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Neuroprotective Potential of Vinpocetine in Drosophila Melanogaster Genetic Model of Parkinson Disease

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ABSTRACT

Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons and dysfunction in both motor and non-motor systems. Current pharmacological treatments are limited by motor complications and do not stop disease progression.
Objectives: This study evaluated the neuroprotective potential of vinpocetine in a genetic *Drosophila* model of PD expressing human α-synuclein in dopaminergic neurons, and also its effect on the fecundity and lifespan of *Drosophila.*
Methods: Transgenic *Drosophila melanogaster* strains (Elav-GAL4<UAS-syn, DDC-GAL4<UAS-syn) and wild-type flies were cultured on normal diet or vinpocetine-supplemented feed at 5, 25, and 50 µM. Fecundity, larva motility, climbing ability, memory performance, and longevity assays were conducted over 28 days. Data were analysed using one way ANOVA and multiple comparison post hoc tests.
Results: Vinpocetine significantly reduced fecundity at 25 and 50 µM. It improved larval motility and climbing activity in a dose-dependent manner. A significant increase in lifespan was observed at 25 µM. Memory assay did not show statistically significant differences across treatment groups.
Conclusion: Vinpocetine demonstrated neuroprotective activity in α-synuclein-expressing *Drosophila* by improving motor function and survival. These findings support its potential utility in PD therapy.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system that affects approximately 1% of the global population, particularly individuals over the age of 60[1]. It is characterized by a combination of motor and non-motor symptoms[2]. PD is the second most common movement disorder after Alzheimer's disease (AD)[3]. Research shows that non-motor symptoms, such as constipation, reduced sense of smell (hyposmia), depression, anxiety, and sleep disturbances, often appear before the onset of motor symptoms. As the disease progresses, motor symptoms—including bradykinesia, resting tremor, rigidity, and freezing—become more pronounced[4,5]. Interestingly, men are about twice as likely to develop PD compared to women. However, women tend to experience faster disease progression and higher mortality rates[6]. As of 2015, PD affected over 6.2 million individuals worldwide and resulted in approximately 117,400 deaths[7]. The average life expectancy following a diagnosis of PD ranges from 7 to 15 years[8]. Diagnosing PD can be challenging due to the variety of motor and non-motor symptoms exhibited by patients, which complicates management. The primary treatment for PD is levodopa, although prolonged use can lead to levodopa-induced dyskinesia[9].

The need for a better understanding of disease pathogenesis, particularly Parkinson's Disease (PD), has led to the development of various laboratory models with face validity. Numerous approaches have been explored, including non-cellular models, cellular models, invertebrates (such as Drosophila melanogaster and Caenorhabditis elegans), and vertebrates (including zebrafish, rodents, and non-human primates). Each of these organisms has unique advantages for modelling PD. Among these, Drosophila melanogaster stands out as an excellent model organism for studying both environmental and genetic factors related to PD. It provides valuable insights into the pathways involved in PD pathogenesis and facilitates the development of therapeutic strategies[10]. The benefits of using Drosophila include a short life cycle, low maintenance costs, and well-defined neuropathology and behavior[11]. Parkinson's Disease results from the dysregulation of the autophagy-lysosome pathway, which is responsible for clearing abnormal aggregated proteins. This dysfunction leads to the formation of insoluble α-Synuclein (αS) fibrillar aggregates in neurons, contributing to the movement disorders observed in PD patients[12]. Drosophila can mimic PD-like movement disorders by expressing αS in dopamine neurons or throughout the entire nervous system. In this study, we utilize the bipartite upstream activating sequence (UAS) combined with the yeast transcription factor GAL4 system for the selective expression of αS mutants in dopaminergic and serotonergic neurons. The inducible gene expression system in Drosophila employs two specific transgenic constructs: an effector gene (EG) and a transactivator gene (TAG), the latter being GAL4. Consequently, the expression of αS is regulated by UAS under the control of GAL4.

Drosophila, also known as the fruit fly, contains approximately 70% of genes that are homologous to those in humans. It has less gene redundancy compared to mammals due to its smaller genome. This characteristic makes fruit flies a valuable model for research, as they have shown great potential in discovering genetically relevant pathways related to various human diseases. They are particularly useful for large-scale genetic and molecular screening, which can lead to the identification of novel therapeutic interventions for these conditions.

Vinpocetine, a derivative of the alkaloid vincamine, acts as a specific inhibitor of phosphodiesterase 1 (PDE1) and is marketed as a dietary supplement for treating cerebrovascular disorders such as stroke, liver fibrosis, and dementia. It has been reported as a safe dietary supplement, prompting investigations into its protective effects against other neurodegenerative diseases, including Parkinson's disease (PD). Research conducted by Ishola IO and colleagues[13,14,15] has demonstrated vinpocetine's ability to alleviate oxidative stress and neuroinflammation in mice induced by haloperidol or paraquat. Additionally, studies[16] have reported its anti-inflammatory properties and its capacity to inhibit pathological changes in vascular and cardiac structure. These findings suggest that vinpocetine may be repurposed for the treatment of neurodegenerative disorders[16]. Therefore, this study aims to investigate the neuroprotective effects of vinpocetine in a progressive model of Parkinson's disease using Drosophila melanogaster.

