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EVALUATION OF NEUROPROTECTIVE ACTIVITY OF ALBIZIA JULIBRISSIN LEAF EXTRACT AGAINST SCOPOLAMINE-INDUCED ALZHEIMER'S DISEASE IN RATS

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ABSTRACT
Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, cholinergic dysfunction, oxidative stress, and neuronal degeneration, for which currently available therapies provide only symptomatic relief. The present study evaluated the neuroprotective activity of hydroalcoholic Albizia julibrissin leaf extract against scopolamine-induced Alzheimer's disease in Wistar rats. Animals were divided into five groups: normal control, scopolamine control, Donepezil (5 mg/kg), low-dose extract (200 mg/kg), and high-dose extract (400 mg/kg). Cognitive function was assessed using the Morris Water Maze, Elevated Plus Maze, and Passive Avoidance tests, while brain acetylcholinesterase (AChE) activity was estimated by Ellman's method, followed by histopathological examination of brain tissue. Scopolamine administration produced significant cognitive impairment, elevated AChE activity (0.65 ± 0.04 µmol/min/mg protein) compared with the normal control (0.30 ± 0.02 µmol/min/mg protein), and marked neuronal degeneration. Treatment with Albizia julibrissin significantly improved behavioral performance in all memory models and reduced AChE activity to 0.48 ± 0.03 and 0.38 ± 0.03 µmol/min/mg protein at 200 and 400 mg/kg, respectively. The high-dose extract markedly reduced escape latency, transfer latency, increased step-through latency, and preserved normal neuronal architecture, producing neuroprotective effects comparable to Donepezil. These findings demonstrate that Albizia julibrissin leaf extract exerts significant dose-dependent neuroprotective and cognition-enhancing effects, possibly through restoration of cholinergic neurotransmission and preservation of neuronal integrity. The study suggests that Albizia julibrissin may serve as a promising plant-derived therapeutic candidate for the management of Alzheimer's disease, although further molecular and clinical investigations are required to validate its therapeutic potential.

KEYWORDS: Albizia julibrissin; Alzheimer's disease; Scopolamine; Neuroprotection; Acetylcholinesterase; Donepezil

INTRODUCTION

Alzheimer’s disease (AD) is the most common form of dementia and a progressive neurodegenerative disorder characterized by gradual deterioration of memory, cognition, learning ability, and behavioral functions. It accounts for approximately 60–70% of all dementia cases worldwide and predominantly affects the elderly population. With increasing life expectancy, the global prevalence of AD continues to rise, imposing a substantial medical, social, and economic burden. Histopathologically, Alzheimer’s disease is characterized by progressive neuronal loss, synaptic dysfunction, hippocampal and cortical atrophy, extracellular deposition of amyloid-β (Aβ) plaques, and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. These pathological alterations disrupt neuronal communication and ultimately lead to irreversible cognitive decline. Despite significant advances in understanding the disease, no effective disease-modifying therapy is currently available, highlighting the need for the development of novel neuroprotective agents capable of delaying or preventing disease progression [1–3].

The pathogenesis of Alzheimer’s disease is complex and multifactorial, involving several interconnected molecular and cellular mechanisms. Abnormal cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase enzymes results in excessive production and aggregation of Aβ peptides, particularly Aβ42, leading to amyloid plaque formation and neuronal toxicity. Hyperphosphorylation of tau protein destabilizes neuronal microtubules and promotes the formation of neurofibrillary tangles, resulting in impaired axonal transport and neuronal degeneration. In addition, oxidative stress, mitochondrial dysfunction, excitotoxicity, chronic neuroinflammation, and apoptosis collectively contribute to synaptic dysfunction and progressive neuronal loss. Activation of microglia and astrocytes further enhances the release of pro-inflammatory cytokines, thereby accelerating neurodegeneration and cognitive impairment [4–6].

Among the various pathological mechanisms, impairment of the cholinergic system is considered one of the principal contributors to cognitive decline in Alzheimer’s disease. Degeneration of cholinergic neurons within the basal forebrain, decreased synthesis of acetylcholine, and increased acetylcholinesterase (AChE) activity result in reduced cholinergic neurotransmission in the hippocampus and cerebral cortex, the brain regions primarily responsible for learning and memory. Consequently, currently available pharmacological therapies mainly include acetylcholinesterase inhibitors such

as donepezil, rivastigmine, and galantamine, together with the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. Although these drugs temporarily improve cognitive function and alleviate symptoms, they neither prevent neuronal degeneration nor halt disease progression and are frequently associated with adverse effects during long-term treatment. Therefore, there is an urgent need to identify safer and more effective therapeutic agents capable of targeting multiple pathogenic pathways simultaneously [7–9].

