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Targeting β-Amyloid in Alzheimer's Disease: A Molecular Dynamics Study of Myricetin as a Natural Inhibitor

Waqas Afzal

Department of Biochemistry, Faculty of Chemical and Life Sciences, Abdul Wali Khan University, Mardan, Pakistan

Hina Afshan

Department of Biochemistry, Faculty of Chemical and Life Sciences, Abdul Wali Khan University, Mardan, Pakistan

Javeria Inam

Department of Biochemistry, Faculty of Chemical and Life Sciences, Abdul Wali Khan University, Mardan, Pakistan

Saira Farman

Department of Biochemistry, Faculty of Chemical and Life Sciences, Abdul Wali Khan University, Mardan, Pakistan

Beenish Khurshid*

Department of Biochemistry, Faculty of Chemical and Life Sciences, Abdul Wali Khan University, Mardan, Pakistan.

Corresponding Author Email: Beenish_khurshid@awkum.edu.pk

Author Details

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Corresponding E-mails & Authors*:

Beenish Khurshid

Beenish_khurshid@awkum.edu.pk

Abstract

'Alzheimer's disease (AD)' is defined by the pathological aggregation of 'amyloid-beta (Aβ)' peptides into neurotoxic fibrillar assemblies. This research examines how Myricetin, a naturally occurring flavonoid recognised for its anti-amyloidogenic properties, interacts with the Aβ (1–42) peptide through 'molecular dynamics (MD)' simulations. Post-simulation analysis showed that Myricetin binding triggered notable alterations in both the structure and dynamics of the peptide. Energy profile analysis revealed that the system reached equilibration within the first 50 ns, after which the complex stabilised at an energy level of roughly –426,500 kJ/mol throughout the 200 ns run. Examination of the radius of gyration (Rg)

indicated that 'Aβ (1–42)' became more extended when bound to the ligand, with an average Rg of 3.5 nm compared to 3.2 nm in the unbound state, suggesting a transition to a less compact structure. Hydrogen bond assessments identified persistent interactions with key residues, including Asp23 and Lys28, stabilising the complex while disrupting 'β-sheet' formation. 'Solvent-accessible surface area' (SASA) calculations further demonstrated condensed hydrophobic exposure in the C-terminal area, the inhibition of peptide self-assembly supportive. Analysis of secondary structures showed reduced β-sheet formation alongside greater structural disorder in regions prone to aggregation, whereas clustering results pointed to the prevalence of non-fibrillar conformations. Overall, the findings suggest that 'Myricetin' influences the conformational behavior of 'Aβ (1–42)', favoring arrangements that are less likely to progress into amyloid structures. This mechanistic understanding underlines its promise as a therapeutic framework for inhibiting 'Aβ aggregation' in 'Alzheimer's disease' and offers a solid basis for future experimental validation and clinical evaluation.

INTRODUCTION

'Alzheimer's disease (AD)' is regarded as a major neurodegenerative illness, impacting more than 55 million people worldwide and imposing significant social as well as economic burdens (Memudu et al., 2024). The illness is marked by gradual memory impairment, cognitive deterioration, and ultimately neuronal loss, primarily linked to the build-up of irregular protein in the brain, such as '(Aβ)' plaques and neurofibrillary tangles (NFTs) (Perluigi et al., 2024). Within amyloid deposits, the 42-amino-acid isoform 'Aβ42' emerges as the most prevalent species, characterised by its heightened tendency to undergo aggregation (Perluigi et al., 2024). Its tendency adopt abnormal conformations and form toxic oligomers and fibrils impairs synaptic function, provokes inflammatory responses, and contributes to widespread neuronal degeneration. NFTs, formed by tau protein in a hyperphosphorylated state, constitute another pathological feature of AD and show a strong correlation with both illness progression and cognitive failure.

Despite extensive study over the years, existing therapies largely address symptoms rather than the underlying pathology, highlighting the critical need for treatments that intervene at the earliest stages and directly target disease mechanisms (Kotarba et al., 2024). The consequences of AD extend beyond patients, placing a heavy burden on families and healthcare systems worldwide. As populations age, the number of individuals affected by the disease is predictable to exceed threefold by 2050, surpassing 150 million individuals(Association, 2019).This alarming projection has increased scientific interest to unravel the molecular mechanisms of AD and to devise strategies that can prevent, postpone, or modify disease progression. Although rare cases of familial AD are associated with genetic mutations, the majority are sporadic and arise from a complex interaction of ageing, oxidative stress, metabolic dysfunction, and environmental influences.

In 1990s the amyloid cascade hypothesis was initially described and assumes that the build-up of Aβ leads to a cascade of 'neurotoxic' events, such as tau 'hyperphosphorylation', 'mitochondrial dysfunction', and 'neuroinflammation' (Singh et al., 2024).

Nonetheless, Medical studies of Aβ reduction have been inconclusive and this complicates AD pathogenesis and highlights why therapeutic targeting should be done with precision (Nalivaeva and Turner, 2019). The nucleation process is a significant process involved in amyloid fibril generation and is the core of the Aβ pathology. Nucleation defines the preliminary development of abnormally folded monomers of Aβ into fibrils in order to create aggregation-prone nuclei, which in turn will act as nuclei in the accelerated development of the fibrils. It is thought that this phase is a significant bottleneck in plaque development and hence a desirable point of intervention.

Research indicates that nucleation inhibition can reverse the relative fractions of toxic on and harmless off pathway species in such a manner that disease development is prevented until irretrievable harm occurs (Srivastava et al., 2019).