MATERIALS AND METHODS

Materials/ Drugs

Vinpocetine (Divine essentials formulations, Lagos State, Nigeria), diethyl-ether (GuandongGuangbua sci. Tech CO. Ltd China), sugar, corn flour (Benchmark foods and spices Ltd, Lagos state), yeast (STK industries Ltd, China), agar (Himedia Laboratories Pvt, Ltd, Mumbai, India), propanoic acid (LOBA Chemic Laboratory Reagents and fine Chemicals, Mumbai, India), methyl-p-hydroxyl benzoate (LOBA Chemic Laboratory Reagents and fine Chemicals, Mumbai, India), orthophosphoric acid (Thermo Fischer Scientific India pvt, Ltd, Mumbai, India).

Fly Stock

The strains of *Drosophila melanogaster* used in this study include UAS-*syn*, Elav-GAL4, DDC-GAL4, and Wild type (WII8) were obtained from Dr. Rakesh Mishra Laboratory, Centre of Cellular and Molecular Biology, India. The flies were maintained at a temperature between 18°C-23°C. Flies were allowed to develop on corn-meal agar medium in 50ml plastic vials and cultured under 12:12 hours light/dark cycles, in a set up of 15-20 flies per vial. The UAS/GAL4 system was utilized for transgene expression.

Preparation of Fly Meal

To prepare 1L of cooked media, the following materials and quantifier were used

- Sugar- 80 g
- Corn-flour- 75 g
- Yeast- 24 g
- Agar- 9 g

The mixture was microwaved under medium heat for 15 minutes. Thereafter, the following preservatives were added:

- Methyl-p-hydroxyl benzoate
- Propanoic acid
- Orthophosphoric acid

Vinpocetine was prepared to result to the following final media concentrations; 5, 25 and 50 µM.

Collection of Virgin Flies
Collection of female virgins were done under anaesthesia using diethyl ether. Female virgin flies only remain so for about 8-10h after eclosion and collected within this time frame. The anaesthetized flies were placed under a microscope and the female virgin separated and collected.

Fecundity Assay
The strains used for this study includes DDC-Gal4<UAS-*syn*, Elav-GAL4<UAS-*syn*, and the wild strain type (W118) used as negative control. The fecundity study began at 24 hours after crossing. The number of egg was counted at 24 and 48 hours after crossing by viewing the vials under the microscope. The number of pupa and adult that emerged were also recorded for each vial in all the strains used for this study

Larval Locomotion Assay
The desired number of individual larvae were collected at 90-96 hours after egg laying, washed in phosphate buffered saline and transferred to the assay stage. The assay stage was prepared on a petri dish by boiling 2% Agar in distilled water and pouring into the petri dish to solidify. The petri dish was placed over a 2B paper with a 0.1cm^2 grid. Third instar larvae were collected from the food media and loosened from food using distilled water and placed individually on the assay stage to be tested. The larvae were first allowed to acclimatize for a minute and then the assay was carried out for one minute, the total number of line crossed by the larvae recorded. Several drops of distilled water were periodically added to the stage to keep it from drying.

Negative geotaxis
To assess climbing behaviour, 20 adult flies were collected upon eclosion and scored for their ability to climb over a period of twenty-eight days. Every seven days, twenty flies cultured on normal feed and drug supplemented feed (5 µM, 25 µM and 50 µM) were assayed for their ability to climb 8cm in 8 seconds in a clean climbing apparatus in three repetition per vial. Analysis was performed using the GraphPad Prism and compared using 95% confidence interval with a 0.05 P value

Ageing Assay
The progeny of the DDC-Gal4<UAS-*syn* and W118<UAS-*syn* as negative control were collected in several vials, in a random ratio of male to female flies. The flies were enclosed at a density of twenty flies per vial on fresh normal feed media and also on the drug supplemented feed of concentration 5 µM, 25 µM and 50 µM. The flies were observed and scored every seven days for a total of twenty-eight days for deceased adults. Flies were considered to be dead when they did not display any activity upon agitation. This assay allows the monitoring of the effect of the genotype and environment as well as the drug on the lifespan of the flies. The data gathered from the longevity assay was analyzed using the GraphPad prism and significance was determined at 95% at P value less than or equal to 0.05.