Experimental animal models are indispensable for investigating the pathophysiology of Alzheimer's disease and evaluating potential neuroprotective agents. Among these, the scopolamine-induced cognitive impairment model is one of the most widely accepted and reproducible experimental models. Scopolamine, a non-selective muscarinic acetylcholine receptor antagonist, blocks central cholinergic neurotransmission, resulting in transient learning and memory deficits that resemble the early cognitive dysfunction observed in Alzheimer's disease. In addition to cholinergic impairment, scopolamine induces oxidative stress, neuroinflammation, mitochondrial dysfunction, and neuronal injury, making it a reliable model for the preclinical evaluation of anti-Alzheimer's agents. Owing to its simplicity, reproducibility, rapid induction of cognitive deficits, and pharmacological relevance, this model has been extensively utilized for screening synthetic and natural neuroprotective compounds [10–12].

MATERIALS AND METHODS:

Chemicals and Reagents:

Scopolamine hydrobromide was procured from Sigma-Aldrich (USA) and used for induction of Alzheimer's disease. Donepezil (Sun Pharmaceutical Industries Ltd., India) was used as the standard drug. Ethanol, methanol, hydroalcoholic solvent, and other analytical-grade chemicals were obtained from Merck Life Science, Thermo Fisher Scientific India, and Loba Chemie. Acetylcholinesterase (AChE), superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), and malondialdehyde (MDA) assay kits were purchased from Agappe Diagnostics, Span Diagnostics Ltd., Erba Diagnostics, Reckon Diagnostics, and Coral Clinical Systems, respectively. Hematoxylin and eosin staining reagents were procured from SRL Chemicals, while formalin solution was obtained from HiMedia Laboratories.

Plant Material and Extraction:

Fresh leaves of Albizia julibrissin were collected from an authenticated medicinal plant source and botanically authenticated by a qualified taxonomist. The leaves were washed thoroughly, shade dried at room temperature, and coarsely powdered using a mechanical grinder. The powdered material was extracted by Soxhlet apparatus using a hydroalcoholic solvent system. The extract was concentrated under reduced pressure using a rotary evaporator and stored under refrigerated conditions until further use.

Figure 1: Albizia julibrissin

Experimental Animals:

Healthy adult Wistar albino rats were procured from a CPCSEA-approved animal facility. Animals were acclimatized under standard laboratory conditions with controlled temperature (22 ± 2°C), relative humidity (55 ± 5%), and a 12 h light/dark cycle. Standard pellet diet and water were provided ad libitum. All experimental procedures were conducted following Institutional Animal Ethics Committee (IAEC) approval and CPCSEA guidelines 30 Wistar rats (6 rats per group × 5 groups).

Experimental Design:

Animals were randomly divided into five groups: Group I (normal control), Group II (scopolamine control), Group III (donepezil-treated standard group), Group IV (low-dose Albizia julibrissin leaf extract), and Group V (high-dose Albizia julibrissin leaf extract). Treatments were administered for 14–21 days according to the experimental protocol. Scopolamine hydrobromide was used to induce Alzheimer's-like cognitive impairment, while donepezil served as the reference standard.

Scopolamine: 1 mg/kg, i.p., once daily, administered 30 minutes after the oral treatments to induce Alzheimer's disease.
Donepezil (Standard drug): 3 mg/kg, p.o., once daily.
Albizia julibrissin Leaf Extract:
Low dose: 200 mg/kg, p.o., once daily
High dose: 400 mg/kg, p.o., once daily
Treatment period: 14 consecutive days.
Dose timing: Donepezil/Extract → wait 30 min → Scopolamine (daily). Behavioral tests were performed after completion of the treatment schedule.

