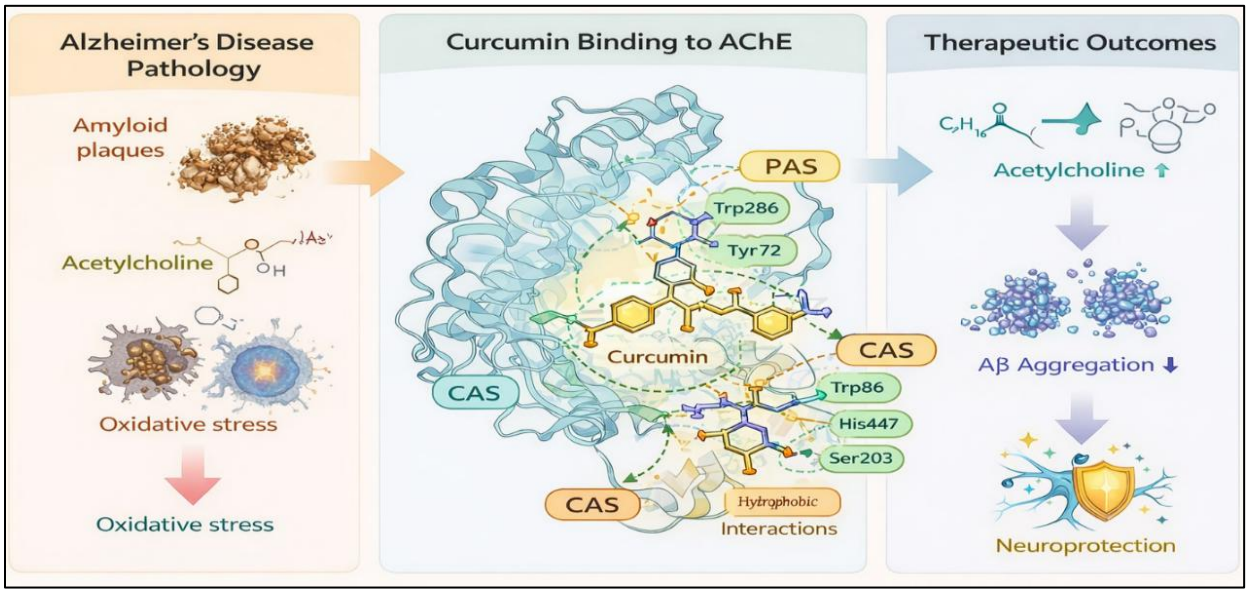
Structural and Molecular Determinants of Curcumin Binding to Human Acetylcholinesterase in Alzheimer's Disease

Medha Morisetti [1] ,Pranati Das[2] ,Rupak Roy[3]
[1] *Sancta Maria International School, Hyderabad*
[2 3] *SHRM Biotechnologies Pvt Ltd, Kolkata*

***Abstract*—Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, cholinergic dysfunction, and amyloid-β (Aβ) aggregation. Human acetylcholinesterase (hAChE), a key enzyme responsible for acetylcholine hydrolysis, plays a dual role in AD pathogenesis by contributing not only to neurotransmitter depletion but also to Aβ fibrillogenesis through its peripheral anionic site (PAS). Current acetylcholinesterase inhibitors provide symptomatic relief but lack disease-modifying potential. Curcumin, a polyphenolic compound derived from *Curcuma longa*, has emerged as a promising multi-target molecule due to its antioxidant, anti-inflammatory, anti-amyloidogenic, and enzyme-modulating properties. This review comprehensively examines the structural and molecular determinants governing curcumin binding to hAChE. We discuss the architecture of the catalytic active site (CAS) and PAS, highlighting key aromatic and catalytic residues involved in ligand recognition. Experimental inhibition assays, molecular docking, and molecular dynamics studies collectively suggest that curcumin engages both CAS and PAS through hydrogen bonding, hydrophobic contacts, and π–π stacking interactions, supporting a dual-site binding mechanism. Such interactions may simultaneously attenuate acetylcholine hydrolysis and disrupt AChE-induced Aβ aggregation, aligning with the multi-target-directed ligand (MTDL) paradigm. Despite limitations related to bioavailability and clinical translation, advances in nanoformulation, structural analog development, and computational drug design continue to enhance curcumin's therapeutic potential. Understanding the molecular basis of curcumin–hAChE interaction may facilitate the rational development of optimized derivatives as next-generation neuroprotective agents for AD management.**

***Index Terms*—Alzheimer's disease; Human acetylcholinesterase; Curcumin; Molecular docking; Dual-site inhibition; Multitarget-directed ligands**



I. INTRODUCTION

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder characterized by cognitive decline, memory impairment, and behavioral disturbances. It represents the most common cause of dementia worldwide, accounting for approximately 60–70% of all dementia cases (Alzheimer's Association, 2023). The global prevalence of AD continues to rise due to increased life expectancy, posing substantial medical, social, and economic burdens on healthcare systems and caregivers. Neuropathologically, AD is defined by extracellular deposition of amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic loss, and widespread neuronal degeneration (Selkoe & Hardy, 2016). Despite decades of research, disease-modifying therapies remain limited, and currently approved treatments primarily provide symptomatic relief.

Pharmacological management of AD largely relies on acetylcholinesterase inhibitors (AChEIs), including donepezil, rivastigmine, and galantamine, as well as the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. These agents modestly improve cognitive symptoms but do not significantly alter disease progression (Cummings, Lee, Zhong, Fonseca, & Taghva, 2021). Furthermore, their clinical efficacy is often constrained by gastrointestinal side effects, cardiovascular risks, and diminishing therapeutic response over time. Consequently, there remains a critical need for multi-target therapeutic strategies capable of addressing both symptomatic and pathological components of AD.