Memory test
The strains used for this test include DDC-Gal4<UAS-*syn* and W118<UAS-*syn*as negative control. Ten (10) flies from each vial used for the experiment were introduced into the fly t-maze which contained sugar on one side of the maze, and chloroquine on the other side. The flies were allowed to get acclimatized to their new environment, until it was confirmed that all flies had visited both wings of the t-maze before they were removed from the maze. Twenty-four hours later, the same set of flies were introduced into the fly t-maze and the number of flies that turned into the sugar wing were recorded, alongside the number of flies that turned into the chloroquine wing.

Statistical analysis
Data analyses were performed using Graphpad Prism software (Graphpad Software, Inc.). The results were expressed as mean and standard deviation values. One-way ANOVA was adopted for column analysis, while the grouped data were analyzed with the Two-way ANOVA. The results were analyzed by Tukey's and Dunnet's *Post hoc* multiple comparison test.

RESULTS
Fecundity assay
Vinpocetine showed a dose dependent negative effect on the fecundity of Elav-GAL4<UAS-*syn* flies.
Vinpocetine at 25 µM or 50 µM concentration showed a significant reduction in the number of eggs laid by the female flies post-mating at 24 hours and 48 hours [$F(4, 10) = 3.263, p<0.01$) (Fig1a). There was also a significant reduction in the amount of dark pupa in the vinpocetine supplemented feed at 25 µM and 50µM ($F(4, 10) = 1.709$) (Fig1b), when compared to the flies cultured on normal feed. The number of flies that emerged from the dark pupa was also affected by the introduction of vinpocetine into the feed with a significant reduction of the adult that emerged at 50µM concentration of drug supplemented media.

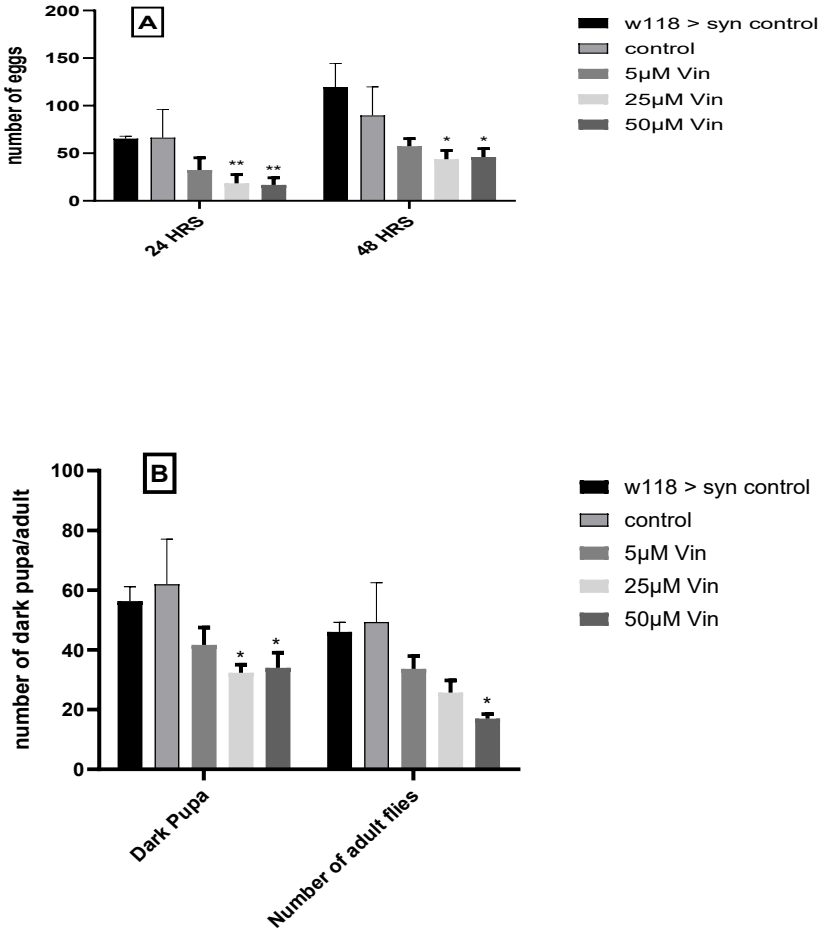

Figure 1A–B: Effect of vinpocetine on fecundity in Elav Gal-4 Drosophila melanogaster. **(A)** Number of eggs laid at 24 h and 48 h. **(B)** Number of pupae formed and adult flies that emerged. Data are presented as mean ± SD. *P < 0.05, *P < 0.01 versus control. Statistical analysis was performed using two-way ANOVA followed by Dunnett's multiple comparisons test.

Vinpocetine showed a dose dependent negative effect on the fecundity of DDC-Gal4<UAS-*syn* flies.

