Beni-Suef University Journal of Basic and Applied Sciences

REVIEW

Open Access

Huperzine A: a natural acetylcholinesterase inhibitor with multifunctional neuroprotective effects

Suvaiv[1*], Kuldeep Singh[1*], Syed Misbahul Hasan[1], Arun Kumar[1], Abdullah khan[1], Mo. Shahanawaz[1], Syed Mehdi Hasan Zaidi[1] and Kausal Verma[2]

Abstract

Background Huperzine A, a naturally derived compound, has garnered interest for its capacity to inhibit cholinesterase with multifaceted neuroprotective effects and is obtained from Huperzia serrata (Chinese club moss plant). This review highlights its pharmacological potential in the treatment of neurodegenerative disorders, particularly Alzheimer's disease (AD). Huperzine A was used in various neurological conditions in traditional Chinese treatments.

Findings Acetylcholinesterase is responsible for the breakdown of acetylcholine, a neurotransmitter critical for cognitive functions such as memory, learning, and attention. Huperzine A exhibits neuroprotective effects by preserving acetylcholine levels, and also offers antioxidant and anti-inflammatory benefits. These pharmacological actions suggest a potential role in modifying disease progression in AD and vascular dementia (VD). Although preclinical and clinical studies have demonstrated promising cognitive benefits, discrepancies in outcomes still exist. While considered safe at therapeutic dosages, excessive intake may lead to adverse effects, e.g., nausea, diarrhea, and muscle cramps.

Conclusion Research on its effectiveness in various neurological conditions is ongoing, and its use should be approached with caution and professional guidance.

Keywords Huperzine A, Neuroprotection, Acetylcholinesterase (AChE), Alzheimer's disease, Herbal drug, Traditional medicine, Neurotransmitters

1 Introduction

Alzheimer's disease (AD) and other forms of neurodegenerative disorders like vascular dementia (VD), posed significant challenge to public health due to the progressive decline in cognitive function [1]. AD is the most prevalent form of dementia, accounting for 60–70% of cases globally and based on the overall dementia numbers, this suggests that in 2021, roughly 34 to 40 million people worldwide may have had Alzheimer's disease, [2] with projections indicating an increase to 22.51 million cases by 2033, reflecting an annual growth rate of 4.08% [3]. It is the most prevalent form of dementia, is characterised by the degeneration of cholinergic neurons, accumulation of β-amyloid plaques, and the formation of neurofibrillary tangles, leading to significant cognitive decline. Unlike, VD is the second most common form of dementia and primarily arises from cerebrovascular insufficiencies, resulting in ischaemic damage and impaired neuronal function [4]. Acetylcholine in cholinergic signaling, crucial for cerebral blood flow, neuronal communication, and neuroplasticity. Damage to brain blood vessels in Vascular Dementia (VD) disrupts

*Correspondence:
Suvaiv
suvaiv@student.iul.ac.in
Kuldeep Singh
kulintegral@gmail.com
[1] Integral University, Lucknow, India
[2] Shree Krishna College of Pharmacy, Sitapur, India

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

cholinergic pathways, particularly in areas like the basal forebrain. This leads to reduced acetylcholine levels, mirroring the cognitive decline seen in Alzheimer's disease, and the severity of this decline is linked to the degree of cholinergic dysfunction [5].

Depletion of acetylcholine is a major pathological hallmark of both the condition. Huperzine A combined with hyperbaric oxygen has a synergistic effect on improved cognitive function and reduced serum hypoxia-inducible factor-1α (HIF-1α) levels in elderly patients with vascular dementia, suggested enhanced neuroprotection and improved cerebral oxygenation [6]. Alongside acetylcholine depletion, AD pathology also involves β-amyloid plaque accumulation, neurofibrillary tangles, synaptic dysfunction, and progressive neuronal loss [7].

Acetylcholinesterase (AChE) inhibitors have been widely explored as therapeutic agents to slow cognitive decline by preventing the breakdown of acetylcholine [8].

A newly discovered Lycopodium alkaloid with established medical benefits is called Huperzine A (HupA). It is potent, reversible, and specific acetylcholinesterase inhibitor, extracted from the Chinese herb *Huperzia serrata* (Fig. 1) and its cognitive improvement effect has been proven in various animalstudies [9–11].

Study conducted in China, have shown that HupA, when compared to other Acetylcholinesterase Inhibitor (AChEI) now in use, dramatically reduces peripheral cholinergic adverse effects while enhancing memory deficits in older adults and individuals experiencing benign senescent forgetfulness [12].

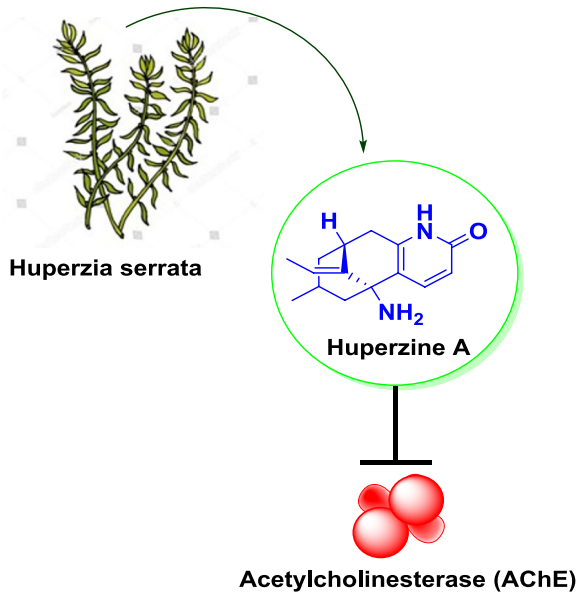


Fig. 1 Huperzine A (*Huperzia serrata)*, a natural acetylcholinesterase inhibitor (AChEI)

HupA's protective benefits are linked to its ability to reduce oxidative stress [13], regulate apoptotic proteins (Bcl-2, Bax, P53, and caspase-3), shield mitochondria, and obstruct APP. It protected cells from ischemia, glutamate, β-amyloid protein (or peptide), hydrogen peroxide, and staurosporine-induced cytotoxicity and apoptosis [14]. Although the exact cause and method of neuronal death in Alzheimer's disease are still unknown, Aβ has been shown to have a crucial role in the pathophysiology of the disease. Even with its complex etiology, genetics is a major factor in the course of the illness [15].

Acetylcholinesterase (AChE) is strongly, selectively, and reversibly inhibited by the active principle, HupA [16]. Its inhibitory potency AChE is on with or more potent than that of tacrine, galanthamine, donepezil, and physostigmine [17, 18].

The multifaceted pharmacological profile of HupA underpins its potential to serve not only as a symptomatic treatment but also as a disease-modifying agent in neurodegenerative conditions [19]. Despite its therapeutic efficacy, the clinical application of Huperzine A remains an area of active research, with studies assessing its efficacy, optimal dosage, and long-term safety [20]. This article aims to review the pharmacological properties of Huperzine A, its therapeutic potential in neurodegenerative conditions and the current state of research on its efficacy and safety.

2 Chemistry and structure of Huperzine A

Huperzine A is an alkaloid found in nature that is a member of the sesquiterpene chemical class [21]. Its molar mass is roughly 242.32 g/mol, and its chemical formula is $C_{15}H_{18}N_2O$. Huperzine A is distinguished by its distinct and intricate structure (Fig. 2), which includes a tetracyclic ring system that has fused. A fused 5,6,9,10-tetrahydro-1H,5H,10H-5,10-ethano-1,3-diazacycloocta [1,2-b] quinoxaline moiety makes up the core moiety of the compound [22]. It occurs naturally as a

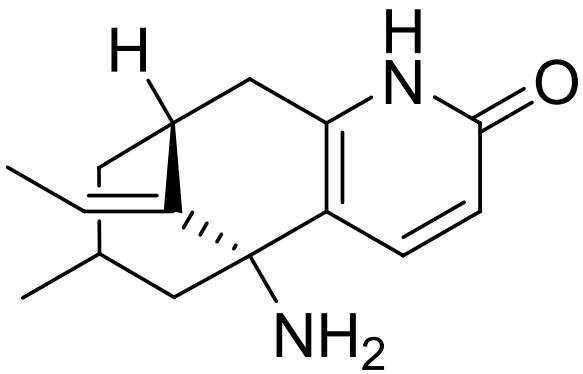


Fig. 2 Chemical structure of Huperzine A

combination of stereoisomers and enantiomer with the (S)-configuration, (−)-Huperzine A, is frequently the most prevalent biologically active form [23]. Two distinct side chains are present in huperzine A: an ethyl group (–C2H5) and a methoxy group (–OCH3). At position eleven, the side chain is fastened to the quinazoline ring. Huperzine A has a bicyclic quinazoline ring that is made up of a pyrimidine ring, in which two nitrogen are fused within a benzene ring [24]. One more addition completes the tetracyclic structure: a ring with six members. Potential hydrogen bonding sites are provided by the nitrogen atoms in the quinazoline ring, which may aid in interactions with biological targets. Different stereoisomers can result from isomerization at the side chain's double bond. Understanding Huperzine A's precise chemical makeup is essential to understanding its pharmacological effects, particularly its function in the central nervous system as an acetylcholinesterase inhibitor [25]. Its unique interactions with biological targets involved in neuroprotection and cognitive function are partly explained by the intricacy of its structure.