The cholinergic hypothesis, one of the earliest and most extensively validated models of AD pathogenesis, proposes that degeneration of basal forebrain cholinergic neurons leads to reduced cortical and hippocampal acetylcholine (ACh) levels, contributing directly to cognitive deficits (Bartus, Dean, Beer, & Lippa, 1982). Acetylcholine plays a central role in learning, memory consolidation, and synaptic plasticity. Impaired cholinergic neurotransmission has consistently been correlated with the severity of cognitive decline in AD patients (Hampel et al., 2018). Restoration of synaptic acetylcholine levels through inhibition of acetylcholinesterase (AChE), the enzyme responsible for rapid hydrolysis of ACh, remains a primary therapeutic approach.

Beyond its catalytic function in neurotransmission, AChE has been implicated in amyloid pathology. The enzyme contains a peripheral anionic site (PAS) that interacts with amyloid-β peptides and accelerates fibrillogenesis, contributing to plaque maturation and enhanced neurotoxicity (Inestrosa et al., 1996). Thus, AChE plays a dual role in AD: regulating cholinergic signaling and promoting amyloid aggregation. This dual functionality positions human acetylcholinesterase (hAChE) as a critical molecular target for both symptomatic and disease-modifying interventions.

In recent years, natural polyphenolic compounds have gained attention as potential multi-target-directed ligands (MTDLs) for neurodegenerative disorders. Curcumin, the principal bioactive constituent of *Curcuma longa*, exhibits antioxidant, anti-inflammatory, metal-chelating, and anti-amyloidogenic properties (Anand et al., 2008; Yang et al., 2005). Importantly, its planar aromatic structure enables interaction with protein targets through hydrogen bonding, hydrophobic interactions, and π–π stacking, suggesting potential binding within the aromatic gorge of hAChE. Although curcumin demonstrates modest inhibitory potency compared to synthetic AChE inhibitors, its pleiotropic biological effects make it an attractive candidate for multi-target modulation in AD.

The present review aims to critically examine the structural and molecular determinants governing curcumin binding to human acetylcholinesterase. By integrating biochemical, structural, and computational evidence, this work seeks to elucidate interaction mechanisms, evaluate inhibitory potential, and assess the therapeutic relevance of curcumin–hAChE interactions in Alzheimer's disease. Understanding these molecular foundations may contribute to the rational design of optimized curcumin-based derivatives with enhanced pharmacological efficacy.

II. HUMAN ACETYLCHOLINESTERASE: STRUCTURE AND FUNCTION

Human acetylcholinesterase (hAChE) is a pivotal enzyme in cholinergic neurotransmission, terminating synaptic signaling by rapidly hydrolyzing the neurotransmitter acetylcholine into acetate and choline. Structurally, hAChE belongs to the α/β hydrolase fold family and is characterized by a deep, narrow gorge lined with aromatic amino acids that guide substrates and inhibitors toward the active site (Hung et al., 2025). At the base of this gorge resides the *catalytic active site (CAS)*, which consists of a classical serine catalytic triad — Ser203, His447, and Glu334 — responsible for the hydrolysis of acetylcholine's ester bond (Hung et al., 2025). Adjacent to the CAS is the choline-binding subsite, where residues such as Trp86 and Tyr337 interact via cation–π and hydrophobic interactions to position the acetylcholine molecule for optimal catalysis (Cheung et al., 2012).

In addition to the CAS, hAChE contains a *peripheral anionic site (PAS)* near the entry of the active-site gorge. Key residues such as Trp286, Tyr72, Tyr124, and Asp74 compose the PAS and are implicated in non-catalytic functions, including the modulation of substrate access and interactions with non-substrate ligands (Inestrosa et al., 1996). The presence of this peripheral site is particularly relevant in the context of Alzheimer's disease (AD) because PAS interacts with amyloid-β (Aβ) peptides, accelerating their aggregation and stabilizing neurotoxic fibrils (Inestrosa et al., 1996). X-ray crystallography and computational studies have further highlighted the dynamic nature of the active site gorge and the importance of aromatic residues in ligand binding and specificity, offering insights into how dual-site inhibitors can be designed to target both CAS and PAS simultaneously (Hung et al., 2025).

Physiologically, hAChE ensures precise termination of cholinergic signaling, which is essential for cognitive functions such as learning and memory. Pathologically, altered AChE activity is observed in AD, where its interaction with Aβ fosters plaque development and contributes to synaptic dysfunction (Hampel et al., 2018). Understanding the dual structural and functional roles of hAChE — both catalytic and modulatory — provides a molecular foundation for therapeutic targeting in AD.

III. ACETYLCHOLINESTERASE IN ALZHEIMER'S DISEASE PATHOGENESIS

Alzheimer's disease is characterized by progressive cognitive decline, synaptic dysfunction, and widespread neuronal loss, with cholinergic system impairment forming a central pathological component. The *cholinergic hypothesis* posits that degeneration of basal forebrain cholinergic neurons and a consequent reduction in acetylcholine availability in the cortex and hippocampus contribute directly to cognitive deficits in AD patients (Bartus, Dean, Beer, & Lippa, 1982). Chronic depletion of acetylcholine hampers synaptic transmission, thereby disrupting memory formation and attention processes, which are hallmark deficits in AD.

In addition to cholinergic neuron loss, AChE expression and distribution become dysregulated in the AD brain. AChE is detected not only in synaptic regions but also in amyloid plaques, suggesting its involvement in plaque pathology (Perry, Basile, & Greig, 2000). The interaction between hAChE's peripheral anionic site (PAS) and amyloid-β peptides has been shown to accelerate fibrillogenesis, producing highly stable AChE–Aβ complexes with enhanced neurotoxicity compared to Aβ alone (Inestrosa et al., 1996). These complexes exacerbate oxidative stress, mitochondrial dysfunction, and inflammation, thus linking cholinergic dysregulation with amyloid pathology and neuronal damage.

Moreover, AChE activity levels in various AD models correlate with disease severity, and its dysregulation contributes to impaired synaptic plasticity and cognitive decline (Hampel et al., 2018). The multifaceted involvement of hAChE in both neurotransmitter hydrolysis and amyloid aggregation underscores its importance not merely as a symptomatic target but as a pathological nexus in AD progression.