Vinpocetine at 25 μM and 50 μM concentration showed a significant reduction in the number of eggs laid by the female DDC-Gal4 flies after mating with the UAS-*syn* male flies at 24 hours and 48 hours post-mating (F (4, 10) = 1.084) (Fig2a), when compared to the number of eggs laid by female flies cultured on the normal feed. There was also a significant reduction in the amount of dark pupa in the vinpocetine supplemented feed at 25μM and 50μM concentration (F (4, 10) = 0.7297) (Fig. 2b)., when compared to the flies cultured on normal feed. The number of flies that emerged from the dark pupa were also affected by vinpocetine supplementation evidenced in a significant reduction at 5μM, 25μM and 50μM.

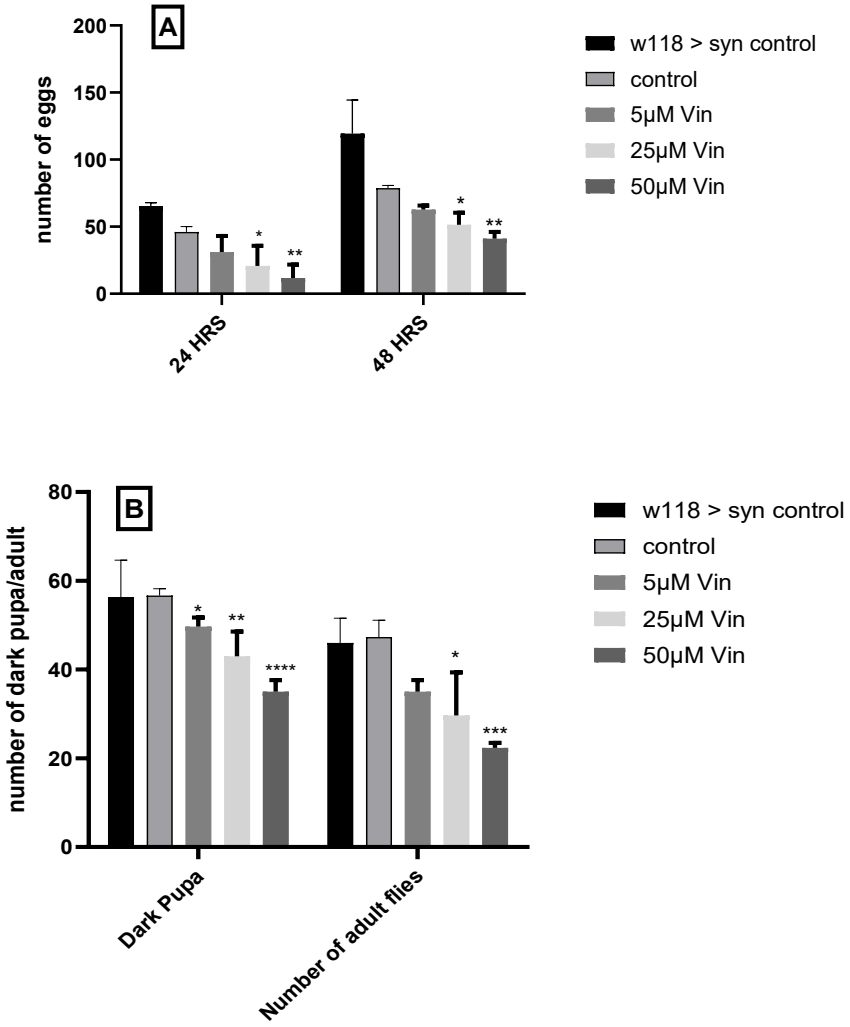

Figure 2A-B: Vinpocetine showed a negative effect on **(A)** number of eggs laid by female DDC Gal-4 *Drosophila melanogaster* in 24 and 48 hrs **(B)** the number of pupa and number of flies that emerged in the fecundity assay. Bar chart represent mean ± SD; *P <0.05, **P <0.01,, ***P <0.001, ****P <0.0001 versus control. Two-way ANOVA was used for the statistical analysis followed by Dunnett's multiple comparisons test.

Larva motility assay

Vinpocetine rescue locomotor activity in Elav-GAL4<UAS-*syn* larva

The exposure of the Elav-GAL4<UAS-*syn* larva to 25μM and 50μM concentration of vinpocetine supplemented feed showed an ameliorative effect when assayed for locomotor activities using a hardened 2% agar stage (F (4, 10) = 0.2184) ((Fig.3). The results showed a decrease in spontaneous locomotive activity of Elav-GAL4<UAS-*syn* pathological control when compared to the non-pathological model W118<UAS-*syn*, however, supplementation of feed with vinpocetine caused dose related increase in motor activity when compared with pathological with Elav-GAL4<UAS-*syn* group.