3 Reported pharmacological properties of Huperzine A

Huperzine A and its derivatives exhibit several pharmacological activities (Fig. 3), including potent acetylcholinesterase (AChE) inhibitory activity [26, 27]. Huperzine A demonstrates neuroprotective properties, protecting neurons from oxidative stress and excitotoxicity, which may help preserve cognitive function [28]. It possessed anti-inflammatory effects by modulating inflammatory pathways, contributing to reduced neuroinflammation implicated in neurological disorders [9]. Its antioxidant activity alleviates oxidative brain damage, providing further neuroprotective benefits [29]. Huperzine A alleviates oxidative brain damage through direct free radical scavenging and by enhancing endogenous antioxidant defense systems (e.g., superoxide dismutase, catalase, glutathione peroxidase), thereby protects neuronal lipids, proteins, and DNA from oxidative damage. This contributes to overall neuroprotection by preserving neuronal integrity and function in conditions associated with increased oxidative stress, such as traumatic brain injury, neurodegenerative diseases, and stroke [30]. It inhibited the formation of beta-amyloid plaques, addressing Alzheimer's disease and other neurodegenerative conditions. Huperzine A has been reported to increase nerve growth factor levels, supporting neurogenesis and neuronal survival, with potential applications in nerve regeneration [31]. It also has potential to show anticonvulsant properties by modulating cholinergic neurotransmission, influencing central nervous system excitability [32]. While these findings highlight the promising pharmacological activities of Huperzine A, further study is needed to fully validate its mechanisms of action and pharmacological potential in various neurological conditions. Its use should be approached

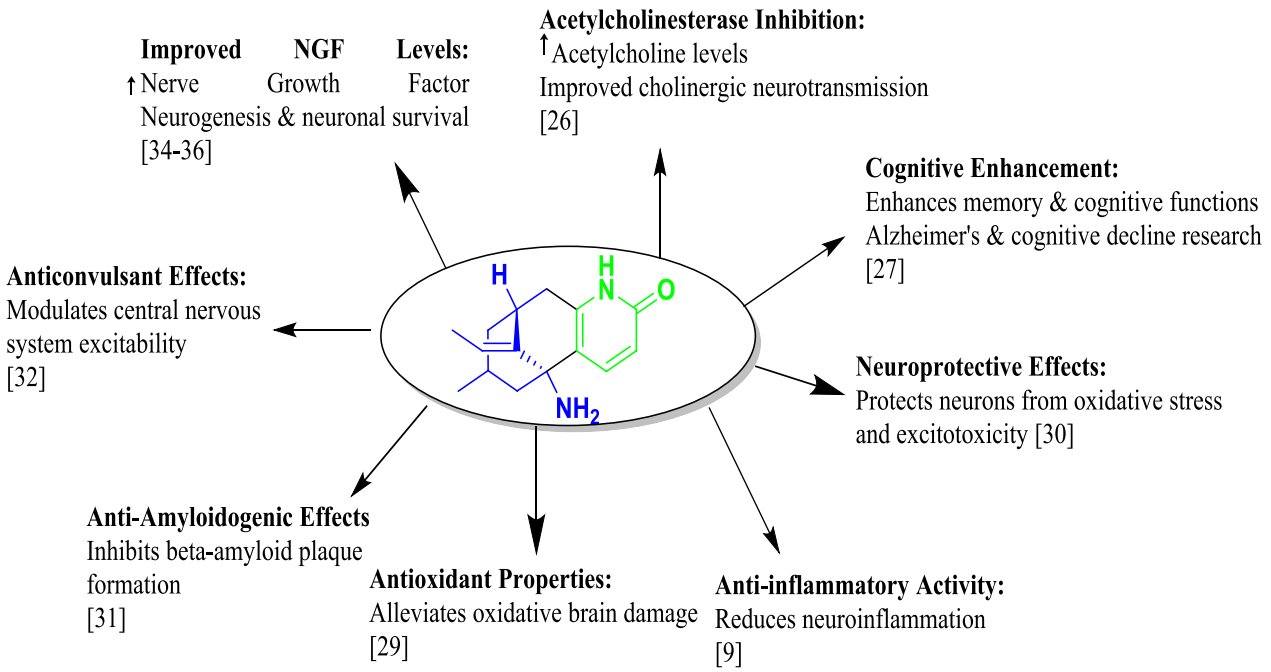


Fig. 3 Various pharmacological properties shown by Huperzine A

cautiously, with consultation from healthcare professionals due to potential side effects and drug interactions [33].

3.1 Cholinergic effects of Huperzine A

HupA has been tested for cholinesterase inhibition, in comparison to other AChE inhibitors used for AD treatment; HupA demonstrated potency that was equal to or greater in both in vitro and in vivo assays [37]. Regarding Half Maximal Inhibitory Concentration (IC_{50}) values, HupA was more effective at inhibiting AChE activity than tacrine, physostigmine, galantamine, and rivastigmine. However, HupA was the weakest inhibitor of Butyrylcholinesterase (BuChE) among those tested [8]. The BuChE:AChE IC_{50} ratio for HupA was significantly higher than that of the other four inhibitors. AChE inhibition by HupA was consistent across various sources. Acetylcholinesterase (AChE) exists in multiple structural forms, which are categorized based on subunit associations and hydrodynamic properties [38, 39]. The monomeric form of AChE (G1, 4S) is present in smaller amounts in the mammalian brain, while the predominant form is tetrameric (G4 form, 10S) [40, 41]. This observation prompted researchers to explore whether HupA could differentially inhibit various forms of acetylcholinesterase (AChE) [42] (Fig. 4).Findings indicated that HupA exhibited a preference for inhibiting the tetrameric acetylcholinesterase (G4 form) whereas tacrine and rivastigmine showed a preference for inhibiting the monomeric AChE (G1 form) [28]. In the striatum and hippocampal regions, donepezil displayed strong selectivity for G1 AChE, although this selectivity was not observed in the cortex. Physostigmine did not exhibit any form-selectivity in any brain region [44]. Huperzine A (HupA) exhibits multiple neuroprotective mechanisms (Fig. 5). It also interferes with amyloid precursor protein (APP) processing, reducing Aβ accumulation (Fig. 4). These combined effects contribute to its therapeutic effect in neurodegenerative disorders.

3.2 Apoptosis inhibition effect of Huperzine A

Beyond its acetylcholinesterase (AChE) inhibition, exhibits notable anti-apoptotic effects, HupA's anti-apoptotic effects result from its capacity to suppress the generation or actions of reactive oxygen species (ROS) [45], regulated apoptosis through the Bcl-2 family of proteins, where high levels of Bcl-2 prevent apoptosis, while proteins like Bax promote it [46]. HupA appears to influence these proteins, reduced apoptosis-associated markers like Bax and p53 and increased Bcl-2 levels (Fig. 6) [47]. It inhibited caspase-3 activation, reduces Aβ-induced caspase-3 activity in neurons, and contributed to its neuroprotective effects [48]. Pre-incubating cells with HupA before H_2O_2 exposure, significantly reduced apoptosis and restored normal levels of Bcl-2, demonstrated its role in countering oxidative damage [46].

3.3 Neuroprotective role of Huperzine A via PKC-mediated APP processing in hypoxic-ischaemic brain injury

HupA upregulates Protein Kinase C (PKC), particularly PKCα, affected the amyloid precursor protein (APP) processing (Fig. 7). A VD model is established in rats by permanent common carotid arteries (CCA) ligation, caused cerebral ischemia, reduced blood flow, cognitive impairment, and neuronal damage [27] Daily oral HupA

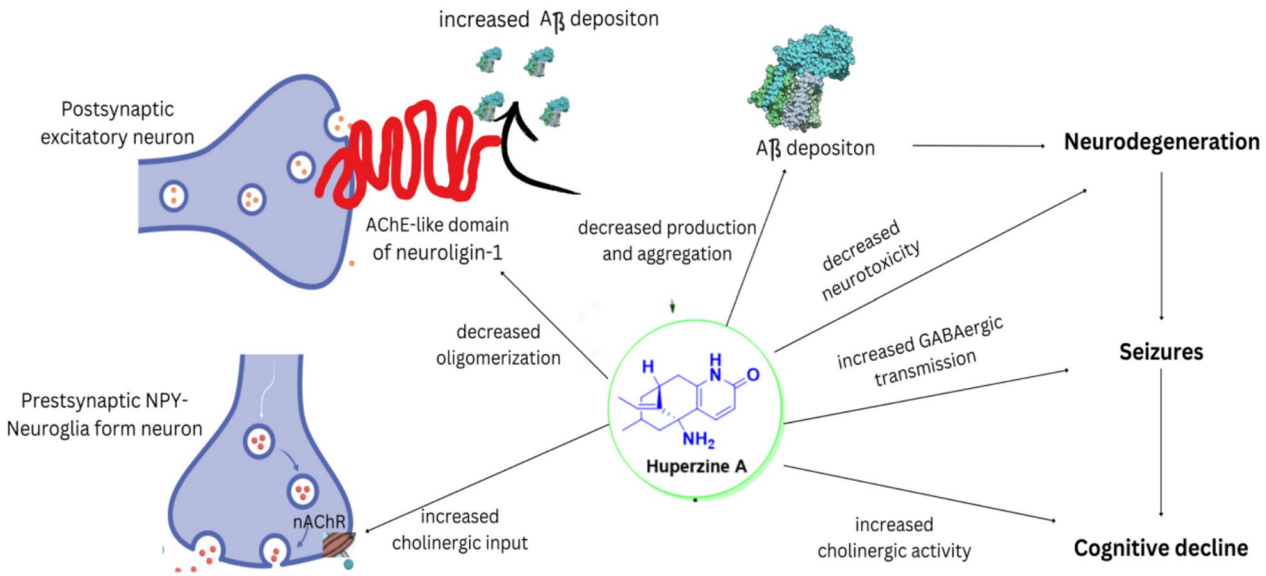


Fig. 4 Disease-modifying capabilities of Huperzine A in neurodegenerative disorders, nAChR; nicotinic acetylcholine receptor

