Research Article

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# Neuroprotective Effect of Farnesol Against Rotenone Induced Parkinson's Disease in Drosophila Melanogaster

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**ABSTRACT**

The current study aimed to investigate the neuroprotective effects of farnesol on rotenone-induced neurotoxicity in Drosophila melanogaster. Neurotoxicity was induced in Drosophila melanogaster by administering 500 µmol of rotenone and then the flies were administered either 300 µmol or 600 µmol of farnesol in the diet for the duration of the experiment. The study measured the effect of farnesol on longevity through a survival rate study, and locomotor function through a negative geotaxis assay. In addition, the study also estimated in vivo antioxidant parameters to determine the impact of farnesol on oxidative stress. The results showed that farnesol improved both longevity and locomotor function in the flies treated with 300 µmol or 600 µmol of test compound compared to control. The antioxidant studies also demonstrated that farnesol enhanced the catalase and superoxide dismutase activity and decreased lipid peroxidation. Based on these findings, it is concluded that farnesol might exhibit a significant neuroprotective effect against Parkinson's disease.

**Keywords:** Farnesol, Drosophila melanogaster, negative geotaxis, survival rate, antioxidants

## 1. INTRODUCTION

A progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) is the characteristic feature of Parkinson's disease. The symptoms of PD are tremors, hypokinesia and muscle rigidity[1]. The etiology of PD has not been clearly established yet but several factors like elevated oxidative stress, impaired degradation of proteins, neuroinflammation mediated by microglia cells, disturbance in calcium metabolism and mitochondrial dysfunction are implicated[2–6]. PD is characterized by pathological hallmarks, which include degeneration of dopaminergic neurons, build-up of α-synuclein and elevated oxidative stress.[7] Oxidative stress affects the stability of nucleic acids through oxidation of RNA and increasing the rate of mutations in mitochondrial DNA. Oxidative stress also disturbs homeostasis of protein by accelerating α-synuclein aggregation. Oxidative stress also affects the release of dopamine through activation of ATP-sensitive potassium channels and inactivation of neuronal nicotinic acetylcholine receptors[8]. Because oxidative stress is a well-established factor in the pathogenesis of PD, treatments that counteract the effects of free radicals and oxidative stress may be useful in managing PD[9]. Numerous plant-based components have the ability to act as antioxidants, which may be beneficial in mitigating the damaging effects of oxidative stress caused by reactive oxygen species in PD

Farnesol is a naturally occurring sesquiterpene compound with 15 carbon atoms that can be found in essential oils extracted from ambrette seeds and citronella[10]. Previous research has indicated that farnesol possesses noteworthy anti-inflammatory and antioxidant properties[11]. It has also been observed to provide protection to renal cells against oxidative stress induced by ferric nitrilotriacetate, mitigate inflammation and lung damage caused by cigarette smoke extract in rats, and demonstrate effectiveness in treating colon, liver, pancreas, and skin cancers by inhibiting cell proliferation and inducing apoptosis in various malignant cell types[12–14].

The cellular structure of flies and vertebrates bears a striking resemblance, which has made *D. melanogaster* a valuable experimental model for evaluating the effectiveness of possible treatments for Parkinson's disease. Moreover, using *D. melanogaster* for experiments raises fewer ethical issues than using rodents such as rats and mice. The ECVAM (European Centre for the Validation of Alternatives Models) has endorsed and sanctioned the use of *D. melanogaster* because it adheres to the 3Rs protocol [15]. Earlier research has indicated that exposing *D. melanogaster* to non-lethal amounts of rotenone for seven days led to a decline in dopamine levels, a loss of dopaminergic neurons, and impaired locomotor function[16]. The simpler genetic system of *Drosophila melanogaster* helps in unravelling fundamental cellular pathways.[17] Flies are used to investigate the effect of potential therapeutic agents against neurodegenerative diseases. The hypothesis of this work is that farnesol would decrease oxidative stress in rotenone induced neurodegeneration through its antioxidant and anti-inflammatory property.