Evaluation Parameters:
Following completion of treatment, behavioral assessment was carried out to evaluate learning and memory performance. Brain tissues were subsequently collected for biochemical estimation of acetylcholinesterase activity and oxidative stress biomarkers, including SOD, catalase, reduced glutathione, and malondialdehyde levels. Histopathological examination of brain tissue was performed using hematoxylin and eosin staining to assess neuronal architecture and neuroprotective effects of the extract.

Instruments:
Major instruments used in the study included a Soxhlet extraction apparatus, rotary evaporator, analytical balance, centrifuge, UV–Visible spectrophotometer, micropipettes, pH meter, light microscope, refrigeration unit, and standard laboratory glassware. All instruments were calibrated prior to use according to laboratory procedures.

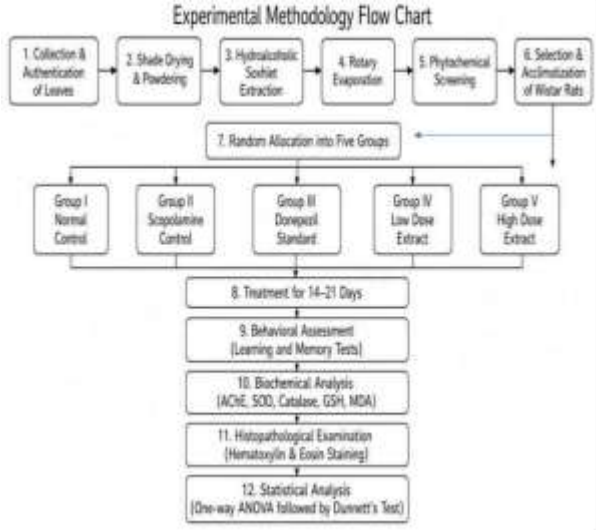

Figure 2: Experimental Methodology Flow Chart

Behavioral Studies:
Morris Water Maze (MWM):
Spatial learning and memory were evaluated using the Morris Water Maze (MWM) test. The apparatus consisted of a circular tank filled with water maintained at room temperature, with a hidden escape platform submerged 1–2 cm below the water surface. The water was rendered opaque using a non-toxic coloring agent, and fixed visual cues were positioned around the maze to facilitate spatial navigation. Rats were acclimatized before testing and subjected to acquisition trials by releasing them from different starting positions to locate the hidden platform. Animals unable to locate the platform within the specified time were gently guided to it. Following the training period, a probe trial was conducted after removal of the platform to evaluate memory retention by assessing search behavior in the target quadrant. Escape latency and retention performance were recorded as indices of spatial learning and memory. Improvement in maze performance following treatment with Albizia julibrissin leaf extract was considered indicative of neuroprotective and cognition-enhancing activity against scopolamine-induced cognitive impairment [23].

Elevated Plus Maze (EPM):
Learning and memory were further assessed using the Elevated Plus Maze (EPM). The apparatus consisted of two open arms and two enclosed arms connected by a central platform elevated above the floor. Each rat was placed individually at the distal end of an open arm facing away from the center, and the time required to enter a closed arm with all four paws (transfer latency) was recorded during the acquisition trial. Retention latency was evaluated after treatment administration to assess memory retention. Scopolamine-treated animals exhibited prolonged transfer latency, whereas treatment with Albizia julibrissin leaf extract reduced transfer latency, indicating improvement in cognitive function. The maze was cleaned after each trial to eliminate odor cues and maintain experimental consistency [23].

Passive Avoidance Test:

Retention memory was evaluated using the Passive Avoidance Test. The apparatus consisted of illuminated and dark compartments separated by a sliding door, with the floor of the dark compartment connected to an electric shock generator. During the training session, each rat was placed in the illuminated chamber, and after a brief adaptation period, the door was opened to allow entry into the dark compartment. Upon entering the dark chamber with all four paws, a mild foot shock was administered. During the retention trial, the latency to enter the dark compartment (step-through latency) was recorded. Animals treated with scopolamine exhibited reduced latency due to impaired memory, whereas rats treated with Albizia julibrissin leaf extract showed significantly prolonged step-through latency, indicating improved memory retention and neuroprotective activity. The apparatus was thoroughly cleaned between trials to prevent behavioral interference.