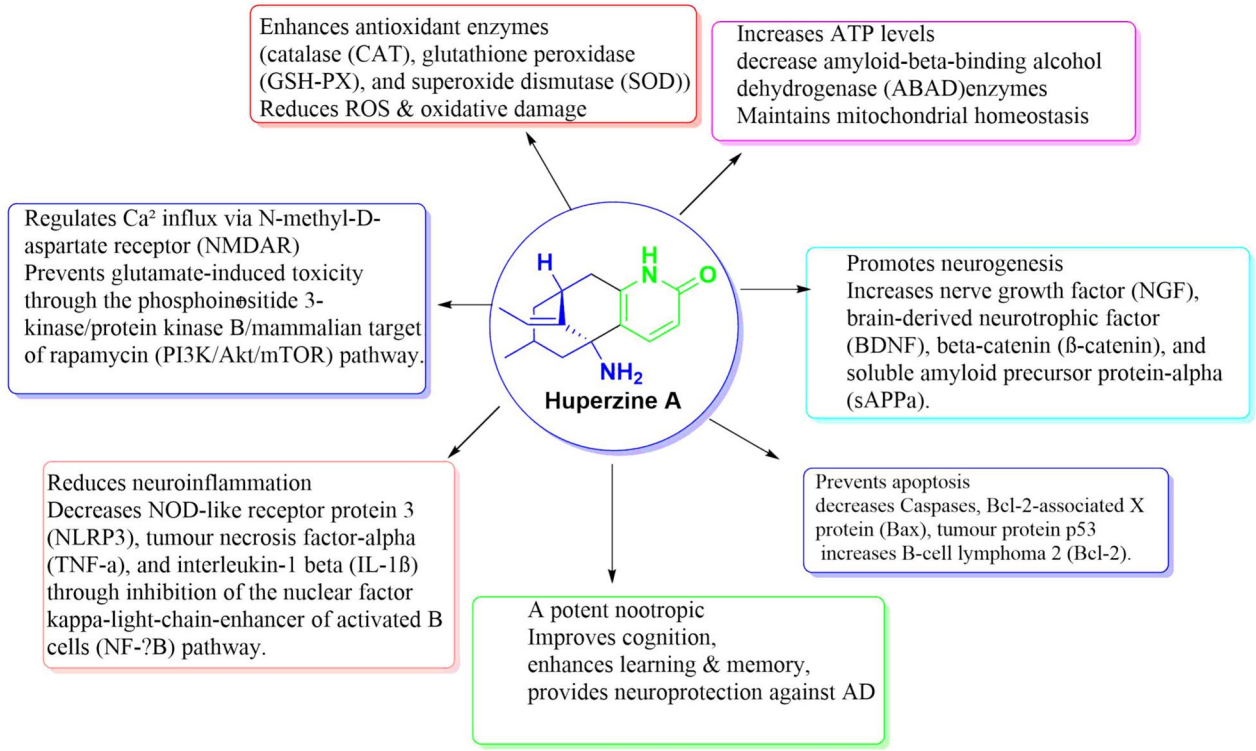


Fig. 5 Miscellaneous neuroprotective mechanisms of Huperzine A in AD

(0.1 mg/kg) for 14 days restored hippocampal choline acetyltransferase activity and normalized superoxide dismutase (SOD), lipid peroxide, lactate, and glucose levels [49]. A study involving rats infused with β-amyloid protein-(1–40) (Aβ 1–40) and human embryonic kidney 293 (HEK293sw) cells, daily administration of HupA for 12 days significantly reversed the Aβ 1–40-induced down-regulation of secretory Amyloid Precursor Protein (APP) and PKC [50]. Results suggested that HupA have a positive effect on the non-amyloidogenic pathway of APP processing. HupA's intervention in the APP metabolic pathway has shown primarily through the up-regulation of PKC, particularly PKCα, which promotes the non-amyloidogenic processing of APP. This effect may benefit AD, by producing neuroprotective soluble APP alpha (sAPPα) [51].

In ischaemic stroke, experimental models have demonstrated that Huperzine A attenuates neuronal apoptosis by upregulating Bcl-2, downregulating pro-apoptotic Bax and p53, and inhibiting caspase-3 activation, thereby preserving mitochondrial membrane potential and promoting neuronal survival under hypoxic conditions [35, 44, 46]. It has also been shown to restore cognitive function in rats subjected to chronic cerebral hypoperfusion, a model relevant to vascular dementia and post-stroke cognitive decline [46]. In the context of traumatic brain injury (TBI), Huperzine A has been reported to reduce oxidative brain damage, enhance superoxide dismutase (SOD) activity, and inhibit lipid peroxidation, which are key contributors to secondary brain injury [52]. The ability of HupA to modulate glutamatergic toxicity through NMDA receptor antagonism further supports its potential in acute CNS injury, where glutamate excitotoxicity is a major driver of neuronal death. Moreover, its enhancement of protein kinase C (PKC) signalling, especially PKCα, promotes non-amyloidogenic APP processing and may benefit long-term synaptic maintenance post-injury [49].

3.4 Effects of Huperzine A on nerve growth factor

HupA enhances Nerve Growth Factor (NGF) induced neuron survival and functional recovery, aid in neurodegenerative disease treatment. Studies have shown, HupA promotes neuronal outgrowth in undifferentiated PC12 cells, enhances NGF expression and secretion, and increases p75NTR mRNA levels in primary astrocytes. Cholinergic mechanisms regulate NGF, supports cholinergic neuron survival and its decline in aging contributes to neurodegeneration [31, 39]. In vitro studies using rat PC12 cells have shown that Huperzine A promotes neurite outgrowth and increases NGF secretion in astrocytes. It upregulates p75 neurotrophin receptor

