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Neuroprotective effects of farnesol on motor and cognitive impairment against 3-nitropropionic acid-induced Huntington's disease

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ABSTRACT

Objective: The purpose of this study is to evaluate the role of farnesol as a potential neuroprotective agent against 3-nitropropionic acid (3-NP) acid-induced Huntington's disease (HD) by *in vitro, in vivo,* and *in silico* models. 3-NP acid-induced Huntington's disease in male Wistar rats was used to evaluate the neuroprotective potential of farnesol. **Materials and Methods:** 3-NP (10 mg/kg/day) was used for the induction of disease, followed by treatment with 50 mg/kg and 100 mg/kg of farnesol for 7 days. The effect of farnesol on motor symptoms was evaluated using actophotometer and rotarod apparatus and effect of farnesol on learning and memory was evaluated using elevated plus maze apparatus. **Results:** Body weight of animals showed significant gain after treatment with farnesol. Animals showed a significant improvement in locomotor activity, grip strength, and transfer latency after treatment with farnesol compared to disease control. Animals treated with farnesol significantly attenuated 3-NP-induced alterations in the levels of nitrite and reduced glutathione (GSH) level. The binding affinity of farnesol and the standard dimethyl fumarate was found to be −6.1 kcal/mol and −4.6 kcal/mol. **Conclusion:** Based on the effect of farnesol on neurobehavioral and biochemical parameters in 3-NP acid-induced Huntington's disease, we conclude that farnesol is effective against 3-NP acid-induced Huntington's disease in male Wistar rats.

Keywords: 3-nitropropionic acid, Farnesol, Huntington's disease, Nrf2, oxidative stress

INTRODUCTION

An increasing number of studies in the last few decades have ascertained the significant role of elevated oxidative stress in the pathogenesis of Huntington's disease.[1-3] The mutations in the huntingtin gene (HTT) that encode huntingtin protein leads to the accumulation of abnormal huntingtin protein that carries greater than 36 CAG (Cytosine adenine guanine) repeats.[4] Despite the well-known genetic origin, the exact pathogenesis by which the abnormal protein leads to Huntington's disease remains unclear and inconclusive.[5] The motor abnormality originates from dysfunction of the control of involuntary movements in a brain region known as the striatum and is manifested as a hallmark feature of uncontrollable dance-like movements (chorea). The most prominent neuropathological feature induced by mutant huntingtin (mHTT) in patients with HD is atrophy of the striatum (caudate nucleus and putamen), with extensive loss of GABAergic medium spiny neurons, which make up 90–95% of striatal neurons, although cortical atrophy and damage to other brain regions including the thalamus, hippocampus, and amygdala, also occurs as the disease progresses.[6-8]

Several studies indicate that huntingtin protein causes mitochondrial dysfunction(MD) by interacting with the outer membrane of mitochondria, by interfering with the transport of mitochondria and interfering with the production of ATP.[9-12] Similarly, several postmortem analyses of brains of Huntington's disease patients have revealed the definitive role of oxidative stress in the pathogenesis of Huntington's disease.[13] A decrease in the level of activities of complex II, complex III, and complex IV was also observed in the striatal region of Huntington's disease patients.[14] Many autopsy studies have also revealed the enhanced accumulation of iron and copper in the brains of patients with Huntington's disease.[15,16] Iron is believed to mediate oxidative damage through Fenton chemistry and copper through increased production of reactive oxygen species (ROS).[17] It is still not conclusive whether oxidative stress is cause or effect of Huntington's disease but it is widely accepted that oxidative stress plays a definitive role in the pathogenesis of Huntington's disease. As there are no current treatments available to reverse the progression of Huntington's disease and tetrabenazine is the only drug approved by the US Food and Drug Administration (FDA) for its use in Huntington's disease,[18] there exists a quintessential and unavoidable need to discover new molecules for the management of patients with Huntington's disease.

