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ORIGINAL ARTICLE

Neuroprotective Role of Ranolazine in Parkinson Disease: *Drosophila Melanogaster* Model

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Abstract

Background/Aim: Among the neurological ailments, Parkinson disease (PD) might be one of the most mysterious and intricate ones. The brain produces less dopamine as PD worsens, making it harder for a person to control their movements. In literature the effect of ranolazine (Rn) in the CNS has been proposed for the management of pain and epilepsy. So, it was hypothesised that ranolazine could act in neuroprotection. Aim of this study was to explore ranolazine effect in Parkinson and neuronal cells.
Methods: *Drosophila melanogaster* has been employed. Five groups, each with 100 flies were: Group 1: control; Group 2: vehicle treated; Group 3: PD + ranolazine treated (1 mg/mL); Group 4: PD + ranolazine treated (2 mg/mL); Group-5: PD + ranolazine treated (4 mg/mL). PD was induced by paraquat. Part A involved the estimation of mortality index at 2-6 h. Estimation of climbing assay at 2 h, 4 h and 6 h and biochemical parameters such as oxidative stress were performed at 6 h.
Results: At different concentration of ranolazine percentage climbing of flies was found improved. Ranolazine at dose of 4 mg/mL showed significant reduction in percentage mortality at 24 h. Ranolazine at dose of 4 mg/mL showed a significant effect on total protein content level. Ranolazine 1 mg/mL showed significant effect and 2 mg/mL showed significant reduction in superoxide dismutase (SOD) level as compared to vehicle group. Ranolazine 1 mg/mL, 2 mg/mL and 4 mg/mL showed significant reduction in malondialdehyde (MDA) level as compared to vehicle group.
Conclusion: The present findings suggest that ranolazine has a good neuroprotective potential in the treatment of PD in flies. Further studies still required to be performed so as to explore its potential in clinical trials.

Key words: Ranolazine; *Drosophila melanogaster*; Leucine-rich repeat kinase 2; LRRK2; Neuroprotection; Parkinson disease.

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Introduction

Parkinson disease is one of the intricate neurological disorders affecting approximately 1 % of the total population with age of more than 60 years. Only about 5 % to 10 % of patients reported with genetic predisposition and especially in men.[1] In India, Bangalore in 2004, the prevalence rate of Parkinson reported to be 33 per 100,000.[2] The disease prevalence rate in Europe is 1.8 per 100 in peoples above 65 years of age.[3] The four main symptoms are rigidity in the limbs and trunk; tremor in the hands, arms, legs, jaw and face, postural instability, coordination and bradykinesia.[4-7]

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Parkinson disease is associated with elevated glutathione and malondialdehyde (MDA) levels, which can lead to neuronal death and dysfunction of essential brain nerve cells.[8, 9] The *Substantia nigra* is the name of the region of the brain where Parkinson disease mostly affects neurons.[10] Patients who experience dopamine loss are unable to direct or control their motions normally because the striatal nerve cells fire erratically. It is believed that oxidation damages tissues, including neurons. Antioxidants, which are substances that shield cells from harm caused by free radicals, normally regulate this type of damage.[11] Although depression might not be severe, medications used to treat other Parkinson disease symptoms may make it worse.[12-14]

The term "neuroprotection" describes the methods and techniques used to protect the central nervous system (CNS) against harm brought on by both acute (such as a stroke or trauma) and chronic (such as dementia, Parkinson, Alzheimer's, epilepsy, etc) neurodegenerative diseases. Ranolazine currently utilised in the treatment of chronic angina. Effect of ranolazine in the CNS has been proposed for the management of pain and epilepsy. As the hypothesised that ranolazine could act in neuroprotection, its effects in Parkinson and neuronal cells were studied.[15] The majority of scientific research has been done on mice, fruit flies and worms utilising different disease models. *Drosophila melanogaster* exhibits promising qualities as a model organism for investigating the mechanisms involved in Parkinson disease pathogenesis and aiding in the creation of treatment approaches.[16]

Molecular based *in silico* studies made it easy to screen and postulate the mechanism behind the pharmacological activity of novel compounds. Docking studies of ranolazine towards inhibition of leucine-rich repeat kinase 2 (LRRK2) were performed in current study and its neuroprotective role was evaluated in Parkinson disease *Drosophila* fly model.

Methods

Drug and chemicals

Ranolazine, as a gift sample was collected from *Belco Pharma*, Bahadurgarh. The entire chemical used for the study were of analytical grades.

In-silico studies

The Glide module in Schrodinger suite 2022-1 was used to illustrate the activity of the interaction between ranolazine and LRRK2 for the treatment of Parkinson disease. The PDB selected for inhibition was 8E80, obtained from protein data bank. The ranolazine and PDB ligand were docked into the catalytic domain of 8E80. The Dock score, Glide score and MMGBSA were recorded for studies.[17-20]

Drosophila melanogaster

Flies of both sexes Oregon R^+ strains of wild type included in the study were received from *Drosophila* stock centre situated in Shimla, Himachal Pradesh, India. The flies were raised on a defined food medium at a temperature of 25 °C with alternate light and dark cycle in glass bottles.

Induction of Parkinson disease using paraquat

The dose of paraquat was calculated. Food media was prepared and required concentration of paraquat mixed in food and then inserted in the bottle and kept it in hot air oven for solidification. After solidification the flies were transferred into the bottle and kept it for 24 h at 21 °C. The mortality rate of flies was counted; behaviour and biochemical parameters were estimated.[21, 22]
Step 1: Parkinsons disease induced flies 24 h later were taken in plastic vial and then mortality data was observed at 2 h, 4 h and 6 h.