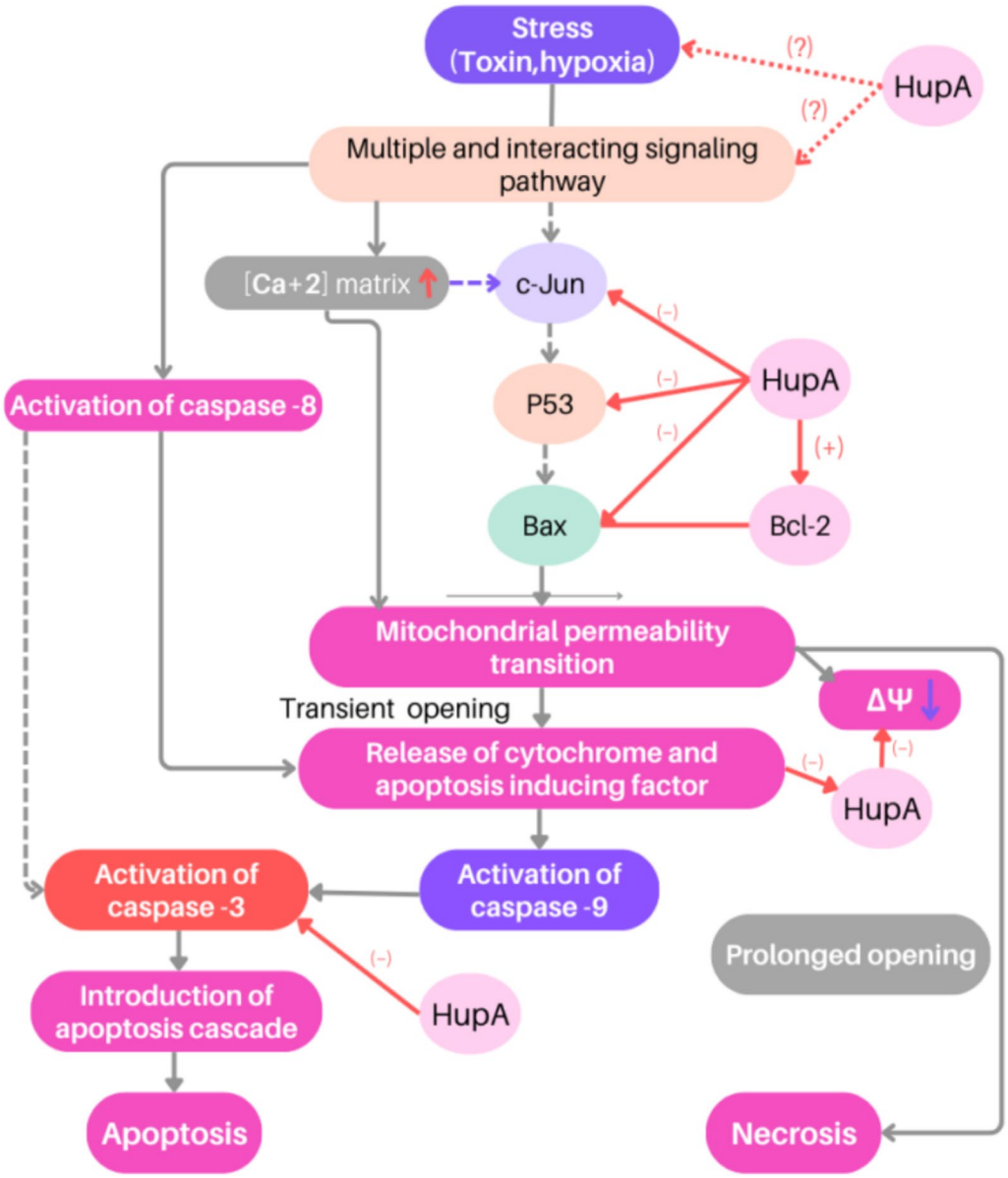


Fig. 6 Anti-apoptotic mechanism of HupA. Stress signals (e.g., toxins, hypoxia) initiate multiple interacting signalling pathways, including calcium ion (Ca^{2+}) matrix influx and c-Jun activation. This modulate tumour protein p53 (P53) and Bcl-2-associated X protein (Bax), leading to mitochondrial permeability transition, results in transient or prolonged opening of the mitochondrial membrane, causing release of cytochrome c and apoptosis-inducing factors, which promote apoptosis. HupA inhibits caspase-3 and caspase-9 activation, downregulates P53 and Bax, and upregulates B-cell lymphoma 2 (Bcl-2), thereby mitigating mitochondrial dysfunction. The figure also shows a decrease in mitochondrial membrane potential (Δψ) and the possible involvement of HupA in modulating these apoptotic events

(p75NTR) mRNA expression, plays a crucial role in NGF-mediated neuronal survival and differentiation [33]. Additionally, by increasing acetylcholine (ACh) levels through acetylcholinesterase (AChE) inhibition, Huperzine A indirectly enhances NGF signalling via activation of muscarinic ACh receptors, which are known to regulate neurotrophic factor release. This cholinergic activation contributes to synaptic plasticity and supports cholinergic neuron survival in the ageing brain, a key target in Alzheimer's pathology [35].

4 Structure activity relationship of Huperzine A

The Structure–Activity Relationship (SAR) study of Huperzine A (Fig. 8) is essential for rational design of derivatives that possess better pharmacological attributes, such as increased AChE inhibition, enhanced

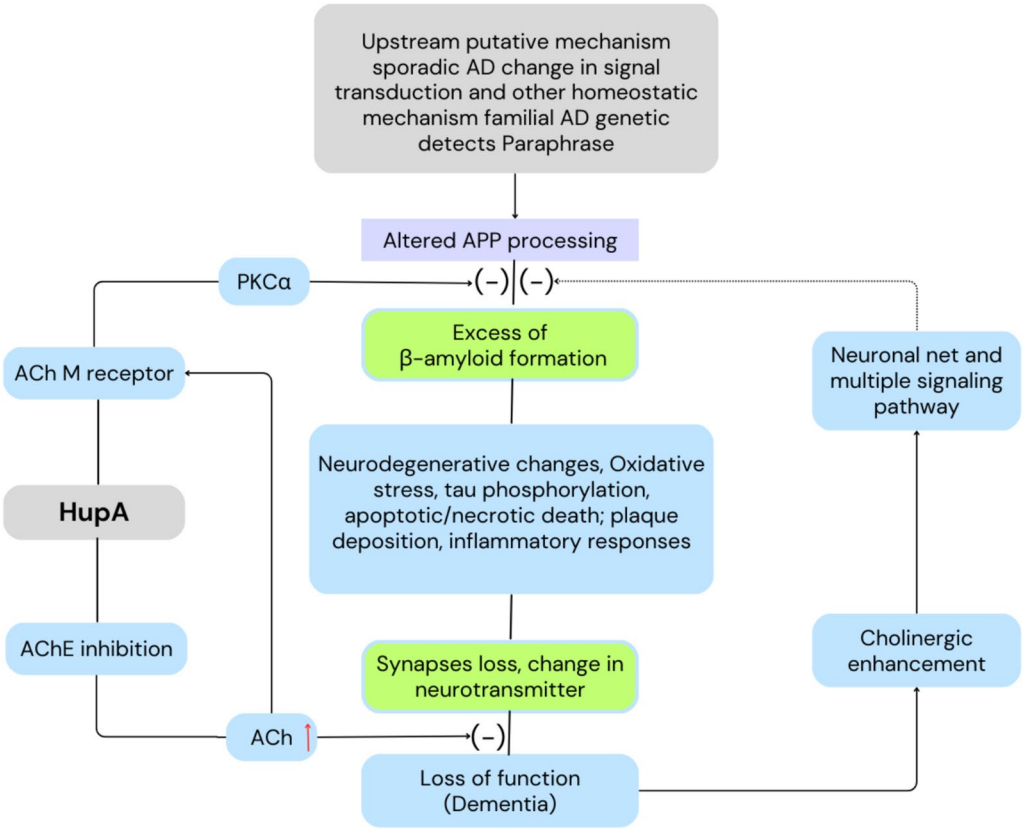


Fig. 7 Effect of HupA by intervention to APP metabolic pathway. The diagram illustrates upstream putative mechanisms in sporadic Alzheimer's disease (AD), involving altered signal transduction and genetic regulation in familial AD. HupA inhibits acetylcholinesterase (AChE), thereby increasing acetylcholine (ACh↑) levels and activating muscarinic acetylcholine (ACh M) receptors. This stimulates protein kinase C alpha (PKCα), modulating APP processing and reducing β-amyloid formation. The resultant effects include prevention of neurodegenerative changes, oxidative stress, tau protein phosphorylation, apoptotic/necrotic neuronal death, plaque deposition, and inflammatory responses. By maintaining synaptic function and neurotransmitter levels, HupA reduces synapse loss and cognitive decline, thus potentially preventing functional loss and dementia. Additionally, HupA supports neuronal network integrity and enhances cholinergic signalling pathways

bioavailability, and decreased side effects. The pharmacological activity of Huperzine A is closely linked to its unique structural features. Its tetracyclic structure and nitrogen-containing heterocycles enhance binding affinity to acetylcholinesterase (AChE) via hydrogen bonding and hydrophobic interactions within the enzyme's active site. The presence of methoxy and ethyl side chains increases lipophilicity, contributing further to membrane permeability and CNS bioavailability [25, 53]. Additionally, the (−)-Huperzine A enantiomer exhibits stronger AChE inhibitory activity, indicating that stereochemistry plays a crucial role in receptor binding and pharmacodynamics [23].

Researchers continue to explore structural modifications to optimize Huperzine A for therapeutic applications in conditions associated with cholinergic dysfunction, such as Alzheimer's disease and other cognitive disorders [25].

5 Pharmacokinetics of Huperzine A

In both rats and healthy human volunteers, HupA is quickly absorbed, widely distributed across the body, and moderately eliminated [54]. On i.v. or oral HupA in rats, a biphasic decline (distribution phase and an elimination phase) was seen in the blood levels of HupA. In mice, 96.9% oral bioavailability was found, with the highest levels of radioactivity observed in the kidney and liver. After intravenous administration of [3H] Only 2.4% of HupA's radioactivity was recovered from the faeces, while the majority was detected in the urine within 24 h [3H]. HupA was excreted partly as its metabolite and the unchanged compound, as indicated by paper chromatography of rat urine [54]