Farnesol ($C_{15}H_{25}OH$) is acyclic sesquiterpene alcohol that is predominantly found in essential oils of various plants such

as citronella, lemongrass, tuberose, cyclamen, rose, neroli, balsam, and musk. Farnesol is also produced in humans as an intermediate in the cholesterol synthesis pathway. Many studies have reported the ability of farnesol to alleviate oxidative stress, inflammation, and apoptosis in several animal models. Farnesol has been found effective in prostate, pancreatic, and lung cancer. It has also been reported to be effective in animal models of allergic asthma, diabetes, atherosclerosis, obesity, and hyperlipidemia.[19] This study hypothesizes that the antioxidant and anti-inflammatory properties of farnesol might be effective in alleviating the signs and symptoms of Huntington's disease. *In silico* docking study was carried out to explore the molecular targets of farnesol. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that regulates the expression of antioxidant and anti-inflammatory genes. Kelch-like ECH-associated protein 1(Keap1) is a cytosolic inhibitor of Nrf2 and causes degradation of Nrf2 by proteasomal degradation. 3VNH was obtained from protein data bank for molecular docking studies and 3VNH was used to test the ability of farnesol to activate Nrf2 through inhibition of keap1. Dimethyl fumarate (DM) was used as a standard as dimethyl fumarate is the only proven drug to activate Nrf2 through interacting with Keap1.[20]

MATERIALS AND METHODS

Chemicals and Reagents

Farnesol was purchased from Sigma-Aldrich and the percentage purity of farnesol is 95%. GSH, sodium nitrite, 3-nitro propionic acid, farnesol, Griess reagent, trichloroacetic acid (CCl_3COOH), sodium phosphate dibasic ($Na_2HPO_{4),}$ 5,5'-Dithiobis-(2-Nitrobenzoic Acid) (DTNB), sodium citrate ($Na_3C_6H_5O_7$), corn oil, and sodium chloride (NaCl) were obtained from Sigma-Aldrich.

Chemical Preparations

Farnesol was dissolved in corn oil and administered orally[21] and 3-NP was dissolved in normal saline (pH 7.4) and administered intraperitoneally (i.p).[22] Similarly, DTNB, 1% (w/v) of sodium citrate, 0.3 M Na_2HPO_4 (8.4 pH), 10% (w/v) CCl_3COOH, and 100 μM of GSH were prepared according to the literature.[22]

Animal Acquisition and Care

Male Wistar rats (200–250 g) were acquired from the animal house facility of JSSCP, Ooty, Tamil Nadu. Animals were housed in polypropylene cages in groups of three rats per cage and were kept in a room maintained at 25 ± 2°C with a 12 h light/dark cycle. Further, animals were acclimatized to laboratory conditions for 1 week before the commencement of experimental studies and standard housing conditions were maintained for the entire period of research work. Six animals per group were used for all the experiments. The experimental procedure for this research work was approved by the Institutional Animal Ethics Committee (JSSCP/OT/IAEC/25/2019-20) and the research work was carried out according to regulations set by committee for the purpose of control and supervision of experiments on animal's ethics.

Animal Grouping

The experimental animals were divided into four groups of six animals each. Group I served as normal and was treated orally with vehicle (corn oil) and NaCl (0.9%) i.p. Group II served as control and was treated with 3-NP (10 mg/kg/day, i.p), the inducing agent for 14 days. Group III and Group IV served as test groups that were treated with 50 mg/kg and 100 mg/kg p.o of farnesol for 7 days after induction of Huntington's disease with 3-NP. All the laboratory parameters were assessed on the 1st day before treatment and then on day 15 after the last dose of 3-NP and again on day 22 after the last dose of farnesol.

Induction of Huntington's Disease

All the groups except Group I were treated with 10 mg/kg/day of 3-NP for 14 days to induce Huntington's disease. After the induction period of 14 days, only those animals that showed definitive signs and symptoms of Huntington's disease,[23] such as weight loss, hind limb weakness, weak grip strength, abnormal posture, and motor abnormalities,[24,25] were included for further studies. This was done to ensure that only animals that display positive signs and symptoms of HD are grouped into Group II (disease control), Group III (farnesol 50 mg/kg farnesol), and Group IV (100 mg/kg farnesol). All animals treated with 3-NP displayed definitive signs and symptoms of HD. Hence, six animals were added to Group II, Group, III, and Group IV for further studies.