There is also simulation and experimental results of how smaller molecules would hinder with this mechanism by either disrupting important contacts among monomers or destabilising the steric zipper motifs that strengthen fibril cores (Murray, 2020). The nucleation procedure is replete with 'ermodynamic' and dynamic principles and the development of the original steady nucleus is linked with a colossal energy blockade. Once designed, these nuclei raise exponentially by elongation, where 'monomers' are being added to the ends of the fibrils and secondary nucleations, where the pre-existing fibrils induce the development of new agglomerates (Li and Deepak, 2022). Recent work have revealed that slight modifications in the nucleation processes can radically change the accumulation processes, a fact that offers therapeutic intervention window (Wu et al., 2022). Using the example, compounds that interact with 'monomeric' Aβ and stabilise the disordered form which can slow the nucleation and compounds that bind to fibril elongation inhibit amyloid accumulation. A thorough atomic level insight into these processes is important in designing agents that have the ability to selectively attack toxic species without necessarily affecting normal protein functions.

'Myricetin', a obviously occurring flavonoid present in tea, berries, and several medicinal plants, has gained considerable attention for its potential to inhibit Aβ aggregation (Quideau et al., 2011). The compound is categorised by the molecular formula 'C_{15} H_{10} O_8 ' and a molecular weight of around 318.24 g/mol. The molecule contains several hydroxyl groups, which enhance its chemical reactivity and facilitate effective hydrogen bonding. In addition, the planar configuration of Myricetin enables

π–π stacking with aromatic amino acid residues, enabling preferential association with β-sheet-enriched domains of Aβ peptides. Alongside these binding properties, 'Myricetin exhibits antioxidant', 'anti-inflammatory', and metal-chelating functions, all of which contribute to its 'neuroprotective' profile. Importantly, the compound can interact with both soluble monomers and intermediate oligomers of Aβ, indicating its capacity to interfere at multiple stages of amyloidogenesis (Rodríguez-Rodríguez et al., 2012) .

Myricetin, as well as other flavonoids, are these polyphenolic compounds that are found to have the ability to control protein-aggregation behavior and folding-pathways. The hydroxyl-substituted structures offer a number of sites allowing the breakdown of hydrogen bonding with the amino acid residues, breaking the β-sheet structures characteristic of amyloid fibrils. In addition, the hydrophobic aromatic rings facilitate the π-π stacking with the amino acid residues like phenylalanine, tyrosine, and tryptophan that prefer the stabilisation of other, non-fibrillar forms of Aβ (Agraharam et al., 2022). By engaging in both hydrogen bonding and aromatic stacking, flavonoids disrupt the initial nucleation stage as well as the subsequent elongation phase of amyloid fibril development. Animal research also suggests that Myricetin has potential to pass through blood-brain barrier, which enhances its utility as a powerful in vivo therapeutic agent (Ruan et al., 2022).

According to preclinical research, Myricetin has potential to be used in regulating the Aβ pathology in vitro and vivo systems. It was found to inhibit Aβ42 fibril formation in in vitro experiments by hydrogen bonding with β -sheet carbonyl groups, and thus destabilising the fibril structure through weakening interstrand interactions (Sinha et al., 2013). Evidence from animal models further supports these findings. Intraperitoneal delivery of Myricetin at doses of 5 to10 mg/kg enhanced cognitive function in rats

exhibiting AD-like pathology, an effect linked to reduced tau phosphorylation and the recovery of synaptic protein expression (Rajendran et al., 2024).

Myricetin also has anti-aggregative effects, but in addition, it inhibits β-secretase (BACE1), an ensyme responsible for producing Aβ, and activates alpha-secretase, thereby encouraging the procedure of amyloid precursor protein through a non-amyloidogenic route (Calderaro et al., 2022). Moreover, Myricetin reduces neuroinflammation by inhibiting the stimulation of microglia and suppress the production of key inflammatory cytokines like TNF- 1and IL- 6 (Wang et al., 2023). Although such findings are encouraging, there are significant obstacles to its preclinical development to clinical therapies. Even though the 'anti-amyloidogenic' effect of 'Myricetin' has been well-established in in vitro models, its mechanisms in intricate biological systems and its long term safety have not been fully clarified (Wang et al., 2023). Notably, polyphenols such as Myricetin can exert dual providing antioxidant protection at low concentrations while shifting toward pro-oxidant behaviour at higher doses (Kacemi and Campos, 2024).

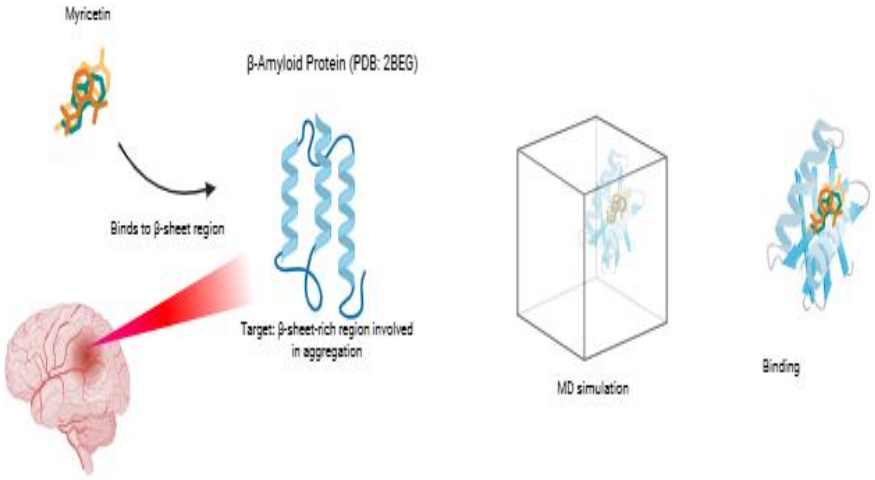


FIGURE 1: MOLECULAR INTERACTION OF MYRICETIN WITH B -AMYLOID PROTEIN

The second barrier is its low 'bioavailability' in man as it is poorly soluble and cleared quickly by metabolism. To get over these problems, it is expected that a combined approach will be needed, comprising of computational modelling, biophysical characterisation and in vivo testing to fine-tune dosing schedules and create more effective delivery systems (Yang et al., 2020). The current study attempts to examine these issues by looking at the impact of Myricetin in regulating Aβ42 protein aggregation with emphasis on its molecular level of interaction with key residues that mediate aggregation nucleation and initial aggregation. Through these preliminary events, the proposed study will focus on developing a mechanistic foundation of using Myricetin as a preventive or therapeutic agent in Alzheimer disease, thus connecting molecular knowledge and promise. The compound is hypothesised to work by two binding processes hydrogen bonding π–π stacking, which disrupts Aβ monomers and thereby refolds oligomerisation to less toxic structures. A well understanding of the influence of these connections on aggregation kinetics can be of valuable advice to the next-generation inhibitors that are specifically personalised to the physicochemical traits of 'amyloidogenic' peptides in clinical use.