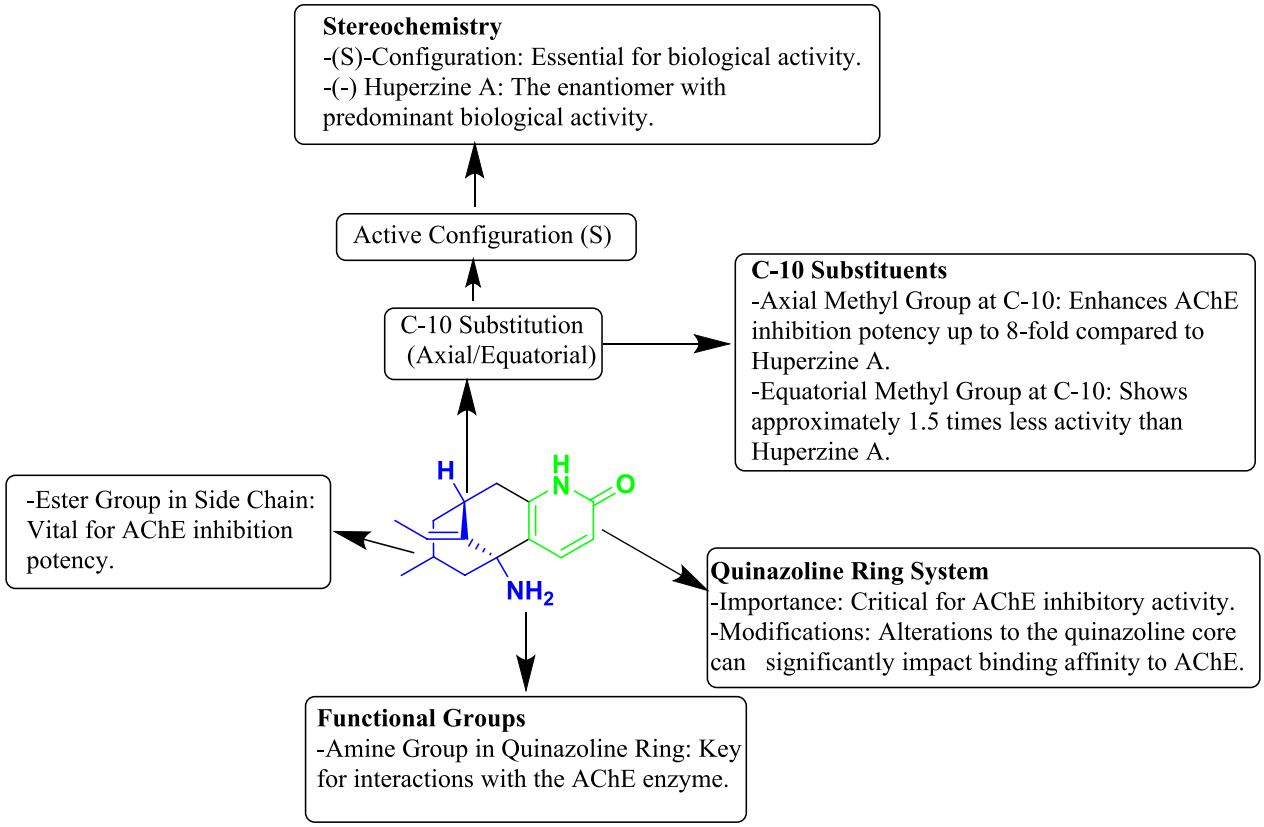


Fig. 8 Structural Components of Huperzine A for better Acetylcholinesterase (AChE) Inhibitory activity

5.1 Comparative profile of Huperzine A with standard AChE inhibitors

To enhance the robustness of our comparative evaluation of Huperzine A and standard acetylcholinesterase inhibitors (AChEIs), a systematic literature review was conducted following the PRISMA 2020 guidelines. Searches were performed across PubMed, Scopus, and Web of Science databases using the keywords: "Huperzine A," "acetylcholinesterase inhibition," "IC_{50}," "blood–brain barrier permeability," "bioavailability," and "comparative studies." Records published between 1995 and 2024 were screened. Inclusion criteria were: (i) English-language articles; (ii) studies reporting IC_{50} values or pharmacokinetic data of Huperzine A and comparators; and (iii) in vitro, in vivo, or clinical studies comparing Huperzine A with other AChEIs. After removing duplicates and irrelevant articles, a total of 8 studies were included in the final analysis. The extracted data were used to construct an updated comparative Table 1 detailing IC_{50} values, blood–brain barrier permeability, oral bioavailability, and key pharmacological insights.

Huperzine A demonstrates a competitive IC_{50} for AChE inhibition compared to tacrine and is more potent than galantamine. It possesses excellent blood–brain barrier permeability and notably high oral bioavailability, especially in rodent models, suggesting good CNS exposure following oral administration. These properties, combined with its antioxidant and neuroprotective mechanisms, support its potential as a strong candidate in the treatment of neurodegenerative diseases such as Alzheimer's.

5.2 Clinical Studies on Huperzine A: efficacy and safety in alzheimer's treatment

Huperzine A has been investigated in several clinical studies for its potential benefits in treating Alzheimer's disease (Table 2) but variations in study design, sample sizes, dosages, and durations contribute to inconsistent findings. Most reported adverse events were mild, moderate, and transient. Robust, large-scale randomized controlled trials are required to validate the efficacy and safety of Huperzine A. Some potential novel combinations with Huperzine A for AD management are discussed in Table 3. Some of the clinical trials are discussed here in details;

Table 1 Comparative properties of Huperzine A and standard AChE inhibitors

Authors	Study Type	Drug	IC_{50} for AChE (nM)	BBB Permeability	Oral Bioavailability (%)	Key Outcomes
Wang and Tang [56]	In vivo (Rat)	Huperzine A	82–112	High	~96.9	High potency; excellent CNS delivery
Zhang et al. [61]	Clinical Trial	Huperzine A	–	High	~96.9	Effective in mild–moderate AD; mild side effects
Rafii et al. [60]	Clinical Trial	Huperzine A	–	High	–	400 µg/day improved cognition at 11 weeks
[58]	Review (Human)	Donepezil	~6	High	~100	Reversible AChEI; long half-life
Desilets et al. [57]	Review (Human)	Galantamine	~600	Moderate	~80–90	Dual mechanism; less potent than HupA
Wang and Tang [56]	In vivo (Rat)	Tacrine	~77	High	~30–40	Withdrawn in some countries due to hepatotoxicity
Wang and Tang [56]	In vivo (Rat)	Rivastigmine	~4.1	High	~36	Short half-life; dual AChE and BuChE inhibition
Mak et al. [18, 55]	In silico & preclinical	Huprines (Tacrine-Huperzine hybrids)	< 1–10	High	–	Highly potent hybrids; potential for drug development

Clinical data for Huperzine A show cognitive improvements at doses of 300–500 µg/day with mild adverse events

Preclinical IC_{50} values of HupA are competitive with standard inhibitors

Compared to galantamine and tacrine, HupA exhibits superior safety, BBB penetration, and neuroprotective effects

Data collected via PubMed and Scopus (search terms: "Huperzine A", "AChE inhibition", "IC_{50}", "Alzheimer", "bioavailability") from 1995 to 2024

Table 2 Clinical trial data of Hup A in AD treatment

Sample Size	Duration	Dosage	Cognitive Function Improvement (MMSE)	ADL improvement	Adverse events	Comparison to placebo	References
210	16 weeks	200 µg BD and 400 µg BD	No significant improvement at 200 µg BD; 400 µg BD showed improvement at 11 weeks but not at 16 weeks	No significant change	Mild to moderate, transient adverse events	HupA > Placebo at 400 µg BD	[59, 60]
202	8–12 weeks	200 µg daily	Significant improvement at 8, 12, and 16 weeks	Significant improvement at 6, 8, and 12 weeks	No severe adverse events reported	HupA > Placebo	[61]
131	12 weeks	400 mg/day	Significant improvement at 8, 12 weeks	Significant improvement at	No severe adverse events reported	HupA > Placebo	[64]
733 (AD)	8–24 weeks	300–500 µg daily	Significant improvement; longer durations resulted in better efficacy	Significant improvement	Mild to moderate, transient adverse events	HupA > Placebo	[66]
4 RCTs Data	8–24 weeks	300–500 µg daily	Significant improvement	Significant improvement	Mild to moderate, transient adverse events	HupA > Placebo	[67]

MMSE: Mini-Mental State Examination, ADL: Activities of Daily Living scale, RCTs: Randomized Controlled Trials

5.3 Rafii et al. 2011—US Phase II RCT

Design Multicenter, randomized, double-blind, placebo-controlled (3-arm dose-escalation) trial. Patients and raters were blinded; allocation was 1:1:1. [59, 60]

Sample 210 patients with mild-to-moderate Alzheimer's disease (AD) (mean age ~ 74–75 years, ADAS-Cog and Mini-Mental State Examination (MMSE) defined) were randomized; 177 completed 16 weeks. Participants