Dose Selection of Farnesol

The test dose of farnesol (50 mg/kg and 100 mg/kg) for experimental studies was selected based on acute toxicity reports published in the literature.[26,27] Corn oil was used as a vehicle for the administration of farnesol to Groups III and IV and administered orally from day 15 to day 21 after 14 days of the induction period.

Measurement of Body Weight (bw)

The bodyweight of the rats was weighed on day 1, day 15, and day 22. The percentage change in body weight was evaluated by comparing the bodyweight of the rats with the initial bodyweight that was weighed on the 1st day.[36]

$$\% \text{ Change in Body Weight} = \frac{\text{Body Weight}}{\text{Initial Body Weight}} \times 100$$

Assessment of Locomotor Activity

The locomotor activity of all the animals was evaluated using actophotometer on day 1, day 15, and day 22. The locomotor activity was measured using an actophotometer which operates on photoelectric cells which are connected in circuit with a counter. When the beam of light falling on the photo cell is cutoff by the animal, a count is recorded. The locomotor activity was measured for 5 min and the values are expressed as the number of counts/5 min. The locomotor activity on day 1 was used as the baseline for comparing the locomotor activity after induction of disease and after treatment with farnesol.[22,27-36]

Assessment of Spatial Memory Using Elevated Plus Maze

Elevated plus maze was used to evaluate the effect of farnesol on learning and memory in animals induced with Huntington's disease using 3-NP. The animals were tested for acquisition of memory by placing them in one of the open arms facing away from the central platform. The time taken by the animals to move from open arm and enter the closed arm is recorded as initial transfer latency. The rats were then allowed to explore the maze for 30 s. Retention of this learned task each animal was noted on the next day and at the end of the study.[28]

$$\%\text{Change in transfer latency} = \frac{\text{Transfer latency on day 1, day 15, day 22}}{\text{Transfer latency 1}} \times 100$$

Assessment of Grip Strength Using Rotarod

The animals were first trained to walk on a rotating rod at 25 rpm speed. Once the animals were successfully trained, the effect of a farnesol on their motor performance was evaluated. Animals that experienced impaired motor coordination were unable to cope with the rotating rod and dropped off when the speed of rotation exceeds their capacity to coordinate motor performance. When the animal drops from rod safely into its own lane, the time latency to fall is automatically recorded. The animals were placed on the rod rotating at a speed of 25 rpm with a cutoff time of 180 s. The average of three trials was taken as the fall-off time to assess the grip strength on day 1, day 15, and day 22.[22,36]

Dissection and Homogenization for Estimation of Biochemical Parameters

After the assessment of behavioral parameters, the rats were sacrificed by cervical dislocation under anesthesia and the whole brain tissue was isolated and the striatum was separated. 0.1 M phosphate buffer maintained at pH 7.4 was used for preparing a 10% (w/v) of tissue homogenate. An aliquot of the supernatant was separated after centrifugation (10,000 G) of homogenate for 15 min.[28]

Estimation of nitrite level

Griess reagent was used as an agent for determining the accumulation of nitrite in the supernatant of the brain homogenate. The supernatant and Griess reagent were mixed in equal volumes, followed by incubation for 10 min at room temperature in the dark. The nitrite level was determined by measuring the absorbance at 540 nm. The standard curve of sodium nitrite (5 to 50 μM) was used for determining the concentration of nitrite in the supernatant and the values obtained were expressed as a percentage of the control.[22]

Estimation of GSH level

The supernatant obtained from tissue homogenate after centrifugation was mixed with CCl_3COOH of 10% w/v in a 1:1 ratio. The tubes were centrifuged for 10 min at 10,000 G. After centrifugation, 2 ml of 0.3 M Na_2HPO_4 was taken and mixed with 0.5 ml of the supernatant. Then 0.25 ml of 0.001 M freshly prepared DTNB dissolved in 1% sodium citrate was added and absorbance was measured at 412 nm. The results were compared to that of the standard curve of GSH (10–100 μm).[22]

In silico Docking Study

The ligand, farnesol was downloaded in its natural form from the PubChem database and the crystal structure of Nrf2 (PDB ID: 3VNH) was downloaded from https://www.rcsb.org/. The target was prepared for docking using BIOVIA Discovery Studio 2016 v16.1.0.15350 and the binding pose, interactions, and the binding affinity of the protein-ligand complex were predicted using PyRX v.0.8.[29]

Histological Estimation

Rotary microtome was used for sectioning the striatal region with 10 µm thickness. The sections were then stained with hematoxylin and eosin stain (H & E) and viewed under the microscope.

