The animals were maintained under standard environmental conditions of 50 ± 10% relative humidity and 12 h light and 12 h dark cycle throughout the experiment. The animals were used after an acclimatization period of five days in propylene gages on the laboratory environment.

Acclimatization were provided with standard rat pellets diet (Hindustan Lever Pvt Ltd., Bangalore) and clean drinking water. All procedures was conducted according to CPCSEA guidelines.

Experimental Design

Haloperidol induced Parkinson's disease

The animals were divided into 5 groups of 6 animals each as follows:

Group I*:* 0.9% w/v Normal saline (1mg/kg b.w; i.p) for 14 days, served as Normal control

Group II*:* Haloperidol (1mg/kg b.w; i.p) and vehicle for 14 days, served as Negative control

Group III*:* Levodopa + Carbidopa (100+10mg/kg b.w; p.o) and then followed by haloperidol (1mg/kg b.w; i.p) after 30 min for 14 days, served as Positive control

Group IV*:* Farnesol (50mg/kg b.w; p.o) and then followed by haloperidol (1mg/kg b.w; i.p) after 30 min for 14 days, served as Low dose

Group V*:* Farnesol (100mg/kg; p.o) and then followed by haloperidol (1mg/kg b.w; i.p) after 30 min for 14 days, served as High dose

Pharmacological Evaluation

Actophotometer

This test measures the exploration and the voluntary locomotion within an enclosed area. The objective value for the spontaneous motor activity was obtained using actophotometer. The animal was placed individually into a 30cm× 30cm black metal chamber with a screen floor and a light-tight lid. Six beams of red light were focused 2cm above the floor into a photocells on the opposite side. Each beam interruption was registered as an event on the external counter. The light beam breaks were counted for 5 minutes.

Rota rod test

The rota rod apparatus consists of a motor rod with a drum of 7cm diameter. It was adjusted to a speed of 12 revolutions per min during the test session. The latency to fall in a test session of 180sec was taken as a measure of motor coordination.

Open field test

The open field apparatus consists of a big square area with walls 42 cm high. The floor was divided into 9 equal squares. To determine activity, an animal was placed at the corner of a square of the open field and immediately after the placement the number of squares crossed was scored for 5 min.

Preparation of Brain Tissue Homogenate

Animals were sacrificed by cervical dislocation after 14 days of drug treatment. Whole brain were dissected and removed out quickly, then washed with ice cold normal saline and homogenized with 0.1M phosphate buffer (pH 7.4) at 4˚ C. Brain tissue homogenate was centrifuged at 10,000 rpm for 20 min, supernatant was separated and aliquots were used for biochemical estimations.

Estimation of Neurotransmitters

Estimation of Dopamine

The aqueous phase was then taken for dopamine assay. All steps were carried out at 0˚ C (on ice). To the 0.2ml of aqueous phase, 0.05 ml of 0.4 M Hcl, and 0.1 ml of Sodium acetate buffer (pH 6.9) were added, followed by 0.1ml of iodine solution (0.1 M in ethanol) for oxidation. The reaction was stopped after 2 min by addition of 0.1 ml of 0.1 ml sodium sulphite solution. 0.1 ml acetic acid is added after 1.5 min. The solution was then heated to 100˚ C for 6 min. When the sample again reached room temperature, excitation and emission spectra were read from the spectrofluorimeter at 330-375 nm. Tissue blanks for dopamine were prepared by adding the reagents of the oxidation step in reversed order (sodium sulphite before iodine).

Calculation

The neurotransmitter level is calculated using the following formula:

$$X_{dopamine} = \text{Sample O.D} - \text{Blank O.D} / \text{Standard O.D} - \text{Blank O.D} \times \text{Conc. Of Standard}$$

This gives the amount of dopamine present in 1ml of the sample.

