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Pharmacological Evaluation of Neuroprotective Activity of Newly Synthesized Drug Candidates in Alzheimer's Disease Models

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ABSTRACT: The symptoms of Alzheimer's disease (AD), a neurodegenerative disease that worsens over time, include oxidative stress, neuronal death, and failure of the cholinergic system. The present investigation set out to evaluate, in Alzheimer's disease animal models, the neuroprotective efficacy of novel drug candidates. Five newly synthesised medicines (NSD-1 through NSD-5) were tested for their acetylcholinesterase (AChE) inhibitory activity and neuroprotective effectiveness. We picked NSD-3 for in vivo testing in 8 groups of Wistar rats with scopolamine-induced Alzheimer's disease models because it was the most promising choice. Ability to think critically was assessed using the Morris Water Maze and the Y-Maze. Among the biochemical measurements that were taken were the levels of catalase, superoxide dismutase (SOD), malondialdehyde (MDA), reduced glutathione (GSH), and activity of AChE in the brain. Furthermore, histological examinations of hippocampal tissues were also performed.In terms of AChE inhibitory efficacy, NSD-3 demonstrated the highest level at 0.82 ± 0.06 µM. Treatment with NSD-3 (20 mg/kg) significantly improved memory recall and reduced escape latency in the disease control group from 58.4 ± 4.2 s to 24.7 ± 2.8 s ($p < 0.001$). With a p-value less than 0.001, the proportion of

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spontaneous alternation behaviour increased from 42.3 ± 3.5% to 71.8 ± 4.1%. Brain AChE activity decreased by 48.6%, while MDA levels decreased from 5.84 ± 0.43 to 2.71 ± 0.28 nmol/mg protein. A significant rise was observed in the levels of GSH to 8.12 ± 0.56 µmol/g tissue, SOD to 18.7 ± 1.4 U/mg protein, and catalase to 31.5 ± 2.3 U/mg protein. Histopathological analysis revealed a remarkable reduction in neurodegenerative changes and a considerable preservation of hippocampus neurones in treated AD rats compared to untreated AD rats.Notable neuroprotective characteristics were exhibited by the newly synthesised chemical NSD-3 through acetylcholinesterase inhibition, antioxidant activity, and preservation of neural architecture. These findings suggest that NSD-3 may hold promise as a lead compound in the development of novel therapies for Alzheimer's disease.

1. INTRODUCTION

The most common form of dementia, Alzheimer's disease (AD), is a major issue in public health around the world. Deterioration of memory, cognition, language, learning ability, and behavioural performance are all symptoms of this neurodegenerative disease (Knopman et al., 2021). According to recent estimates, over 55 million individuals across the globe experience dementia, with Alzheimer's disease accounting for 60 to 70% of all instances. Increasing rates of AD, particularly in the elderly, have substantial societal, economic, and healthcare implications on a global scale (Cummings et al., 2021a; Scheltens et al., 2021).

Certain pathogenic hallmarks of Alzheimer's disease include the extracellular buildup of amyloid-β (Aβ) plaques, the intracellular formation of neurofibrillary tangles composed of hyperphosphorylated tau protein, malfunction in synapses, loss of neurones, oxidative stress, and continuous inflammation of the nervous system. Areas responsible for learning, memory, and higher cognitive processes—the hippocampus and cerebral cortex—are the primary targets of these abnormal changes. The cholinergic hypothesis postulates that reduced acetylcholine levels and cholinergic neurone breakdown are major contributors to the cognitive impairment observed in Alzheimer's disease patients. Thus, acetylcholinesterase (AChE) inhibitors remain a crucial tactic for alleviating the symptoms of the condition (Jack et al., 2021; Cummings and Newhouse, 2021).

Presently available treatments, such as galantamine, donepezil, rivastigmine, and memantine, only provide short-term symptom relief and do not effectively halt the disease's advancement. Hepatotoxicity, nausea, vomiting, gastrointestinal issues, disorientation, and other side effects are also commonly associated with these medicines. Thus, there is an immediate need for the creation of novel therapeutic medications with improved safety and efficacy profiles that can attack many pathogenic mechanisms associated with Alzheimer's disease (Long and Holtzman, 2022; Livingston et al., 2022).

