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# Investigation on the efficacy of *Barleria cristata* leaves in preventing and treating memory loss in chronic stress induced rats

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**Abstract**

Alzheimer's disease (AD) is responsible for approximately 60-70% of memory loss cases. Chronic amnesia is a severe form of memory impairment that is characterized by difficulties with language, memory, and behaviour. Aging is the primary risk factor for Alzheimer's disease (AD). The incidence rate exhibits age-dependent variation. As soon as individuals attain the age of 65, the incidence rate doubles. The disease's prevalence is also differentiated by gender. The purpose of this study was to evaluate the influence of a methanolic extract of *Barleria cristata* leaves on memory and learning deficits in animal models. *Barleria cristata* is a shrub that belongs to the Acantharean flower family. The plant extract is employed for its hypoglycaemic and antispasmodic properties. Anaemia and edema are managed through the utilization of root extract. Additionally, it serves as an advantageous treatment for pneumonia, rheumatism, and snake stings. Employed to alleviate otitis media. *Barleria cristata* were collected, authenticated, desiccated, and isolated using methanol extraction. The cognitive abilities associated with learning and memory were examined in the context of the investigation of the impact of methanolic extract from *Barleria cristata* leaves at concentrations of 200 and 400 mg/kg, administered orally once daily for 84 days. For the purpose of comparison, we implemented the Morris Water Maze Apparatus and the Modified Elevated Plus Maze Apparatus. Learning and memory were impaired as a consequence of prolonged obsessive-compulsive stress. In the Modified Elevated Plus Maze Apparatus, rats that received treatment demonstrated a decreased number of entries and a shortened duration of time spent in the closed arm, while they spent a greater amount of time and entered in the open arm. In the Morris Water Maze Apparatus, rats that were treated demonstrated an extension of their stay duration and a reduction in their escape latency. The methanolic extract of *Barleria cristata* leaves exhibited remarkable mild to moderate effects on learning and memory at both low (200 mg/kg) and high (400 mg/kg) concentrations, as demonstrated by the present study. Consequently, *Barleria cristata* has significant potential as an herbal alternative in the field of alternative medicine.

**Keywords**

*Barleria cristata*, Alzheimer's Disease, Elevated Plus Maze Apparatus, Morris Water Maze Apparatus, Learning and Memory Improvement Activity.

## Introduction

Alzheimer's disease (AD) is a persistent neurological disorder that is commonly referred to as cognitive impairment. Memory function decline is the result of Alzheimer's disease in 60-70% of patients. Dr. Alois Alzheimer, a German neuropathologist and physiotherapist, is credited with the initial description of memory loss. Alzheimer's disease (AD) is a form of memory loss that is swiftly progressive and is distinguished by memory impairments (1,2). The development of neurofibrillary tangles (NFTs) and the degeneration of neuronal cells are the hallmark features of Alzheimer's disease, which is characterized by the accumulation of amyloid peptides (A-peptides) and tau protein. The accumulation of these aberrant proteins and the subsequent neuronal injury are the result of impaired clearance. Cholinergic insufficiency in the brain also affects glutamate and neuropeptide levels. Amyloid beta (Aβ), a peptide composed of 39-43 amino acid residues, is present in the healthy human brain. The fragmentation of a larger amyloid precursor protein is the cause of the presence of Aβ fibrils. The degeneration of synapses, impaired synaptic function, inflammatory reactions, and nerve cell mortality are all strongly associated with the accumulation of amyloid fibrils as amyloid plaques in the extracellular space of brain cells in Alzheimer's disease (AD). In contrast, tau protein is highly concentrated in specific spatial configurations within the central nervous system (CNS) and plays a critical role in the stabilization of microtubules. The tau protein undergoes substantial hyperphosphorylation in the pathogenesis of Alzheimer's disease (AD), which leads to its aggregation and the formation of intracellular neurofibrillary tangles (NFTs). The disordering of microtubules, the collapse of dendritic spines, and the degeneration of axons are the consequences of the intracellular production of neurofibrillary tangles (NFTs). Amnesia, anxiety, mood fluctuations, financial management difficulties, and impaired decision-making are among the partial manifestations of Alzheimer's disease. During the advanced stages of Alzheimer's disease, patients experience a decreased ability to respond to their environment, disorientation, restlessness, and difficulties in modulating physical movements, as well as in verbal and cognitive functions. (3,4). Advanced age is the primary risk factor for Alzheimer's disease. The incidence rates are contingent upon age. As soon as individuals attain the age of 65, the incidence rate doubles. Gender also influences the disease incidence rate. Women are at a higher risk of developing the condition, particularly after the age of 85. The Hispanic population is less susceptible to Alzheimer's disease than the non-Hispanic white population; however, the non-