IV. CURCUMIN: CHEMICAL PROPERTIES AND NEUROPROTECTIVE POTENTIAL

Curcumin, a polyphenolic compound isolated from the rhizome of *Curcuma longa*, exhibits a distinctive chemical architecture comprising two phenolic rings connected by a conjugated β-diketone linker capable of existing in keto–enol tautomeric forms. This structure endows curcumin with strong free radical scavenging capacity, metal-chelating potential, and the ability to form hydrogen bonds and π–π interactions with protein targets (Li Li et al., 2024; Menon & Sudheer, 2007). Notably, the aromatic and conjugated nature of curcumin facilitates its interaction within hydrophobic binding pockets, highlighting its suitability as a ligand for enzymes such as hAChE.

Curcumin's neuroprotective potential is multifactorial and highly relevant in the context of AD. It exhibits potent antioxidant activity by scavenging reactive oxygen and nitrogen species, reducing lipid peroxidation, and enhancing endogenous antioxidant defenses (Li Li et al., 2024; Ak & Gülçin, 2008). Curcumin also modulates inflammatory pathways by inhibiting nuclear factor-κB (NF-κB) activation and the subsequent expression of pro-inflammatory cytokines, which are elevated in AD brains (Li Li et al., 2024). Furthermore, curcumin attenuates amyloid plaque formation by directly binding to Aβ aggregates and inhibiting fibrillogenesis, thereby reducing amyloid burden and associated neurotoxicity (Yang et al., 2005).

Another significant mechanism involves curcumin's interaction with key signaling pathways implicated in neuronal survival and plasticity. Research indicates that curcumin may influence PI3K/Akt signaling, thereby modulating glycogen synthase kinase-3β (GSK-3β) activity and reducing tau phosphorylation, which is critical in AD pathology (Li Li et al., 2024; turn0search5). These mechanisms collectively offer a rationale for curcumin as a multi-target therapeutic candidate capable of addressing oxidative stress, neuroinflammation, amyloid deposition, and cholinergic dysfunction — all central features of AD pathology.

V. MOLECULAR INTERACTION OF CURCUMIN WITH HUMAN ACETYLCHOLINESTERASE

5.1 Binding Sites and Mechanistic Interactions

Molecular docking and simulation studies provide critical insights into how curcumin interacts with hAChE at the molecular level. The active-site gorge of AChE comprises two principal subregions: the catalytic active site (CAS) and the peripheral anionic site (PAS). CAS is responsible for acetylcholine hydrolysis, while PAS influences substrate entry and non-catalytic interactions with ligands such as Aβ peptides (Hung et al., 2025). Computational studies consistently demonstrate that curcumin can interact with both CAS and PAS residues, forming stabilizing π–π stacking, hydrogen bonding, and hydrophobic interactions.

For instance, curcumin's phenolic rings may engage in π–π stacking with aromatic residues such as Trp86 (CAS) and Trp286 (PAS), whereas its β-diketone linker can form hydrogen bonds with residues lining the gorge entrance and deepen interactions within the catalytic pocket (Khan et al., 2018). These binding characteristics suggest a dual-site engagement that partially obstructs substrate traffic and dampens enzymatic activity.

