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RESEARCH ARTICLE

Therapeutic Influence of *Nyctanthes arbor-tristis* against Aluminum Chloride-induced Impairment in Wistar Rats

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Abstract

Background: Alzheimer's Disease (AD) is a neurological illness that causes cognitive decline and memory loss. The identification of potential therapeutic agents with neuroprotective properties is of great interest in AD research. This study aimed to evaluate the neuroprotective activity of the ethanolic extract of *Nyctanthes arbor-tristis* in an aluminium chloride-induced dementia model in Wistar rats. **Materials and Methods:** *Nyctanthes arbor-tristis* plant specimens were collected, and ethanolic extract was prepared using standard extraction procedures. Four groups of Wistar rats were formed: control, aluminium chloride-induced dementia, extract-treated, and standard drug-treated groups. Neurobehavioral changes were measured using the elevated plus maze test and Hebb's William apparatus. Plasma levels of amyloid-beta 1-42 (Aβ1-42) were measured. A histopathological examination of brain tissues was conducted to assess structural changes. **Results:** The ethanolic extract of *Nyctanthes arbor-tristis* demonstrated significant neuroprotective effects in the aluminium chloride-induced dementia model. Treatment with the extract improved neurobehavioral changes associated with memory impairment and improved learning and memory performance in the Hebb's William apparatus and elevated plus maze. Moreover, the extract significantly reduced plasma levels of Aβ1-42, indicating its potential as an anti-Alzheimer's agent $p < 0.001$. Histopathological analysis revealed a reduction in neuronal damage and restoration of normal brain tissue architecture in the extract-treated group. **Conclusion:** The ethanolic extract of *Nyctanthes arbor-tristis* exhibits neuroprotective activity in an aluminium chloride-induced dementia model in Wistar rats. The extract improves neurobehavioral changes related to memory, decreases plasma levels of Aβ1-42, and ameliorates histopathological alterations in the brain.

Keywords: Aluminum Chloride-induced Dementia Model, Alzheimer's Disease, Memory Impairment, Neuroprotective Activity, *Nyctanthes arbor-tristis*

1. Introduction

The number of studies investigating natural products as a means to manage dementia, both in preclinical and clinical settings, has steadily increased over time. Notably, there has been a significant surge in such research in the years 2020 and 2021. Dementia is a chronic and debilitating neurological condition that progressively impairs an individual's cognitive and mental abilities. As the disease advances, memory loss hampers a person's independence and functioning. Traditional medicine, rooted in natural sources like plants, animals, and microbes, has long been fundamental in addressing global healthcare needs[1]. Despite the existence of a vast array of natural commodities, only a limited number, such as galantamine and huperzine A, had been approved as drugs for dementia. However, this should not be disheartening, as numerous natural products including alkaloids, terpenoids, polyphenols, phytocannabinoids and isothiocyanates, are currently undergoing drug development stages to combat dementia and related disorders. These natural compounds exhibit a range of promising and diverse biological activities, including antioxidative properties, inhibition of acetylcholinesterase, and anti-amyloidogenic effects, all of

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which have a strong correlation with preventing dementia syndrome[2]. Alzheimer's Disease (AD) represents the highest prevalent form of dementia, and its frequency is projected to affect 131.5 million individuals by 2050 if effective therapies are not developed. Currently, only four agents approved by Food and Drug Administration are available for AD treatment, but they offer limited cognitive improvement. Despite extensive efforts, AD remains an inevitable and incurable condition[3].

Nyctanthes arbor-tristis, commonly known as night-flowering jasmine, is a shrub or small tree native to Southeast Asia and India. It is a member of the Oleaceae family, and its flowers have been traditionally used in herbal medicine to address various ailments like fever, indigestion, and arthritis. The leaves of *Nyctanthes arbor-tristis* are employed to create a medicinal tea known for its therapeutic properties in treating fevers and other health issues. Ayurvedic medicine also utilizes this plant to address a range of diseases[4]. The scientific community has acknowledged its medicinal potential, particularly in traditional remedies for malaria, wound healing, menstrual problems, bronchitis, rheumatism, persistent fever, sciatica, digestive disorders, astringent effects, liver ailments, skin conditions and biliary disorders. Overall, *Nyctanthes arbor-tristis* is a culturally significant plant appreciated for its aesthetic appeal, medicinal value, and traditional applications[5].