Step 2: After the Parkinson-induced flies were placed in plastic vials, the locomotor activity was assessed using the slightly modified negative geotaxis assay method as previously reported by Bland et al. In order to measure the locomotor activity during vertical climbing, a single fly was kept in empty glass vials without medium for six months. The time it took the flies to climb up 8 cm of the vial wall was measured after they were lightly tapped to the bottom of the vial to elicit a negative geotactic climbing response. Every fly was examined four times, separated by one minute. The ascending mean for every experiment was computed. The climbing assay was run 2 h, 4 h and 6 h following the injury.

Step 3: After the Parkinson-induced flies were placed in plastic vials, they were anesthetised 6 h later and all of their legs and wings were severed from their bodies using a sharp knife. The flies were then homogenised in sodium phosphate

buffer (0.1M, pH 8.0) and centrifuged at 2500 g for ten minutes at 40 °C. The biochemical parameters were measured using the supernatant.

Experimental plan

The experimental study consisted of five groups, each with 100 flies: Group 1: control; Group 2: vehicle treated; Group 3: Parkinson disease + ranolazine treated (1 mg/mL); Group 4: Parkinson disease + ranolazine treated (2 mg/mL); Group 5: Parkinson disease + ranolazine treated (4 mg/mL). Part A involved the estimation of mortality index at 2-6 h. And estimation of climbing assay at 2 h, 4 h and 6 h and biochemical parameters such as oxidative stress were performed at 6 h.

Climbing assay

After injury maximum flies were evaluated for time to climb in 10 s, 30 s and 60 s in different groups as compared to control group. At different concentration of drug percentage climbing of flies was evaluated. At 6 h, in vehicle group percentage climbing of flies was evaluated as compared to 4 h after injury and 2 h.[23, 24]

Estimation of biochemical parameters

Total protein content[25, 26]

The Lowry method was used was used for estimation of total proteins. The protein concentration was expressed in mg/mL. The concentration of protein in test sample was determined by using the formula:

$$\text{Protein concentration in test sample} = \frac{\text{Absorbance of test sample}}{\text{Absorbance of standard solution}} \times 2$$

Superoxide dismutase (SOD) estimation[27]

SOD activity was measured using Kono et al's 1978 methodology. Units/mg protein was used to express the results. An enzyme is defined as the amount of enzyme that inhibits a reaction 50 % of the time.

$$\%\ \text{inhibition} = \frac{(\text{Absorbance of control reaction} - \text{Absorbance of test reaction})}{(\text{Absorbance of control reaction})} \times 100$$

$$\text{SOD} = \frac{\%\ \text{inhibition}}{(\text{Units/min/mg of protein})\ 50 \times \text{vol. of sample used} \times \text{incubation time} \times \text{protein (mg/mL)}}$$

Catalase estimation[28]

By heating dichromate in acetic acid in the presence of hydrogen peroxide, this process reduces dichromate to chromic acetate while producing per chromic acid as an unstable intermediate. The catalase concentration was given in µmol of catalase/mg of protein.

Malondialdehyde (MDA)[29]

As a gauge of lipid peroxidation, the MDA content was measured using thiobarbituric acid-reactive compounds, a technique that was refined by Gupta et al and first reported by Okhawa et al. Tetra -methoxy propane was used to produce a standard curve that was used to calculate the MDA concentration in (nmol/mg) protein.

Results

Docking result

Docking results were interpreted by using PDB: 8E80 and showed the interaction of drug with the receptor. Ranolazine showed good docking score with comparison with PDB ligands shown in Table 1. Inhibition of LRRK2 kinase activity is a chemically tractable and potentially disease-modifying mechanism to treat Parkinson disease can be easily determined by looking at the amino acids in the binding site.

In the binding pattern of ranolazine with PDB id 8E80 wrapped by HIE 134, ASN 135, LEU 137, VAL 23, ASP 148, ALA 87, SER 88, GLY 90, SER 91, ASP 94, GLN 13, THR 14, LEU 15, GLY 16, GLU 16 of the LRRK2 inhibitors. LEU 5 and ALA 87 formed hydrogen bond with the electronegative atom shown in Figure 1.

Table 1: Docking results

PDB	Ligand	Docking score	Glide score	MMGBSA_dG_Bind
8E80	8E80 ligand	-9.25757	-9.25757	-83.8824
	Ranolazine	-7.1269	-7.1269	-75.3197

After injury maximum flies were taken more time to climb so percentage climbing in 60 s was higher as in 30 s and in 10 s. In vehicle group minimum flies was climb in 10 s compared to control group. At 2 h RA 1 (5.35 ± 3), ($p < 0.001$) and RA 2 mg/mL (24.9 ± 1.5), ($p < 0.001$) and 4 mg/mL concentrations were found to be significantly increasing % climbing in

10 s as compared to vehicle group. Same results were observed in 30 s climbing. At 6 h RA 1 mg/mL (32.34 ± 2.90), ($p < 0.01$) and RA 2 mg/mL (27.48 ± 3.76), ($p < 0.01$) and 4 mg/ml concentrations were found to be significantly increasing % climbing in 10 s and same result observed in 30 s at dose RA 1 (41.72 ± 3.30) ($p < 0.05$) and RA 2 (42.05 ± 2.40), ($p < 0.05$) respectively as compared to vehicle group (Figure 2).