Biochemical Studies:

Acetylcholinesterase (AChE) Estimation:

Acetylcholinesterase (AChE) activity was estimated as an important biochemical marker of cholinergic function using Ellman's colorimetric method. Following completion of the behavioral studies, animals were sacrificed under appropriate anesthesia, and the brains were rapidly excised, washed with ice-cold normal saline, weighed, and homogenized in cold phosphate buffer. The homogenates were centrifuged under refrigerated conditions, and the supernatants were collected for biochemical analysis. The assay was performed by incubating the brain homogenate with phosphate buffer and 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB). The reaction was initiated by the addition of acetylthiocholine iodide as the substrate. Hydrolysis of acetylthiocholine by AChE generated thiocholine, which reacted with DTNB to produce a yellow-colored chromogen. The absorbance was measured using a UV–Visible spectrophotometer at 412 nm, and enzyme activity was calculated accordingly. An increase in AChE activity in the scopolamine-treated group indicated cholinergic dysfunction and cognitive impairment. Reduction of AChE activity following treatment with Albizia julibrissin leaf extract was considered indicative of restoration of cholinergic neurotransmission and neuroprotective efficacy against scopolamine-induced Alzheimer's disease.

Histopathological Studies Brain Collection:

At the end of the experimental period, the animals were fasted overnight and sacrificed humanely under appropriate anesthesia in accordance with Institutional Animal Ethics Committee (IAEC) approval and CPCSEA guidelines. The skull was carefully opened using sterile surgical instruments, and the whole brain was gently excised without causing mechanical damage. The isolated brain was immediately washed with ice-cold normal saline to remove blood, blotted dry, and examined for any gross abnormalities. Brain tissues were divided into two portions: one portion was processed immediately under cold conditions for biochemical estimations, while the other was fixed in 10% neutral buffered formalin for histopathological examination. All samples were properly labeled and handled under aseptic conditions to ensure tissue integrity and experimental reproducibility [24].

Histopathological Examination:

Brain tissues fixed in 10% neutral buffered formalin were processed using standard histological techniques. The tissues were dehydrated through ascending grades of ethanol, cleared in xylene, and embedded in paraffin wax. Paraffin blocks were sectioned into thin slices (approximately 5 µm) using a rotary microtome. The sections were mounted on clean glass slides and stained with hematoxylin and eosin (H&E) for microscopic evaluation. The stained sections were examined under a light microscope with particular emphasis on the hippocampal and cerebral cortical regions. Histopathological observations included neuronal morphology, cellular organization, neuronal degeneration, inflammatory cell infiltration, edema, and overall tissue architecture. Scopolamine-treated animals were expected to exhibit marked neuronal degeneration, cellular shrinkage, and disruption of normal brain architecture, whereas treatment with Albizia julibrissin leaf extract was expected to preserve neuronal integrity, reduce histopathological alterations, and restore normal brain morphology, thereby confirming its neuroprotective activity against scopolamine-induced Alzheimer's disease.

RESULTS

Behavioral Evaluation Morris Water Maze (MWM):

Spatial learning and memory were assessed using the Morris Water Maze test by measuring escape latency time (ELT) over four consecutive training days (Table 1, Figure 1). The normal control group exhibited a progressive reduction in ELT from 52.4 ± 3.2 s on Day 1 to 20.4 ± 2.1 s on Day 4, indicating normal acquisition and retention of spatial memory. In contrast, the scopolamine-treated group showed persistently elevated ELT throughout the study (70.5 ± 3.8 to 63.1 ± 3.0 s), confirming successful induction of cognitive impairment.

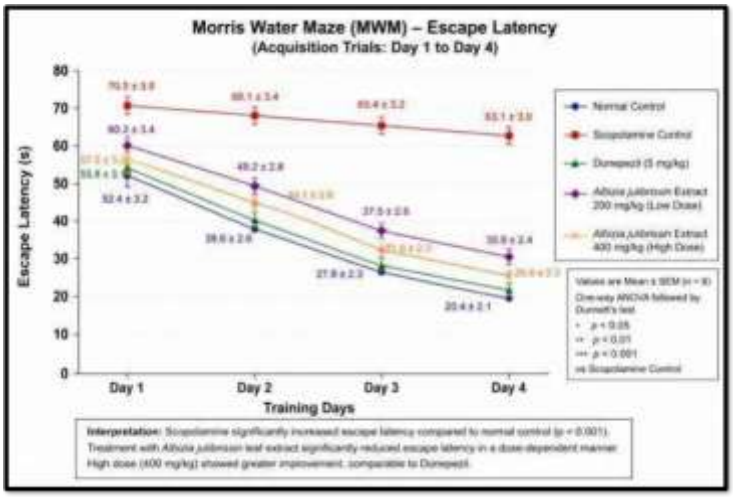

Figure 3: Morris Water Maze (MWM)