2. Materials and Methods

2.1 Human End Point

To ensure the animals' well-being, specific parameters were established as human endpoints before initiating the experiment. If an animal reached the human endpoint before the experimental endpoint, it was important to inform the veterinarian promptly. Furthermore, if the calculated endpoint did not return to normal levels within 24 hours, the animal would be humanely euthanized using appropriate doses of ketamine.

2.2 Collection of Plant

Upon procurement, the *Nyctanthes arbor-tristis* plant specimens were carefully gathered from the Samastipur district in Bihar. Subsequently, herbarium samples were carefully prepared and dispatched to the esteemed ICAR-National Bureau of Plant Genetic Resources located in New Delhi for authentication. Following a thorough examination and analysis, the samples were conclusively identified as *Nyctanthes arbor-tristis*, and an official report bearing the distinguished serial number AC-74/2022 was duly generated. Fresh leaves of *Nyctanthes arbor-tristis* are meticulously collected and thoroughly cleaned to eliminate any impurities or foreign substances. Subsequently, the leaves are carefully dried in a shaded environment for a duration of two weeks. Once fully dried, the leaves are finely powdered utilizing a mortar and pestle. To extract the bioactive compounds, the powdered leaf material is combined with ethanol and left to stand for a period of six hours within a soxhlet apparatus. Following this extraction process, the mixture undergoes filtration, and the solvent is removed through the application of a rotary evaporator, resulting in the acquisition of a concentrated extract.

2.3 Experimental Animals

A total of 140-160 g male Wistar rats, aged 4-5 weeks, were acquired from the animal facility at NIET Institute. These animals were sheltered in a controlled environment with regulated temperature and lighting (22 ± 5 °C, a 12-hour light-dark cycle beginning at 08:00 h). They were given full access to food and water by the standards set out by the Committee for the Purpose of Control and Supervision of Experiments on Animals. All procedures involving the experimental animals were carried out with the approval of the Institutional Animal Ethics Committee, under the protocol number IAEC/NIET/2022/02/04.

2.4 Grouping and Treatment Regimen of Experimental Animals

Each group consisted of six animals. A random assignment was performed to ensure consistent body weights among the experimental groups prior to treatment, resulting in four distinct groups: Group 1, Group 2, Group 3, and Group 4. In Group 1, the animals received purified water orally throughout the entire 42-day study period, serving as the Normal Control (NC) group. This group was unaffected by any additional substances. To induce neurotoxicity in the experimental rats, aluminium chloride obtained from Central Drug House (P) Ltd. was utilized. A fresh solution of aluminium chloride in water, with a dosage of 100 mg/kg, was orally administered daily for 42 days to the rats in Groups 2, 3, and 4. It is important to note that the aluminium chloride solution was freshly prepared each day to maintain its potency.

As a standard drug, Donepezil HCl supplied by GLR Innovation Pvt. Ltd. was employed in the study. Group 2 served as the Disease Control (DC) group, receiving no additional treatment beyond the aluminium chloride. In Group 3, Donepezil hydrochloride was administered orally at a dose of 1 mg/kg for 42 days, one hour after the administration of aluminium chloride. This group was considered the Standard Control (SC) group, serving as a reference for the effects of Donepezil in mitigating neurotoxicity induced by aluminium chloride. Group 4 received an ethanolic extract of *Nyctanthes arbor-tristis* at a dose rate of 500 mg/kg, for 42 days, one hour after the dose of aluminium chloride. Based on the most recent body weights of the animals in each group, the needed amount of extract was administered orally daily. Rats were given the medication orally, a stainless-steel gavage needle was utilized, ensuring precise delivery of the substances under investigation.