Effect of ranolazine on percentage mortality

After injury, the mortality of flies was started at 2-6 h. In vehicle group, 49.67 % mortality was after Parkinson disease. The percentage mortality reduces at with respect to different drug dose concentrations. Maximum mortality was observed at 24 h after disease which was 49.67 % in vehicle

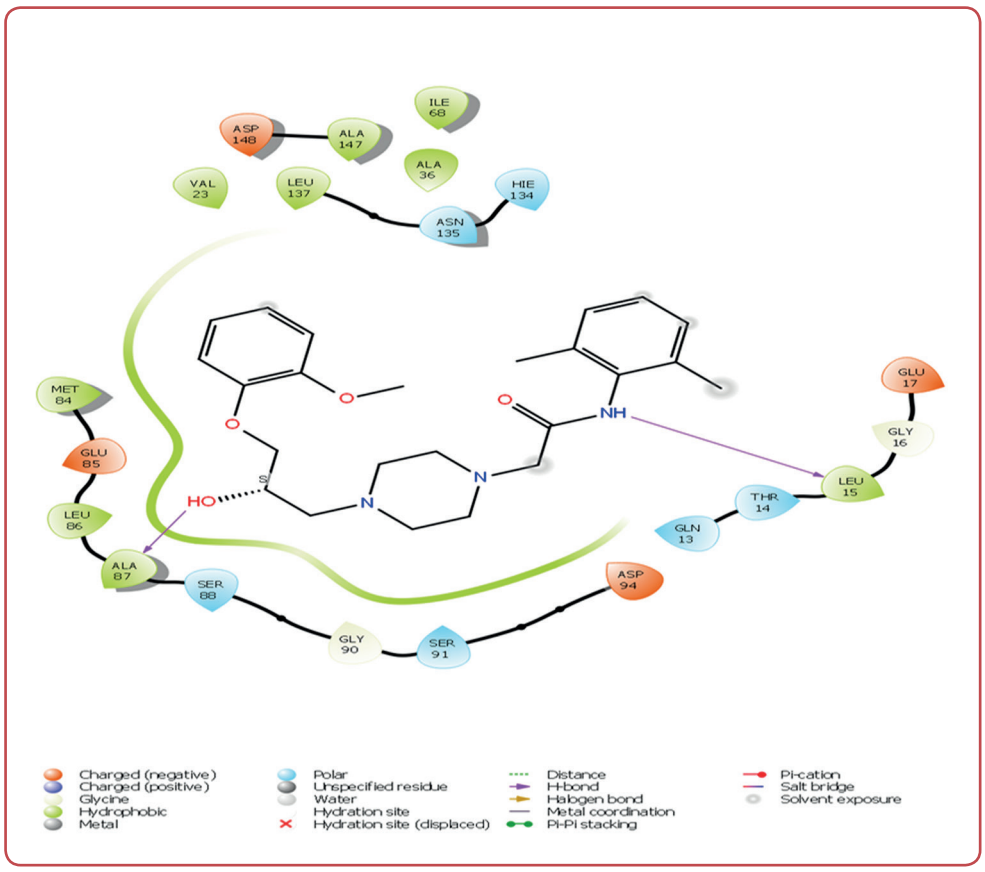

Figure 1: Ranolazine docking results with 8E80 PDB

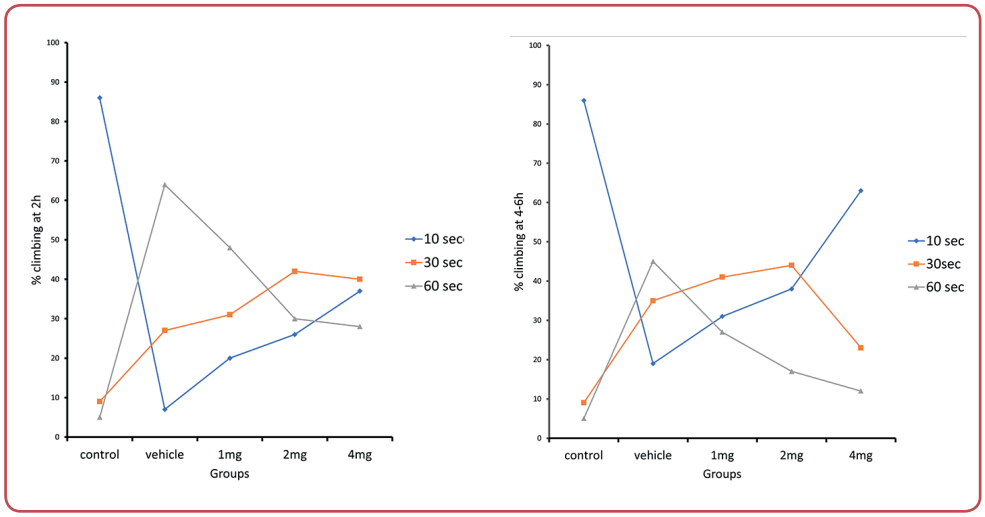

Figure 2: Effect of ranolazine on climbing response of flies in 10, 30, and 60 s at 2 h and 4-6 h after Parkinson's disease. At 2 h, the F value was found to be (4, 10) = 0.004389. At 4-6 h, the F value was found to be (3, 8) = 0.0002910.

group. Ranolazine 4 mg/mL (30.59 ± 0.882), ($p < 0.001$) was shown significant reduction in percentage mortality at 24 h (Figure 3).