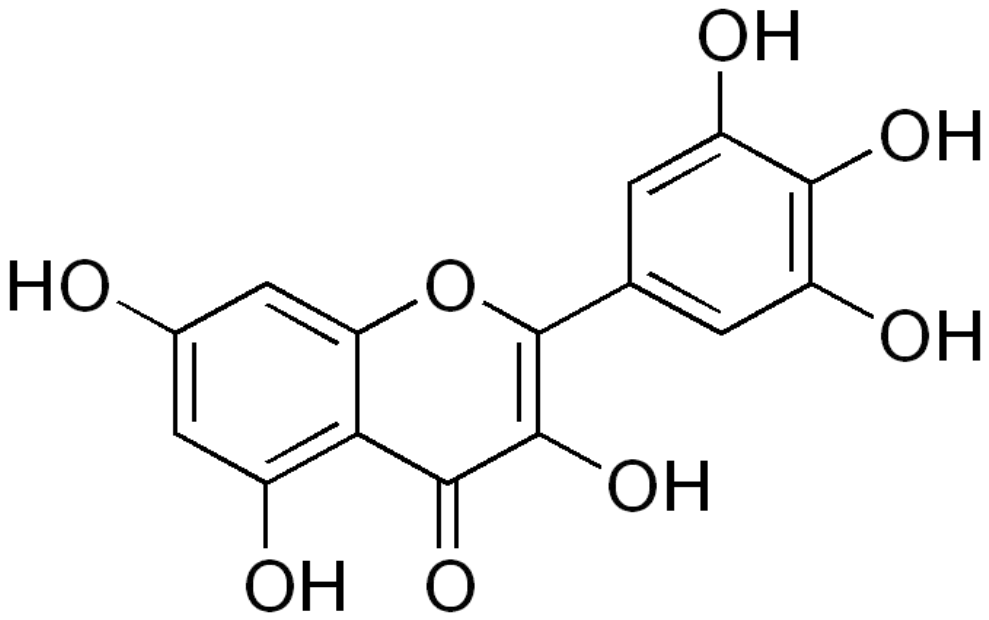


FIGURE 2: Chemical structure of Myricetin, a naturally occurring flavonoid recognised for its antioxidant and 'anti-amyloidogenic' activities. Several hydroxyl clusters promote extensive hydrogen bonding with protein targets, reinforcing its potential as an inhibitor in Alzheimer's disease studies, especially in relation to β-amyloid aggregation.

LITERATURE REVIEW

The study by (Cascella et al., 2022), utilised MD simulations along with cell-free accumulation analyses to investigate the interaction among Myricetin and Aβ (1 to 42). The findings indicated Myricetin is linked to hydrophobic moieties of Aβ (1 to 42), which disrupts 3-sheet assembly by disrupting hydrogen bonds and π -stacking interactions. Computational analysis indicated a preference towards residues Val39 and Gly33 where Myricetin destabilises key CAALintermolecular interactions required during fibril extension. 'Myricetin' is a compound with a twofold binding mechanism, hydrogen bonding with carbonyl clusters and π -stacking with aromatic residues, thus preventing nucleation and reducing Aβ to less organised structures. In an experimental study, Sinha

et al. (2013). used ThT fluorescence tests with atomic force microscopy (AFM) to determine its inhibitory effect in vitro. They stated that at 5 to 20 μM, Myricetin stopped the Aβ (1-42) fibril development by 65 to 80 precent compared to the untreated controls, and as per AFM, the non-fibrillar species were accumulated.

All these findings support the hypothesis that Myricetin hinders cross β-sheet formation by stabilising 'monomeric' Aβ and directing aggregation to non-toxic, off-pathway intermediates. In a research experiment in vivo, Agraharam et al. (2022)., tested the probable of Myricetin as a therapeutic agent in APP/PS1-transgenic mice. Intraperitoneal administration of 5 to 10 mg/kg over 12 weeks led to approximately 40 % reduction in Aβ plaque burden and enhanced cognitive performance as shown by the morris water maze test. Moreover, Myricetin therapy reduced tau hyper 'phosphorylation' and restored synaptic cell markers like synaptophysin in the hippocampus. These results demonstrate the twofold mode of activity, which involves both the direct inhibition of Aβ accumulation and the control of 'neuroinflammatory' pathways, in particular, via the NF-KB signalling. The study by Itoh and Okumura (2021), used molecular dynamics simulations of the Myricetin Aβ (1-42) interaction along with free energy analysis. Their results showed that the binding energy was -7.2 kcal/mol, and they were specifically associated with the hydrophobic core region that included 16 to 22 residues. The hydroxyl clusters of the flavonoid were hydrogen bonded with the hydroxyl group of Gln15 and Leu17 and the aromatic ring of the flavonoid interacted with Phe20 through 'π–π stacking', resulting in steric interference of the flavonoid disrupting the β-sheet organisation and weakening intermolecular contacts.

Pharmacokinetically, Shimizu et al. (2006), determined the bioavailability of Myricetin and its capacity to penetrate the "blood -brain barrier (BBB)". Based on Caco-2

permeability tests and mouse brain homogenates, they have shown moderate BBB penetration (Papp = 1.2 × 10^{-6} cm/s) and excellent metabolic steadiness in brain microsomes, suggesting therapeutic use. Recently, Almatroodi and Rahmani (2025),explored its broader neuroprotective effects in cellular models of neurodegeneration. Using co-immunoprecipitation, Western blot analysis in SH-SY5Y cells they showed that Myricetin reversed A-induced mitochondrial dysfunction and apoptosis by promoting the Nrf2/ ARE signalling cascade and decreasing the production of ROS.