2.5 Elevated Plus Maze

To evaluate the impact of the treatments on neurobehavioral changes related to memory, the Elevated Plus Maze (EPM) test was conducted on days 20 and 42 of the trial. The EPM utilized in this study consisted of walls measuring 40 cm in height, featuring both open and closed arms. The maze's central square had dimensions of 10x10 cm^2 and was positioned at a height of 50 cm beyond the ground. During the acquisition phase of the test, the animal was placed at the end of one of the arms, facing away from the central square. This positioning allowed for the assessment of the animal's Initial Transfer Latency (ITL), which refers to the duration it took for the animal to move from an open arm to a closed arm. By carefully measuring the ITL, we aimed to gain insights into the effects of the administered treatments on memory-related behaviours. This approach provided valuable information regarding the animals' cognitive responses and their ability to adapt to the maze's structure and navigate between different arm types. Once the Initial Transfer Latency (ITL) was noted, a period of 20 seconds was allocated for each animal to freely explore the maze before being safely returned to its home cage. As part of the memory assessment, the Retention Transfer Latencies (RTLs) were measured on day 42, while the ITLs were re-evaluated on day 20. By observing the RTLs on day 42 and comparing them to the baseline ITLs measured on day 20, we aimed to gauge the effectiveness of the treatments in preserving or enhancing memory function. These measurements served as valuable indicators of the animal's ability to remember and recall spatial information and their proficiency in navigating the maze[6].

2.6 Hebb's William Maze

The mice were placed in the start box at the start of each trial, and their progress towards the goal box was recorded. The time it took the mice to reach the goal box was meticulously documented. Following that, the mice were given 30 seconds to devour the reward before being returned to the start box for the next attempt. Each trial had a time limit of 120 seconds, during which the mice were expected to complete the task. If a mouse was unable to reach the goal box within the designated time frame, the trial was promptly concluded, and the mouse was gently returned to the start box without receiving the reward. This ensured consistency in the experimental protocol and maintained the integrity of the data collected. The acquisition phase of the task was deemed complete when the mice consistently demonstrated their ability to complete trials within a 60-second timeframe for two consecutive days. This specific criterion served as a significant milestone, signifying that the mice had successfully acquired the necessary skills to accomplish the task. It highlighted their progress and proficiency in mastering the maze navigation, rewarding their persistence and adaptability throughout the learning process.

2.7 Animal Sacrifice, Blood and Organ Collection

Upon completion of the 42-day study period, the animals were anaesthetized using appropriate doses of ketamine. Following anaesthesia, a 26G needle was employed to obtain blood samples via the cardiac puncture technique. This technique entails the careful insertion of a needle into the heart to collect blood samples for subsequent analysis. The collected blood samples were carefully transferred into appropriate blood collection tubes and subsequently sent to the laboratory for biochemical analysis. These analyses would provide valuable insights into various biochemical parameters and help in evaluating the physiological and pathological aspects of the samples. The kidney, liver, and brain were meticulously taken and weighed after euthanasia. To facilitate histopathological examination, the brain samples were preserved in 10% neutral buffered formalin. This preservation method ensures the tissues maintain their structural integrity for subsequent analysis and observation under a microscope.

2.8 Histopathology

For histopathological analysis, the collected brain samples were trimmed to remove excess tissue and processed using a series of increasing concentrations of alcohol and xylene. Subsequently, the samples were embedded in paraffin blocks, allowing for precise sectioning. These sections were then stained with routine hematoxylin and eosin, a commonly used staining method, which enabled detailed evaluation through histopathological examination.

2.9 Phytochemical Analysis

The phytochemical analysis of *Nyctanthes arbor-tristis* was conducted to identify and quantify its bioactive compounds. The obtained extract was subjected to various phytochemical tests and assays to determine the existence of different classes of bioactive compounds, containing flavonoids, alkaloids, phenols, terpenoids, and glycosides. Specific tests were employed to identify and quantify the respective compounds[7].

2.10Statistical Analysis

The data obtained from the experiment underwent statistical analysis using the one-way analysis of variance (ANOVA) method, followed by a Tukey post hoc test. The analysis was conducted using GraphPad Prism V9.0 software. All Values are in Mean ± S.E.M. A statistical significance level of 95% confidence interval was applied, meaning that results with a p-value below 0.05 were deemed statistically significant.

3. Results

3.1 Phytochemical Analysis

Phytochemicals play a crucial role in promoting human health. They have been recognized for their ability to combat various diseases effectively. Unlike conventional medicines, phytochemicals offer therapeutic benefits without causing harm to the human body, earning them the reputation of being "man-friendly medicine[8]. In the present study, the phytoconstituents present in the ethanol extract were identified and documented in Table 1. This tabulation provides valuable information about the specific phytochemical components present in the extracts, aiding in the understanding of their potential therapeutic properties.