Statistical Analysis

Data are expressed as mean ± SD. Data were analyzed by Analysis of Variance (ANOVA) followed by Tukey's test. $P < 0.05$ was considered significant. $^{*}P < 0.05$ versus Normal Control; $^{\#}P < 0.05$ versus Diseases Control.

RESULTS

Induction of Huntington's Disease

The treatment of the rats with 10 mg/kg/day for 14 days resulted in successful induction of Huntington's disease. Only those animals that exhibited the signs and symptoms of Huntington's disease were selected for further studies [Figure 1].

Effect of Farnesol on Body Weight

No change in body weight was observed in the normal group. However, disease control and test groups that were treated with 3-NP exhibited a significant ($P < 0.05$) loss in body weight during the induction period compared to normal. After treatment with 50 mg/kg and 100 mg/kg of farnesol for 7 days, the animals showed a significant gain in body weight compared to disease control [Table 1].

Effect of Farnesol on Locomotor Activity

No change in locomotor activity was observed on days 15, 22 compared to day 1 in the normal group. A significant decrease

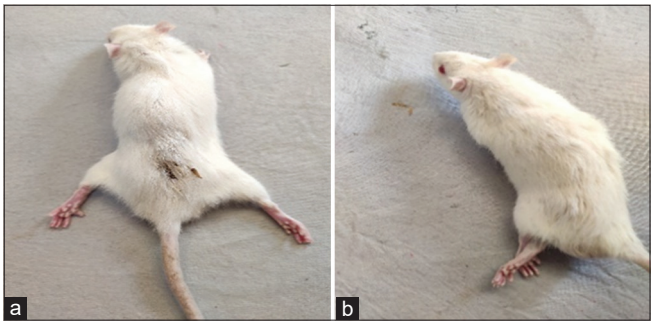

Figure 1: Signs and symptoms observed after 14 days of disease induction

in locomotor activity was observed in disease control and test groups were observed during the induction period. The treatment with 100 mg/kg of farnesol significantly increased the locomotor activity in but no significant improvement was observed in the group treated with 50 mg/kg of farnesol compared to the disease control group [Table 2].

Effect of Farnesol on Spatial Memory

All groups except normal showed a significant increase in transfer latency after treatment with 3-NP during the induction period. The treatment with 100 mg/kg of farnesol resulted in a significant improvement in transfer latency compared to the disease control group but no significant improvement in memory was observed in the group treated with 50 mg [Table 3].

Effect of Farnesol on Grip Strength

The normal group showed no change in grip strength on day 15 and day 22 compared to day 1. However, a significant reduction ($P < 0.05$) in grip strength was observed in the remaining groups compared to normal after induction of Huntington's disease with 3-NP (10 mg/kg) for 14 days. After treatment with 100 mg/kg of farnesol, a significant improvement in grip strength was observed compared to the disease control group but the group treated with 50 mg/kg of farnesol did not show significant improvement in grip strength [Table 4].

Table 1: Effect of farnesol on body weight

Group/Days	Day 1	Day 15	Day 22
Normal control	230.5±4.970	232.2±4.596	233.7±4.967
Disease control	233.7±7.118	209±8.710*	207.3±8.779*
Farnesol (50 mg/kg)	228.2±7.765	200±14.48*	224.3±4.179#
Farnesol (100 mg/kg)	228.7±5.680	199±5.419*	231.2±6.555#

Values are expressed as mean±SD. statistical analysis was performed by one-way analysis of variation (ANOVA), followed by Tukey's test. $n=6$; * $P<0.05$ was considered significant. *$P<0.05$ versus Normal Control; #$P < 0.05$ versus Diseases Control. The disease control was compared with normal and the treated groups were compared with disease control.