Hispanic white population is at a higher risk of mortality from Alzheimer's disease than the non-Hispanic black population (5,6). A shrub belonging to the Acanthaceae family is known as *Barleria cristata*. This plant's root extract is employed as a hypoglycaemic and antispasmodic medication. Root extract is employed to alleviate anaemia. In the event of swelling, the roots and foliage are administered. Additionally, it is highly effective in the treatment of pneumonia, rheumatism, and snake stings. Used in the treatment of otitis media and ocular disorders. In order to alleviate congestion, an infusion is administered. According to reports, it has a diuretic, tonic, and blood purifying effect (7,8). Flavones, luteolin, 7-methoxyluteolin, phenolic acids, β-sitosterol, quercetin, apigenin, naringenin, and malvidin are present in the foliage of *Barleria cristata*. Flavonoids are extensively documented in the literature to predominantly contribute to the improvement of memory and learning. Flavonoids are distinguished into six categories according to their chemical composition: flavanones, anthocyanidins, flavones, flavanols, Iso-flavonoids, and flavanols. These therapies are effective in slowing the progression of neurodegenerative diseases, such as Alzheimer's disease, by strategically targeting multiple targets. The antioxidant and anti-inflammatory properties of flavonoids are currently under investigation as a result of their influential role in the development of Alzheimer's disease (AD). Flavonoids are promising candidates for the prevention of neurodegenerative diseases due to their capacity to cross the blood-brain barrier (BBB). The anti-Alzheimer's disease (AD) properties of specific flavonoids, such as apigenin, catechins, rutin, fisetin, quercetin, kaempferol, and myricetin, have been previously documented (9). The purpose of this study is to investigate the effect of administering a methanolic extract of *Barleria cristata* leaves on the improvement of learning and memory in Alzheimer's disease using a rat model.

**Methods**

leave samples of *Barleria cristata*, a member of the Acanthaceae family, were collected from the Amravati district in Maharashtra, India. The botanical specimen was authentically identified and verified. The foliage was pulverized to produce a coarse powder after being desiccated. This substance was stored in a container that was hermetically sealed and was used for extraction. Methanol and water were the solvents used to extract *Barleria cristata* leaves. A 7:3 ratio of water to methanol was implemented. The extraction procedure necessitated the use of a glass bottle. Methanol and water were combined with dried leaves of *Barleria cristata* in a glass vessel

for extraction processing. During the maceration procedure, powdered leaves were agitated at predetermined intervals. It was purified through concentration and filtration. Subsequently, it was dried through evaporation (10). The presence of numerous phytoconstituents was ascertained through the quantification of the methanolic extract (11).

**Animals**

This investigation used healthy female Sprague-dawley rats that were 8 weeks old and weighed between 150 and 250 grams. The animals were housed in polypropylene enclosures with a wire mesh top and husk bedding. They were maintained in controlled conditions of temperature (25±2ºC), humidity (60±5%), and light (12 hours of day and 12 hours of twilight). They were provided with unrestricted access to water and were exclusively fed a standard pellet diet. During daylight hours (8.00-16.00 hrs), experimental procedures were implemented. In compliance with the established guidelines and standards of CPCSEA and IAEC, the rodents were housed and cared. The Institutional Animal Ethics Committee (IAEC) approved all animal study protocols required for the study.

**Experimental design**

For this study animals were divided into five groups

**Group I** (Vehicle control group)-Rats received only saline solution.

**Group II** (Negative control group)-Rats were subjected to restraint stress using saline bottle for 84 days.

**Group III** (Low dose group)- Rats were subjected to restraint stress and treated with 200mg/kg methanolic extract of *Barleria cristata* orally for 84 days.

**Group IV** (High dose group)-Rats were subjected to restraint stress and treated with 400mg/kg methanolic extract of *Barleria cristata* orally for 84 days.