Table 1. Preliminary phytoconstituents of extrac

Phytochemicals	Phytochemicals Tests	Ethanol
Glycosides	Legal's test	+
Terpenoids	Salkowski's test	+
Flavonoids	Alkaline reagent test	+
Saponins	Frothing Test	-
Tannins	Ferric chloride test	+
Sterols	Salkowski test	+
Alkaloids	Dragendorff's test	+

The symbol "+" indicates the presence of a phytoconstituent in the sample, while the symbol "-" indicates the absence of a phytoconstituent in the sample.

3.2 Elevated Plus Maze

In the Elevated Plus Maze (EPM) test, a noteworthy finding emerged during the assessment of the Initial Transfer Latency (ITL) on day 20. Specifically, the Disease Control group exhibited a significantly higher ITL compared to the other groups, including the Normal Control group. Notably, the ITL in both the Standard Control and extract groups exhibited similar values to that of the Disease Control group. However, on day 42, the Retention Transfer Latency (RTL) in the Standard Control and Extract groups showed a significant decrease compared to the Disease Control group. These findings indicate that the treatment with *Nyctanthes arbor-tristis* extract yielded similar effects to the treatment with donepezil hydrochloride in enhancing memory function, as depicted in Figure 1.

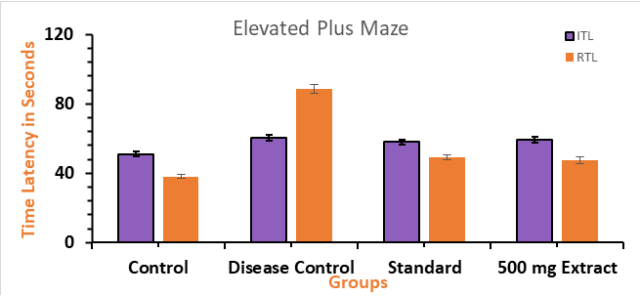

Figure 1. The graph illustrates the latency in the Elevated Plus maze Apparatus.

3.3 Hebb's William Maze

Following the completion of the acquisition phase, the rats underwent testing on the final day of the study, day 42. They were placed in the Hebbs William apparatus, and

the time latency was measured as an indicator of their performance. Interestingly, the disease control group exhibited the highest time latency matched to the control group. In contrast, both the standard drug group and the extract group demonstrated positive effects in mitigating $AlCl_3$-induced dementia, as evidenced by improved performance with reduced time latency. These findings suggest that the standard drug and the *Nyctanthes arbor-tristis* extract have beneficial effects on cognitive function in the experimental model of dementia induced by $AlCl_3$ (Figure 2).

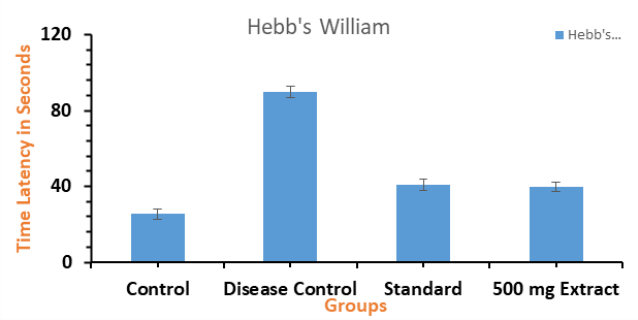

Figure 2. The figure presents a graphical representation depicting the latency observed in Hebb's William maze apparatus.

3.4 Plasma Biochemical Analysis

Consistent with previous reports, our findings in Table 2 indicate that higher levels of Aβ1-42 or an increased Aβ1-40/Aβ1-42 ratio relate to the onset of AD[9]. Specifically, in our study, we observed elevated levels of plasma Aβ1-42 in the Disease Control group compared to the Control group. On the other hand, the Standard Control group and the Extract-treated group exhibited lower levels of Aβ1-42. These results suggest that the administration of the standard drug and the *Nyctanthes arbor-tristis* extract may contribute to reducing the levels of plasma Aβ1-42, which could have potential implications for managing AD and its associated pathology (Figure 3).