In Parkinson's disease, total protein content level decreases. In present study, it was found to be protein level in vehicle group (3.477 ± 0.2896) was significantly decreased ($p < 0.001$) as compared to control group (10.52 ± 0.5759). Effect of ranolazine 1 mg/mL was (6.096 ± 0.1017), ($p < 0.01$), Ranolazine 2 mg/mL (7.293 ± 0.360), ($p < 0.001$) and ranolazine 4 mg/mL (8.996 ± 0.061), ($p < 0.001$) showed a significant effect on total protein content level (Figure 4).

Effect of ranolazine on activity of SOD

SOD is a family of metalloproteins that catalyse the dismutation of 2 molecules of super oxides (O_2) to form hydrogen peroxide. After injury, SOD level showed extremely significant ($p < 0.0001$)

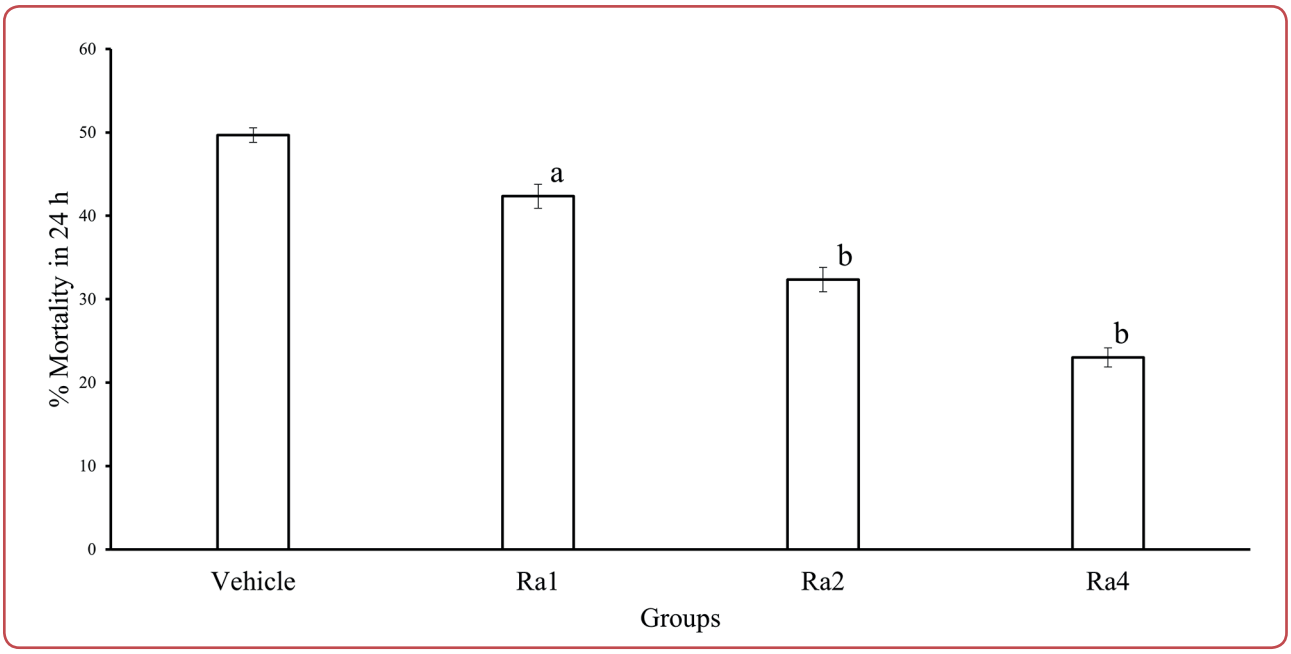

Figure 3: Percentage of flies' mortality at 24 h

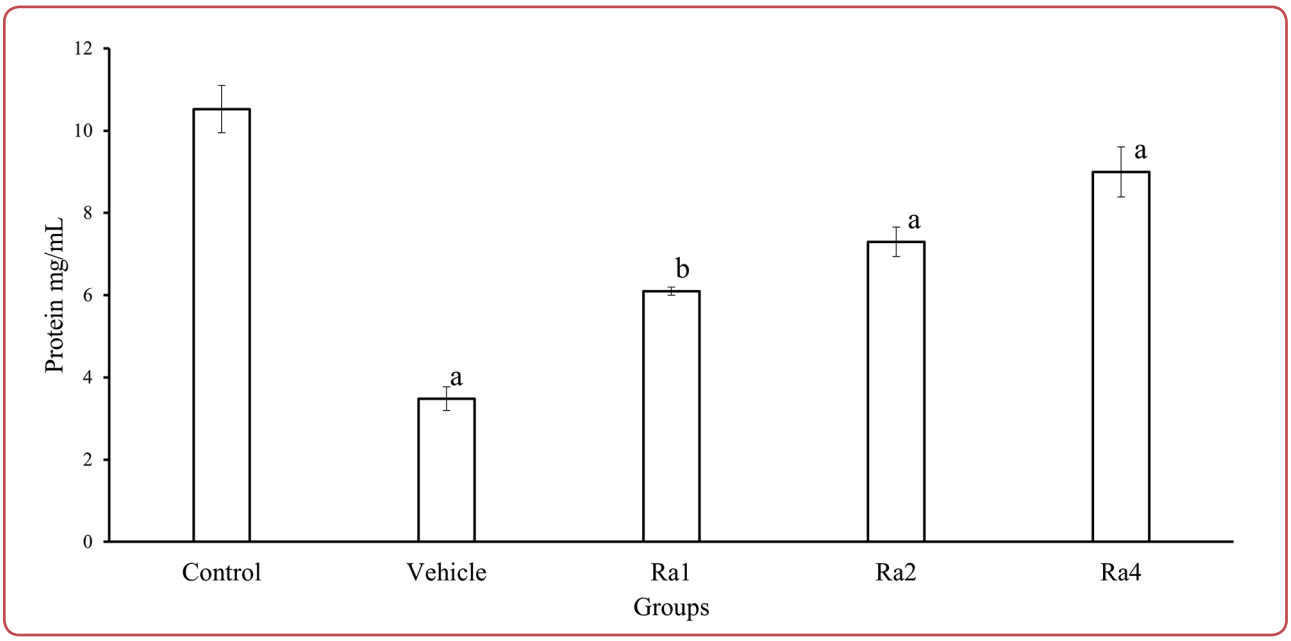

Figure 4: Effect of ranolazine on total protein content in flies' homogenate

The F value was 65.501.

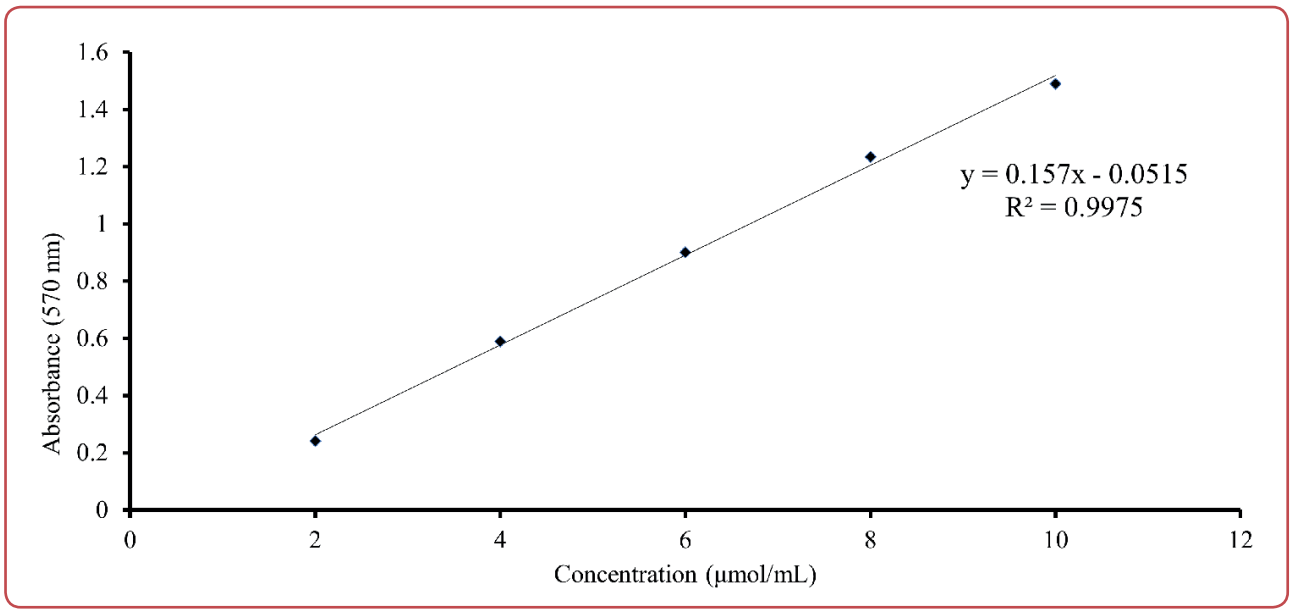

Figure 5: Effect of ranolazine on superoxide dismutase (SOD) level in flies' homogenate

The F-value was found to be F (4, 10) = 87.294.