**Group V** (Standard group) Rats were subjected to restraint stress and treated with 5mg/kg Donepezil for 84 days.

**Induction of memory impairment state**

All groups were subjected to restraint stress for a period of 84 days, with the exception of the normal control group, which was maintained in a normal state within the animal house. A saline container was administered to female Sprague-Dawley rats in order to specifically induce memory impairment. Rats were securely enclosed in a saline container for six hours each day for a period of 84 days. Within a securely sealed saline bottle, the animal model of depression is subjected to persistent stress, which includes food and water deprivation (12).

**Drugs and dosing**

The standard medication was donepezil at a dosage of 5 mg/kg. Distilled water was employed to dilute the compound donepezil. In order to attain two distinct concentrations (200 and 400 mg/kg), liquid extracts of *Barleria cristata* leaves were dissolved in distilled water. On the day of the investigation, each solution was generated from fresh and subsequently delivered orally. The dosage of *Barleria cristata* leaf extract was determined by the body weight of the rodents in each group. The low dose extract group was administered at a rate of 200mg/kg, while the high dose group received 400mg/kg of extract. Utilizing a particular model, an examination of the enhancement of memory and learning abilities after 84 days.

**Modified Elevated plus maze apparatus**

The Modified Elevated Plus Maze Apparatus (MEPMA) was employed to assess the learning and memory improvement activity. The rat was positioned in one of the unobstructed arms of the maze, typically facing the opposing direction of the closed arm, and the experiment was conducted. The animal is granted the opportunity to investigate the instrument upon its discharge. The transfer latency is a further parameter that is employed to evaluate memory. This parameter measures the time it takes for the rat to walk from the open arm to one of the closed arms with all four legs, measured in seconds (13).

**Morris Water Maze Apparatus**

The Morris water maze apparatus (MWMA) is a test that evaluates the learning and memory capabilities of rodents as they navigate from their initial starting points around the exterior of an

open swimming area to locate a submerged Escape Platform. The determination of reference memory is based on the preference for the platform region in the absence of the platform, and the assessment of learning and memory is conducted through repeated trials. (14)

## Results

**Table 1 Effect of methanolic extract of *Barleria cristata* on transfer latency (TL) of rats in EPM apparatus.**

| SN | Groups | Transfer latency in seconds on Day 0 | Transfer latency in seconds on Day 28 | Transfer latency in seconds on Day 84 |
|---|---|---|---|---|
| 1 | Normal Control | 21.61 ± 2.22 | 21.35± 2.26 | 21.32± 2.15 |
| 2 | Negative Control | 23.36± 2.89$^{ns}$ | 36.1± 2.37$^{@}$ | 48.47± 1.44$^{@}$ |

| | | | | |
|---|---|---|---|---|
| 3 | MBC (200 mg/kg) | 23.1± 1.79$^{ns}$ | 20.67± 1.37$^{**}$ | 36.27± 2.27$^{**}$ |
| 4 | MBC (400 mg/kg) | 21.67± 1.37$^{ns}$ | 16.67± 2.74$^{**}$ | 31.12± 1.95$^{**}$ |
| 5 | Donepezil (5 mg/kg) | 22.67 ± 1.87$^{ns}$ | 12.67± 1.87$^{**}$ | 27.93± 1.45$^{**}$ |

Results are expressed as mean ± SD, (n=6), @$p$<0.01 Compared with corresponding normal control group, **$p$<0.01 Compared with negative control group, *$p$<0.05 compared with negative control group