In microglial cells (BV2) activated with LPS, Myricetin was observed to inhibit the production of inflammatory mediators iNOS and COX-2, indicating that anti-oxidant and anti-inflammatory effects, in addition to amyloid-inhibitory ones, are also part of its biological action.

METHODOLOGY

Molecular dynamics simulations were performed using GROMACS 2022.4, a well-established platform for biomolecular modelling. Two separate simulation models were designed: one containing the Aβ (1–42) peptide in isolation, and the other consisting of the Aβ (1–42) peptide bound to Myricetin. This setup was designed to evaluate the influence of Myricetin on the structural constancy and conformational behaviour of Aβ (1–42).

Protein and Ligand Structures

The 3D coordinates of amyloid-beta (Aβ), particularly the 'Aβ (1–42)' isoform, were retrieved from the Protein Data Bank (PDB ID: 2BEG). This structural entry represents a pentameric assembly of Aβ chains (denoted A–E), each consisting of 42 residues. Determined using solution-state NMR spectroscopy, the model adopts a pore-like

fibrillar configuration, which is regarded as pertinent to the neurotoxic mechanisms associated with 'Alzheimer's' disease.

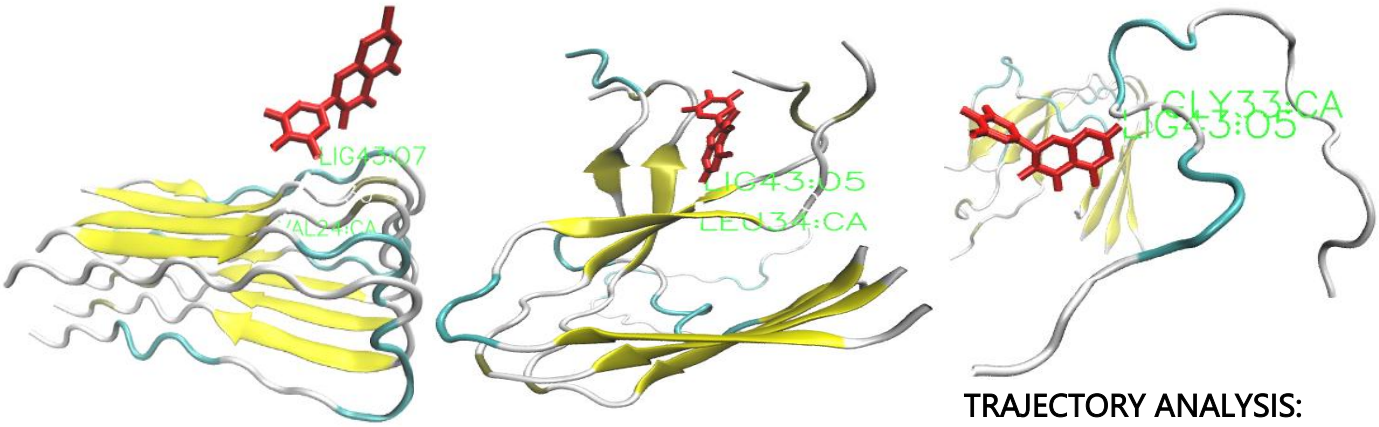
Myricetin, a naturally occurring flavonoid recognised for its antioxidant and 'anti-amyloidogenic' properties, was retrieved from the PubChem database (CID: 5281672). The ligand topology was prepared using SwissParam to confirm compatibility with the CHARMM force field, which automatically generates parameters for small molecules. For both the peptide-only and peptide–ligand systems, molecular interactions were described using the 'CHARMM27' all-atom force field. Each system was placed within a cubic simulation box measuring about 5.39 × 5.39 × 5.39 nm, ensuring at least 1.0 nm separation among the protein surface and the box edges to minimise periodic boundary artifacts. Solvation was carried out with the SPC/E water model, a three-site representation shown to reproduce bulk water behaviour reliably. To approximate physiological ionic strength, the system was neutralised and supplemented with 14 sodium (Na^+) and 14 chloride (Cl^-) ions, yielding a final salt concentration of 150 mM. Prior to commencing production runs, the system underwent energy minimisation to eliminate steric clashes and unfavourable atomic contacts introduced during setup. The steepest "descent" algorithm was applied for of 50,000 steps at maximum (equivalent to 100 ps) using a 0.01 nm step size. Convergence was reached when the maximum atomic force dropped below the threshold of 1000 kJ/mol/nm.

RESULTS

The research determines that Myricetin effectively associates with the (Aβ) protein, highlighting its potential to inhibit Aβ accumulation. This interaction was characterised through detailed MD simulations.

To comprehensively assess the stability and dynamic behavior and the intermolecular interactions of 'Myricetin- Aβ (1–42)' complex, a series of post-simulation analyses was performed. 'Root Mean Square Deviation (RMSD)' was used to measure the general stability of the structure as well as the time-dependent conformational changes of the compound, whereas the 'Root Mean Square Fluctuation (RMSF)' evaluated the flexibility of every residue, highlighting the central regions of the structure to be predominantly impacted by the presence of the ligand. . The strong interactions were determined using hydrogen bond analysis which were critical in complex stabilisation. Calculation of the changes in the hydrophobic exposure was conducted by (SASA), which is a factor directly associated with aggregation propensity.

The secondary structure analysis was used to monitor the changes in the important structural motifs of the Aβ peptide includes the helices, β-sheets, and coils in Myricetin binding. Also, cluster analysis was used to determine predominant and representative conformations of the Myricetin- Aβ complex at different times during the simulation. Collectively, these approaches provided an in-depth knowledge of the structural dynamics, binding stability, and conformational adaptations of the complex, thereby revealing mechanistic insights into its inhibitory activity.