decreased in vehicle group (11.026 ± 0.352 units/min/mg protein) as compared to control group (17.373 ± 0.336). Ranolazine 1 mg/mL (13.203 ± 0.132 units/min/mg protein), ($p < 0.01$) showed significant effect and 2 mg/mL (14.68 ± 0.277 units/min/mg protein), ($p < 0.001$) was shown significant reduction compared to vehicle group and RA 4 mg/mL (15.823 ± 0.096 units/min/mg of protein), ($p < 0.001$). Significant effect was observed between ranolazine treated groups (Figure 5).

Effect of ranolazine on level of catalase

Standard curve for catalase was plotted using external standard H_2O_2 (2-10 µmol/mL). The concentration of catalase was determined by linear standard curve (y = 0.157x - 0.051) (Figure 6). The enzyme catalase is responsible for breaking down hydrogen peroxides into water and oxygen. This enzyme plays a crucial role in shielding the cell from reactive oxygen species-induced oxidative damage. This antioxidant enzyme is depleted in traumatic brain damage. In the vehicle group, there was a significant ($p < 0.001$) drop in the catalase level to (9 ± 0.199 µmol/mg protein) compared to control group (15.343 ± 0.359). Ranolazine 1mg/mL (10.603 ± 0.217 µmol/mg protein), ($p < 0.05$) and 2 mg/mL (12.193 ± 0.327 µmol/mg protein) ($p < 0.001$) and ranolazine 4 mg/mL (13.55 ± 0.27 µmol/mg of protein), ($p < 0.001$) was shown significant increase in catalase level compared to vehicle group (9 ± 0.199 µmol/mg protein) (Figure 7).