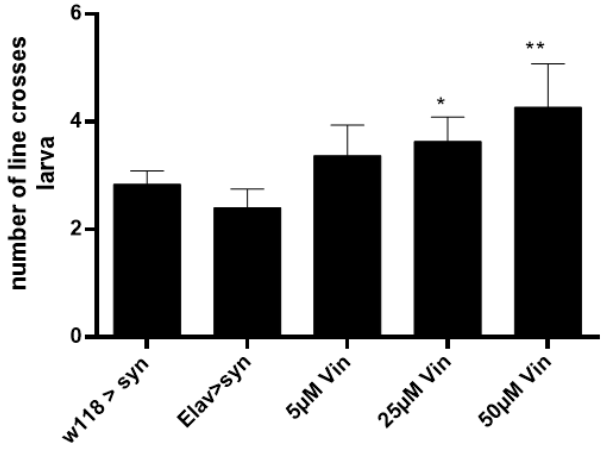

Figure 3: Vinpocetine showed a dose dependent increase in the number of line crosses in Elav-GAL4<UAS-*syn* larva. Bar chart represent mean ± SD; *P <0.05, **P <0.01 versus control. Statistical analysis by one-way ANOVA followed by *Tukey's* multiple comparisons test.

Rescue of locomotor activity in DDC-GAL4<UAS-*syn* larva.

Larva motility assay was also carried out on DDC-GAL4<UAS-*syn* larva in order to test for the neuroprotective effect of vinpocetine. Figure 4 shows the effect of vinpocetine (5 μM, 25 μM and 50 μM) on the locomotive activity of DDC-GAL4<UAS-*syn*. Post hoc analysis showed that there was a significant difference in the number of line crosses in the larva cultured on vinpocetine feed media (5 μM, 25 μM, 50 μM) when compared to the number of line crossings made by the larva of the normal feed (F (4, 10) = 0.5857)

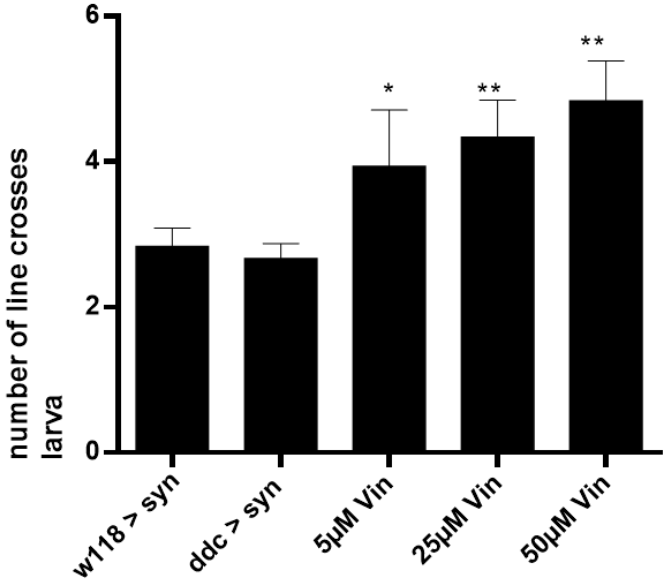

Figure 4: Vinpocetine showed a dose dependent increase in the number of line crosses in DDC-GAL4<UAS-*syn* larva. Bar chart represent mean ± SD; *P <0.05, **P <0.01 versus control. One-way ANOVA was used to analyze followed by *Tukey's* multiple comparisons test.

Climbing assay

Vinpocetine increased the climbing ability in synuclein expressing flies

Vinpocetine increased the climbing ability of synuclein expressing flies over the period of twenty-eight days, with the most significant improvement seen on day 21 by the flies cultured on 25 μM and day 28 by the flies cultured on both 5 μM and 25 μM concentration (F (12, 30) = 1.194) (Fig.5). Two-way ANOVA (P < 0.05)

was used in this analysis. Figure 6 showed that there was a general increase in the amount of flies that climbed from day 7 to day 21 across all the concentration administered (5 µM, 25 µM and 50 µM) when compared to the control cultured on normal feed.