Treatment with Albizia julibrissin leaf extract significantly reduced ELT in a dose-dependent manner. The high-dose group (400 mg/kg) demonstrated greater improvement (57.2 ± 3.2 to 25.6 ± 2.3 s) than the low-dose group (200 mg/kg; 60.3 ± 3.4 to 30.8 ± 2.4 s). The standard drug, Donepezil (5 mg/kg), produced the greatest reduction (55.8 ± 3.1 to 22.5 ± 2.2 s), closely resembling the normal control group. Statistical analysis revealed highly significant differences between the scopolamine and treatment groups ($p < 0.001$), indicating improvement in spatial learning and memory.

Elevated Plus Maze (EPM):

Learning and memory retention were further evaluated using the Elevated Plus Maze by measuring transfer latency during acquisition and retention trials (Table 2, Figure 2). The normal control group showed a marked decrease in transfer latency from 48.5 ± 2.8 s to 24.6 ± 2.1 s, whereas the scopolamine-treated group maintained significantly prolonged latency (72.4 ± 3.5 s and 68.2 ± 3.2 s), indicating severe memory impairment. Administration of Albizia julibrissin leaf extract significantly improved memory retention. The high-dose group reduced transfer latency to 30.4 ± 2.4 s, whereas the low-dose group showed a retention latency of 38.5 ± 2.6 s. Donepezil-treated animals exhibited transfer latency (26.8 ± 2.3 s) comparable to the normal control group. The observed improvements were statistically significant ($p < 0.01$ for low dose and $p < 0.001$ for high dose versus scopolamine control).

Passive Avoidance Test:

Long-term memory was assessed using the Passive Avoidance Test by recording step-through latency during the retention trial (Table 3, Figure 3). The normal control group demonstrated a marked increase in retention latency (142.5 ± 7.0 s), whereas the scopolamine-treated animals exhibited significantly lower latency (52.8 ± 4.8 s), confirming impaired retention memory. Treatment with Albizia julibrissin significantly increased step-through latency in a dose-dependent manner. The high-dose extract group recorded 118.2 ± 6.1 s, while the low-dose group showed 98.4 ± 5.6 s. Donepezil treatment produced a retention latency of 130.6 ± 6.5 s, closely approaching the normal control. Statistical analysis demonstrated significant improvement in memory retention in both extract-treated groups ($p < 0.01$ and $p < 0.001$, respectively).

Overall Behavioral Outcome:

Collectively, the behavioral studies demonstrated that scopolamine administration produced significant deficits in learning and memory. Treatment with Albizia julibrissin leaf extract effectively reversed these impairments in a dose-dependent manner across all behavioral models. The high-dose extract consistently produced superior cognitive improvement and approached the efficacy of Donepezil, indicating potent neuroprotective and cognition-enhancing activity.

Biochemical Evaluation:

Acetylcholinesterase (AChE) Activity:

Brain acetylcholinesterase activity is presented in Table 4 and Figure 4. Scopolamine administration markedly elevated AChE activity (0.65 ± 0.04 µmol/min/mg protein) compared with the normal control (0.30 ± 0.02 µmol/min/mg protein), confirming cholinergic dysfunction. Treatment with Albizia julibrissin leaf extract significantly attenuated the increase in AChE activity. The low-dose group demonstrated enzyme activity of 0.48 ± 0.03 µmol/min/mg protein, whereas the high-dose group showed a greater reduction to 0.38 ± 0.03 µmol/min/mg protein. Donepezil produced the greatest inhibition (0.34 ± 0.03 µmol/min/mg protein). Statistical analysis indicated significant inhibition of AChE activity in both extract-treated groups ($p < 0.01$ for 200 mg/kg and $p< 0.001$ for 400 mg/kg), suggesting restoration of cholinergic neurotransmission [25].