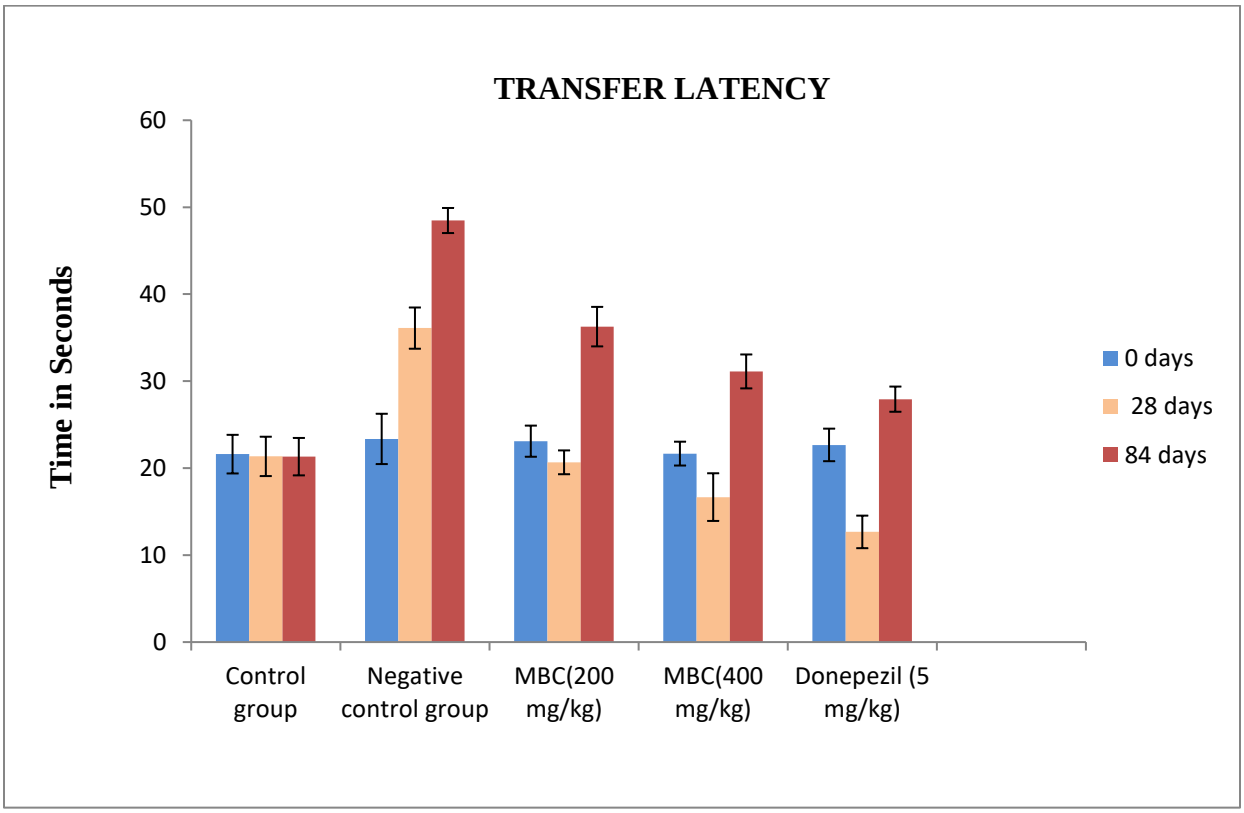


**Figure1 Effect of *Barleria cristata* on transfer latency of rats in EPM apparatus**

**Table 2 Effect of methanolic extract of *Barleria cristata* on Escape latency and retention time in Morris water maze in memory impairment rats.**

| SN | Groups | Escape latency in seconds on Day 0 | Escape latency in seconds on Day 28 | Escape latency in seconds on Day 84 |
|---|---|---|---|---|
| 1 | Normal Control | 31.31± 2.60 | 30.31± 3.62 | 29.43± 2.7 |
| 2 | Negative Control | 31.64± 0.52$^{ns}$ | 69.67± 2.39$^{@}$ | 78.92± 2.39$^{@}$ |

| | | | | |
|---|---|---|---|---|
| 3 | MBC (200 mg/kg) | 31.13± 2.70$^{ns}$ | 35.98± 1.79$^{**}$ | 54.10±1.29$^{**}$ |
| 4 | MBC(400 mg/kg) | 30.94± 1.05$^{ns}$ | 32.40± 1.43$^{**}$ | 48.23 ± 2.25$^{**}$ |

| **Sr. No.** | **Groups** | **Retention time in seconds on Day 0** | **Retention time in seconds on Day 21** | **Retention time in seconds on Day 84** |
|---|---|---|---|---|
| 5 | Donepezil (5 mg/kg) | 31.21±2.29$^{ns}$ | 30.64± 2.26$^{**}$ | 32.31± 2.26$^{**}$ |

Results are expressed as mean ± SD, (n=6), @$p$<0.01 Compared with corresponding normal control group, **$p$<0.01 Compared with negative control group, *$p$<0.05 compared with negative control group