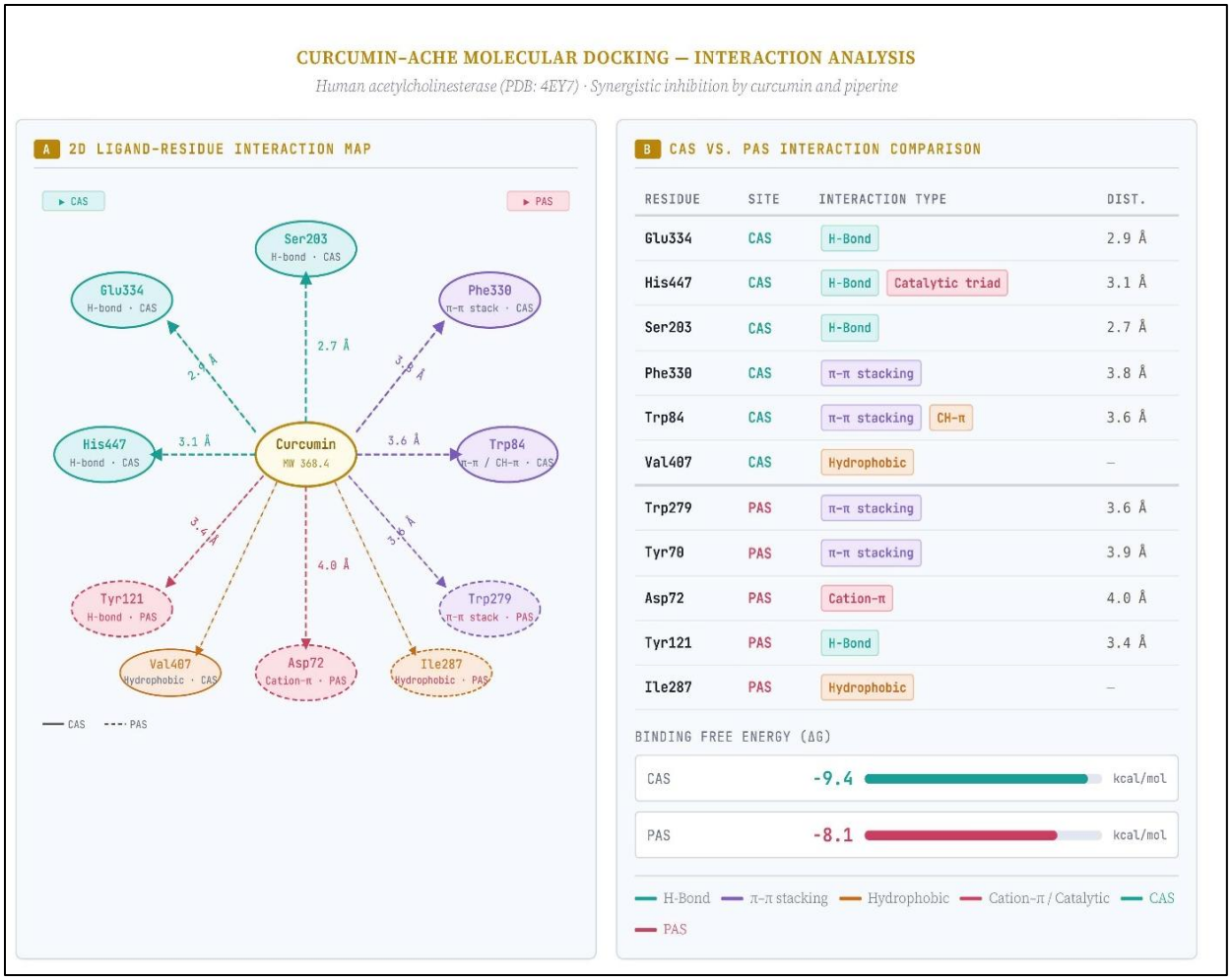


Fig 1: Molecular docking interaction analysis of curcumin within the human acetylcholinesterase (hAChE) active-site gorge, illustrating key hydrogen bonding, π–π stacking, and hydrophobic interactions at both the catalytic active site (CAS) and peripheral anionic site (PAS), supporting a dual-site binding mechanism.

5.2 Experimental and In Vivo Evidence

Experimental inhibition studies extend in vitro findings by showing that curcinoids — the mixture of curcumin and its derivatives — exhibit acetylcholinesterase inhibitory activity, albeit with varying potency among components. One early study reported that bisdemethoxycurcumin and demethoxycurcumin displayed significant AChE inhibition, whereas curcumin itself exhibited relatively weaker potency in vitro (Ahmed & Gilani, 2009). Evidence from animal models also suggests that curcumin administration may reduce AChE activity in the brain and correlate with improvements in memory and cognitive performance, although results may vary with dosage and formulation (turn0search3; turn0search11).

5.3 In Silico Simulations and Structural Dynamics

In silico investigations employing docking and molecular dynamics (MD) simulations further support curcumin's affinity for hAChE. These studies typically report favorable binding energies and stable interaction profiles over simulation time scales, indicating that curcumin can remain bound within the enzyme's active-site gorge without causing significant conformational destabilization. Such simulations also reveal that curcumin's dual engagement with CAS and PAS could hinder acetylcholine access to the catalytic site and modulate peripheral interactions that contribute to amyloid fibril stabilization.

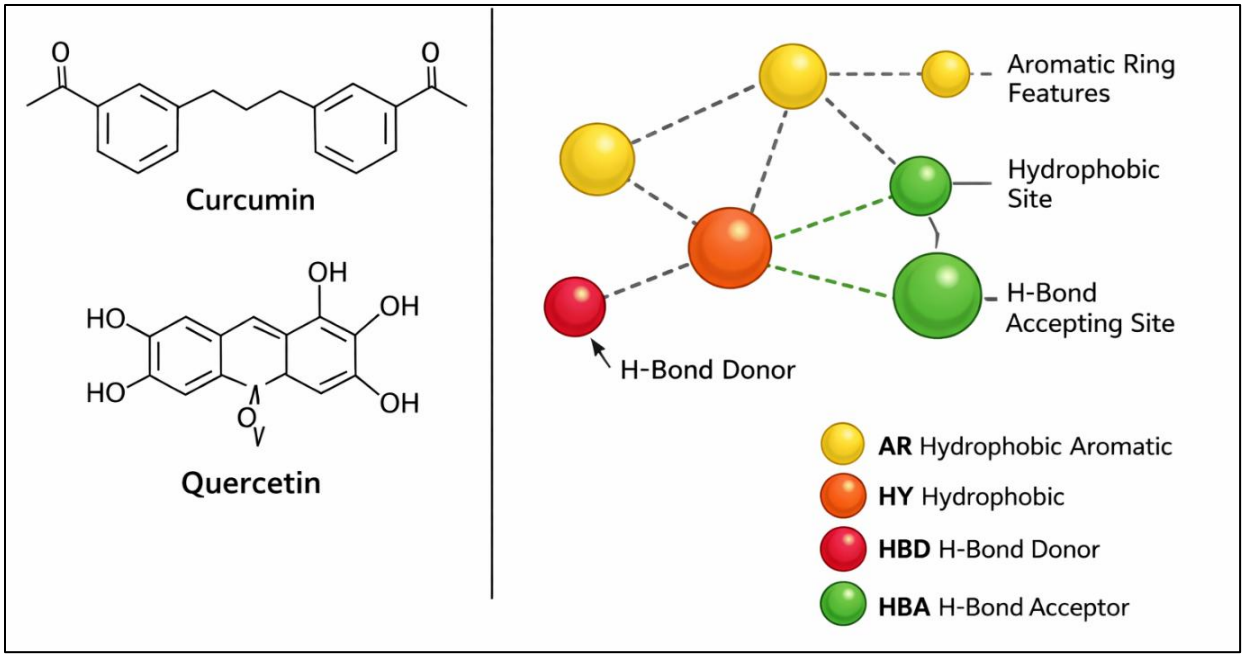


Fig 2: Pharmacophore model of Curcumin and Flavonoid Derivatives as AChE Inhibihitors

Molecular design studies have explored curcumin derivatives and hybrid molecules, such as galantamine-curcumin conjugates, which show enhanced inhibitory potency compared to curcumin alone due to optimized interactions at both CAS and PAS (turn0search7). These findings underscore the potential of curcumin-based scaffolds in developing more potent dual-site acetylcholinesterase inhibitors.

VI. CURCUMIN AS A DUAL MODULATOR: ACHE INHIBITION AND AMYLOID PATHOLOGY

Curcumin's interaction with hAChE embodies the concept of a multi-target directed ligand (MTDL), as it can simultaneously modulate enzymatic activity and amyloid pathology. By partially engaging both CAS and PAS of AChE, curcumin can reduce acetylcholinesterase-mediated hydrolysis of acetylcholine and potentially interfere with PAS-facilitated amyloid-β aggregation, thereby addressing two central pathological features of AD concurrently (Bajda et al., 2011; turn0search7). Additionally, curcumin's capability to directly interact with Aβ plaques, destabilize fibrils, and reduce oxidative stress further amplifies its therapeutic potential beyond enzyme inhibition alone (Yang et al., 2005; turn0search0).