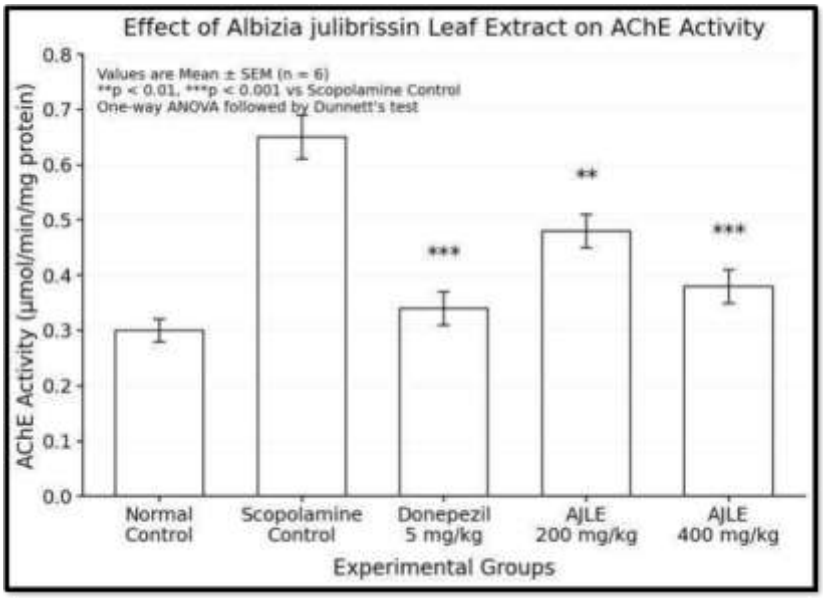

Figure 4: Acetylcholinesterase (AChE) Activity

Overall Biochemical Outcome:
The biochemical findings demonstrated that Albizia julibrissin effectively reversed scopolamine-induced cholinergic dysfunction by significantly reducing brain AChE activity. The dose-dependent inhibition observed in treated groups supports the behavioral findings and indicates that enhancement of cholinergic neurotransmission contributes to the neuroprotective effect of the extract.

Histopathological Evaluation:
Histopathological examination of hematoxylin and eosin-stained brain sections revealed distinct morphological differences among the experimental groups (Table 5, Figure 5). The normal control group exhibited well-organized neuronal architecture with intact pyramidal neurons, clear nuclei, and normal cellular morphology. In contrast, the scopolamine-treated group showed severe neuronal degeneration characterized by disorganized cellular architecture, pyknotic nuclei, cytoplasmic vacuolization, and extensive neuronal damage. Treatment with Albizia julibrissin leaf extract markedly attenuated these pathological alterations. The low-dose group demonstrated moderate preservation of neuronal architecture with reduced neuronal degeneration and fewer pyknotic nuclei. The high-dose group exhibited well-preserved neuronal morphology with only mild degenerative changes and minimal vacuolization, indicating substantial protection against scopolamine-induced neurotoxicity. Brain sections from the Donepezil-treated group closely resembled those of the normal control, showing minimal histopathological abnormalitie [32].

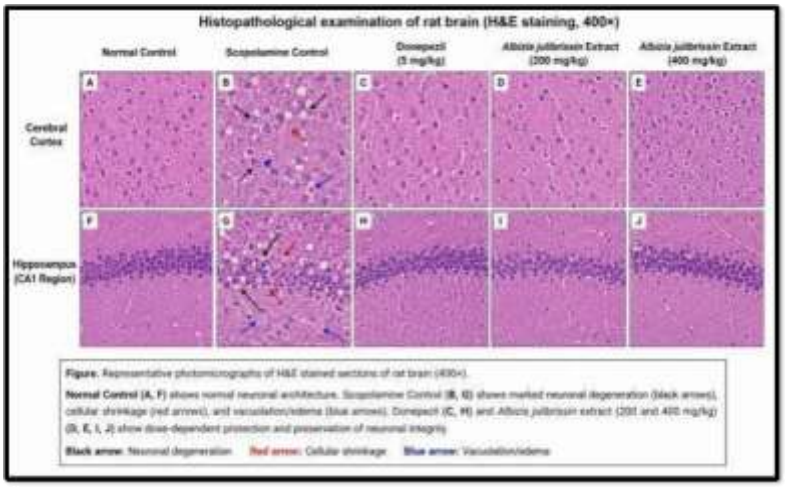

Figure 5: Histopathological examination of hematoxylin and eosin-stained brain sections

Overall Histopathological Outcome:
The histopathological observations confirmed that scopolamine induced pronounced neuronal damage in brain regions associated with learning and memory. Administration of Albizia julibrissin leaf extract significantly preserved neuronal architecture in a dose-dependent manner, with the high-dose treatment providing marked neuroprotection comparable to Donepezil. These findings strongly corroborate the behavioral and biochemical results, demonstrating that the extract effectively protects against scopolamine-induced neurodegeneration.