## 2. MATERIALS AND METHODS

### *2.1 Culturing of Drosophila*

Male adult flies of the wild type (Oregon K), which were 10 days old and synchronized, were acquired from NUCSER, Mangalore. The flies were maintained in a controlled environment at 24±1ºC and a relative humidity ranging from 70 to 80% on a 12-hour light/dark cycle in a laboratory. The flies were raised on a wheat cream agar diet containing yeast granules, which comprised 10% wheat flour (w/v), 10% sucrose (w/v), 2% agar (w/v), 3% yeast granules (w/v), and 0.75% propionic acid (v/v). To 1000 mL of boiling water, 100g of sucrose and 20g of agar were added and mixed thoroughly. 100g of wheat flour and 7.5 mL of propionic acid were added after agar and sucrose were completely melted. To the above media, 30 g of yeast granules was added. The test compound, farnesol was added at the final concentration to the media (45-50 ºC) and stored at 25 ºC.

### *2.2 Estimation of $LD_{50}$*

10-days old flies were exposed to different concentrations of farnesol (150 µmol, 300 µmol, 600 µmol and 1200 µmol in 2 replicates each with each replicate having 30 flies each) for 7 days to determine the median lethal dose. The lethality count was documented every 24 hours, and the lethality rate was determined as the percentage of flies that died.[18].

### 2.3 Rotenone and Farnesol Treatment

The flies were grouped into four sets, each containing 50 flies. The first group, Group I, acted as the normal and was administered a mixture of 5% sucrose and 0.3% DMSO. Group II served as control and received 500µmol of rotenone. The flies were exposed to 500 µmol of rotenone mixed with diet to assess the neuroprotective effect of farnesol. Group III and Group IV received 300 µmol and 600 µmol of farnesol along with 500 µmol of rotenone. The flies were fed treated food and stored in an incubator at 23 ± 1 ºC until they were used for different tests [19].

### 2.4 Survival Rate

Four groups of 100 flies were used to determine the survival rate. The aggregate number of flies is the combination of two separate experiments. Each group received its respective treatment with vehicle, inducing agent and two dose levels of farnesol. To evaluate the effect of farnesol, the number of live and dead flies was counted at 2 days interval for a duration of 28 days. [20].

### 2.5 Negative Geotaxis Assay

The flies were moved to a flat-bottomed glass tube with graduated markings (25 cm in length and 2 cm in diameter) and given a minimum of 5 minutes to acclimate. Then, the base of the tube was lightly tapped, and the flies' climbing behaviour was observed for 60 seconds. Each replicate consisted of three trials with 25 flies per trial. The results were expressed as percent of flies that managed to escape a distance of 10 cm in 20 s.[21].

### 2.6 Biochemical Estimation

#### 2.6.1 Preparation of homogenate for biochemical parameters

To measure the biochemical parameters, the heads of the flies were extracted and mixed in 0.1 M phosphate buffer to create a homogenate.

#### 2.6.2 Estimation of Lipid Peroxidation

To 90 µl of supernatant, 105 µl of water was added and mixed thoroughly. To the above mixture, 600 µl of phosphoric acid and 200 µl of barbituric acid were added. Finally, 105 µl of water was added and incubated for 45 minutes at 90°C. The optical density was measured at 535 nm and the result was expressed as µmol of TBARS formed/h/g tissue [22].

#### 2.6.3 Estimation of Catalase

The rate of conversion of $H_2O_2$ to $H_2O$ and $O_2$ is linked to the amount of catalase present in the specimen. A mixture comprised of sample (17 µl), 333 µl of $H_2O_2$ (0.05 M), and 650 µl of 0.1 M phosphate buffer was used. The absorption level was measured at 240 nm for two minutes, with 30-second intervals, to monitor the reduction in OD. The catalase activity was computed and reported as µmoles of $H_2O_2$ utilized per minute per milligram of protein [23].

#### 2.6.4 Estimation of Superoxide Dismutase

A mixture of 17 µl of the sample and 950 µl of 0.1 M phosphate buffer was prepared. Pyrogallol was added to the mixture to initiate the reaction. The change in optical density was determined for three minutes with 30-second intervals, at 420 nm, and the data was presented as units per milligram of protein.[24].

#### 2.6.5 Statistical analysis

Data were analysed by one way analysis of variance (ANOVA) followed by post-hoc Tukey test using GraphPad Prism. The significance level was established as $p < 0.05$, and the outcomes were presented as mean ± SEM.