Table 2: Effect of farnesol on locomotor activity

Group/ Days	Day 1	Day 15	Day 22
Normal control	623.8±15.22	621.0±9.980	622.5±12.28
Disease control	618.2±10.55	419.3±47.50*	396.5±44.33*
Farnesol (50mg/kg)	617.3±8.091	418.0±40.92*	444.8±37.73ns
Farnesol (100mg/kg)	619.3±9.309	421.0±43.67*	461.8±23.01#

Values are expressed as mean±SD. statistical analysis was performed by one-way analysis of variation (ANOVA) followed by Tukey's test. $n=6$; *$P<0.05$ was considered significant. *$P<0.05$ versuss Normal Control; #$P<0.05$ versus Diseases Control; ns: Non-significant. The disease control was compared with normal and the treated groups were compared with disease control.

Effect of Farnesol on Nitrite and Glutathione

A significant increase in the levels of nitrite and a significant decline in glutathione was observed in the disease control and treatment groups during the induction period. Treatment with 50 mg/kg of farnesol failed to restore the nitrite levels but 100 mg/kg of farnesol significantly restored the nitrite levels. On the other hand, glutathione levels were significantly restored by both 50 and 100 mg/kg of farnesol [Table 5].

Docking Study

The binding affinity of farnesol and dimethyl fumarate was found to be −6.1 kcal/mol and −4.6 kcal/mol [Figure 2 and Table 6].

Histological on the Effect of Farnesol on Rat Striatum

The striatal region of the brain was subjected to histopathological examination. The striatal cells were normal and intact with no signs of apoptosis in the normal group. A high degree of apoptosis was observed in the control group treated only with the inducing agent, 3-NP. A low degree of apoptosis was observed in the animals treated with 3-NP and 50 mg/kg of farnesol. The animals treated 100 mg/kg of farnesol showed almost normal and intact cells with no signs of apoptosis [Figure 3].

DISCUSSION

As tetrabenazine is the only drug approved by the FDA for the management of Huntington's disease, there is a desperate need

Table 3: Effect of farnesol on memory retention

Group/Days	Day 1	Day 15	Day 22
Normal control	21.33±0.8165	23.17±1.169	24.17±1.329
Disease control	22.33±1.862	44.50±2.739*	46.67±2.659*
Farnesol (50 mg/kg)	20.67±1.633	45.17±2.639*	44.50±2.588ns
Farnesol (100 mg/kg)	20.33±1.633	46.17±2.927*	29.33±2.160#

Values are expressed as mean±SD. statistical analysis was performed by one-way analysis of variation (ANOVA) followed by Tukey's test. $n=6$; *$P<0.05$ was considered significant. *$P<0.05$ versus Normal Control; #$P<0.05$ versus Diseases Control; ns: Non-significant. The disease control was compared with normal and the treated groups were compared with disease control.

Table 4: Effect of farnesol on Grip strength

Group/Days	Day 1	Day 15	Day 22
Normal control	243.8±3.312	244.3±2.733	245.3±1.966
Disease control	241.7±2.733	107.5±3.578*	98.33±1.033*
Farnesol (50 mg/kg)	241.3±3.830	107.5±3.834*	108.2±4.579ns
Farnesol (100 mg/kg)	243.5±1.871	106.5±2.588*	247.2±2.041#

Values are expressed as mean ± SD. statistical analysis was performed by one-way analysis of variation (ANOVA) followed by Tukey's test. $n=6$; *$P<0.05$ was considered significant. *$P<0.05$ versus Normal Control; #$P<0.05$ versus Diseases Control; ns: Non-significant. The disease control was compared with normal and the treated groups were compared with disease control.