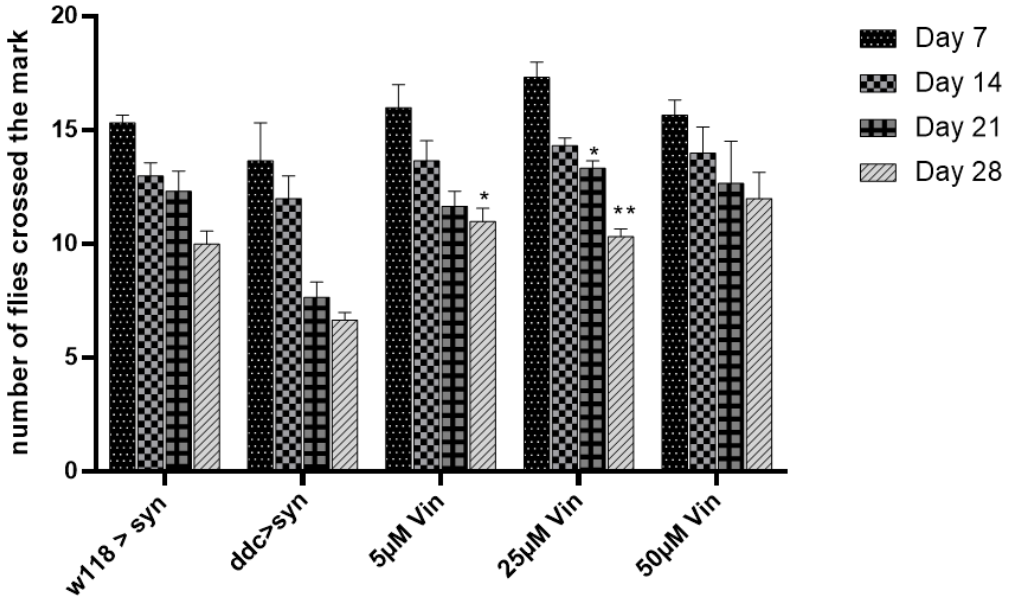

Figure 5: Vinpocetine improved the climbing abilities of synuclein expressing flies. Bar chart represent mean ± SD; *P <0.05, **P <0.01 versus control. Two-way ANOVA was used for the analysis followed by Dunnett's multiple comparisons test.

Longevity Assay

Vinpocetine considerably increased the lifespan of synuclein expressing flies at low doses

Figure 6 shows that vinpocetine played a role on the survival of the synuclein expressing flies. There was a general improvement in the healthspan of the flies placed on the 5 µM and 25 µM concentration of vinpocetine, with the most markedly significant improvement showed by flies on the 25 µM concentration (**P=0.008) when compared to the control flies cultured on normal feed.

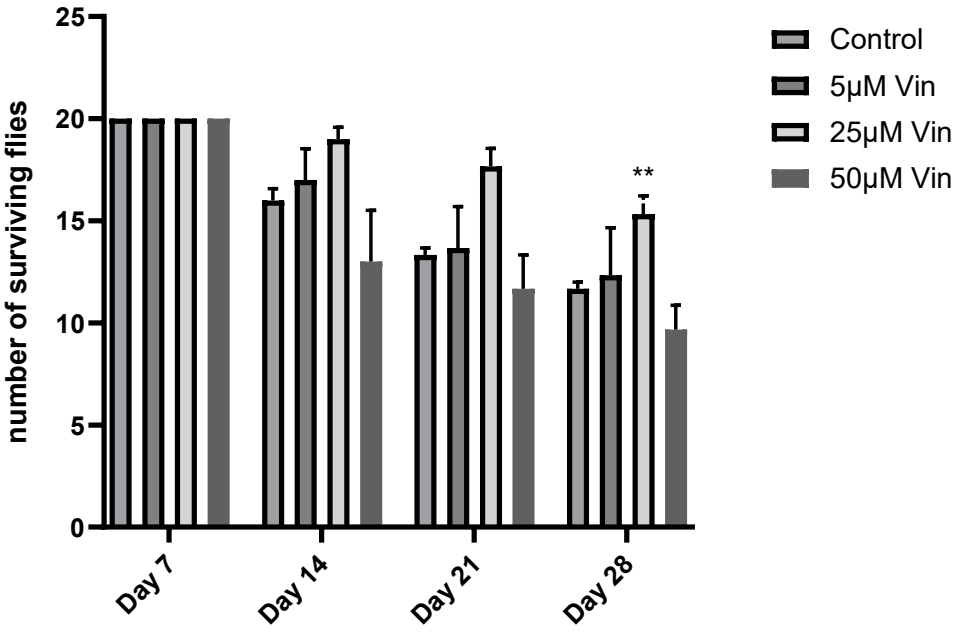

Figure 6: Vinpocetine alters the lifespan of synuclein expressing flies. Bar chart represent mean ± SD;**P <0.008 versus control. Two-way ANOVA was used for the analysis followed by Dunnett's multiple comparisons test.

Memory assay

Vinpocetine showed no significant effect on memory function in synuclein expressing flies

Figure 7 shows the effect of Vinpocetine on the memory of synuclein expressing flies cultured on normal feed and drug feed (5 μM, 25 μM, and 50 μM) and also on the non pathogenic control which were also cultured on normal feed. Vinpocetine did not show a significant improvement in the memory function of the flies cultured on the drug supplemented feed when compared to the flies cultured on normal feed or the non-pathogenic control.