Table 3 Potential Novel Combinations with Huperzine A for AD Management

Combination	Mechanism of action	Evidence summary	Reference
Huperzine A + Curcumin	- Huperzine A: Acetylcholinesterase inhibitor and NMDA receptor antagonist - Curcumin: Anti-inflammatory and antioxidant properties	An open-label study demonstrated cognitive improvements in patients with Alzheimer's disease, dementia with Lewy bodies, and mild cognitive impairment when administered a supplement containing Huperzine A and Curcumin over 6–28 weeks	[68]
Huperzine A + Resveratrol	- Huperzine A: Acetylcholinesterase inhibitor - Resveratrol: Activates sirtuins and reduces β-amyloid accumulation	While direct studies on this combination are limited, resveratrol has shown potential in modulating neurodegenerative pathways relevant to AD. Further research is needed to assess the efficacy of this combination	[69]
Huperzine A + Memantine	- Both agents modulate NMDA receptors; Huperzine A also inhibits acetylcholinesterase	A 24-week randomized trial found that combining Huperzine A with Memantine improved cognitive function and daily living activities more than Memantine alone in AD patients	[70]
Huperzine A + Coenzyme Q10 (CoQ10)	- Huperzine A: Acetylcholinesterase inhibitor - CoQ10: Supports mitochondrial function and reduces oxidative stress	Direct studies on this combination are lacking, CoQ10's role in mitochondrial protection suggests potential benefits when combined with Huperzine A. Clinical trials are needed to validate this hypothesis	[71]
Huperzine A + Probiotics	- Huperzine A: Acetylcholinesterase inhibitor - Probiotics: Modulate gut-brain axis, reduce neuroinflammation	A study involved a human-origin probiotics cocktail in an AD mouse model showed reduced cognitive decline and AD pathology. Combining this with Huperzine A may offer synergistic benefits, though human studies are necessary	[72]
Tacrine – Huperzine	Both agents inhibits acetylcholinesterase	In preclinical studies, Tacrine–Huperzine A hybrids (huprines) showed enhanced AChE inhibition, high selectivity, and brain penetration. These findings suggest potential synergistic benefits for Alzheimer's treatment, though clinical studies are needed to confirm efficacy	[55]

While some combinations have shown promise in preliminary studies, further clinical trials are essential to establish their safety and efficacy in humans

had probable AD (MMSE around 10–26, per ADCS criteria) [60].

Intervention Oral huperzine A, 200 µg twice daily (BID) or 400 µg BID (total 400 or 800 µg/day), for 16 weeks [60].

Control Placebo (matched tablets) in a parallel arm [60].

Outcomes Primary outcome was change in cognitive function (ADAS-Cog) at week 16 (200 µg vs placebo). Secondary outcomes included ADAS-Cog (400 µg arm), MMSE, ADCS-Clinical Global Impression of Change (CGIC), ADCS-Activities of Daily Living (ADL), and Neuropsychiatric Inventory (NPI) [60].

Results The 200 µg dose showed no significant change in ADAS-Cog vs placebo at 16 weeks. In the secondary analysis, the 400 µg dose produced a statistically significant 2.27-point ADAS Cog improvement over placebo at 11 weeks (placebo declined 0.29; $p=0.001$), but the effect was not significant at 16 weeks (1.92 vs. 0.34 points; $p=0.07$). No significant differences were seen on global impression (CGIC), NPI, or ADL at either dose. Overall, the trial "provides Class III evidence" that huperzine A 200 µg BID has no clear cognitive benefit in mild–moderate AD. No serious adverse events were attributed to huperzine A; common mild side effects (nausea, insomnia) were similar in all groups [60].

Limitations Relatively small sample and short duration limit statistical power. The 3-arm design (two active doses plus placebo) reduced power per comparison. High dropout (33/210) may bias results. The trial only tested two doses and did not include an active comparator. Results may not generalize beyond the studied dose/duration. This U.S. trial had rigorous design but found no definitive benefit at the primary dose. It was later included in systematic reviews and meta analyses of huperzine A in AD [59].

5.4 Zhang et al. 2002—Chinese Multicenter RCT

Design Multicenter, randomized, double-blind, placebo-controlled trial. Patients and investigators were masked [61].

Sample 202 patients with "possible or probable" mild-to-moderate AD (Mini-Mental State Examination (MMSE) 11–26), across 15 centers in China. Baseline characteristics (age ~ 68 years, equal gender distribution, mean MMSE ≈18) were similar between groups [61].

Intervention Huperzine A (marketed as "huperzine Alpha") 0.4 mg/day (administered presumably as 200 µg BID) for 12 weeks. The treatment group also received vitamin E 200 mg/day (per Chinese AD practice) [61].

Control Placebo tablets (plus 200 mg/day vitamin E, given to both groups) received equivalent vitamin E, isolating huperzine A vs placebo [61].

Outcomes Cognitive and functional outcomes were measured at baseline and 12 weeks. Reported scales included ADAS-Cog, MMSE, ADAS-Noncog (behavior/mood), CIBIC-Plus (Clinician 1 Interview-Based Impression of Change), and ADL scale. Global impression (CIBIC-Plus) was also assessed [61].

Results The huperzine A group showed statistically significant improvements. Mean ADAS-Cog improved by 4.6 points from baseline ($p \leq 0.001$), versus minimal change in placebo. Notably, 56.1% of huperzine-treated patients improved ≥ 4 points on ADAS-Cog versus 12.5% on placebo ($p \leq 0.001$). MMSE rose by 2.7 points ($p \leq 0.001$). CIBIC-Plus "improved" (scores 1–3) in 59.2% vs 40.6% ($p=0.01$), and ADL ≥ 10% improved in 32.7% vs 17.2% ($p=0.01$). Behavioral (ADAS Noncog) also improved significantly with huperzine A (70.0% vs 36.3% improved; $p \leq 0.001$). Adverse effects were infrequent and mild (e.g. peripheral edema, insomnia in ~ 3%). The authors concluded huperzine A "remarkably improves cognition, behavior, ADL, and mood" [61].

Limitations Concomitant vitamin E (given to both groups) may confound attribution of benefit solely to huperzine A. The 12-week duration is short. Methods reporting is limited (detailed allocation and blinding procedures not shown). Outcomes are reported primarily as comparisons to baseline rather than between-group differences, raising risk of reporting bias. The trial was published in Chinese and not peer-reviewed in Western journals. No long-term follow-up data were provided. Despite positive results, generalizability is uncertain. This trial and its data were included in later reviews [73] noting modest cognitive/functional gains with huperzine A but overall low quality of evidence [59].

5.5 Other Chinese RCTs (1995–2003)

Several small Chinese placebo-controlled RCTs examined huperzine A in AD. These were included in the review (6 trials, 454 patients) [62]. Key examples include:

Liu et al. [63] *(28 pts)* Double-blind RCT in 28 mild AD patients. Patients received huperzine A (0.3–0.4 mg/day) or placebo (duration not stated in abstract). The trial reported no significant differences in adverse cholinergic effects between groups. Cognitive outcomes were not clearly reported in the abstract; likely small improvements were seen [63].

Xu et al. [64] *(131 pts)* Double-blind RCT, comparing 0.4 mg/day huperzine A vs placebo for 12 weeks. Reportedly assessed memory, cognition, behavior. In pooled analysis [62], this trial contributed data on MMSE, Hasegawa Dementia Scale, and others. It showed greater MMSE/ADAS-Cog gains with huperzine, but differences in some scales (HDS, WMS) did not reach significance [64].

Yang et al. [65] *(65 pts)* Single-center RCT of 0.3 mg/day huperzine A vs placebo for 16 weeks. A significant benefit was reported on global dementia stage (CDR): huperzine A improved CDR scores compared to placebo ($p \leq 0.05$). Other cognitive/functional results were not detailed in the English summary [65].

Summary These Chinese trials generally reported that huperzine A improved cognitive scores (MMSE, ADAS-Cog or Chinese equivalents) and ADL more than placebo, with mild and transient side effects. However, all were relatively small (28–131 subjects), short (8–16 weeks), and often of limited quality. The Cochrane review [62] noted that only one trial (Zhang 2002) had adequate randomization, and that overall evidence quality was low. The observed benefits (e.g. 2–3 point MMSE gains or ADAS-Cog improvements) were modest.

Limitations (general to these trials) Small sample sizes and short follow-up limited power and assessment of long-term effects. Many studies were published only in Chinese without full methodological detail. Blinding and allocation procedures were often unclear. Several trials co administered vitamin E or other medicines, confounding attribution of effect to huperzine A. High risk of publication bias is likely (nearly all published trials reported positive findings). Adverse events were reported as mild, but systematic reporting was limited. None of these trials compared huperzine A to standard Western AChE inhibitors.

6 Safety and side effects of Huperzine A

Huperzine A may interact with medications that affect cholinergic neurotransmission or have anticholinergic effects. This includes medications for Alzheimer's disease, antipsychotics, and certain medications for gastrointestinal issues [73, 74]. Responses can vary among individuals; some may be more sensitive to its effects, while others may tolerate it well. Due to limited safety information in pregnancy and lactation, pregnant or nursing individuals should consult healthcare professionals before using Hup A. Huperzine A, potentially lead to cholinergic side effects including excessive salivation, sweating, and muscle twitches [75]. Some individuals may experience gastrointestinal discomfort, including stomach pain. Headaches and dizziness at higher doses or in those sensitive to cholinergic effects, have also been reported [75]. It may cause insomnia or difficult sleep and can influence blood pressure, so individuals with cardiovascular conditions should use it with caution [59]. It is suggested for individuals considering the use of Huperzine A to do so under the guidance of a healthcare professional. Self-medication, especially without proper knowledge of dosage and potential interactions, can lead to adverse effects.