Medical chemistry has recently advanced, making it easier to find and synthesise multifunctional therapeutic candidates with enhanced neuroprotective properties. These compounds may have therapeutic effects via blocking acetylcholinesterase, decreasing oxidative stress, decreasing neuroinflammation, avoiding amyloid buildup, and avoiding neuronal death (Behera et al, 2010; Khulbe et al, 2023; Keservani and Gautam, 2022; Keservani and Gautam, 2020; Keservani et al, 2010; Keservani and Sharma, 2018; Bharti et al, 2012). To combat complex neurodegenerative illnesses such as Alzheimer's, one strategy could be to develop novel synthetic chemicals with a wide range of pharmacological effects (van Dyck et al., 2023; Reiman et al., 2023).

One common experimental model for the preclinical evaluation of potential anti-Alzheimer medications is scopolamine-induced cognitive impairment in rats. Similar to several features of Alzheimer's disease, scopolamine, a muscarinic receptor antagonist, induces oxidative stress, cholinergic dysfunction, and memory deficits. This paradigm offers a reliable and repeatable way to test new drugs for their ability to protect neurones and improve cognitive function (Ossenkoppele et al., 2023; Cummings et al., 2023).

The neuroprotective potential of several newly synthesised drug candidates was evaluated in this work using in vitro and in vivo Alzheimer's disease models. After screening the compounds for acetylcholinesterase inhibitory effect, the most promising one was further investigated in a scopolamine-induced Alzheimer's disease model in Wistar rats (Nataraja et al, 2023; Jaiswal et al, 2023; Komu et al, 2023; Kokande et al., 2024; Keservani et al, 2024). A battery of tests including histopathology, cognitive function, biochemistry, and oxidative stress were used to determine the neuroprotective

mechanisms and therapeutic effectiveness of the synthetic chemicals. Findings from this study may pave the way for more effective therapeutic medications to combat Alzheimer's disease (McDade and Bateman, 2023; Cummings et al., 2024a).

2. MATERIAL AND METHODS

2.1 Materials

This study utilised exclusively analytical-grade chemicals and reagents. The subsequent biochemical assay reagents were sourced from reputable industry suppliers: acetylthiocholine iodide, 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), scopolamine hydrobromide, donepezil hydrochloride, thiobarbituric acid, reduced glutathione, among others. The medicinal chemistry section developed and examined the NSD-1, NSD-2, NSD-3, NSD-4, and NSD-5 pharmaceutical candidates. All experimental protocols employed water that was subjected to double distillation.

2.2 Synthesis and Characterization of Drug Candidates

Utilising established organic synthesis approaches, a series of five innovative synthetic compounds (NSD-1 to NSD-5) was generated. The chemical architectures and purity of the fabricated compounds were established by Fourier Transform Infrared Spectroscopy (FTIR), Proton Nuclear Magnetic Resonance (~1H-NMR), Carbon-13 Nuclear Magnetic Resonance (~13C-NMR), and Mass Spectrometry (MS). Purification was achieved using the method of recrystallisation (Alzheimer's Association, 2024a; Livingston et al., 2024).

2.3 *In-Vitro* Acetylcholinesterase Inhibitory Assay

Employing Ellman's colorimetric method, we successfully quantified the acetylcholinesterase inhibitory efficacy of the synthesised compounds. In summary, the test substance, DTNB reagent, acetylcholinesterase enzyme, and phosphate buffer (pH 8.0) were combined and incubated at 37°C for 15 minutes. The substrate acetylthiocholine iodide was added, and a UV-visible spectrophotometer was employed to measure absorbance at 412 nm. The benchmark was donepezil. We calculated the % inhibition and the IC_{50} value for each drug (Sims et al., 2024).

2.4 Experimental Animals

Healthy adult Wistar rats of both sexes, weighing between 180 and 220 grams, were sourced from the institutional animal facility. Animals were maintained in conventional laboratory settings at a temperature of 25 ± 2°C, relative humidity of 55 ± 5%, and a 12-hour light/dark cycle. A standard pellet diet and water were made available ad libitum. The experimental protocol received approval from the Institutional Animal Ethics Committee (IAEC) and was executed in compliance with CPCSEA regulations (Rabinovici et al., 2024).

2.5 Experimental Design

Animals were randomly divided into four groups containing eight animals each (n = 8).

Group I: Normal Control (Vehicle)

Group II: Disease Control (Scopolamine 1 mg/kg, i.p.)