## 3. RESULTS AND DISCUSSION

The aim of this study is to determine the protective effect of farnesol and the results indicate that farnesol exhibits neuroprotection against rotenone induced PD in *Drosophila melanogaster.* The Current medical therapies and surgical techniques for Parkinson's disease only provide symptomatic alleviation[20,21]. As a result, novel pharmacological medicines based on natural phytoconstituents with fewer or no side effects should be explored to offer protection against Parkinson's disease. Phenols, flavonoids, and tannins are examples of natural antioxidants that can limit the impact of reactive oxygen species (ROS) by blocking oxidative harm to proteins, lipids, and DNA. [22,23]. Examinations of PD brains after death have indicated that oxidative stress is accountable for harm to DNA, lipids, and proteins, as well as a reduction in the effectiveness of glutathione, catalase, and SOD [24–26].



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Todd B. Sherer et al have established the involvement of oxidative stress in rotenone induced PD and supported the testing of antioxidant therapies against rotenone induced PD in flies[27]. This study explored the mechanism of rotenone toxicity using three different models of increasing complexity. In the first model, rotenone exposure from 10 nM to 1 mM led to ATP depletion, oxidative damage, and mortality in SK-N-MC human neuroblastoma cells. The second approach involved introducing rotenone-insensitive NADH dehydrogenase of *Saccharomyces cerevisiae* (NDII) into cells, which can take the place of the mammalian ETC and function as a replacement for the body's own complex I. This was done to identify where exactly rotenone acts on a molecular level. The cells that were transfected with NDII did not show any negative effects such as damage to the mitochondria, oxidative harm or cell death upon exposure to rotenone. This suggests that rotenone causes its deleterious effects through inhibition of complex I. In the third model, the authors used the antioxidant tocopherol reduced oxidative damage and prevented cell death[27]. Taking above findings into consideration, we chose rotenone for the current study.

*Drosophila melanogaster* is currently one of the most widely used organism to investigate the effect of potential therapeutic agents for neurodegenerative disorders[15]. The main advantages of *Drosophila melanogaster* compared to other existing animal models are: a short life span ranging between 40 and 120 days, identical off springs and ability to learn and remember. [28,29]. Because of the above advantages, we decided to use *Drosophila melanogaster* in this study.

## 3.1 Survival Rate

Based on LD50 study, the dose of farnesol was fixed at 300 µmol and 600 µmol to determine the effect of farnesol on survival rate. There was a significant increase in the mortality in the flies that received 500 µmol of rotenone compared to normal group. An increase in survival was observed in the groups treated with low and high doses of farnesol. The results are depicted in Figure 1. Studies have reported that diets enriched with supplements rich in phytoconstituents with significant antioxidant property extend the lifespan in drosophila[30,31]. In longevity assay, farnesol increased the life-span of drosophila at 300 µmol and 600 µmol. The dose dependent increase in longevity of drosophila might be because of its reported antioxidant property.

### *3.2 Negative Geotaxis Assay*

The neuroprotective effect of farnesol on locomotor ability was studied using negative geotaxis assay. No significant changes in locomotor function were observed in any group on day 1. The flies exposed to 500 µmol of rotenone exhibited significant impairment of locomotor functions compared to normal flies on day 28. The flies treated with of farnesol (300 µmol and 600 µmol) exhibited a significant improvement in locomotor function on day 28. The results are represented in Figure 2. Treatment of flies with 500 µmol of farnesol induced significant locomotor deficit and treatment with farnesol showed a dose dependent improvement in flies. This improvement in locomotor activity in the flies might be because of the antioxidant property of farnesol.

A significant decrease in locomotor ability was observed in the group treated with rotenone compared to normal group on day 28 but no significant difference was observed on day 1. The treatment of flies with farnesol reversed the locomotor ability caused by rotenone.

### *3.3 Estimation of LPO, CAT & SOD*

A significant increase was observed in lipid peroxidation in the control group compared to the normal group. The flies exposed to 300 µmol and 600 µmol of farnesol exhibited a dose dependent decrease in the level of lipid peroxidation. The activity of catalase was significantly increased in the control group. The flies exposed to 300 µmol and 600 µmol of farnesol exhibited a dose dependent decrease in catalase activity. The control flies showed a significant increase in the activity of SOD compared to the normal group. The flies treated with 300 µmol and 600 µmol of farnesol exhibited a dose dependent decrease in SOD activity compared to control group. The results are represented in Table 1. The *in vivo* antioxidant studies showed that both low and high doses of the substance increased the activity of antioxidant enzymes, such as catalase and SOD, and significantly reduced lipid peroxidation in flies.