Anti-Oxidant Studies

Assay of Superoxide dismutase

The assay of Superoxide dismutase is based on the inhibition of formation of NADH-phenazinemethosulphate-nitrobluetetrazoliumformazon. The assay mixture contained 1.2 ml of sodium pyrophosphate buffer, 0.1ml of PMS, 0.3 ml of NBT, 0.2 ml of enzyme preparation and water in a total volume of 2.8 ml. the reaction will be initiated by addition of 0.2 ml of NADH. The mixture was incubated at 30˚ C for 90 seconds and arrested by the addition of 1.0 ml of glacial acetic acid. The reaction mixture will be then shaken with 4.0 ml of n-butanol, allowed to stand for 10 min and centrifuged. The intensity of the chromogen in the butanol layer will be measured at 560 nm in a spectrophotometer. One unit of enzyme activity is defined as the amount of enzyme that gives 50% inhibition of NBT reduction in one min.

Assay of Catalase

The assay of catalse is based on the disappearance of hydrogen peroxide into hydrogen and oxygen. The tissue was homogenized in isotonic buffer and centrifuged. Twenty microliter of 100-fold diluted tissue supernatant added to 980µl of the assay mixture; the assay mixture consists of 900µl of 10mmol/L of H_2O_2, 50µl of TrisHcl buffer (pH 8) and 30µl of water. The degree of decomposition of hydrogen peroxide was monitored spectrophotometrically at 240 nm.

Asaay of lipid peroxidation

To the sample of tissue homogenate, 30% trichloro-acetic acid and 1ml of 0.8% thiobabituric acid reagent were added and centrifuged at 3000 rpm for 15 min. The absorbance of the supernatant was read at 535 nm at room temperature against the blank.

The content of thiobarbituric acid reactive substances expressed as 'n' moles formed per milligram of protein in the tissue calculated.

Statistical Analysis

ANOVA (Analysis of Variance)

The data were analysed using One way ANOVA followed by Dunnett's test. $p<0.05^{*}$, $p<0.01^{**}$, $p<0.001^{***}$ were considered as significant, more significant, most significant respectively.

RESULTS

Haloperidol induced Parkinson's disease

Table No.1 Effect of Farnesol on locomotor activity in haloperidol induced Parkinson's rats

Drug Treatment	Number of Counts/5 Min		
	3rd day	7thday	14th day
Group-I Normal control 0.9% Nacl (1mg/kg i.p)	224±2.9	152.8±2.5	161.6±3.5
Group-II Haloperidol (1mg/kg i.p)	115±1.5**	73.6±2.6**	51±0.9**
Group-III Levodopa+Carbidopa (100+10mg/kg)	174±2.6**	174.5±2.4**	201.1±0.7**
Group-IV Farnesol (50mg/kg p.o)	60.1±2.6**	105.3±1.4	108.5±1.9**
Group-V Farnesol (100mg/kg p.o)	97.3±2.8	124±1.7**	150.6±1.6**

Values are expressed as mean ± S.E.M (n=6) $p<0.05^{*}$, $p<0.01^{**}$ and $p<0.001^{***}$ compared with normal controll

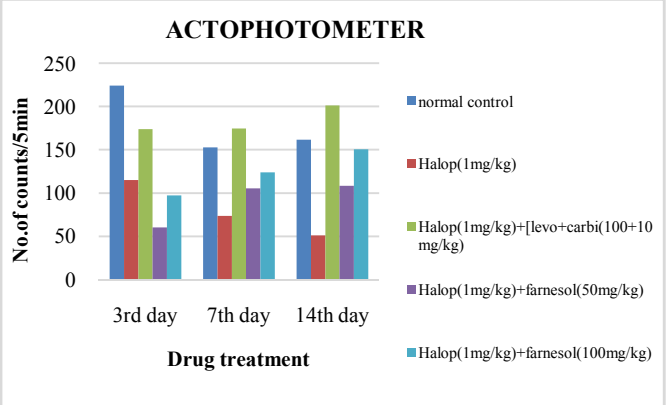

Fig No 1 Effect of Farnesol on haloperidol induced Parkinson's rats in locomotor activity

Table No 2 Effect of Farnesol on Grip Strength in haloperidol induced Parkinson's model