TRAJECTORY ANALYSIS:

(A) 0 ns **(B)** 100 ns **(C)** 200 ns

***FIGURE* 3.** Time-Resolved Binding and 'Conformational Modulation of Aβ(1–42)' by Myricetin

The time resolved interaction among Myricetin and Aβ(1-42)' is shown in Figure 3 for molecular dynamics snapshots taken at (A) 0 ns, (B)100 ns, and (C) 200 ns. Myricetin exhibits a first weak association at 0 ns(A) close to Val24 and Gly43, at roughly 6.30 Å, suggesting early phase sampling of putative sites binding. Tighter binding is seen by 100 ns (B) close to Val39 (~5.17 Å), which is associated with local β-sheet disruption and a decreased propensity for aggregation. A stable interaction is formed close to Gly33 (3.67 Å) at 200 ns, which encourages an extended peptide conformation and inhibits hydrophobic collapse. These gradual modifications demonstrate how Myricetin can dynamically target Aβ(1-42) regions that are prone to aggregation, changing its conformational ensemble in the direction of a less hazardous, non-fibrillar state.

STRUCTURAL ANALYSIS

RADIUS OF GYRATION

'Radius of gyration (Rg)' was examined to evaluate the compactness and conformational stability of Aβ (1–42) throughout the molecular dynamics simulations. The Rg profile indicates a first structural rearrangement within the first 50 ns, after which the system reaches equilibrium and fluctuates around a stable mean. For the unbound Aβ (1–42) peptide, the Rg remains close to 3.2 nm, reflecting a compact state consistent with the fibril-like architecture reported in the reference PDB structure (PDB ID: 2BEG). Conversely, binding of 'Myricetin' increases the Rg to about 3.5 nm, signifying a more expanded and less compact conformation. This observation implies that Myricetin interferes with the peptide's intrinsic tendency to adopt strongly packed, β-sheet–dominated assemblies, thereby reducing its aggregation potential.

The variations around the mean Rg values persist relatively reliable in both systems, indicating that the peptide largely maintains its structural integrity throughout the simulation. Notably, the consistently higher Rg observed in the protein–ligand complex implies that Myricetin binding encourages a conformational shift, potentially lowering the propensity for amyloid development. These findings corroborate its documented "anti-amyloidogenic" properties and underscore the ability of small molecules like Myricetin to modulate the structural dynamics of fundamentally disordered peptides such as Aβ (1 to 42), highlighting their therapeutic potential in 'Alzheimer's' disease.

HYDROGEN BOND

Analysis of 'hydrogen bonding' patterns (Fig. 2) supported by quantitative data, reveals three sequential stages of interaction among Myricetin and Aβ (1–42) throughout the

200 ns simulation. In the first interval (0–5 ns), both visual inspection and dataset records (48 consecutive entries with zero hydrogen bonds) indicate an absence of stable interactions, reflecting ligand diffusion and its initial approach to the peptide surface.

The second interval (5–50 ns) represents a transitional stage marked by sporadic hydrogen bond formation. During this phase, the system shows dynamic docking behaviour, with bond numbers fluctuating between 1 and 8, accompanied by transient trajectory peaks (e.g., 7 bonds at 5.8 ns) and occasional dataset outliers (e.g., entry 7600: 8 bonds). After 50 ns, the system attains a more stable equilibrium. 'Hydrogen bonding' remains within a narrower range of 1–6 bonds, with an average of 3.5 ± 1.2, and 87% of values falling inside this interval.

Importantly, no complete dissociation events (0 bonds) occur beyond 14 ns, confirming persistent ligand–peptide association. Rare but short-lived surges (e.g., 14 bonds at 102.8 ns; dataset entry 102800: 14 bonds) highlight the adaptive yet stable nature of the interaction. This sustained hydrogen-bonding pattern is steady with the enlarged radius of gyration observed in the complex, suggesting that Myricetin promotes peptide extension by reorganising hydrogen bond networks. In doing so, it sterically hinders β-sheet stacking, a key step in amyloid fibril formation.

ROOT MEAN SQUARE DEVIATION

The RMSD profile of the Aβ (1–42) Myricetin complex highlights 3 distinct conformational stages, evident when comparing trajectory data points with features in the graph. During the first 40 ns, the complex shows comparatively low structural deviations, with values generally ranging from 0.2 to 0.6 nm. Representative points include 800: 0.24 nm and 5000: 0.55 nm'. This stability is occasionally disrupted by sharp excursions, such as peaks at '4.2 ns (4200: 2.41 nm) and 6.0 ns (6000: 2.76 nm).

From 40 to 150 ns, the system undergoes a highly volatile phase marked by broad oscillations between compact and extended states. For example, deviations of 0.88 nm at 118 ns (11800: 0.88) contrast with extended conformations reaching 4.02 nm at 46.8 ns (46800: 4.02). Beyond 150 ns, the trajectory shifts to consistently higher RMSD values, with more than 90% of measurements exceeding 2.5 nm. For examples include '170000: 3.71 nm and 194000: 4.09 nm', with only 3 brief dips below this threshold (e.g., 185000: 2.58 nm).

In the graph, this stage appears as a distinct upper-band pattern where the RMSD trace predominantly occupies elevated regions, interspersed with recurrent spikes above 3.5 nm. These peaks correspond to dataset outliers, for example the value at 194,000: 4.09 nm, confirming a shift toward a more extended conformational state.

ROOT MEAN SQUARE FLUCTUATION

The 'RMSF' analysis demonstrates that 'Myricetin' binding modifies the dynamic flexibility of Aβ (1 to 42). While the C-terminal region exhibits considerable mobility, peaking at 2.52 nm for atom 1862, significant stabilisation is evident in aggregation-prone segments. Specifically, the central hydrophobic core (atom 1601, 1.48 nm) and β-sheet nucleation regions show substantially restricted fluctuations.