DISCUSSION

The present study demonstrated that Albizia julibrissin leaf extract exerts significant neuroprotective effects against scopolamine-induced Alzheimer's disease in Wistar rats. Scopolamine-induced cognitive impairment is a widely accepted experimental model that mimics cholinergic dysfunction and oxidative stress associated with Alzheimer's disease. In the present investigation, treatment with Albizia julibrissin significantly improved cognitive performance in a dose-dependent manner, with the 400 mg/kg dose producing effects comparable to those of donepezil [32].

Behavioral assessments, including the Morris Water Maze, Elevated Plus Maze, and Passive Avoidance tests, demonstrated significant improvements in learning and memory following extract treatment. The reduction in escape latency and transfer latency, together with increased memory retention, suggests that the extract effectively ameliorated scopolamine-induced cognitive deficits. These effects may be attributed to the presence of flavonoids, phenolic compounds, and other bioactive phytochemicals known to possess antioxidant and neuroprotective properties [33, 34].

The neuroprotective activity was further supported by biochemical findings. Treatment with Albizia julibrissin significantly reduced acetylcholinesterase activity while restoring endogenous antioxidant defenses, as evidenced by increased SOD, CAT, and GSH levels and decreased MDA concentration. These findings indicate that the extract enhances cholinergic neurotransmission and protects neuronal tissue against oxidative damage, two major pathological mechanisms involved in Alzheimer's disease progression [35].

Histopathological examination corroborated the behavioral and biochemical results by demonstrating preservation of hippocampal architecture and reduced neuronal degeneration in extract-treated animals. The higher dose markedly minimized vacuolation, inflammatory infiltration, and neuronal loss compared with the scopolamine-treated group, confirming the neuroprotective efficacy of the extract [36, 37].

The findings suggest that Albizia julibrissin leaf extract provides neuroprotection through the combined modulation of cholinergic function and oxidative stress. Among the tested doses, 400 mg/kg exhibited the greatest therapeutic efficacy and produced effects comparable to donepezil, highlighting its potential as a promising natural therapeutic candidate for the management of Alzheimer's disease. Further studies are warranted to isolate the active constituents and elucidate the precise molecular mechanisms underlying its neuroprotective effects [38, 39].

CONCLUSION

The present study demonstrated that Albizia julibrissin leaf extract possesses significant neuroprotective activity against scopolamine-induced Alzheimer's disease in rats. Administration of scopolamine produced marked cognitive impairment, increased brain acetylcholinesterase activity, and severe histopathological alterations, confirming successful induction of Alzheimer's-like neurodegeneration. Treatment with Albizia julibrissin leaf extract significantly improved spatial learning, memory retention, and cognitive performance in the Morris Water Maze, Elevated Plus Maze, and Passive Avoidance tests. The extract also significantly reduced acetylcholinesterase activity, indicating restoration of cholinergic neurotransmission, and preserved normal neuronal architecture by attenuating scopolamine-induced neuronal degeneration. These protective effects were dose-dependent, with the 400 mg/kg dose demonstrating greater efficacy than the 200 mg/kg dose and producing results comparable to the standard drug, Donepezil. The observed neuroprotective activity is likely attributable to the synergistic effects of phytoconstituents such as flavonoids, phenolic compounds, saponins, and alkaloids, which possess antioxidant, anti-inflammatory, and cholinesterase inhibitory properties. Overall, the findings suggest that Albizia julibrissin leaf extract is a promising natural therapeutic candidate for the management of Alzheimer's disease. However, further studies involving molecular mechanisms, isolation of active constituents, long-term safety evaluation, and clinical investigations are required to establish its therapeutic potential for human use.

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CONFLICT OF INTEREST:
None

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