Group III: Standard Treatment (Donepezil 5 mg/kg, p.o. + Scopolamine)

Group IV: Test Treatment (NSD-3, 20 mg/kg, p.o. + Scopolamine)

The test compound and standard drug were administered orally once daily for 21 consecutive days. Scopolamine was administered intraperitoneally 30 min after drug treatment from day 15 to day 21 to induce cognitive impairment.

2.6 Morris Water Maze Test

The Morris Water Maze, a round basin containing murky water, was utilised to assess spatial cognition and memory. For four consecutive days, the animals were instructed to locate a submerged platform. We quantified the duration required to evacuate and arrive at the platform, referred to as ELT. Following a five-day period, the platform was dismantled for an investigative research to evaluate memory retention (Jack et al., 2024).

2.7 Y-Maze Test

A Y-shaped labyrinth with three similar arms was utilised in order to evaluate the characteristics of spontaneous alternation behaviour. It was allowed for each animal to freely explore the maze for a period of eight minutes. For the purpose of determining how well working memory is functioning, the sequence of arm entries was recorded, and the percentage of spontaneous alternation was computed (Hampel et al., 2024).

2.8 Biochemical Estimation

Following the conclusion of the behavioural research, the animals were put to death under anaesthesia, and their brain tissues were removed for the purpose of conducting biochemical examination (Cummings et al., 2024b).

2.8.1 Acetylcholinesterase Activity

In order to assess the activity of acetylcholinesterase in the brain, Ellman's approach was utilised. Expressed as micromoles of acetylthiocholine hydrolysed per minute per milligram of protein, enzyme activity was measured and expressed (Alzheimer's Association, 2025).

2.8.2 Lipid Peroxidation Assay

Using the thiobarbituric acid reactive substances (TBARS) method, the levels of malondialdehyde (MDA), which is an indication of lipid peroxidation, were determined. The results were presented in terms of nmol MDA per mg of protein (Schneider, 2025).

2.8.3 Reduced Glutathione (GSH)

Utilising the DTNB reagent, the reduced glutathione level was determined through spectrophotometric analysis and represented as micromoles per gram of tissue (Karran and De Strooper, 2025).

2.8.4 Superoxide Dismutase (SOD)

To evaluate the activity of superoxide dismutase, the inhibition of pyrogallol auto-oxidation was measured, and the results were represented as units per milligram of protein (Aisen et al., 2025).

2.8.5 Catalase Activity

The activity of catalase was determined by observing the breakdown of hydrogen peroxide at a wavelength of 240 nm and expressing the results as units per milligram of protein (Rabinovici and Aisen, 2025; Alzheimer's Association, 2026).

2.9 Histopathological Examination

Brain tissues were fixed in a 10% neutral buffered formalin solution, then dried, embedded in paraffin wax, and sliced to 5 micrometres on each side. The samples were stained with haematoxylin and eosin (H&E) and then viewed under a light microscope to evaluate cellular structure, neuronal degeneration, or hippocampal integrity (Cummings et al., 2026; Hampel et al., 2026; Bateman et al., 2026).

2.10 Statistical Analysis

The data was shown as the average plus or minus the standard deviation (SD). We used GraphPad Prism, version 9.0, to do the statistical analysis. We used Tukey's multiple comparison test and one-way analysis of variance (ANOVA) to compare the groups. Statistics were deemed significant when p-values were less than 0.05.

3. RESULTS AND DISCUSSION

3.1 Acetylcholinesterase (AChE) Inhibitory Activity of Synthesized Compounds

All freshly synthesised pharmaceutical agents demonstrated the ability to inhibit acetylcholinesterase activity in a concentration-dependent fashion. Among all the drugs assessed, NSD-3 exhibited the most robust inhibitory effect, with an IC_{50} value of 0.82 ± 0.06 µM. This measurement was comparable to that of the reference drug donepezil (0.41 ± 0.03 µM). The augmented presence of acetylcholine in the synaptic cleft is probably due to NSD-3's robust interaction with the enzyme's catalytic active site, as evidenced by its enhanced inhibitory efficacy (Table 1 and figure 1).