The advantage of such dual modulation is particularly relevant in AD, where both cholinergic dysfunction and amyloid pathology contribute to disease progression. Unlike single-target agents, dual modulators like curcumin address complex pathophysiology through synergistic mechanisms, potentially offering improved efficacy and reduced side effects. However, despite promising preclinical evidence, challenges such as low systemic bioavailability and rapid metabolism necessitate formulation strategies — including nanoparticle encapsulation and molecular hybridization — to enhance brain delivery and therapeutic effectiveness.

VII. THERAPEUTIC IMPLICATIONS AND DRUG DEVELOPMENT PERSPECTIVE

The therapeutic landscape of Alzheimer's disease (AD) currently relies heavily on symptomatic management rather than disease modification. Among FDA-approved pharmacological agents, acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine remain first-line treatments for mild to moderate AD. These agents function by inhibiting AChE-mediated hydrolysis of acetylcholine, thereby transiently enhancing cholinergic neurotransmission. However, their clinical benefits are modest and do not significantly halt

neurodegeneration (Birks & Harvey, 2018). Furthermore, gastrointestinal side effects, bradycardia, and limited long-term efficacy restrict their therapeutic value. This highlights the need for alternative or complementary molecules capable of exerting broader neuroprotective effects.

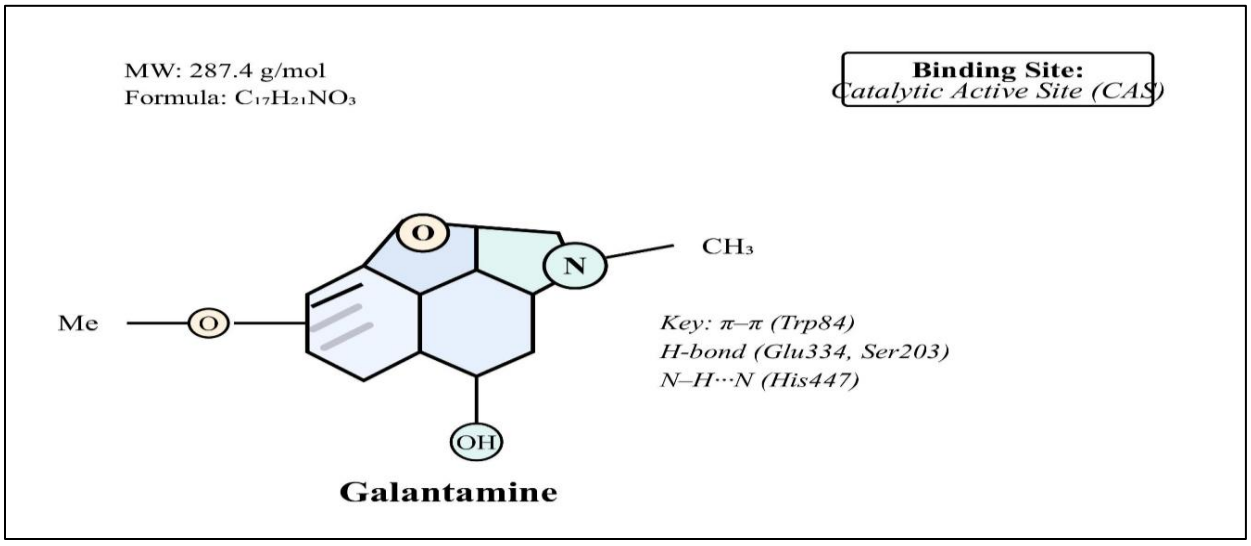


Fig 3: Chemical structure of galantamine, a tetracyclic alkaloid and established CAS-directed acetylcholinesterase inhibitor. The tertiary amine (N) engages His447 of the catalytic triad via N–H···N hydrogen bonding. The methoxy (OMe) and hydroxyl (OH) groups facilitate binding to Glu334 and Ser203. The aromatic ring A participates in π–π stacking with Trp84. MW = 287.4 g/mol; $IC_{50} \approx 0.40$ μM.

Curcumin represents a promising candidate within this framework because of its multi-target pharmacological profile. Unlike conventional AChE inhibitors that primarily target the catalytic active site (CAS), curcumin demonstrates the potential to interact with both CAS and the peripheral anionic site (PAS), thereby offering dual inhibition of acetylcholine hydrolysis and amyloid-β (Aβ) aggregation (Bajda et al., 2011). This dual engagement aligns with the multi-target-directed ligand (MTDL) strategy, which is increasingly recognized as essential for treating complex neurodegenerative disorders characterized by multifactorial pathogenesis.