All values are expressed as the mean ± standard error of the mean (SEM). Statistical significance was denoted as follows: $p < 0.01$ represented by the symbol α, $p < 0.001$ represented by the symbol a, and $p < 0.05$ represented by the symbol *. These symbols indicated significant differences when compared to the Control group. Additionally, statistical significance was denoted as follows: $p < 0.01$ represented by the symbol β, $p < 0.001$ represented by the symbol b, and $p < 0.05$ represented by the symbol #. These symbols indicated significant differences when compared to the Disease Control group.

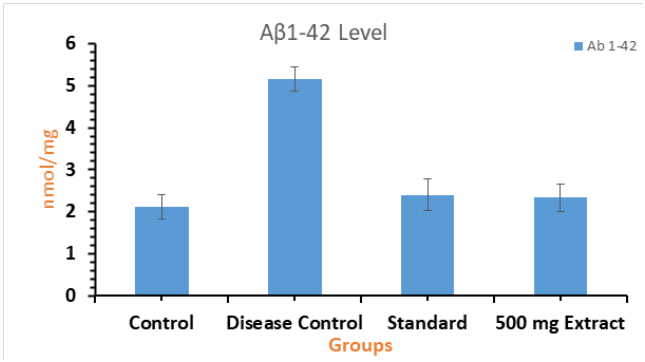

Figure 3. The figure presents a graphical representation depicting the Aβ1-42 level in plasma.

3.5 Histopathology Report

Histopathological examination Figure 4 was conducted to assess the effects of *Nyctanthes arbor-tristis* treatment at a dosage of 500 mg/kg on brain tissues. In the control group (Group I), the brain tissues exhibited normal and intact cellular arrangements. However, in the $AlCl_3$-induced group (Group II), brain tissues displayed various pathological changes, including glial scarring, edema, cell loss, and active inflammation, (indicated by blue arrows). In contrast, treated groups (Groups III and IV) exhibited a notable reduction in cellular alterations and no significant pathology was observed. This suggests that the administration of *Nyctanthes arbor-tristis* at the

Table 2. The table presents a comprehensive overview of various parameters associated with the experimental animals utilized in the study

Parameters	Control	Disease Control	Standard	500mg/kg
Elevated Plus Maze				
ITL	51.16±1.55	60.5±1.56 $^{\alpha}$	58±1.46*	59.33±1.74 $^{\alpha}$
RTL	38.16±1.04	88.5±2.51^{a}	49.16±1.47 ^{ab}	47.66±1.99 ^{ab}
Hebb's William	25.33±2.52	89.83±2.82^{a}	40.83±3.00 ^{ab}	39.83±2.46 ^{ab}
Aβ1-42	2.11±0.28	5.15±0.29^{a}	2.4±0.37^{b}	2.33±0.32^{b}

given dosage resulted in a beneficial effect, mitigating the histopathological changes induced by $AlCl_3$ in the brain tissues. These findings highlight the potential therapeutic value of *Nyctanthes arbor-tristis* in ameliorating the detrimental effects of $AlCl_3$-induced brain pathology.

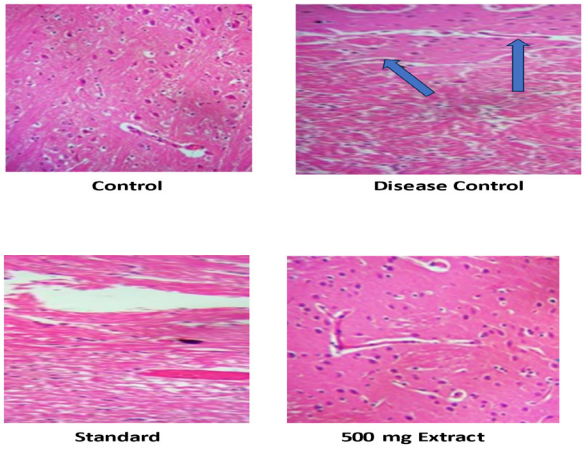

Figure 4. Brain tissues from the control group (Group I) showed normal cellular arrangements. In the $AlCl_3$-induced group (Group II), brain tissues exhibited pathological changes including oedema, inflammation, cell loss, and glial scarring (blue arrows). Treated groups (Group III and IV) showed reduced cellular alterations and no significant pathology.