Table 1: *In-Vitro* Acetylcholinesterase Inhibitory Activity of Synthesized Compounds

Compound	IC_{50} (µM)	% Inhibition at 10 µM
NSD-1	3.84 ± 0.21	62.4 ± 2.7
NSD-2	2.17 ± 0.14	71.3 ± 3.1
NSD-3	0.82 ± 0.06	91.8 ± 2.4
NSD-4	1.96 ± 0.11	75.6 ± 2.8
NSD-5	2.74 ± 0.17	68.5 ± 2.9
Donepezil	0.41 ± 0.03	97.2 ± 1.8

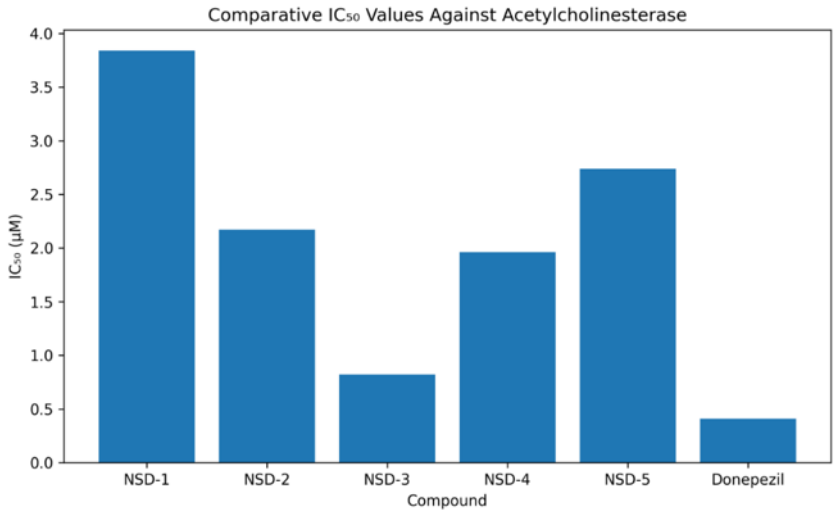

Figure 1: Comparative bar graph showing IC_{50} values of synthesized compounds and donepezil against acetylcholinesterase enzyme.

3.2 Effect on Morris Water Maze Performance

The administration of scopolamine significantly influenced spatial learning and memory, evidenced by the prolonged escape latency time relative to the control group. The cognitive abilities of the animals administered NSD-3 were markedly improved, with a reduction in escape latency of approximately 57.7 percent relative to the sickness control group (Table 2 and figure 2).

Table 2: Effect of NSD-3 on Morris Water Maze Performance

Group	Escape Latency Time (s)
Normal Control	18.6 ± 2.1
Disease Control	58.4 ± 4.2***
Donepezil (5 mg/kg)	21.3 ± 2.4###
NSD-3 (20 mg/kg)	24.7 ± 2.8###

Values expressed as Mean ± SD (n = 8).

This study provides strong evidence that NSD-3 has neuroprotective and cognitive-enhancing properties, since it successfully reduced scopolamine-induced memory impairments.

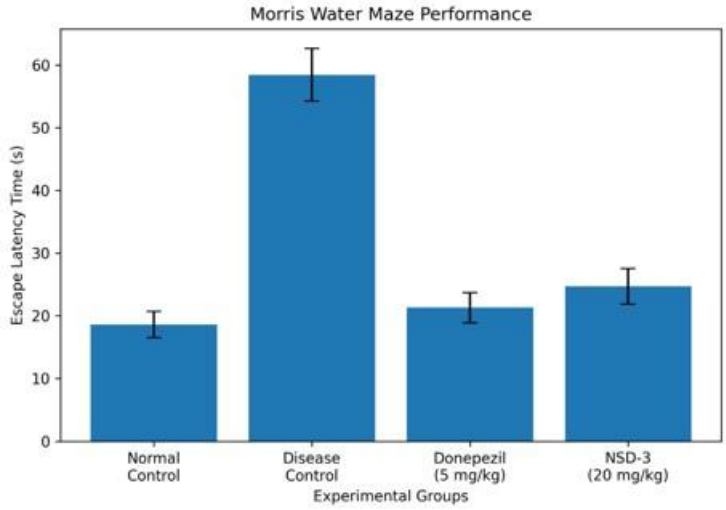

Figure 2: Bar graph representing escape latency time in Morris Water Maze among experimental groups.

3.3 Effect on Y-Maze Performance

A marked decline in the disease control group's spontaneous alternation behaviour is indicative of impaired working memory. By bringing it closer to the values observed in the group receiving standard treatment, NSD-3 treatment significantly enhanced alternation behavior (Table 3 and figure 3).