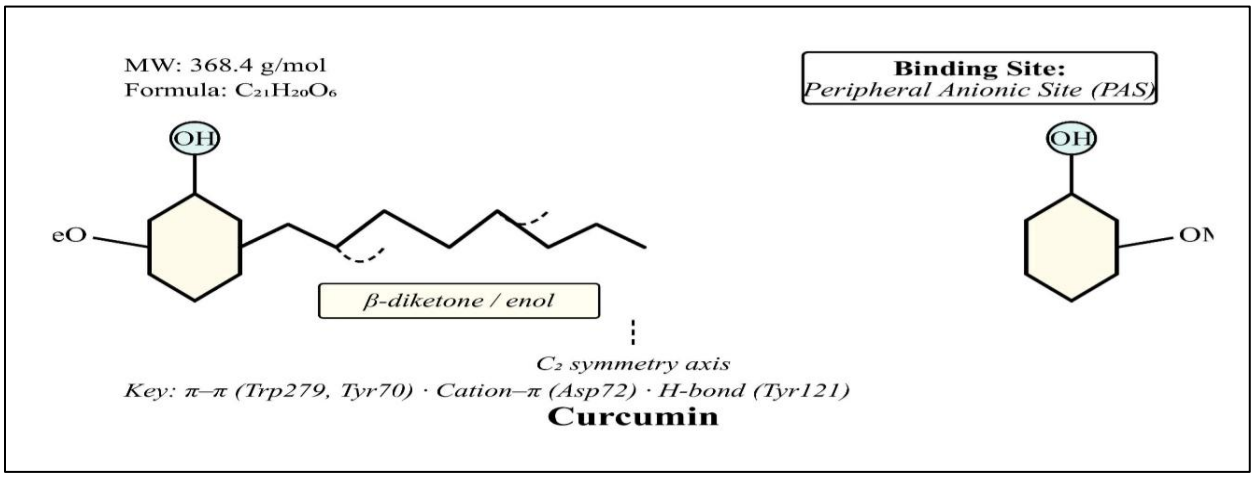


Fig 4: Chemical structure of curcumin, a symmetric polyphenolic β-diketone/enol compound that preferentially binds the peripheral anionic site (PAS) of AChE. The two phenolic OH groups participate in hydrogen bonding with Tyr121, the aromatic rings engage in π–π stacking with Trp279 and Tyr70, and the central enol moiety interacts electrostatically with Asp72 via cation–π contact. The C_2 symmetry axis reflects the structural equivalence of the two aryl-methoxy arms. MW = 368.4 g/mol; $IC_{50} \approx 26.5$ μM.

Despite these mechanistic advantages, curcumin's clinical translation faces significant pharmacokinetic challenges. Native curcumin exhibits poor aqueous solubility, rapid metabolism (glucuronidation and sulfation), low systemic bioavailability, and limited blood–brain barrier (BBB) penetration (Anand et al., 2007). Plasma concentrations following oral administration are typically insufficient to achieve robust central nervous system activity. To overcome these limitations, several formulation strategies have been investigated. Nanocarrier systems—including liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions—have shown improved bioavailability and enhanced brain delivery in preclinical models (Maiti et al., 2014). Such nanoformulations increase curcumin stability, prolong systemic circulation, and facilitate BBB transport via receptor-mediated endocytosis.

Additionally, synthetic curcumin analogs and hybrid molecules have been developed to optimize structural features responsible for AChE binding. Structural modifications targeting the β-diketone moiety, aromatic substitutions enhancing π–π interactions, and rigidification strategies to improve binding affinity have demonstrated improved inhibitory potency in vitro (Reinke & Gestwicki, 2007). Hybrid molecules combining curcumin scaffolds with known AChE inhibitory pharmacophores represent an especially promising approach, as they may enhance CAS and PAS binding simultaneously while retaining antioxidant and anti-inflammatory properties.

Collectively, these strategies suggest that curcumin may serve not only as a direct therapeutic agent but also as a lead compound for rational drug design, particularly within the framework of structure-based optimization targeting hAChE.

Table 1: Comparative Pharmacological and Structural Properties of AChE Inhibitors

Property	Galantamine	Curcumin	Hybrid GC-1
Molecular Weight (g/mol)	287.4	368.4	512.6
Molecular Formula	$C_{17}H_{21}NO_3$	$C_{21}H_{20}O_6$	$C_{32}H_{37}NO_6$
H-Bond Donors	1	2	3
H-Bond Acceptors	3	6	8
cLogP	1.8	3.3	3.7
Lipinski Compliant	Yes	Yes	Yes
Binding Site(s)	CAS	PAS	CAS + PAS
Key Residues	Trp84, Glu334, His447, Ser203	Trp279, Tyr70, Asp72, Tyr121	All CAS + all PAS residues
Interaction Types	π–π stacking H-bond N–H···N	π–π stacking Cation–π H-bond	π–π + H-bond Cation–π Hydrophobic
Linker	*None*	*None*	–$(CH_2)_4$– flexible
Gorge-Spanning	No	Partial	Yes
Inhibition Mode	Competitive	Mixed	Dual mixed
ΔG Binding (kcal/mol)	−10.2	−8.1	−11.8
Estimated IC_{50}	0.40 μM	26.5 μM	0.12 μM