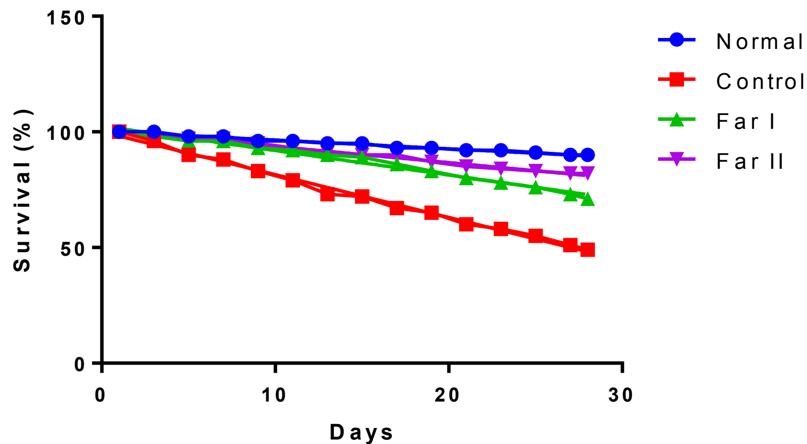


**Fig 1.** Effect of Farnesol on Survival Rate in Drosophila Melanogaster
A significant decrease in survival was observed in the group treated with rotenone compared to normal group. The treatment of flies with 300 µmol and 600 µmol of farnesol on survival reversed the increased mortality caused by rotenone.
Results are represented as the percentage of flies alive counted every 2 days (n=100) for a period of 28 days.

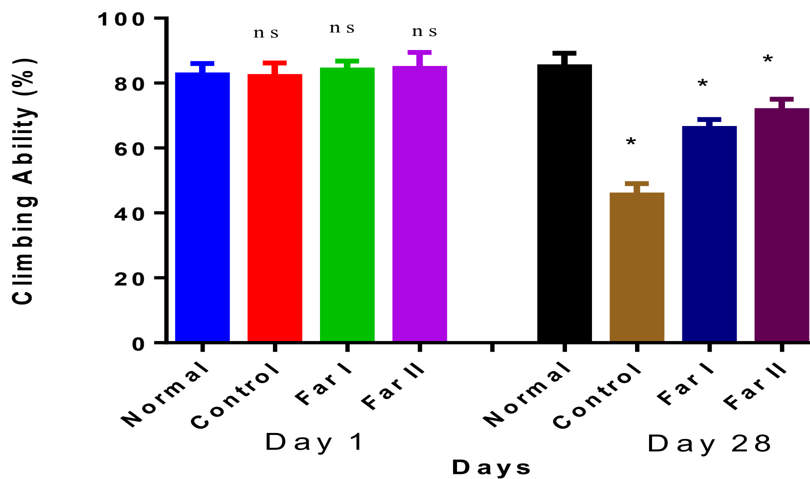


**Fig 2.** Effect of Farnesol on Negative Geotaxis Assay
Data are represented as Mean±SD. Data were analyzed by one-way analysis of variation (ANOVA), followed by Tukey's test. *n*=25; ns – non-significant; * *P* <0.05 was considered significant. Control vs Normal; Treated vs Control.

## 4. CONCLUSION

In conclusion, farnesol in diet could extend longevity and improve locomotor functions in flies against rotenone induced neurotoxicity.

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## Conflict of Interest

The authors declare that the contents in this article have no conflict of interest.



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**Table 1.** Effect of farnesol on Oxidative Stress Markers

| Group | LPO (n moles of TBARS formed/hour/ gram tissue) | CAT (µmoles of $H_2O_2$ consumed/min/ mg protein) | SOD (units/mg Protein) |
|---|---|---|---|
| Normal | 1.33±0.15 | 5.46±0.15 | 10.53±0.35 |
| Control | 4.63±0.11* | 12.67±0.41* | 19.30±0.45* |
| Farnesol I | 3.26±0.25* | 9.56±0.18* | 14.30±0.36* |
| Farnesol II | 2.40±0.26* | 7.26±0.15* | 11.73±0.40* |

Values are expressed as Mean±SD. Statistical analysis was performed by one-way analysis of variation (ANOVA), followed by Tukey's test. $n$=3; * $P$ <0.05 was considered significant. The control group was compared with the normal and the treated groups were compared with the control.

## Statement of Contribution of Researchers

P.T.K.: supervisor, conception, design, execution and interpretation of the results; S.J.: conception, pharmacology experiments, execution of the results collecting the data, and writing

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