Long-term safety data on Huperzine A, particularly in elderly populations, remain limited but encouraging. Several clinical trials involving elderly patients with Alzheimer's disease or vascular dementia have reported favourable safety profiles over treatment durations of 8 to 24 weeks, with most adverse events being mild, transient, and cholinergic in nature (e.g., nausea, dizziness, gastrointestinal discomfort) [60, 66]. Notably, a large-scale meta-analysis encompassing over 1,800 elderly participants indicated no severe adverse events directly attributed to Huperzine A, even at dosages up to 500 µg daily [59, 67]. Due to the age-related decline in hepatic and renal function, and the potential for polypharmacy in elderly individuals, cautious monitoring is advised. Continued longitudinal studies and post-marketing surveillance are essential to fully establish the safety of chronic Huperzine A administration in geriatric populations.

7 Conclusion and future perspectives

Huperzine A, a naturally derived and reversible acetylcholinesterase inhibitor, demonstrates strong neuroprotective and cognitive-enhancing effects, particularly in Alzheimer's disease (AD). The compound's preferential inhibition of the tetrameric AChE form (G4), along with excellent blood–brain barrier permeability and high oral bioavailability, distinguish it from conventional AChE inhibitors. Preclinical models validate its therapeutic effects in diverse neuropathologies, including hypoxic–ischaemic brain injury and traumatic brain injury. Combinations with agents such as curcumin, memantine, resveratrol, CoQ10, and probiotics suggest synergistic potential in enhancing neuroprotection and cognitive function. The emergence of tacrine–huperzine hybrid with enhanced potency further highlights the importance of structure–activity relationship (SAR) optimisation. Despite encouraging results from early trials, larger and well-designed randomised studies are needed to confirm its efficacy, define optimal dosing, and evaluate long-term safety particularly in elderly and comorbid populations. Future research should also explore novel delivery systems to improve brain targeting and investigate biomarkers for personalised therapeutic approaches. Phase IV trials and post-marketing surveillance will be essential to ensure safe clinical translation.

7.1 Limitations

Despite encouraging findings, limitations exist. Many clinical studies are small, short-term, and vary in quality, often lacking standard comparators. Long-term safety data remain limited, particularly in elderly and comorbid populations. Further well-designed randomized controlled trials are required to confirm its efficacy, optimize dosing, and assess long-term outcomes.

Acknowledgements
The authors extend their sincere gratitude to Integral University, Lucknow, India, for assigning the manuscript communication number to this article.... IU/R&D/2025-MCN0003450.

Author contribution
Suvaiv: Writing—Original Draft, Review & Editing. Kuldeep Singh: Visualization, Supervision, Project administration, Investigation Syed Misbahul Hasan: Visualization, Supervision, Arun Kumar: Conceptualization Abdullah khan: Review & Editing, Mo. Shahanawaz:, Software, Validation Syed Mehdi Hasan Zaidi: Visualization, Formal analysis Kausal Verma: Resources, Formal analysis.

Funding
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 21 March 2025 Accepted: 5 August 2025
Published online: 16 August 2025

References

1. Ahmad FB, Cisewski JA, Xu J, Anderson RN (2023) Provisional mortality data—United States, 2022. MMWR Morb Mortal Wkly Rep 72(18):488
2. (https://www.who.int/news-room/fact-sheets/detail/dementia)
3. GlobalData. Alzheimer's disease total prevalent cases across 8MM to reach 22.51 million in 2033, forecasts GlobalData. GlobalData. 2025 Jan 6. Available from: https://www.globaldata.com/media/pharma/alzheimers-disease-total-prevalent-cases-across-8mm-to-reach-22-51-million-in-2033-forecasts-globaldata/)
4. Ornello R et al (2018) Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes: a systematic review and meta-analysis. Stroke 49(4):814–819
5. Bir SC, Khan MW, Javalkar V, Toledo EG, Kelley RE (2021) Emerging concepts in vascular dementia: a review. J Stroke Cerebrovasc Dis 30(8):105864
6. Li J, Meng X, Li F, Liu J, Ma M, Chen W (2021) Huperzine A combined with hyperbaric oxygen on the effect on cognitive function and serum hypoxia-inducible factor-1α level in elderly patients with vascular dementia. Am J Transl Res 13(6):6897
7. Hampel H et al (2018) The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain 141(7):1917–1933
8. Khanal P et al (2021) Integration of system biology tools to investigate huperzine A as an anti-Alzheimer agent. Front Pharmacol 12:785964
9. Zhang H, Wang D, Sun J, Wang Y, Wu S, Wang J (2022) Huperzine—A improved animal behavior in cuprizone-induced mouse model by alleviating demyelination and neuroinflammation. Int J Mol Sci 23(24):16182
10. Wei DX, Cai D, Tan Y et al (2024) Poly (3-hydroxybutyrate-co-3-hydroxyvalerate-co-3-hydroxyhexanoate)-based microspheres as a sustained platform for Huperzine A delivery for alzheimer's disease therapy. Int J Biol Macromol 282:136582
11. Ghassab-Abdollahi N et al (2021) The effects of Huperzine A on dementia and mild cognitive impairment: an overview of systematic reviews. Phytother Res 35(9):4971–4987
12. Zhang K, Wang H (2024) Development and validation of a highly sensitive UPLC–MS/MS method for the determination of Huperzine A in rat plasma. Biomed Chromatogr 38(11):e6011
13. Su J, Chen K, Sang X et al (2024) Huperzine A ameliorates sepsis-induced acute lung injury by suppressing inflammation and oxidative stress via α7 nicotinic acetylcholine receptor. Int Immunopharmacol 141:112907
14. Wongjaikam S, Nopparat C, Boontem P, Panmanee J, Thasana N, Shukla M, Govitrapong P (2024) Huperzine A regulates the physiological homeostasis of amyloid precursor protein proteolysis and tau protein conformation—a computational and experimental investigation. Biology 13(7):518
15. Kamatham PT, Shukla R, Khatri DK, Vora LK (2024) Pathogenesis, diagnostics, and therapeutics for Alzheimer's disease: breaking the memory barrier. Ageing Res Rev 101:102481
16. Dadlani VG, Pawar HA, Tripathi PK (2023) Huperzine-based derivatives: design, synthesis, and anti-alzheimer activity. In: Natural product-based synthetic drug molecules in Alzheimer's disease: therapeutic & theranostic agents (pp. 213–244). Singapore, Springer Nature Singapore..
17. Grigorev VY, Rasdolsky AN, Grigoreva LD, Tinkov OV (2021) Structural fractal analysis of the active site of acetylcholinesterase in complexes with huperzine A, galantamine, and donepezil. Mol Inform 40(11):2100127
18. Mak S et al (2021) Promising tacrine/huperzine A-based dimeric acetylcholinesterase inhibitors for neurodegenerative disorders: from relieving symptoms to modifying diseases through multitarget. J Neurochem 158(6):1381–1393
19. Tun MKM, Herzon SB (2012) The pharmacology and therapeutic potential of (−)-huperzine A. J Exp Pharmacol. https://doi.org/10.2147/JEP.S27084
20. Gul A, Bakht J, Mehmood F (2019) Huperzine-A response to cognitive impairment and task switching deficits in patients with Alzheimer's disease. J Chin Med Assoc 82(1):40–43
21. https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:78330.
22. National Center for Biotechnology Information (2025) PubChem Compound Summary for CID 854026, Huperzine A. Retrieved March 20, 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/854026
23. Raves ML, Harel M, Pang YP, Silman I, Kozikowski AP, Sussman JL (1997) Structure of acetylcholinesterase complexed with the nootropic alkaloid, (–)-huperzine A. Nat Struct Biol 4(1):57–63
24. Sarfraz M, Sultana N, Rashid U, Akram MS, Sadiq A, Tariq MI (2017) Synthesis, biological evaluation and docking studies of 2, 3-dihydroquinazolin-4 (1H)-one derivatives as inhibitors of cholinesterases. Bioorg Chem 70:237–244
25. Zhu X, Xu JB, Gao F, Wan LX (2024) Advances in the structural modification of Alzheimer's disease drug–Huperzine A. Bioorgan Chem 108012
26. Li Y, Li Q, Sun M, Song G, Jiang S, Zhu D (2004) 1H NMR relaxation investigation of acetylcholinesterase inhibitors from huperzine A and derivative. Bioorg Med Chem Lett 14(6):1585–1588
27. Wessinger CM, Inman CL, Weinstock J, Weiss EP (2021) Effect of huperzine A on cognitive function and perception of effort during exercise: a randomized double-blind crossover trial. Int J Exerc Sci 14(2):727
28. Friedli MJ, Inestrosa NC (2021) Huperzine A and its neuroprotective molecular signaling in Alzheimer's disease. Molecules 26(21):6531
29. Yang Y, Dai L, Wu D, Dong L, Tu Y, Xie J, Luo X (2021) In vitro propagation, Huperzine A content and antioxidant activity of three genotypic *Huperzia serrata*. Plants 10(6):1112
30. Pohanka M, Hrabinova M, Zemek F, Drtinova L, Bandouchova H, Pikula J (2011) Huperzine induces alteration in oxidative balance and antioxidants in a guinea pig model. Neuro Endocrinol Lett 32(Suppl 1):95–100
31. Qian ZM, Ke Y (2014) Huperzine A: is it an effective disease-modifying drug for Alzheimer's disease? Front Aging Neurosci 6:216
32. Damar U, Gersner R, Johnstone JT, Schachter S, Rotenberg A (2017) Huperzine A: a promising anticonvulsant, disease modifying, and memory enhancing treatment option in Alzheimer's disease. Med Hypotheses 99:57–62
33. Yang G et al (2025) Improved protective effects and pharmacokinetics of Huperzine A derivative H14 in soman poisoning: a comparative study with Huperzine A in rats. Rapid Commun Mass Spectrom 39(9):e9995
34. Tang LL, Wang R, Tang XC (2005) Effects of huperzine A on secretion of nerve growth factor in cultured rat cortical astrocytes and neurite outgrowth in rat PC12 cells. Acta Pharmacol Sin 26(6):673–678
35. Ma T et al (2013) Huperzine A promotes hippocampal neurogenesis in vitro and in vivo. Brain Res 1506:35–43