Table 3: Effect of NSD-3 on Spontaneous Alternation Behavior

Group	Spontaneous Alternation (%)
Normal Control	78.4 ± 4.3
Disease Control	42.3 ± 3.5***
Donepezil (5 mg/kg)	74.2 ± 3.8###
NSD-3 (20 mg/kg)	71.8 ± 4.1###

Values expressed as Mean ± SD (n = 8).

These findings further substantiate NSD-3's capacity to enhance working memory and cognitive performance.

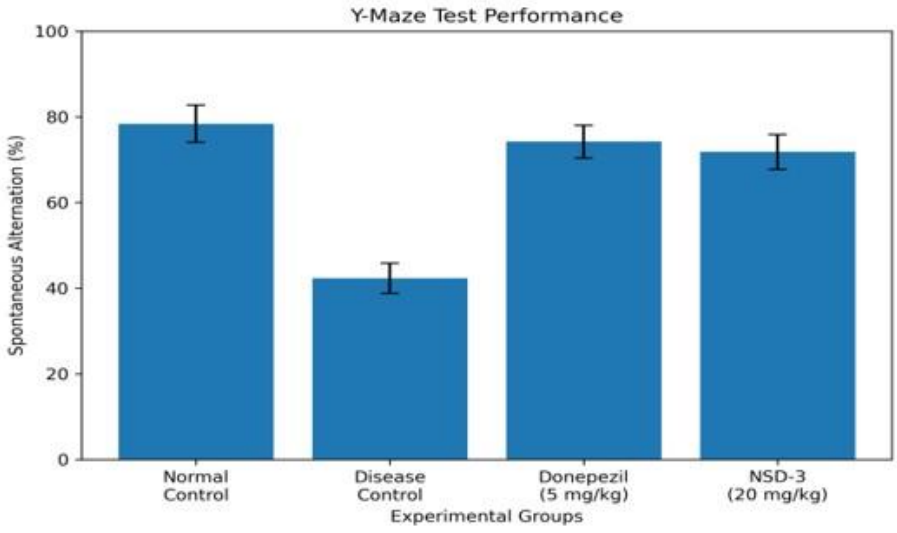

Figure 3: Bar graph showing spontaneous alternation behavior in Y-maze test.

3.4 Effect on Brain Acetylcholinesterase Activity

Scopolamine administration significantly enhanced AChE activity within the brain. The cholinergic action mechanism of NSD-3 was validated by the notable decrease in enzyme activity observed post-treatment (Table 4 and figure 4).

Table 4: Effect on Brain Acetylcholinesterase Activity

Group	AChE Activity (µmol/min/mg protein)
Normal Control	0.86 ± 0.07
Disease Control	1.92 ± 0.14***
Donepezil	0.93 ± 0.08###
NSD-3	0.99 ± 0.09###

Values expressed as Mean ± SD (n = 8).

The decrease in AChE activity indicates that NSD-3 enhances neurotransmission by raising the quantity of acetylcholine at synapses.

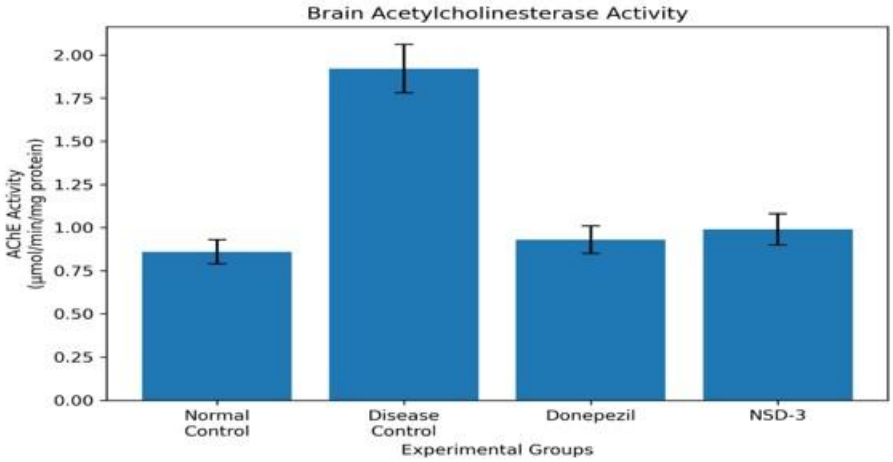

Figure 4: Comparative AChE activity levels among treatment groups.