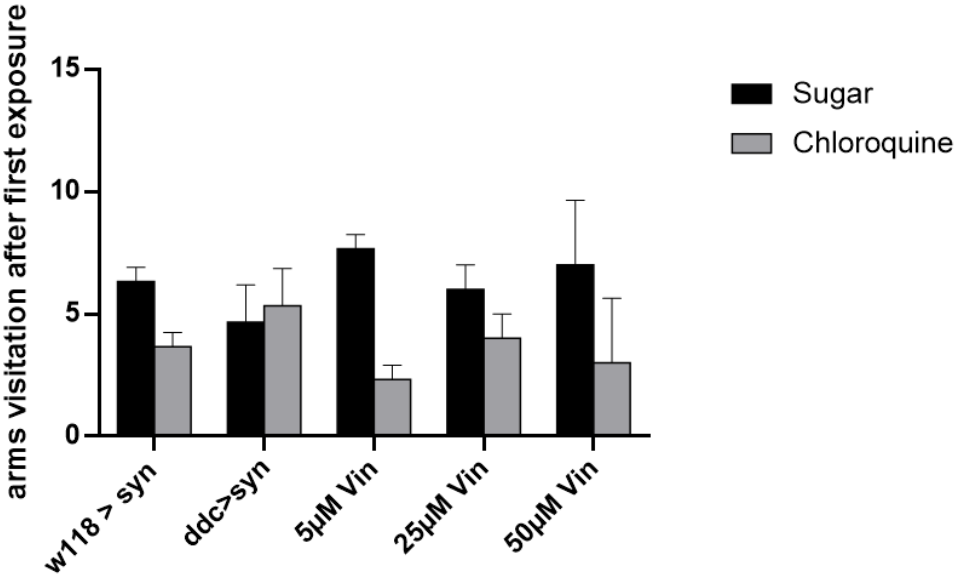

Figure 7: Vinpocetine showed no significant effect in the improvement of memory in synuclein expressing flies. Bar chart represent mean ± SD. Two-way ANOVA was used to analyze followed by Dunnett's multiple comparisons test.

DISCUSSION

The present study investigated the effect of vinpocetine on the UAS-GAL4 genetic model of PD. The ability of alpha-synuclein to form aggregates in dopaminergic neurons has always been a key pathological factor in the development of PD, and this has been confirmed by the lack of toxic effect on the neurons by aggregates of the beta-synuclein and non-aggregated alpha-synuclein in the neurons[17]. The overexpression and presence of mutations in dopaminergic neurons leads to the loss of synaptic function of alpha-synuclein, thereby resulting in an increase in the synthesis and availability of dopamine, causing an impairment of the synaptic vesicles and increasing the susceptibility of the neurons to oxidative conditions[18,19,20].

Our results showed that vinpocetine reduced fecundity in drosophila expressing α-synuclein and dose-dependent possibly linked to oxidative stress, mitochondrial dysfunction, and altered signalling pathways[18]. In fact, flies raised on vinpocetine-supplemented food demonstrated a dose-dependent reduction in the number of eggs laid, particularly at 25μM and 50μM concentrations, across both 24- and 48-hour counts. Correspondingly, there was a general decline in the number of dark pupae and adult emergence in drug-fed flies compared to controls, with statistical significance noted at the higher drug concentrations. Reproduction in *Drosophila* is tightly regulated by juvenile hormones and genes involved in oogenesis and vitellogenesis. vinpocetine may alter courtship and mating behaviour in *Drosophila*, further contributing to decreased fecundity. More importantly, interfere with endocrine signalling or transcriptional regulators. These findings suggest that vinpocetine affect the reproductive capacity of the flies and may potentially impact fertility or developmental viability. Factors influencing fecundity, such as temperature, humidity, female mating receptivity, and other physiological regulators[21], may interplay with vinpocetine's systemic effects, warranting further mechanistic investigation.

In *Drosophila melanogaster*, the Elav-GAL4 driver is a pan-neuronal promoter used to express target genes in neurons. The UAS-syn construct typically refers to the UAS-human alpha-synuclein (α-syn) transgene, a model for Parkinson's disease (PD) or synucleinopathies, characterized by impaired dopaminergic signaling, locomotor deficits, and neurodegeneration. Larval motility (e.g., number of line crosses in a grid-based assay) is a surrogate marker for neurophysiological integrity, and decreased motility is a hallmark in PD models due to dopaminergic neuronal loss[17]. The dose-dependent increase in line crosses observed in Drosophila larvae expressing α-synuclein under the Elav-GAL4 driver following vinpocetine treatment suggests that vinpocetine alleviates synuclein-induced neurotoxicity. In the Elav-GAL4 > UAS-syn model, α-syn overexpression leads to synaptic dysfunction and impaired larval crawling. Vinpocetine's neuroprotective effect may restore synaptic signalling and mitochondrial function, leading to: improved neuronal excitability, increased locomotor activity. This correlates with a dose-dependent increase in the number of line crosses, as observed in the larval motility assay. This is most likely via neuroprotective, antioxidant, anti-inflammatory, and PDE1-inhibitory actions[13,14]. These findings support the potential of vinpocetine as a modulator of motor function in neurodegenerative conditions, warranting further translational research.