36. Yan YP, Chen JY, Lu JH (2022) Disease-modifying activity of huperzine A on Alzheimer's disease: evidence from preclinical studies on rodent models. Int J Mol Sci 23(23):15238
37. Ellman GL, Courtney KD, Andres V Jr, Featherstone RM (1961) A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem Pharmacol 7(2):88–95
38. Brimijoin S (1983) Molecular forms of acetylcholinesterase in brain, nerve and muscle: nature, localization and dynamics. Prog Neurobiol 21(4):291–322
39. Mufson EJ, Bothwell M, Kordower JH (1989) Loss of nerve growth factor receptor-containing neurons in Alzheimer's disease: a quantitative analysis across subregions of the basal forebrain. Exp Neurol 105(3):221–232
40. Bon S, Vigny M, Massoulié JEAN (1979) Asymmetric and globular forms of acetylcholinesterase in mammals and birds. Proc Natl Acad Sci U S A 76(6):2546–2550
41. Grassi J, Vigny M, Massoulié J (1982) Molecular forms of acetylcholinesterase in bovine caudate nucleus and superior cervical ganglion: solubility properties and hydrophobic character. J Neurochem 38(2):457–469
42. Graham SH, Chen J (2001) Programmed cell death in cerebral ischemia. J Cereb Blood Flow Metab 21(2):99–109
43. Xi-Can T, Kindel GH, Kozikowski AP, Hanin I (1994) Comparison of the effects of natural and synthetic huperzine-A on rat brain cholinergic function *in vitro* and *in vivo*. J Ethnopharmacol 44(3):147–155
44. Xiao XQ, Zhang HY, Tang XC (2002) Huperzine A attenuates amyloid β-peptide fragment 25–35-induced apoptosis in rat cortical neurons via inhibiting reactive oxygen species formation and caspase-3 activation. J Neurosci Res 67(1):30–36
45. Wang R, Tang XC (2005) Neuroprotective effects of huperzine A: a natural cholinesterase inhibitor for the treatment of Alzheimer's disease. Neurosignals 14(1–2):71–82
46. Wang LS, Zhou J, Shao XM, Tang XC (2002) Huperzine A attenuates cognitive deficits and brain injury in neonatal rats after hypoxia–ischemia. Brain Res 949(1–2):162–170
47. Zamzami N, Kroemer G (2001) The mitochondrion in apoptosis: how Pandora's box opens. Nat Rev Mol Cell Biol 2(1):67–71
48. Wang LM, Han YF, Tang XC (2000) Huperzine A improves cognitive deficits caused by chronic cerebral hypoperfusion in rats. Eur J Pharmacol 398(1):65–72
49. Zhang HY, Yan H, Tang XC (2004) Huperzine A enhances the level of secretory amyloid precursor protein and protein kinase C-α in intracerebroventricular β-amyloid-(1–40) infused rats and human embryonic kidney 293 Swedish mutant cells. Neurosci Lett 360(1–2):21–24
50. Al-Kuraishy HM et al (2023) Evaluation and targeting of amyloid precursor protein (APP)/amyloid beta (Aβ) axis in amyloidogenic and non-amyloidogenic pathways: a time outside the tunnel. Ageing Res Rev 92:102119
51. Ohba T, Nakamura S, Shimazawa M, Hayashi Y, Kono H, Hara H (2020) Protective effects of *Huperzia serrata* and its components against oxidative damage and cognitive dysfunction. PharmaNutrition 13:100203
52. de Sousa LF, Paschoal DF, Novato WT (2024) Molecular modeling of multitarget analogs of huperzine A and applications in Alzheimer's disease. J Mol Model 30(7):200
53. Camps P et al (1999) Synthesis, in vitro pharmacology, and molecular modeling of very potent Tacrine−Huperzine A hybrids as acetylcholinesterase inhibitors of potential interest for the treatment of Alzheimer's disease. J Med Chem 42(17):3227–3242
54. Wang YE, Feng J, Lu WH, Tang XC (1988) Pharmacokinetics of huperzine A in rats and mice. Zhongguo yao li xue bao= Acta Pharmacologica Sinica 9(3):193–196
55. Camps P et al (2000) New tacrine− huperzine A hybrids (huprines): highly potent tight-binding acetylcholinesterase inhibitors of interest for the treatment of Alzheimer's disease. J Med Chem 43(24):4657–4666
56. Wang H, Tang XC (1998) Anticholinesterase effects of huperzine A, E2020, and tacrine in rats. Zhongguo yao li xue bao= Acta pharmacologica Sinica 19(1):27–30
57. Desilets AR, Gickas JJ, Dunican KC (2009) Role of huperzine A in the treatment of Alzheimer's disease. Ann Pharmacother 43(3):514–518
58. PubChem: Compound Summary for CID 3152 (Donepezil). Retrieved May 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/3152
59. Yang G, Wang Y, Tian J, Liu JP (2013) Huperzine A for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials. PLoS ONE 8(9):e74916
60. Rafii MS, Walsh S, Little JT, Behan K, Reynolds B, Ward C (2011) Alzheimer's disease cooperative study. A phase II trial of huperzine A in mild to moderate Alzheimer disease. Neurology 76(16):1389–1394
61. Zhang Z, Wang X, Chen Q, Shu L, Wang J, Shan G (2002) Clinical efficacy and safety of huperzine Alpha in treatment of mild to moderate Alzheimer disease, a placebo-controlled, double-blind, randomized trial. Zhonghua Yi Xue Za Zhi 82(14):941–944
62. Li J, Wu HM, Zhou RL, Liu GJ, Dong BR (2008) Huperzine A for Alzheimer's disease. Cochrane Database Syst Rev
63. Liu FG, Fang YS, Gao ZX, Zuo JD, Sou ML (1995) Double-blind control treatment of huperzine-A and placebo in 28 patients with Alzheimer disease. Chin J Pharmacoepidemiol 4:196–198
64. Xu SS et al (1995) Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Zhongguo yao li xue bao = Acta Pharmacologica Sinica 16(5), 391–395
65. Yang CY, Lu ZP, Zheng CG (2003) Efficacy and reliability of huperzine A in mild and moderate Alzheimer's disease. Chin J Clin Rehabil 7:4258–4259
66. Xing SH, Zhu CX, Zhang R, An L (2014) Huperzine A in the treatment of alzheimer′ s disease and vascular dementia: a meta-analysis. Evid Based Complement Alternat Med 2014(1):363985
67. Wang BS, Wang H, Wei ZH, Song YY, Zhang L, Chen HZ (2009) Efficacy and safety of natural acetylcholinesterase inhibitor huperzine A in the treatment of Alzheimer's disease: an updated meta-analysis. J Neural Transm 116:457–465
68. Tabira T, Kawamura N (2018) A study of a supplement containing huperzine A and curcumin in dementia patients and individuals with mild cognitive impairment. J Alzheimers Dis 63(1):75–78
69. Roy KK, Mehta DK, Das R (2025) Reevaluating Alzheimer's disease treatment: can phytochemicals bridge the therapeutic gap? Neuroscience 575:1–18
70. Shao ZQ (2015) Comparison of the efficacy of four cholinesterase inhibitors in combination with memantine for the treatment of Alzheimer's disease. Int J Clin Exp Med 8(2):2944
71. Tripathi PN et al (2024) Review of pharmacotherapeutic targets in Alzheimer's disease and its management using traditional medicinal plants. Degenerat Neurol Neuromusc Dis. https://doi.org/10.2147/DNND.S452009
72. Prajapati SK, Wang S, Mishra SP, Jain S, Yadav H (2025) Protection of Alzheimer's disease progression by a human-origin probiotics cocktail. Sci Rep 15(1):1589
73. Zhang L et al (2013) The effects of huperzine A on gastrointestinal acetylcholinesterase activity and motility after single and multiple dosing in mice. Exp Ther Med 5(3):793–796
74. Chu Z et al (2024) Pharmacology, phytochemistry, and traditional uses of Huperzia serrata (Thunb. ex Murray) Trev. Fitoterapia: 106304
75. Bredsdorff L, Pilegaard K (2018) Concern for adverse effects of huperzine A when sold as an ingredient in food supplements. Toxicol Lett 295(Suppl. 1):S145

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.