Drug Treatment	Number of Seconds/3 MIN		
	3rd day	7thday	14th day
Group-I Normal control 0.9% Nacl (1mg/kg i.p)	54.1±0.6	73.6±0.9	106.8±1.5
Group-II Haloperidol (1mg/kg i.p)	52.6±1.8*	21.6±0.9**	6±1.5**
Group-III Levodopa+carbidopa(100+10mg/kg p.o)	45±3.1**	143.8±1.5*	162.31±0.9*
Group-IV Farnesol (50mg/kg p.o)	34.5±2.2	52.1±1.9	57.3±1.7
Group-V Farnesol (100mg/kg p.o)	36.5±2.9	128.5±1.5*	140.3±1.3**

Values are expressed as mean ± S.E.M (n=6)$p<0.05^{*}$, $p<0.01^{**}$ and $p<0.001^{***}$ compared with normal control

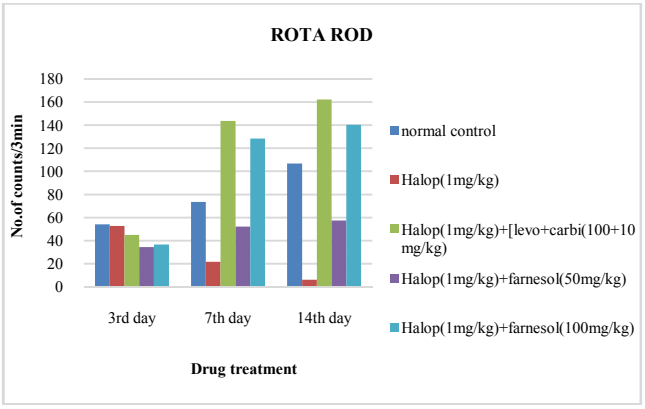

Fig No 2 Effect of Farnesol on haloperidol induced Parkinson's rats in Rota rod

Table No 3 Effect of Farnesol on Open field in haloperidol induced Parkinson's model

Drug Treatment	Number of Squrae Traversed/5 Min		
	3rd day	7thday	14th day
Group-I Normal control 0.9% Nacl (1mg/kg i.p)	7.83±0.47	8.16±0.30	7.83±0.47
Group-II Haloperidol (1mg/kg i.p)	2.16±1.07**	1.83±0.79**	1.66±0.55**
Group-III Levodopa+carbidopa (100+10mg/kg p.o)	5.8±1.44**	7.16±0.70**	7.83±0.47**
Group-IV Farnesol (50mg/kg p.o)	3±0.93	4±1.36	5±0.85**
Group-V Farnesol (100mg/kg p.o)	3.66±1.2	4.5±1.11	5.66±1.52**

Values are expressed as mean ± S.E.M (n=6)$p<0.05^{*}$, $p<0.01^{**}$ and $p<0.001^{***}$ compared with normal control

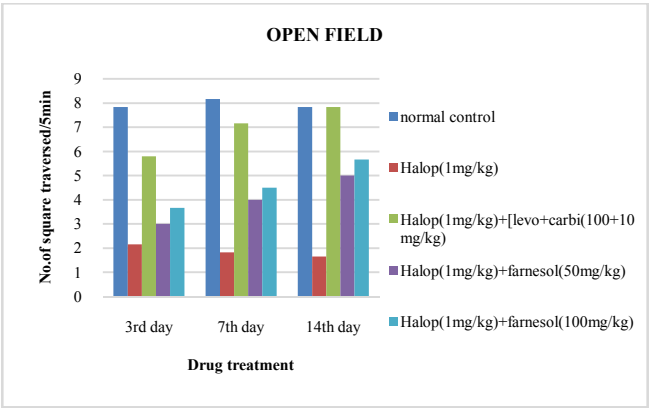

Fig No 3 Effect of Farnesol on haloperidol induced Parkinson's rats in Open field test

Estimation of Neurotransmitter

Estimation of Dopamine

Table No 4 Effect of Farnesol on Dopamine levels in Brain tissue homogenate

DRUG TREATMENT	DOPAMINE (mg/g of brain tissue)
Group-I Normal control 0.9% Nacl (1mg/kg i.p)	24.21±1.09
Group-II Haloperidol (1mg/kg i.p)	8.96±2.8**
Group-III Levodopa+carbidopa (100+10mg/kg p.o)	22.54±0.63**
Group-IV Farnesol (50mg/kg p.o)	17.01±0.3
Group-V Farnesol (100mg/kg p.o)	19.14±0.17*