Effect of ranolazine on level of MDA

Standard curve for MDA was plotted using external standard ie, tetramethoxy-propane (2-10 nmol/mL). The concentration of MDA was determined by linear standard curve (y = 0.019x + 0.058) (Figure 8). After Parkinson disease, MDA level was found to be increased in vehicle group (1.717 ± 0.029 nmol/mg protein) as compared to control group (1.146 ± 0.006). Changes in MDA level in flies and its modulation by ranolazine was recorded. Ranolazine 1 mg/mL (1.560 ± 0.0298 nmol/mg protein) ($p < 0.05$) and 2 mg/mL (1.295 ± 0.0496 nmol/mg protein) ($p < 0.001$) and 4 mg/mL (1.238 ± 0.032), ($p < 0.001$) showed significant reduction compared to vehicle group while when compared to each other significant effect was observed between ranolazine treated group (Figure 9).

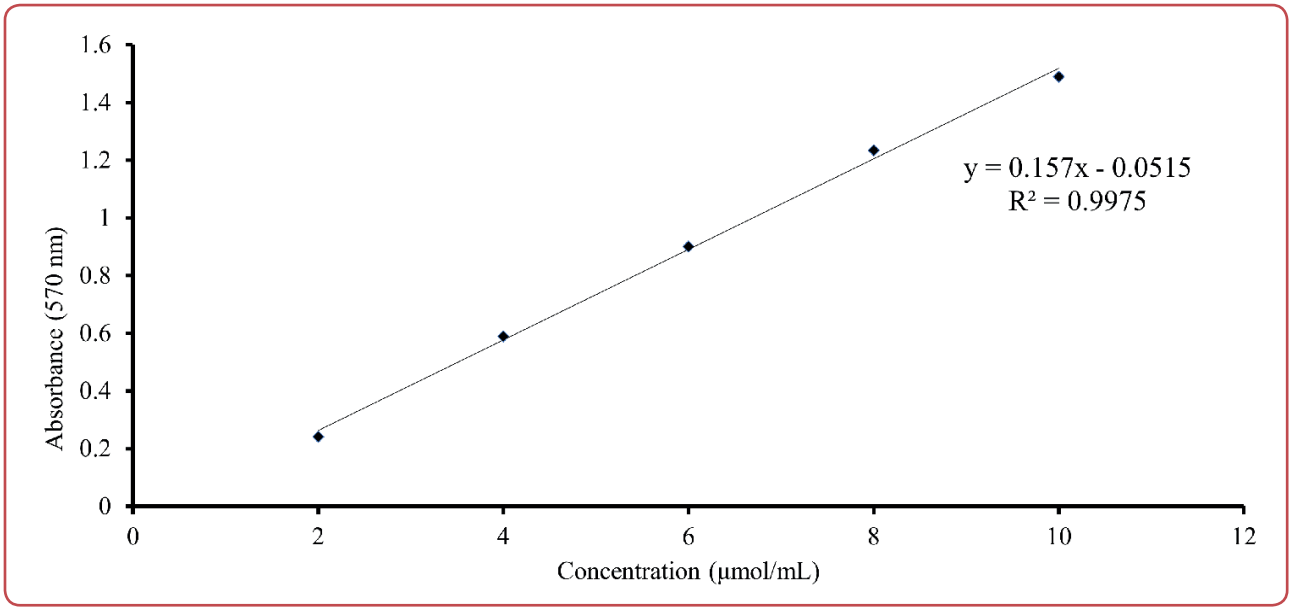

Figure 6: Standard plot of catalase

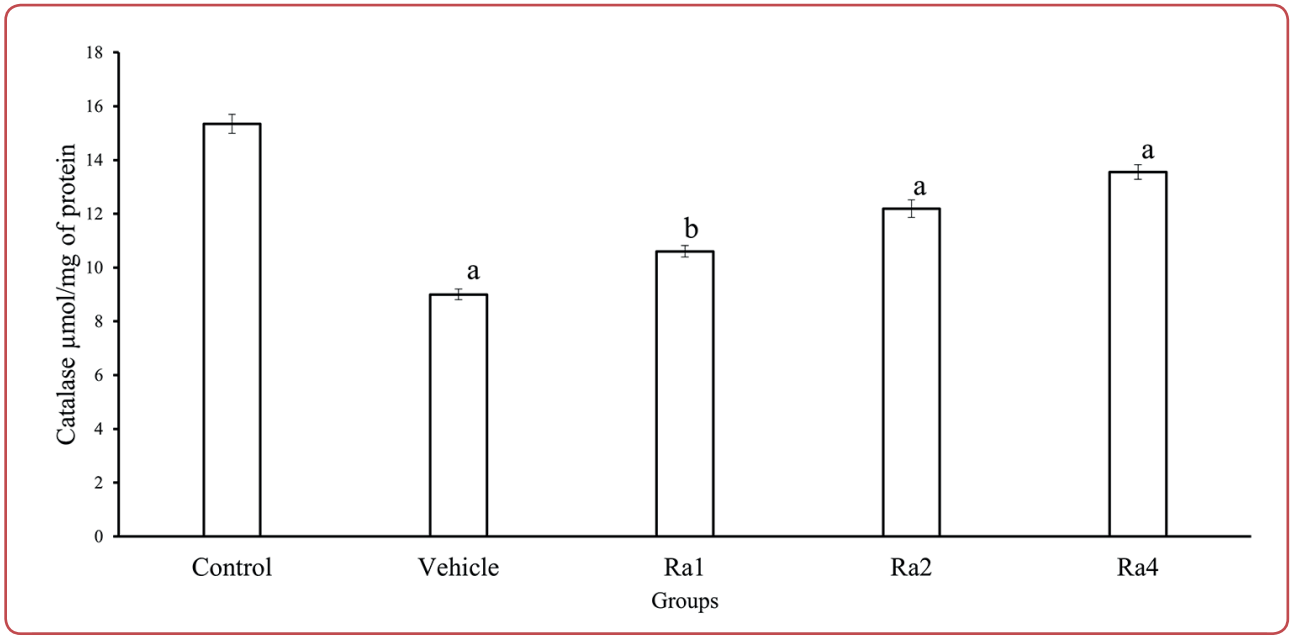

Figure 7: Effect of ranolazine on level of catalase

The F-value was found to be F (4, 10) = 76.825.