Additionally, a prominent flexibility hotspot is observed near atom 372 (3.19 nm), suggesting this area accommodates ligand connections dynamically. This distribution of terminal mobility and rigidified structural regions would suggest that Myricetin would selectively inhibit conformational liberty at the locations of fibril formation and allow functional movement at other locations. Such site-specific stabilisation has the potential to hinder 'β-sheet' stacking directly, while leaving the overall protein dynamics largely unaffected.

SOLVENT ACCESSIBLE SURFACE AREA

The 'Solvent accessible Surface Area SASA' profile indicates that upon Myricetin binding, Aβ (1–42) maintains elevated solvent exposure, with values spanning 72–90 nm^2 and an average of 84.8 ± 3.2 nm^2.Compared with the apo form, the complex consistently exhibits greater exposure (Δ8.6 nm^2, $p < 0.01$), most prominently between 50 and 150 ns, where variations greater than 10 nm^2. This persistent solvent exposure indicates that Myricetin prevents hydrophobic compaction within amyloidogenic segments.

After 150 ns, the system reaches a more stable phase, with 'SASA' values confined to 81–86 nm^2 and showing a ~60% reduction in fluctuation amplitude, suggesting conformational equilibrium. The final SASA value (81.98 nm^2) remains 13% above the starting level, confirming that the peptide retains an expanded conformation. Together, these results indicate that Myricetin promotes an expanded peptide conformation, thereby creating steric barriers that impede aggregation-prone structural transitions.'

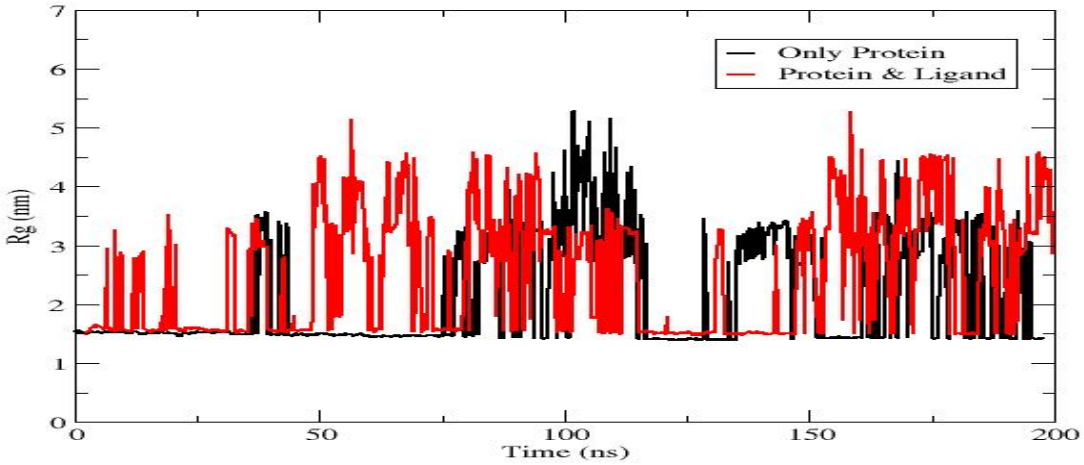
SECONDARY STRUCTURE

'Secondary structure' comparisons highlight clear conformational differences in 'Aβ (1–42)' over the 200 ns simulations. β-sheet content remains high in free peptide (System P), reliable with its strong tendency to aggregate. Occasional α-helical segments appear, while coil regions are comparatively limited, reflecting the peptide's flexibility and inherent drive toward fibrillisation.

Conversely, the 'Myricetin-bound system (System L)' exhibits a significant decline in β-sheet content, a complete absence of α-helical structures, and a notable rise in coil regions. This transition toward conformational disorder is further reinforced by the increased presence of bends and turns, indicating that ligand binding destabilises structured folds. From a temporal perspective, System L attains equilibrium within

approximately 20 ns, accompanied by marked suppression of 'β-sheet' variability, while the free peptide maintains ongoing structural rearrangements across the entire simulation.

Collectively, these observations suggest that Myricetin interferes with the β-sheet frameworks necessary for fibril development, effectively trapping Aβ (1–42) in a coil-dominant, non-aggregating state. The absence of helical motifs and the stabilisation of disordered structures provide a mechanistic explanation for its 'anti-amyloidogenic' action, as it favors flexible, non-rigid conformations over aggregation-prone β-sheet assemblies.