Values are expressed as mean ± SEM $p<0.05^{*}$, $p<0.01^{**}$ and $p<0.001^{***}$ compared with normal control

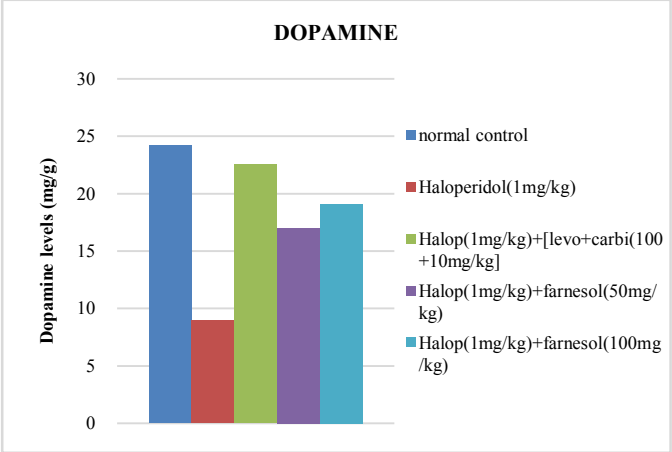

Fig No 4 Effect of Farnesol on Dopamine levels in brain tissue homogenate

Anti-Oxidant Studies

Table No.5 Effect of Farnesol on oxidative parameters in brain tissue homogenate

Drug Treatment	SOD (µ/mg protein)	LPO (n moles/mg protein)	CAT (µ/mg protein)
Group-I Normal control 0.9% Nacl (1mg/kg i.p)	1.86±1.5	1.64±±0.55	1.92±1.31
Group-II Haloperidol (1mg/kg i.p)	0.56±0.23**	4.33±0.28**	0.21±0.22**
Group-III Levodopa+carbidopa (100+10mg/kg p.o)	1.79±0.51**	1.83±0.06**	1.89±0.25**
Group-IV Farnesol (50mg/kg p.o)	1.14±0.80	3.11±0.91	1.58±0.19
Group-V Farnesol (100mg/kg p.o)	1.57±0.29	2.56±0.70**	1.62±0.37**

Values are expressed as mean ± SEMp<0.05*, p<0.01** and p<0.001*** compared with normal control

Effect of Farnesol on Superoxide dismutase

Superoxide dismutase is an anti-oxidant enzyme, which plays a important role in detoxifying superoxide anions. Animals treated with Haloperidol (1mg/kg, i.p) significantly ($p<0.001$) decreased the Superoxide dismutase levels in brain homogenate when compared to normal control. Levodopa + carbidopa (100+10 mg/kg, p.o) administered rats significantly ($p<0.01$) increased Superoxide dismutase levels when compared to haloperidol treated animals. In treatment group, Farnesol (50mg/kg, p.o) administration showed remarkable increased ($p<0.01$) in Superoxide dismutase levels when compared to haloperidol treated animals. Animals treated with Farnesol (100mg/kg, p.o) significantly ($p<0.01$) increased in Superoxide dismutase levels when compared to negative control group.

Effect of Farnesol on lipid peroxidation

Thiobarbituric acid (TBARS) is an indicator of lipid peroxidation. Haloperidol (1mg/kg, i.p) administration of animals showed increased ($p<0.001$) level of TBARS when compared to normal control. Levodopa + carbidopa (100+10 mg/kg, p.o) significantly ($p<0.01$) decreased the TBARS level contrast to haloperidol treated animals. Further, Farnesol (50mg/kg, p.o) treated animals significantly ($p<0.01$) decreased the TBARS level when compared to haloperidol treated group. Farnesol (100mg/kg, p.o) showed decreased ($p<0.01$) level of TBARS when compared to negative control group.