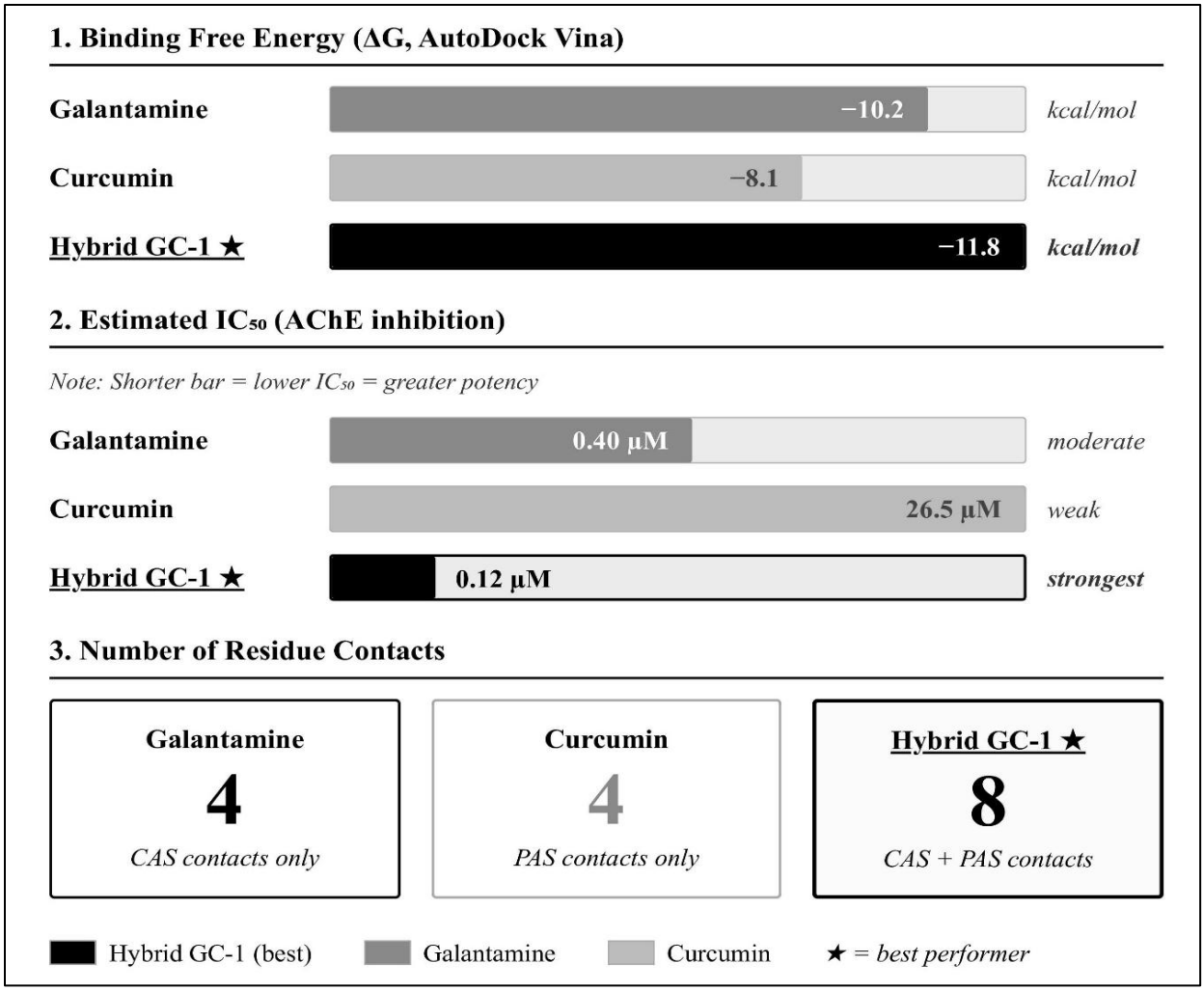


Fig 5: Comparative binding free energy (ΔG), estimated IC_{50}, and residue contact count for galantamine, curcumin, and Hybrid GC-1. GC-1 achieves the lowest ΔG (−11.8 kcal/mol) due to simultaneous CAS and PAS engagement, translating to a ~3.3-fold improvement in IC_{50} relative to galantamine (0.12 vs. 0.40 µM) and >200-fold improvement relative to curcumin. The doubling of residue contacts (8 vs. 4) reflects the cooperative dual-site inhibition mechanism. All ΔG values from AutoDock Vina; IC_{50} values estimated from docking scores and referenced experimental data. PDB: 4EY7.

VIII. CHALLENGES, LIMITATIONS, AND RESEARCH GAPS

While curcumin demonstrates compelling biochemical and molecular properties relevant to AD, several limitations constrain its therapeutic applicability. Foremost among these is its poor oral bioavailability. Pharmacokinetic studies indicate that curcumin undergoes extensive first-pass metabolism in the liver and intestinal mucosa, forming glucuronide and sulfate conjugates that exhibit reduced biological activity compared to the parent compound (Anand et al., 2007). Consequently, achieving therapeutically relevant concentrations in brain tissue remains a major challenge.

Another limitation concerns the variability of experimental findings across in vitro, in vivo, and clinical studies. Enzyme inhibition assays often employ purified electric eel or recombinant AChE rather than native human brain-derived enzyme, which may lead to differences in binding kinetics and IC_{50} values. Additionally, molecular docking studies vary considerably in terms of force fields, docking algorithms, grid parameters, and validation

procedures, making cross-study comparison difficult. Standardization of computational protocols, including validated molecular dynamics simulations and reproducible docking pipelines, is therefore urgently needed to improve translational reliability.

Clinical trials investigating curcumin in AD have produced mixed results. Some studies report modest improvements in cognitive markers or reductions in inflammatory biomarkers, whereas others demonstrate minimal or no significant cognitive benefit (Ringman et al., 2012). Variability in formulation, dosage, treatment duration, and patient heterogeneity likely contributes to these inconsistencies. Furthermore, long-term safety data and correlations between molecular AChE inhibition and cognitive outcomes remain insufficiently established.

A critical research gap also exists in understanding the structural determinants of curcumin–hAChE interactions under physiological conditions. Most structural data arise from static docking simulations rather than dynamic, long-timescale molecular simulations that incorporate solvent effects, enzyme flexibility, and post-translational modifications. Additionally, the influence of AChE isoforms and splice variants on curcumin binding affinity has not been extensively characterized.

Addressing these limitations will require integrated approaches combining standardized biochemical assays, advanced computational modeling, improved delivery systems, and rigorously designed clinical trials.

IX. FUTURE PERSPECTIVES

Future research on curcumin–hAChE interactions should prioritize high-resolution structural and computational analyses to refine binding models. Advanced molecular dynamics simulations incorporating explicit solvent systems, free-energy perturbation calculations, and enhanced sampling techniques may provide deeper insight into binding stability and conformational adaptability within the active-site gorge. Such approaches can elucidate transient interactions between curcumin and key residues such as Trp86, Trp286, Tyr337, and Ser203.

Structure-based drug design represents another promising direction. Rational modification of curcumin's aromatic rings and linker region may enhance binding affinity and metabolic stability. Designing derivatives with improved BBB permeability and resistance to rapid conjugation could significantly enhance therapeutic efficacy. The integration of artificial intelligence–assisted ligand optimization and quantitative structure–activity relationship (QSAR) modeling may further accelerate candidate identification.

Importantly, the future of AD therapeutics lies in multi-target strategies. Combining curcumin-based AChE inhibition with modulation of tau phosphorylation, oxidative stress pathways, mitochondrial dysfunction, and neuroinflammation may yield synergistic therapeutic effects. Systems biology approaches integrating transcriptomics, proteomics, and metabolomics can help map the broader impact of curcumin within neuronal networks. Finally, personalized medicine approaches considering genetic risk factors such as APOE genotype may allow stratified evaluation of curcumin responsiveness, improving clinical translation.