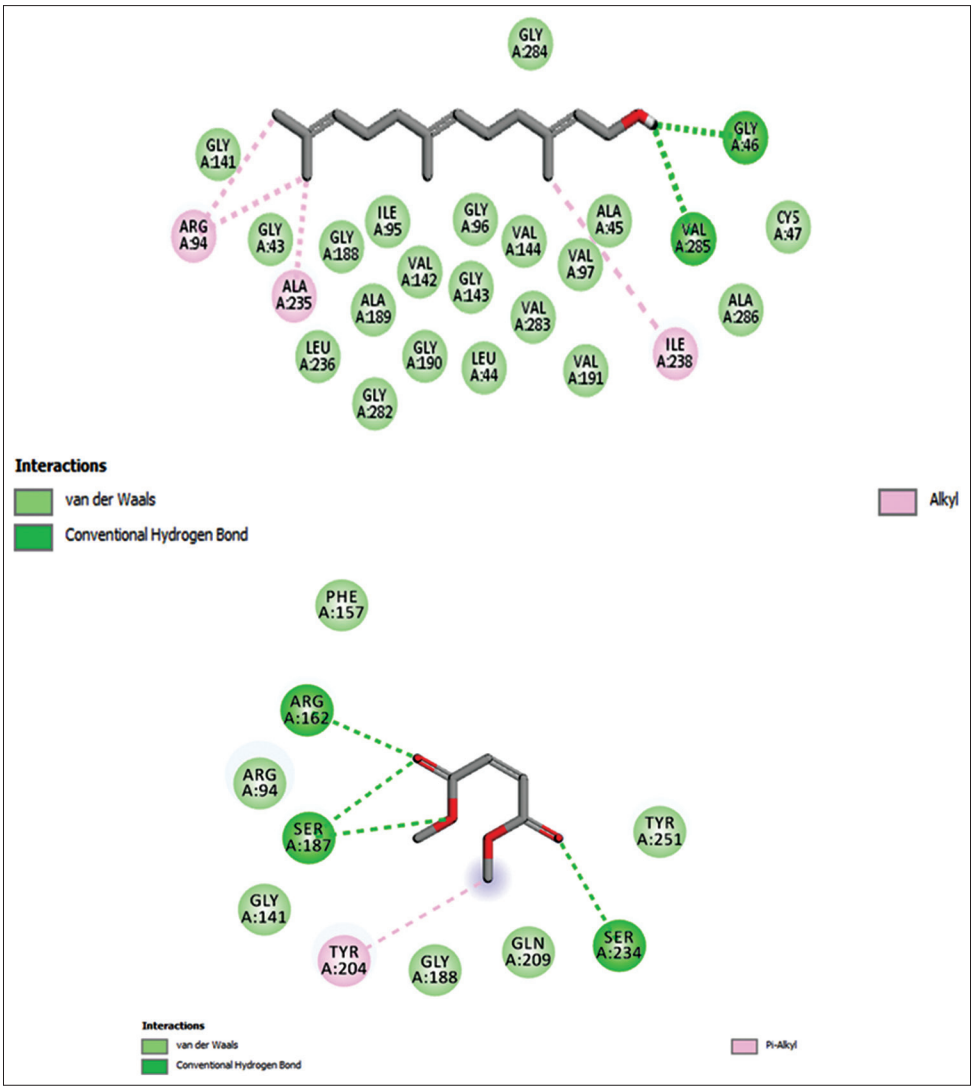

Figure 2: Interaction of farnesol and dimethyl fumarate with 3VNH amino acids

Table 5: Effect of farnesol on nitrite level

Group/Days	Nitrite	Glutathione
Normal control	100±0.000	120.8±2.639
Disease control	188±1.265*	54±4.262*
Farnesol (50 mg/kg)	183±1.265^{ns}	69.83±1.472$^{\#}$
Farnesol (100 mg/kg)	129±1.265$^{\#}$	90±4.926$^{\#}$

Values are expressed as mean ± SD. statistical analysis was performed by one-way analysis of variation (ANOVA) followed by Tukey's test. $n = 6$; *$P<0.05$ was considered significant. *$P<0.05$ versus Normal Control; $^{\#}P<0.05$ versus Disease Control; ns – non-significant. The disease control was compared with normal and the treated groups were compared with disease control.