Effect of Farnesol on Catalase activity

Catalase is an anti-oxidant enzyme which has capability to detoxify oxidative free radicals. Animals treated with haloperidol (1mg/kg, i.p) showed remarkable decrease ($p<0.001$) in catalase level when compared to normal control. Levodopa+carbidopa (100+10 mg/kg, p.o) treated group showed significant ($p<0.01$) increase in catalase level when compared to haloperidol treated animals. Meanwhile, Farnesol (50mg/kg, p.o) treated group significantly ($p<0.01$) increased the catalase level when compared to haloperidol treated group. Farnesol (100mg/kg, p.o) showed significant ($p<0.01$) increase level of catalase when compared to negative control group.

DISCUSSION

Haloperidol induced Parkinson's disease is the drug induced model. Haloperidol is a neuroleptic drug, which block central dopamine receptors, produces a behavioural state in animals in which they fail to correct externally imposed postures. Haloperidol works by antagonizing dopamine D2 and, to a lesser extent, D1 receptors in medium spiny neurons that comprise the indirect and direct pathways of the motor circuit respectively. The resultant block of striatal dopamine transmission results in abnormal downstream firing within the basal ganglia circuits that manifest as symptoms of muscle rigidity and catalepsy.

Evaluation of anti-Parkinson's activity of Farnesol was performed by using behavioural models such as Actophotometer, Rota rod and Open field test. As haloperidol decreased the locomotor activity in Actophotometer as compared to the respective normal control group. Treatment of farnesol significantly reduced the haloperidol induced Parkinson's in contrast to the normal control. The increase in the locomotor activity indicating the kinetic improvement. Farnesol 50 mg/kg showed the values near to the standard drug levodopa+carbidopa (100+10 mg/kg). Therefore, this indicates that farnesol significantly increases the locomotor activity. While in Rota rod, rats treated with farnesol 50 mg/kg and levodopa+carbidopa (100+10 mg/kg) showed significant increase in the motor coordination as compared to the normal control group. Effects of farnesol at the doses of 50 and 100 mg/kg respectively were comparable to the standard drug levodopa+carbidopa (100+10 mg/kg).In Open field test, the animals treated with farnesol 100 mg/kg and levodopa+carbidopa (100+10 mg/kg) showed significant increase in the locomotor activity compared to the normal control group. Thus the farnesol could be agreed to improve the locomotor activity of the animals. The results of anti-Parkinson's activity of farnesol at a dose of 100 mg/kg showed the value near to the standard levodopa+carbidopa (100+10 mg/kg) in comparative study. This study indicates that farnesol having a significant impact in increasing the motor coordination and locomotor activity in rats.

Estimation of neurotransmitter such as Dopamine play a important role in dopaminergic function, dopamine activity was measured by using brain tissue in the present day.In the present study, haloperidol treated animals showed decreased dopamine level in the rat brain tissue when compared to the normal control group. Levodopa+carbidopa (100+10 mg/kg) treated animals showed significant increase in the level of dopamine when compared to negative control group. Meanwhile, the animals treated with farnesol at a doses of 50

and 100 mg/kg showed significant increase in the dopamine level when compared to negative control group.

In the present anti-oxidative study, the animals treated with haloperidol for 14 days showed decreased levels of Superoxide dismutase, Catalase and increased level of lipid peroxidation as compared to the normal control group. The enzymatic degradation by MAOs was associated with the production of hydrogen peroxide, which is readily converted into hydroxyl radical in the presence of iron. Further, Levodopa+carbidopa (100+10 mg/kg) treated group significantly increased the superoxide dismutase, Catalase and decreased the lipid peroxidation levels as compared to the haloperidol treated group. Meanwhile, farnesol 50 and 100 mg/kg treated animals increased the superoxide dismutase, Catalase and decreased the lipid peroxidation levels as compared to the haloperidol treated group.

CONCLUSION

The results of the present study concluded that farnesol has anti-oxidant and neuroprotective effect in haloperidol induced Parkinson's model. However, further advanced research have need of to promise the neuroprotective effect of farnesol in Parkinson's disease.

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