4. Discussion

The present study investigated the *in vivo* neuroprotective activity of the ethanolic extract of *Nyctanthes arbor-tristis* using a male Wistar rat model of aluminium chloride-induced neurotoxicity. The rats received a daily oral administration of the ethanolic extract of *Nyctanthes arbor-tristis* at a dosage of 500 mg/kg body weight for a time of 42 days. Following the treatment phase, memory assessment was conducted using the Elevated Plus Maze test and Hebb's William maze. Subsequently, the animals were euthanized to collect blood samples and perform histopathological evaluations. The procedures outlined in the study were designed with the specific objective of assessing the potential neuroprotective effects of the extract derived from *Nyctanthes arbor-tristis* and understanding its impact on memory-related behaviours and histological changes in the brain.

The phytochemical analysis of the extract unveiled the existence of diverse compounds that have been identified to impact brain functions through various mechanisms. Flavonoids, including quercetin[10] and kaempferol[11], present in *Nyctanthes arbor-tristis*, have exhibited positive effects on brain health. Additionally, triterpenoids like oleanolic acid and ursolic acid found in *Nyctanthes arbor-tristis*, have demonstrated promising neuroprotective properties in preclinical investigations[12]. Amyloid beta-peptide (1–42), also known as Aβ (1–42), is believed to have a crucial role in the development of AD, a neurological disease that causes cognitive decline and ageing. The brain of individuals with AD experiences significant oxidative stress, and Aβ (1–42) has been found to contribute to the process by inducing lipid peroxidation, protein oxidation, and generation of reactive oxygen species in neurons and synaptosomes[13].

The current study's findings are compatible with previous literature reports that highlight the detrimental effects of chronic oral administration of $AlCl_3$ on memory and learning functions in male albino rats. The Hebb's William test and Elevated Plus Maze revealed that animals treated with $AlCl_3$ experienced significant learning and memory impairments compared to the control group. However, intriguingly, all treated groups, including the $AlCl_3$-treated rats, displayed notable resilience against these deficits induced by $AlCl_3$[14]. The brain, being highly oxygen-dependent and having limited antioxidant defences, is vulnerable to oxidative stress. Consequently, $AlCl_3$'s neurotoxicity causes significant neuronal damage by disrupting the antioxidant defence system. These findings resemble the early stages of AD and correlate with cognitive decline[15].

The memory-related behaviour of rats was assessed using the EPM test, which measures the transfer latency from the open arm to the closed arm[16,17]. In the case of aluminium chloride-induced neurotoxicity, progressive memory loss occurred, leading to an RTL compared to the ITL. This indicates that the rats were unable to memorize and recall the correct path in the maze. Similar observations were recorded using Hebb's William apparatus, where rats in the DC group also exhibited difficulties in memorizing and recalling the maze path. The present study's findings demonstrate that the administration of aluminium chloride to rats resulted in a progressive decline in memory function and subsequent neurobehavioral deficits. Consequently, the rats in the DC group exhibited a higher RTL compared to the rats in the NC group, indicating impaired memory. These EPM test results in the neurotoxicity DC group are consistent with earlier publications, confirming the establishment

of the neurotoxicity model[18]. Treatment with *Nyctanthes arbor-tristis* showed a considerable reduction in RTL when compared with the DC group, indicating a potential improvement in memory function. The study encountered certain limitations primarily related to budget constraints. As a result, certain analyses, such as the AChE Assay and oxidative stress assessment, could not be conducted in this study. These analyses would be valuable for gaining further insights into the biochemical aspects of the study and understanding the exact mechanism of action. Future studies should prioritize the inclusion of these analyses to improve the comprehensiveness of research and provide a more comprehensive understanding of the therapeutic potential of the intervention.

5. Conclusion

In conclusion, our research explored the neuroprotective potential of *Nyctanthes arbor-tristis* in an aluminium chloride-induced neurotoxicity model. The ethanolic extract exhibited promising effects on memory-related behaviours and mitigated histological changes in the brain. Phytochemical analysis revealed the presence of compounds known for their beneficial effects on brain health. These findings contribute to our understanding of neuroprotective interventions for cognitive disorders, highlighting the resilience of treated groups against cognitive deficits. Future studies should focus on elucidating the exact mechanism of action and conducting comprehensive biochemical analyses. Overall, *Nyctanthes arbor-tristis* holds promise as a natural therapeutic agent for promoting brain health and combating neurodegenerative conditions.

6. Acknowledgement

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