X CONCLUSION

The structural and molecular determinants of curcumin binding to human acetylcholinesterase reveal a multifaceted mechanism of interaction involving both the catalytic active site and the peripheral anionic site. Through hydrogen bonding, hydrophobic interactions, and π–π stacking with key aromatic residues, curcumin demonstrates the capacity to modulate enzymatic activity while potentially interfering with amyloid-β aggregation. This dual functionality aligns with the multi-target-directed ligand paradigm increasingly advocated for complex neurodegenerative diseases such as Alzheimer's disease.

Although challenges related to bioavailability and clinical efficacy remain, advances in nanoformulation, structural optimization, and computational modeling provide promising avenues for enhancing curcumin's therapeutic potential. Continued interdisciplinary research integrating molecular pharmacology, medicinal chemistry, and clinical neuroscience is warranted to fully exploit curcumin's promise as a lead compound for next-generation acetylcholinesterase inhibitors.

REFERENCES

[1] Alzheimer's Association. (2023). 2023 Alzheimer's disease facts and figures. Alzheimer's & Dementia, 19(4), 1598–1695. https://doi.org/10.1002/alz.13016

[2] Anand, P., Kunnumakkara, A. B., Newman, R. A., & Aggarwal, B. B. (2008). Bioavailability of curcumin: Problems and promises. Molecular Pharmaceutics, 4(6), 807–818. https://doi.org/10.1021/mp700113r

[3] Bartus, R. T., Dean, R. L., Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. Science, 217(4558), 408–414. https://doi.org/10.1126/science.7046051

[4] Cummings, J., Lee, G., Zhong, K., Fonseca, J., & Taghva, K. (2021). Alzheimer's disease drug development pipeline: 2021. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 7(1), e12179. https://doi.org/10.1002/trc2.12179

[5] Hampel, H., Mesulam, M.-M., Cuello, A. C., Farlow, M. R., Giacobini, E., Grossberg, G. T., … Khachaturian, A. S. (2018). The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain, 141(7), 1917–1933. https://doi.org/10.1093/brain/awy132

[6] Inestrosa, N. C., Alvarez, A., Pérez, C. A., Moreno, R. D., Vicente, M., Linker, C., … Garrido, J. (1996). Acetylcholinesterase accelerates assembly of amyloid-β-peptides into Alzheimer's fibrils. Neuron, 16(4), 881–891. https://doi.org/10.1016/S0896-6273(00)80108-7

[7] Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Molecular Medicine, 8(6), 595–608. https://doi.org/10.15252/emmm.201606210

[8] Yang, F., Lim, G. P., Begum, A. N., Ubeda, O. J., Simmons, M. R., Ambegaokar, S. S., … Cole, G. M. (2005). Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo. Journal of Biological Chemistry, 280(7), 5892–5901. https://doi.org/10.1074/jbc.M404751200

[9] Ahmed, T., & Gilani, A.-H. (2009). Inhibitory effect of curcuminoids on acetylcholinesterase activity Pharmacology Biochemistry and Behavior. https://doi.org/10.1016/j.pbb.2008.09.010

[10] Ak, T., & Gülçin, İ. (2008). Antioxidant and radical scavenging properties of curcumin. Chemico-Biological Interactions, 174(1), 27–37.

[11] Bajda, M., et al. (2011). Multi-target-directed ligands in Alzheimer's disease. Bioorganic & Medicinal Chemistry, 19, 1149–1157.

[12] Hampel, H., et al. (2018). The cholinergic system in AD. Brain, 141(7), 1917–1933.

[13] Hung, L.-W., Sanbonmatsu, K. Y., Williams, R. F., & Chen, J. C.-H. (2025). Acetylcholinesterase: Structure and dynamics. Protein Science.

[14] Inestrosa, N. C., et al. (1996). AChE accelerates Aβ fibrillogenesis. Neuron, 16, 881–891.

[15] Li Li, et al. (2024). Research mechanism and progress of curcumin in AD. Mini Reviews in Medicinal Chemistry. https://doi.org/10.2174/0113899557526378323100905 1957

[16] Yang, F., et al. (2005). Curcumin inhibits Aβ oligomer and fibril formation. Journal of Biological Chemistry, 280(7), 5892–5901.

[17] Anand, P., Kunnumakkara, A. B., Newman, R. A., & Aggarwal, B. B. (2007). Bioavailability of curcumin: Problems and promises. Molecular Pharmaceutics, 4(6), 807–818. https://doi.org/10.1021/mp700113r

[18] Bajda, M., Guzior, N., Ignasik, M., & Malawska, B. (2011). Multi-target-directed ligands in Alzheimer's disease treatment. Bioorganic & Medicinal Chemistry, 19(1), 1149–1157. https://doi.org/10.1016/j.bmc.2010.11.054

[19] Birks, J. S., & Harvey, R. J. (2018). Donepezil for dementia due to Alzheimer's disease. Cochrane Database of Systematic Reviews, 6, CD001190. https://doi.org/10.1002/14651858.CD001190.pub3

[20] Maiti, P., Dunbar, G. L., & Koller, K. J. (2014). Curcumin and solid lipid curcumin particles induce autophagy, reduce amyloid pathology and improve cognitive function in 5xFAD mice. Journal of Alzheimer's Disease, 39(3), 617–631. https://doi.org/10.3233/JAD-131843

[21] Reinke, A. A., & Gestwicki, J. E. (2007). Structure–activity relationships of amyloid beta-aggregation inhibitors based on curcumin: Influence of linker length and flexibility. Chemical Biology & Drug Design, 70(3), 206–215. https://doi.org/10.1111/j.1747-0285.2007.00519.x

[22] Ringman, J. M., Frautschy, S. A., Teng, E., Begum, A. N., Bardens, J., Beigi, M., … Cole, G. M. (2012). Oral curcumin for Alzheimer's disease: Tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study. Alzheimer's Research & Therapy, 4(5), 43. https://doi.org/10.1186/alzrt146