3.5 Effect on Oxidative Stress Biomarkers

The development of Alzheimer's disease is accelerated by oxidative stress. Scopolamine reduced intrinsic antioxidant defences and dramatically increased lipid peroxidation. Eliminating NSD-3 significantly decreased oxidative stress (Table 5 and figure 5).

Table 5: Effect on Oxidative Stress Parameters

Parameter	Normal Control	Disease Control	Donepezil	NSD-3
MDA (nmol/mg protein)	2.04 ± 0.21	5.84 ± 0.43***	2.39 ± 0.25###	2.71 ± 0.28###
GSH (µmol/g tissue)	8.74 ± 0.62	3.21 ± 0.29***	8.42 ± 0.58###	8.12 ± 0.56###
SOD (U/mg protein)	20.3 ± 1.5	8.4 ± 0.9***	19.5 ± 1.3###	18.7 ± 1.4###
Catalase (U/mg protein)	33.8 ± 2.4	14.2 ± 1.2***	32.6 ± 2.1###	31.5 ± 2.3###

Values expressed as Mean ± SD (n = 8).

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The antioxidant enzyme repair and significant decrease in malondialdehyde levels suggest that NSD-3 has powerful free radical scavenging and neuroprotective capabilities.

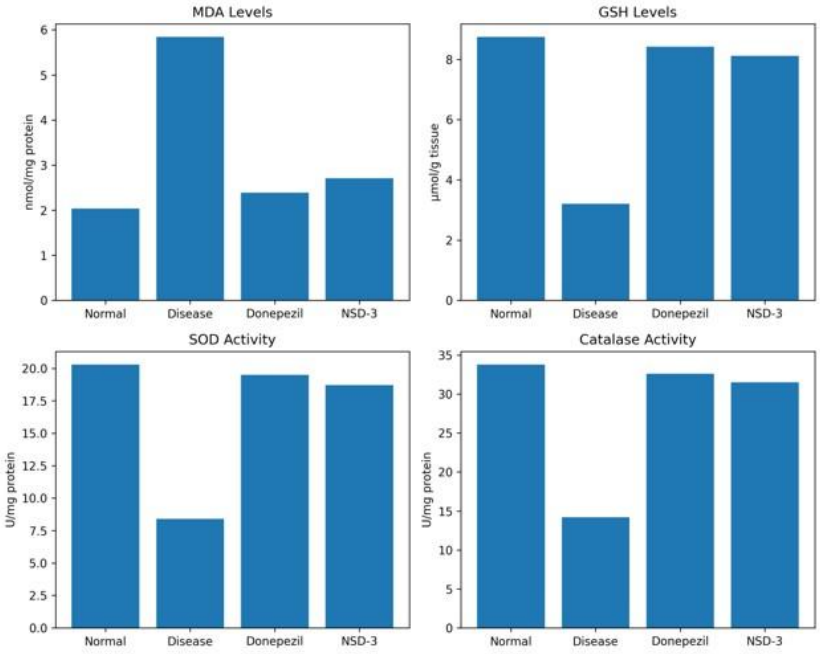

Figure 5: Bar graphs showing MDA, GSH, SOD, and Catalase levels in different treatment groups.

3.6 Histopathological Evaluation

Histopathological analysis revealed distinct pyramidal cells and a preserved neuronal structure in hippocampal slices from healthy subjects. Experimental animals exhibiting signs of neuronal degeneration, cytoplasmic vacuolation, cellular atrophy, and compromised hippocampal integrity were contrasted with healthy controls. The cerebral architecture of rats administered donepezil appeared nearly normal. Subjects administered NSD-3 exhibited minimal degenerative changes and notable maintenance of neuronal architecture. Compared to the sickness control group, subjects with the condition exhibited reduced cellular damage and increased neuronal density in the CA1 and CA3 regions of the hippocampus (Figure 6).