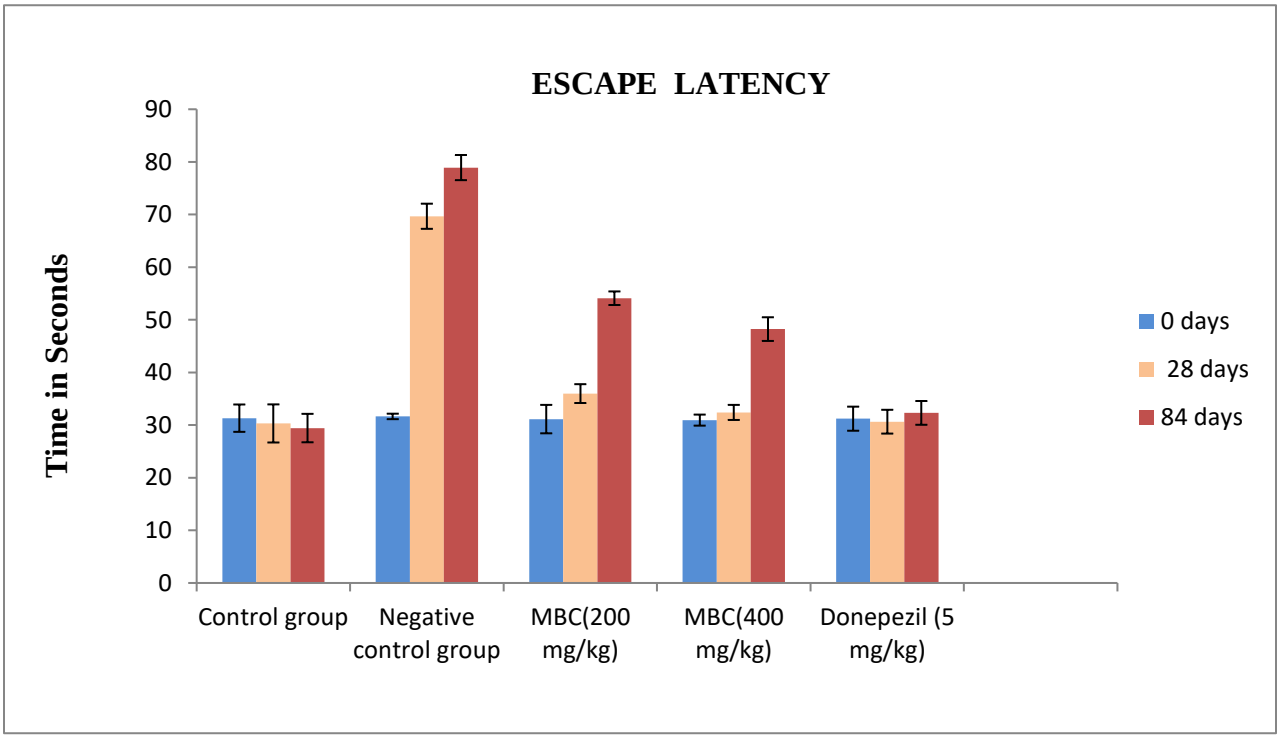


**Figure 2 Effect of *Barleria cristata* on escape latency of rats in MWM apparatus**

**Table 3 Effect of methanolic extract of *Barleria cristata* on retention time in Morris water maze in memory impairment rats**.

| | | | | |
|---|---|---|---|---|
| 1 | Normal Control | 40.31± 0.53 | 44.62± 2.43 | 43.43± 0.61 |
| 2 | Negative Control | 37.80± 1.79$^{ns}$ | 30.64± 0.98$^{@}$ | 27.92± 0.49$^{@}$ |
| 3 | MBC (200 mg/kg) | 40.88±2.23$^{ns}$ | 38.31± 1.31$^{**}$ | 51.64±0.72$^{**}$ |
| 4 | MBC (400 mg/kg) | 42.63± 1.27$^{ns}$ | 39.64± 1.87$^{**}$ | 58.23 ± 0.79$^{**}$ |
| 7 | Donepezil (5 mg/kg) | 41.00± 0.90$^{ns}$ | 44.43± 1.87$^{**}$ | 66.91± 0.47$^{**}$ |

Results are expressed as mean ± SD, (n=6), @$p$<0.01 Compared with corresponding normal control group, **$p$<0.01 Compared with negative control group, *$p$<0.05 compared with negative control group