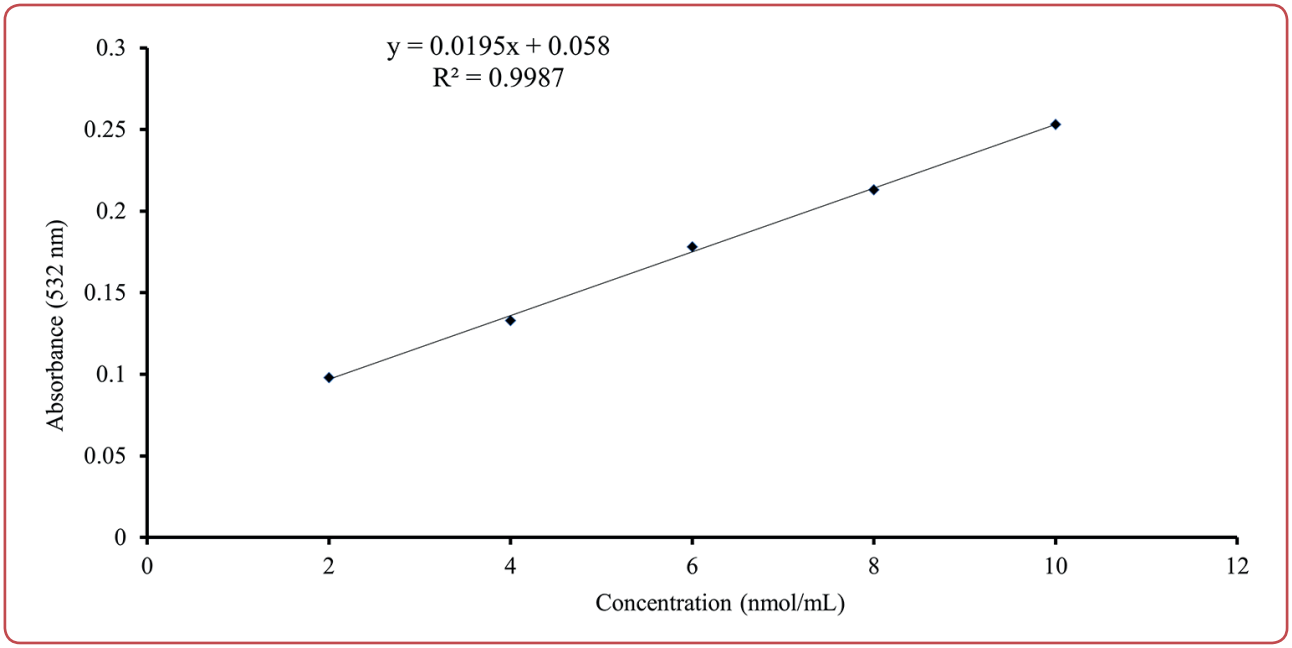

Figure 8: Standard plot of malondialdehyde (MDA)