Table 6: Summary of residues interacting with the farnesol and dimethyl fumarate

Ligand	Conventional hydrogen bond	Dock score
Farnesol	GLY46, VAL285	−6.1 kcal/mol
Dimethyl fumarate	ARG162, SER187, SER234	−4.6 kcal/mol

to explore and discover new synthetic or natural therapeutic agents for the treatment of HD. This study aims to explore the pharmacological effects of the natural sesquiterpene compound, farnesol in 3-nitropropionic acid-induced Huntington's disease in male Wistar rats. Huntington's disease is an autosomal dominant neurological disorder characterized by excessive repetition of cytosine-Adenine-Guanine triplets that encodes for the Huntington gene located in chromosome 4. The number of abnormal triplets determines the penetrance, age of onset and severity of disease.[30,31] Many theories exist to explain the pathophysiology of Huntington's disease but the most widely accepted is the one that indicates the role of elevated oxidative stress due to dysfunction of complex II and complex III of electron transport chain in mitochondria.[13,32] The elevated oxidative stress due to imbalance between oxidant and antioxidant levels as a result of mitochondrial dysfunction leads to progressive neurodegeneration in Huntington's disease.

Kainic acid (KA), quinolinic acid (QA), malonic acid (MA), and 3-nitropropionic acid are widely used toxic agents to induce Huntington's disease in animals to study the effectiveness of potential drugs in Huntington's disease. Apart from these models, genetic models and lower animals such as vinegar

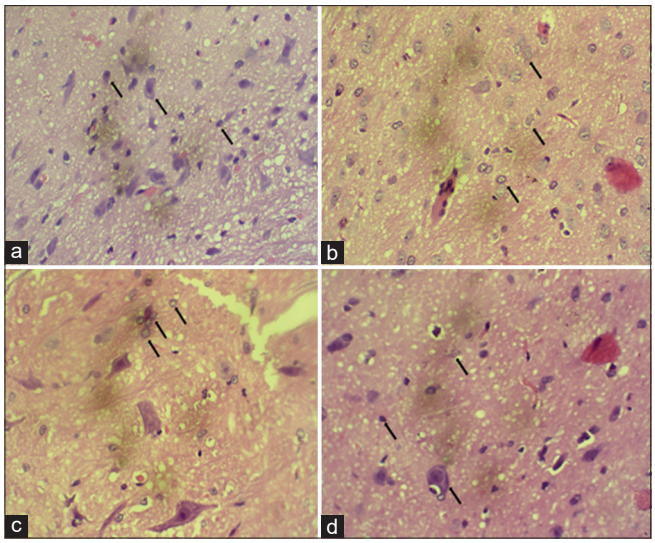

Figure 3: Histopathological report **:** (a) Normal control; (b) disease control; (c) farnesol (50 mg/kg); (d) farnesol (100 mg/kg). In the normal group, arrow sign indicates absence of apoptosis; in disease control group, arrow sign indicates high degree of apoptosis; in the animals treated with 3-NP and 50 mg/kg of farnesol arrow sign indicates low degree of apoptosis; while in animals treated 100 mg/kg of farnesol arrow sign indicates almost normal intact cells with no signs of apoptosis

fly and *Caenorhabditis elegans* are also used in Huntington's research. However, the preferred model is toxin based because of their ease in use and control. Toxins mimic Huntington's disease in animals either by causing excitotoxicity such as kainic acid and quinolinic acid or by causing mitochondrial dysfunction such as malonic acid and 3-nitropropionic acid. 3-NP-induced Huntington's disease in animals mimics the exact chain of processes that leads to progressive neurodegeneration and neuronal death in Huntington's disease. 3-NP mainly mimics the mitochondrial dysfunction but it also imitates the impairment of cognition, histological, and pathological characteristics of this disease making it an excellent model for studying Huntington's disease.[30] Chronic administration of 3-NP (10 mg/kg/day) for 2 to 6 weeks induces clinical features similar to those observed in humans with Huntington's disease in animals by irreversibly blocking succinate dehydrogenase enzyme.[33] Because of the above advantages, we chose 3-NP over other toxins to induce Huntington's disease for this research work. It has also been reported that rats are more sensitive to 3-NP than mice and among different species of rats, Fischer rats are more susceptible but Wistar rats are also more sensitive to 3-NP.[31] Hence, it was decided to use Wistar rats for the current study.