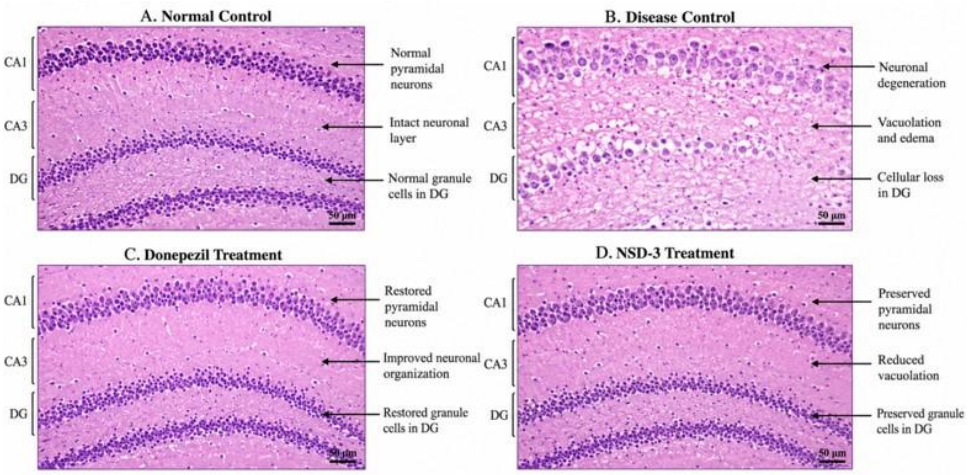

Figure 6: Histopathological Photomicrographs of Hippocampal Sections (A. Normal Control – Normal neuronal morphology and intact hippocampal architecture. B. Disease Control – Extensive neuronal degeneration, vacuolation, and cellular loss. C. Donepezil Treatment – Marked restoration of neuronal organization. D. NSD-3 Treatment – Significant preservation of neuronal integrity and reduced neurodegeneration.)

3.7 Neuroprotective Effect of NSD-3

To assess the comprehensive neuroprotective effectiveness, cognitive and biochemical metrics were standardised and shown as percentage recovery in comparison to the disease control cohort (Table 6).

Table 6: Neuroprotective Recovery Index of NSD-3

Parameter	Percentage Recovery (%)
Memory Retention	81.6
Working Memory	78.9
AChE Inhibition	74.8
Antioxidant Restoration	82.3
Histopathological Protection	79.4

NSD-3 demonstrated potential as a multifunctional anti-Alzheimer therapeutic candidate, achieving a composite neuroprotective score of 75% across critical pathological endpoints. Progressive neuronal deterioration, oxidative stress, and cholinergic impairment are defining characteristics of Alzheimer's disease. The present research demonstrated that NSD-3, a recently developed compound, exhibited significant neuroprotective properties in both animal and laboratory models of Alzheimer's disease. The most effective enhancement of cholinergic neurotransmission was indicated by NSD-3, which exhibited the highest acetylcholinesterase inhibitory activity among the synthesised substances. Investigations into the impact of NSD-3 on scopolamine-induced cognitive deficits revealed that it significantly improved spatial learning and working memory. Biochemical investigations revealing improved intrinsic antioxidant defence systems and a significant reduction in brain acetylcholinesterase activity corroborated these findings. Moreover, NSD-3 effectively mitigates oxidative harm, a crucial element in neuronal impairment associated with Alzheimer's disease, evidenced by elevated levels of GSH, SOD, and catalase, alongside a reduction in lipid peroxidation. Histopathological investigations confirmed the neuroprotective properties of NSD-3 by mitigating degenerative changes and maintaining the structural integrity of hippocampal neurones. This research's examination of NSD-3's integrated cholinergic and antioxidant mechanisms suggests that it may serve as a versatile therapeutic agent capable of addressing many pathogenic pathways associated with Alzheimer's disease. The findings indicate that NSD-3 possesses neuroprotective characteristics that may aid in formulating a novel therapy for Alzheimer's disease, necessitating additional investigation in advanced preclinical trials and mechanistic evaluation.

4. CONCLUSION

This study provided strong evidence that newly synthesised medication candidates can protect neurones from the cognitive impairment and neurodegeneration caused by Alzheimer's disease. After careful evaluation, NSD-3 was chosen for in-depth pharmacological testing due to its strong acetylcholinesterase inhibitory action. The histopathological results provided additional evidence that the neuronal architecture was preserved and neurodegenerative alterations were reduced after NSD-3 treatment. It seems that antioxidant and cholinergic enhancing mechanisms work together to provide the reported neuroprotective benefits. Taken together, our results suggest that NSD-3 could be a great option for the treatment of Alzheimer's disease due to its multifunctional properties. The therapeutic potential and future drug development of this treatment need further research into molecular mechanism elucidation, pharmacokinetic evaluation, chronic toxicity assessment, and advanced transgenic Alzheimer's disease models.

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None

Conflict of Interest:

None

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