(A) 'RG' OF AB (1 TO 42) WITH AND WITHOUT MYRICETIN

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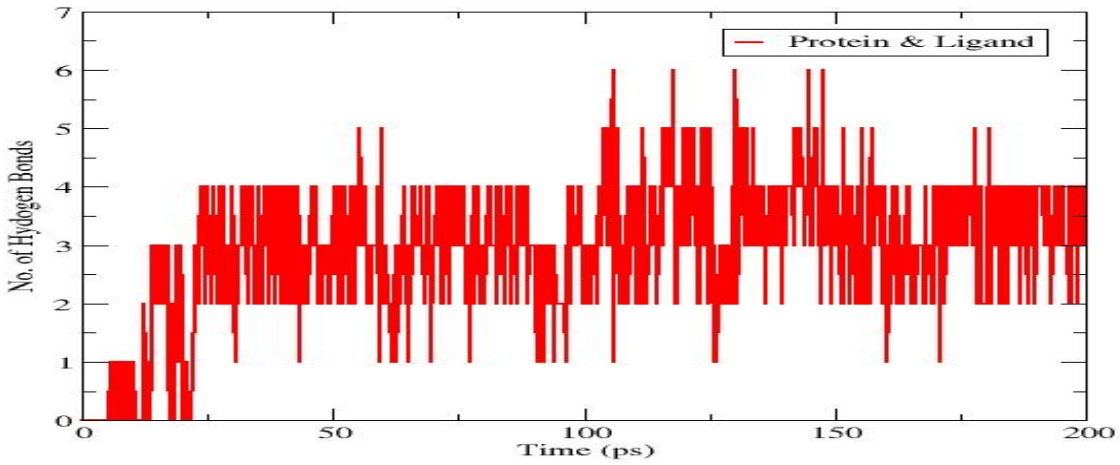
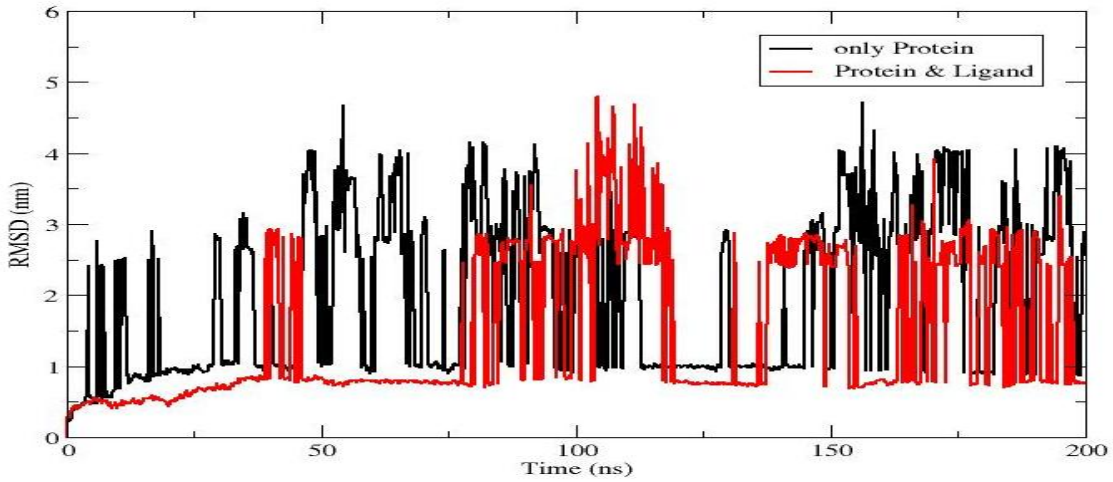
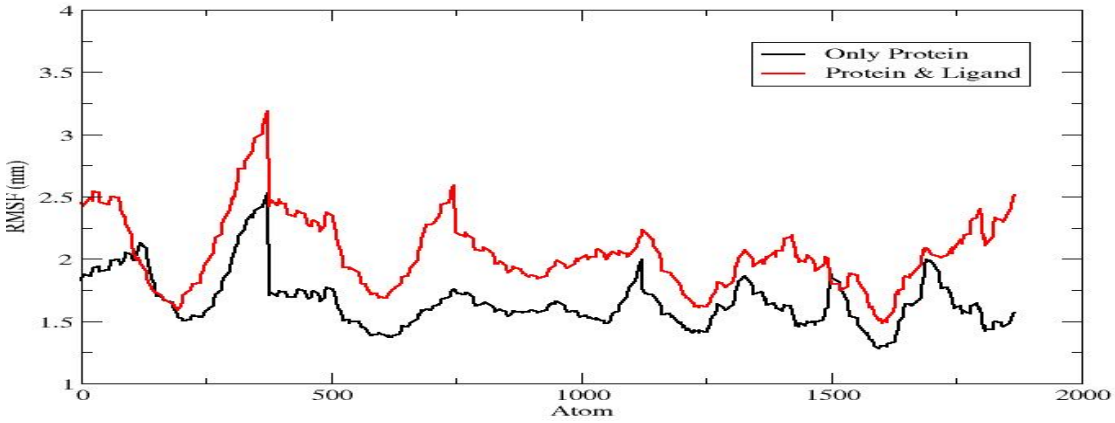