Weight loss is one of the peripheral manifestations of Huntington's disease but the exact cause is unknown. It is believed to be multifactorial and possible causes include chorea, decreased appetite, difficulty in swallowing food, and loss of hypothalamic neuronal control.[34] In this study, the administration of 3-NP resulted in significant weight loss in animals and treatment with 50 and 100 mg/kg of farnesol resulted in significant weight gain. This could due to the negation of oxidative stress by farnesol through its proven antioxidant property.

Huntington's patients develop hypokinesia, akinesia, ataxia, rigidity, and dystonia and these symptoms progressively decline over time. These motor symptoms lead to an ataxic gait, frequent falls, and difficulty in initiating movements.[35] Animals in this study exhibited all motor complications that are characteristic of Huntington's disease confirming the induction of the disease. The motor activity was assessed at the beginning of the study, after successful induction of the disease and at the end of the treatment with farnesol using actophotometer and rotarod. The animals showed a significant improvement in motor activity after treatment with farnesol reflecting a positive neuroprotective effect of farnesol in animal models of Huntington's disease.

A decline in cognitive function is one of the most important signs of Huntington's disease and appears even before motor symptoms appear. Memory is severely compromised and all psychomotor symptoms are impaired in Huntington's disease.[35] In this study, 3-NP treatment led to the loss of learning and memory as reflected in elevated plus maze tests in control and test animals at the end of the induction period. A significant improvement in transfer latency was observed after the treatment period in the animals treated with 100 mg/kg of farnesol confirming its neuroprotective potential but no significant improvement was observed in the group treated with 50 mg/kg of farnesol.

3-NP treatment leads to an elevation in the levels of free radicals and a significant decline in the level of antioxidant enzymes. The treatment with farnesol led to the restoration of normal levels of GSH and nitrite further confirming the antioxidant potential of farnesol. Several compounds such as rivastigmine,[36] sesamol,[37] kaempferol,[38] and lycopene[39] have been reported in the literature for their neuroprotective effects in Huntington's disease through their antioxidant(AO) property. Consistent with the above reports, farnesol could have exerted neuroprotective property in this study through its antioxidant property. However, studies on the protective effect of antioxidants in neurodegenerative disease have been equivocal so recently there is a trend to increase the activity of endogenous antioxidant systems such as nuclear factor erythroid 2-related factor 2 (Nrf2).[40] Nrf2 is a transcription factor that increases the expression of antioxidant response elements such as superoxide dismutase (SOD), thioredoxin (TXN), thioredoxin reductase (TXNRD), sulfiredoxin (SRXN), NAD(P)H:quinone oxidoreductase-1 (NQO1), HO-1, glutathione reductase (GR), glutaredoxin (Grx), glutamate cysteine ligase (GCL), glutathione S-transferase (GST), UDP-glucuronyl transferase, thioredoxin reductase, peroxiredoxin sulfotransferase, and γ-glutamate cysteine ligase catalytic subunit (GCLC) that are involved in negating the effects of free radicals. The binding of a regulatory protein called keap1 to Nrf2 leads to proteasomal degradation of Nrf2. Disruption of this complex through modification of cysteine residues within the Keap1 destabilizes the Nrf2–Keap1 complex thereby allowing the free translocation and nuclear accumulation of Nrf2. Nrf2 once inside the nucleus binds to antioxidant response elements (ARE) and activates the transcription of cytoprotective genes.[41-44] Hence, to check if farnesol might have produced its neuroprotective property indirectly by activating the Nrf2, we performed molecular docking studies. The docking results showed that farnesol binds to keap1

more avidly than the standard dimethyl fumarate. Hence, the beneficial effects of farnesol might partly be due to the activation of Nrf2 which, in turn, might have led to an increase in the levels of antioxidant response elements

SUMMARY AND CONCLUSION

The present study confirms the potential neuroprotective activity of farnesol in HD by *in silico* and the rat model. The treatment of animals with 3-NP for a period of 14 days caused successful induction of HD and development of characteristic signs and symptoms of HD. Animals treated with 100 mg/kg of farnesol displayed significant improvement in behavior and cognitive functions but the group treated with 50 mg/kg of farnesol failed to produce significant improvement in locomotor activity, memory, and grip strength. However, modern and advanced molecular biological studies are required to further confirm the neuroprotective effects of farnesol in Huntington's disease.

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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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