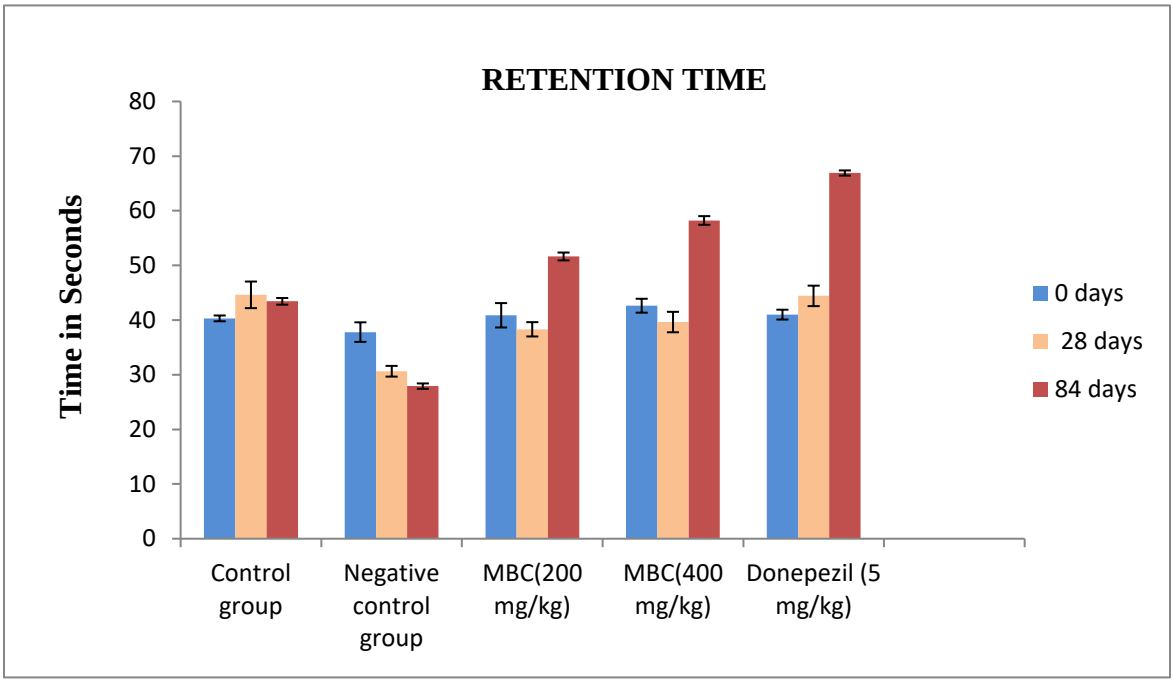


**Figure 3 Effect of *Barleria cristata* on Retention time (RT) of rats in MWM apparatus**

**Interpretation of Results**

Table 1 and Figure 1 illustrate the correlation between the transfer latency of stressed rats on the EPM apparatus and the methanolic extract of *Barleria cristata*. A statistically significant increase (p<0.01) in transfer latency was observed in the negative control group compared to the normal control group on the 84 days. In comparison to the negative control group, transfer latency was significantly reduced (P<0.01) following treatment with the methanolic extract of

*Barleria cristata* at concentrations of 200 mg/kg and 400 mg/kg, and Donepezil at a dosage of 5 mg/kg.

The data in Table 2 and Figure 2 illustrate the effect of *Barleria cristata* leaves extract on escape latency in memory-impaired rodents in the Morris water maze (MWM). The negative control group exhibited a significantly longer escape delay ($P<0.01$) than the control group. Treatment with the methanolic extract of *Barleria cristata* at concentrations of 200 mg/kg and 400 mg/kg, and Donepezil (5 mg/kg), led to a substantial ($P<0.01$) decrease in escape latency in comparison to the negative control group.

The retention time in the Morris water maze (MWM) of experimental rats with memory impairment is influenced by *Barleria cristata* leaves, as illustrated in Table 3 and Figure 3. In comparison to the negative control group, the retention time was significantly reduced following treatment with the methanolic extract of *Barleria cristata* at concentrations of 200 mg/kg and 400 mg/kg, and Donepezil at a dosage of 5 mg/kg.