The climbing assay first described in the 1970s is by far the most commonly used assay to assess the motor function of Drosophila flies[22]. It is used to follow neurodegeneration in the Drosophila model and measure the age dependent deficit in motor activity that is typical of this case. Exposure of the flies to varying concentration of vinpocetine (5μM, 25μM and 50 μM) produced an ameliorating effect across all groups when compared to the pathogenic control. Age dependent motor deficit across all the drug supplemented feed were generally improved. Significant ameliorative effect of vinpocetine was first shown on day 21 by flies exposed to 25 μM concentration and on day 28. Elav-GAL4 > UAS-syn, drives expression of human alpha-synuclein throughout the entire nervous system. This model replicates generalized neurodegeneration, motor dysfunction, and shortened lifespan[17].

DDC-GAL4 > UAS-syn, targets alpha-synuclein expression specifically to dopaminergic and serotonergic neurons (expressing the Dopa decarboxylase gene). This model represents a more focused simulation of Parkinsonian pathology, particularly affecting the dopaminergic system, which regulates motor control and aging. The observation that vinpocetine increases lifespan in both Elav-GAL4 > UAS-syn and DDC-GAL4 > UAS-syn Drosophila models aligns with its neuroprotective, anti-inflammatory, and antioxidant properties. These models mimic features of PD and synucleinopathies, with the overexpression of human alpha-synuclein (UAS-syn) under pan-neuronal (Elav-GAL4) and dopaminergic-specific (DDC-GAL4) promoters, respectively.

A number of studies have confirmed reduction in the memory capabilities of PD patients; this has been shown to be as a result of the difficulty in selecting the optimal strategy for memorizing, leading to an inadequacy in memorization[23]. Studies have confirmed the memory enhancing effect of vinpocetine[13]. This has been shown to be possible via

the facilitation of long-term potentiation by vinpocetine[24], enhancing the cognitive performance in human population[25]. There was an improvement in the general memory retention abilities of the flies placed on the drug feed when placed in the fly t-maze, compared to the pathologic control.

Physiologic deterioration is a hallmark for aging and is seen across most organisms. Aging is measured by observing the life span of age-matched organisms and is dependent on the strict regulation of nutritional, environmental conditions and sometimes on the level of toxicity of agents exposed to. The measurement of the lifespan of DDC-GAL4<UAS-syn progeny cultured on normal feed and those cultured on drug supplemented feed with vinpocetine showed that there was an increase in the lifespan of flies placed on the 25µM concentration of vinpocetine when compared to the other concentrations (5µM and 50µM) and the control group.

These findings align with the pathophysiological framework of Parkinson's disease (PD), where alpha-synuclein aggregation causes dopaminergic neuronal dysfunction, synaptic impairment, and oxidative stress vulnerability[17,18,19,20]. Vinpocetine shows motor and lifespan benefits consistent with previous mammalian studies, and while memory enhancement trends were not statistically significant, they reflect earlier studies that documented cognitive improvements through vinpocetine's effects on synaptic plasticity and cerebral metabolism[13,24,25]. However, the observed reduction in fecundity and developmental viability is less frequently reported and suggests a need for further research, especially since vinpocetine is generally considered safe in mammalian reproductive contexts.

Utilizing a genetically tractable Drosophila model, this study provides a rapid, cost-effective platform to screen neuroprotective compounds and examine their effects on motor, cognitive, and lifespan parameters in a PD context. The combination of Elav-GAL4 and DDC-GAL4 drivers enhances translational relevance. Nonetheless, key questions remain about the molecular mechanisms of vinpocetine's neuroprotective effects. It's unclear if it directly prevents alpha-synuclein aggregation, influences synaptic vesicle dynamics, reduces oxidative stress, or affects neuroinflammation. Future studies should include biochemical analyses—such as measuring aggregated alpha-synuclein, reactive oxygen species, synaptic protein expression, and apoptosis markers—to clarify these mechanisms. The modest, non-significant memory improvements indicate that cognitive outcomes warrant further investigation with more sensitive assays or prolonged treatment.

The translational relevance is limited by its preclinical nature. While vinpocetine shows promise for neurological indications, regulatory scrutiny remains high due to inconsistent clinical efficacy and safety concerns in certain regions. This highlights the need for rigorous validation in mammalian models and clinical trials before recommendations for human use.

CONCLUSION

Findings from this study showed that vinpocetine demonstrates beneficial effects on larval and adult motor function, and lifespan extension in a Drosophila model of Parkinson's disease, suggesting neuroprotective potential.

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Declaration of conflict of interest

We do not have any conflict of interest to declare.

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