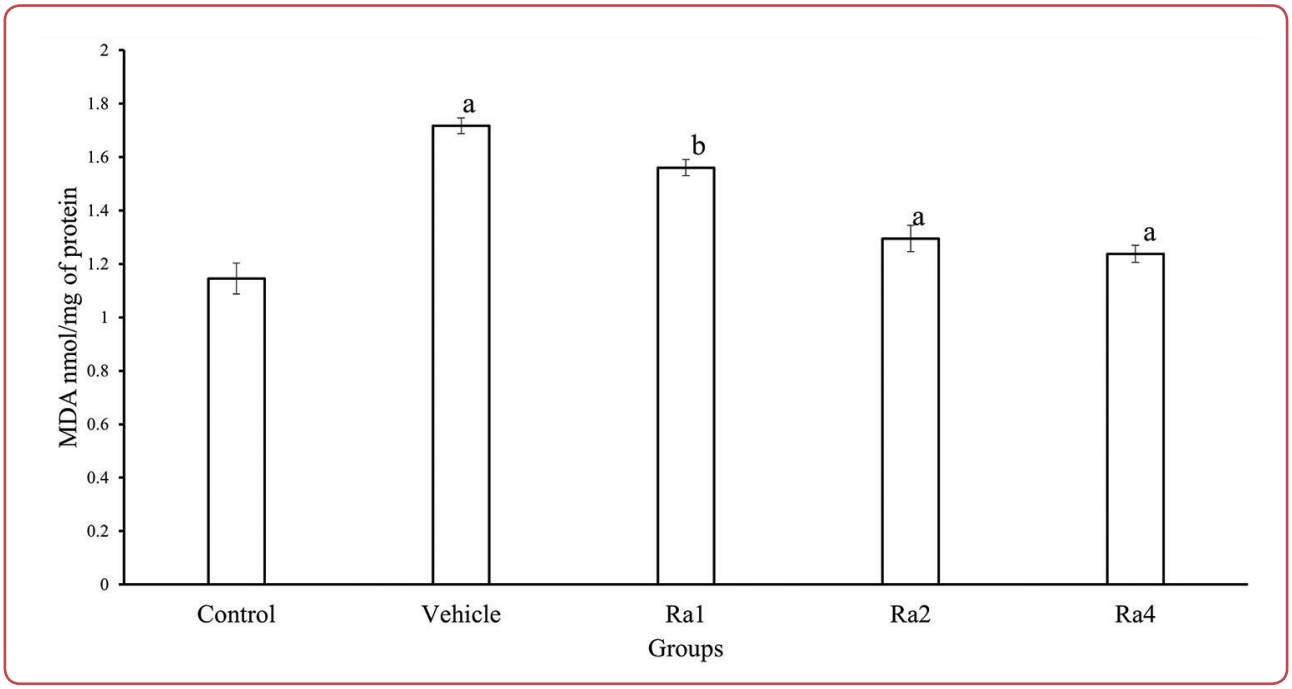

Figure 9: Effect of ranolazine on malondialdehyde (MDA) level in flies' homogenate

The F-value was found to be F (4, 10) = 53.871.

Discussion

Currently in the market, certain therapeutic medications, such as antidepressants, anticonvulsants and antipsychotics, provide symptomatic relief but are unable to stop the progression of neuronal injuries. Therefore, there is a strong need to create novel treatment strategies that stop neuronal degradation especially after trauma and other secondary damages.

The drug ranolazine currently utilised in the treatment of chronic angina. Effect of ranolazine in the CNS has been proposed for the management of pain and epilepsy. As the hypothesised that ranolazine could act in neuroprotection, its effects in Parkinson and neuronal cells were studied. Ranolazine drug was evaluated for their molecular docking and free binding energy of the protein-ligand interactions. The possible binding pattern uncovered that ranolazine within catalytic cavity of enzyme tightly by pi–pi stacking, hydrophobic interaction and hydrogen bonding.

At different concentration of drug percentage climbing of flies was improved. Injured flies take more time to climb while at different drug concentration more flies climb in 10 s and in 30 s and the number of flies' climbs in 60 s got decreases. At 6 h, in vehicle group percentage climbing of flies were improved compared to 4 h after injury but percentage climbing decreased as compared to control group.

After injury, the mortality of flies was started at 2-6 h. In vehicle group, 49.67 % mortality was after Parkinson disease. The percentage mortality reduces at with respect to different drug dose concentrations. Maximum mortality was observed at 24 h after disease which was 49.67 % in vehicle group.

Ranolazine showed its antioxidant potential by decreasing the level of MDA and increasing the level of SOD, catalase. MDA is a naturally occurring product of lipid peroxidation, which is a free radical event. Ranolazine also improved the level of total protein content. In the behavioural paradigms, ranolazine showed effective results by reducing the mortality index at 2 h, 4 h and 6 h after injury and at different concentration of drug percentage climbing of flies was improved. Thus ranolazine aced as a free radical scavenging action by decreasing or increasing the level of auto destructive enzymes via reducing the overloading of sodium and calcium inside in the cells through voltage gated sodium and calcium channel, inhibited nitric oxide production by nitric oxide synthase inhibition and inhibited the release of inflammatory mediators such as TNF-α. Dock score, Glide score and MMGBSA result can be interpreted that ranolazine have a good binding affinity towards LRRK2 inhibitors and inhibition of leucine-rich repeat kinase 2 (LRRK2) activities is a chemically tractable and potentially disease-modifying mechanism to treat Parkinson disease.

Some other studies also postulate the neuroprotective potential of some already reported drugs. Kumar and Singh in 2022 also studied the pharmacological potential of zonisamide and *Nigella sativa* per se and combination in high-impact trauma device induced traumatic brain injury in *Drosophila melanogaster*. They evaluated the pharmacological potential of zonisamide and *Nigella sativa* per se and in combination, using high-impact trauma device (HIT)-induced TBI model in *Drosophila melanogaster*. Their results proved the combined potential of zonisamide and *Nigella sativa* in neuroprotection fruit fly.[30, 31]

The results of current study concluded the neuroprotective potential of ranolazine in the treatment of Parkinson disease in fruit fly. These results are helpful for the researchers working in area of neuroprotection for establishing appropriate studies of already utilised drugs. The concept of drug repurposing also less time consuming and required fewer studies. Hence, further studies are still needed to be performed for exploration of ranolazine potential in neuroprotection *via* clinical trials.

Conclusion

Parkinson disease is a degenerative disorder mainly affecting the motor system. In the present study the ranolazine drug was repurposed for treatment of Parkinson as it has good pharmacological potential as anti-ischaemic and anti-inflammatory potential. Docking studies were carried out on LRRK2 inhibitor (PDB: 8E80) responsible to treat Parkinson disease. Dock score, Glide score and MMGBSA result showed binding potential of drug towards studied receptor. *In vivo* studies confirmed that ranolazine has potential in Parkinson disease protection against the oxidative stress, possibly by reducing the lipid peroxidation and increasing the level of SOD and catalase. The present findings suggest that ranolazine has a good neuroprotective potential in the treatment of Parkinson disease in flies. Further studies are needed to be performed so as to explore its potential in clinical trials.

Ethics

The use of *Drosophila melanogaster* is free of ethical concerns because it is not a vertebrate animal model system and it is in accordance with The Institute of Laboratory Animal Resources Guide for the Care and Use of Laboratory Animals which describes the minimum ethical requirements for animal research.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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