**Discussion**

Stress is a pervasive stressor that is exacerbated by the advancement of industrialization and is activated by a variety of factors, such as environmental, social, or pathological phenomena of life. In the past decade, a substantial amount of research has been conducted on a series of neurochemicals, biochemical, and molecular consequences that are induced by stress in the central nervous system, endocrine system, and immune system (15). A correlation has been established between the advancement of diseases, alterations in the immune system, and exposure to stress, particularly in neurodegenerative disorders such as Alzheimer's disease (AD). This correlation has been extensively researched. Currently, the treatment of Alzheimer's disease (AD) is authorized for only two categories of medications: antagonists of N-methyl d-aspartate (NMDA) and inhibitors of the cholinesterase enzyme. These treatments are only beneficial in alleviating the symptoms of AD; they do not prevent or cure the disease. (16). In the modelling of Alzheimer's disease (AD), scopolamine, streptozotocin, alcohol, and several heavy metals, such as aluminium (Al), copper (Cu), zinc (Zn), lead (Pb), and reducing sugar (D-galactose), are frequently employed agents (17). Flavonoids, the most prevalent and ubiquitous group of phytochemicals found in higher plants, exhibit significant therapeutic potential. Flavonoids are classified into six categories according to their chemical structure: anthocyanidins, flavanols,

flavanones, flavones, and flavanols. Its efficacy in preventing neurodegenerative diseases and in slowing the progression of neurodegeneration by targeting multiple pathways has been demonstrated by experimental evidence. Flavonoids are the subject of extensive research due to their critical anti-inflammatory and antioxidant properties in the development of Alzheimer's disease. The potential utility of flavonoids in the mitigation of neurodegenerative disorders has been demonstrated by experimental studies that have demonstrated their ability to cross the blood-brain barrier (BBB). However, the blood-brain barrier permeation capabilities of various flavonoid subgroups vary (18). *Barleria cristata* is composed of carbohydrates, phenols, flavonoids, steroids, alkaloids, anthraquinones, and amino acids, according to scientific literature. The present investigation has confirmed the presence of alkaloids, carbohydrates, tannins, phenolic compounds, flavonoids, anthraquinones, and saponins. The elevated plus maze apparatus, Morris water maze apparatus, light and dark apparatus, elevated T maze, elevated zero maze, open field test, and white lack box are among the numerous models available for the screening of learning and memory-enhancing activities. The elevated plus maze apparatus and Morris water maze apparatus were employed in this investigation to assess memory enhancement and learning activities. These devices were selected due to their cost-effectiveness, ubiquitous availability, popularity, accuracy, specificity, and their demonstrated positive outcomes (19).

In the elevated plus apparatus, the negative control group exhibited a significantly greater transfer delay than the normal control group. Conversely, the treatment group that received methanolic *Barleria cristata* (at concentrations of 200 mg/kg and 400 mg/kg) and Donepezil (5 mg/kg) daily for 84 days demonstrated a substantial decrease in transfer latency when contrasted with the negative control group.

In the Morris water maze, the negative control group exhibited a significantly higher escape latency than the normal control group. After 84 days, the group that received methanolic *Barleria cristata* (at concentrations of 200 mg/kg and 400 mg/kg) and Donepezil (5 mg/kg) exhibited a substantial decrease in escape latency in comparison to the negative control group. Retention time was significantly reduced in the negative control group within the Morris water maze apparatus in comparison to the normal control group. A significant increase in transfer latency was observed in comparison to the negative control group after 84 days following treatment with the methanolic extract of *Barleria cristata* at concentrations of 200 mg/kg and 400 mg/kg, in conjunction with Donepezil at 5 mg/kg.

## Conclusion

The current findings indicate that the methanolic extract of *Barleria cristata* leaves has significant modest to moderate effects on learning and memory at both low and high doses (200 mg/kg and 400 mg/kg).

## Declarations

### Acknowledgements

Not Applicable

### Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Author's Contribution

"The Concept was discussed by Mr. Rahul Jodh while Dr P. S. Kawtikwar prepared the writing original draft of the article followed by Ms. Ankita Kawtikwar with validation and data analysis, Mr. Rahul Jodh contributes with data curation, then Dr P. S. Kawtikwar Review and edit the article and finally Mr. Rahul Jodh done the formal analysis of the article. All the author read and approved the final manuscript."

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### Ethics Statement

The Institutional Animal Ethics Committee of SNIOP, Pusad, approved all protocols utilized in this work.

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