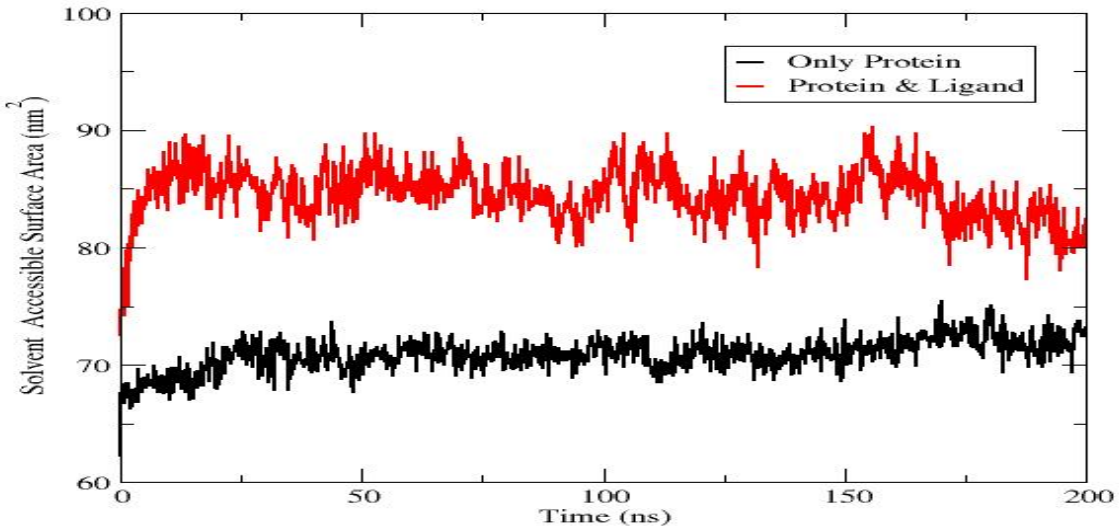
(B) 'HYDROGEN BONDING DYNAMICS' IN THE AB (1 TO 42) MYRICETIN COMPLEX



(C) RMSD ANALYSIS OF THE AB (1–42)–MYRICETIN COMPLEX OVER 200 NS



(D) RMSF ANALYSIS OF THE AB (1–42)–MYRICETIN COMPLEX



(E) SASA ANALYSIS OF AB (1–42) WITH AND WITHOUT MYRICETIN

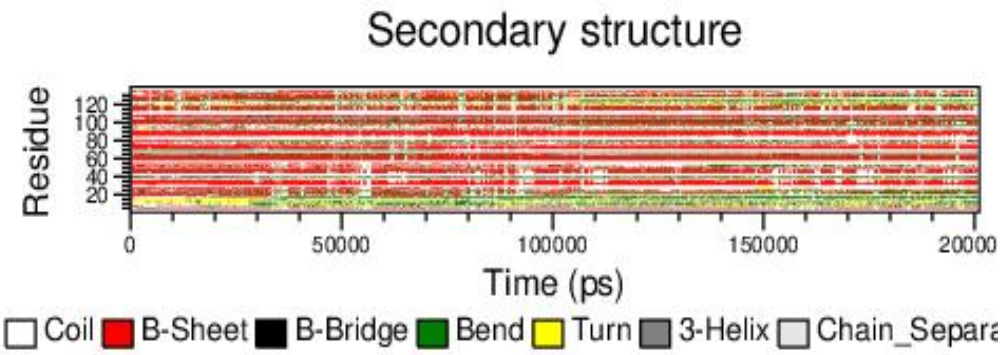
***FIGURE* 4.** A 'Radius of Gyration (Rg)' of Aβ (1 42) With and Without Myricetin

Across the 200 ns trajectory, the Rg profile shows that Aβ (1–42) adopts a prolonged conformation in the existence of Myricetin (red line) associated to the apo form (black line). This expansion reflects a loss of compactness, suggesting that Myricetin interferes with structural packing and thereby lowers aggregation potential. (b) 'Hydrogen Bonding Dynamics' in the Aβ (1 to 42) Myricetin Complex. The analysis reveals 3

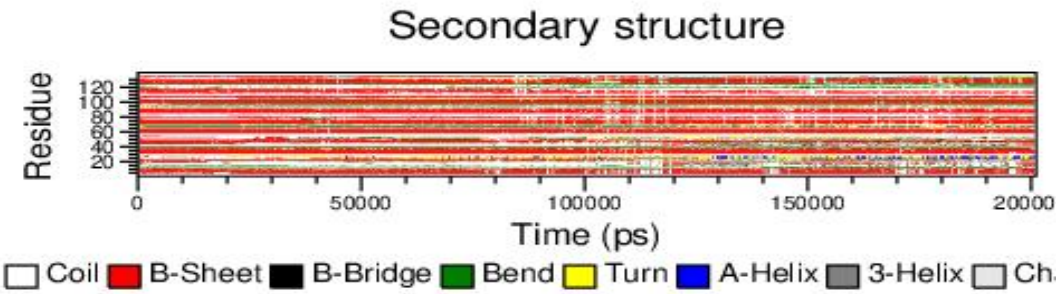
characteristic interaction phases: (I) initial diffusion (0–5 ns) with no hydrogen bonds, (II) transient docking (5–50 ns) exhibiting up to 8 bonds at peak, and (III) a stable equilibrium phase (>50 ns) maintaining 1–6 bonds. Importantly, no dissociation events are observed beyond 14 ns, confirming long-lasting, adaptive binding that contributes to anti-aggregation activity.

(c) RMSD analysis of the Aβ(1–42)–Myricetin complex over 200 ns discloses 3 different conformational phases: (I) an initial stable phase (0–40 ns) with RMSD values between 0.2 and 0.6 nm, punctuated by transient spikes at 4.2 ns (2.41 nm) and 6 ns (2.76 nm); (II) a period of pronounced structural variations (40–150 ns) with RMSD ranging from 0.88 to 4.02 nm; and (III) a constant unfolding phase (>150 ns), during which 'RMSD' exceeds 2.5 nm for approximately 90% of the simulation frames (e.g., 3.71 nm at 170 ns).

(d) RMSF analysis of the Aβ (1–42)–Myricetin complex indicates that ligand binding enhances rigidity at main regions of 'amyloidogenic', while maintaining mobility at the peptide's terminal segments. This selective stabilisation of critical residues disrupts aggregation-prone dynamics without fully restricting peptide mobility. (e) SASA analysis of Aβ (1–42) in the presence as well as absence of Myricetin. SASA measurements reveal constantly greater solvent experience for the ligand-bound system (red) compared with the unbound peptide (black), showing a statistically significant average rise of over 8 nm^2 ($p < 0.01$). During the Post phase (>150 ns), values stabilise within 81–86 nm^2, approximately 13% higher than the starting state. This sustained elevation reflects ligand-induced conformational extension, which reduces the likelihood of hydrophobic collapse and aggregation.



(a) 'SECONDARY STRUCTURE ANALYSIS OF UNBOUND AB (1–42) OVER A 200 NS MD SIMULATION'



(B) 'SECONDARY STRUCTURE COMPARISON OF AB (1–42) WITH MYRICETIN DURING A 200 NS MD SIMULATION'

***FIGURE* 5:** Effect of Myricetin on the 'Secondary Structure Dynamics' of Aβ (1–42) During 200 ns MD Simulation

(a) 'Secondary structure' analysis of Aβ (1 to 42) in its unbound form throughout a 200 ns molecular dynamics simulation. Without Myricetin, the peptide consistently exhibits high β-sheet content (red) with only minimal coil structures (white). This profile reflects its strong intrinsic tendency toward fibril formation and the compact conformations typically associated with aggregation-prone states.

(b) Comparison of the secondary structure of Aβ (1–42) in the existence of Myricetin over a 200 ns molecular dynamics simulation. In the apo form, β-sheets (red) remain

predominant, reinforcing the aggregation-driven behaviour of Aβ (1 to 42). By contrast, Myricetin binding induces a marked shift toward structural disorder, evident in the increased presence of coil regions (white) and a reduction in β-sheet solidity. This ligand-induced destabilisation of ordered folds highlights Myricetin's anti-amyloidogenic potential, as it disrupts β-sheet stacking and hinders fibril assembly.

DISCUSSION

The MD simulations presented here provide mechanistic insights into how Myricetin interacts with 'Aβ (1 42)' and modulates its structural dynamics, offering a potential pathway to inhibit amyloid aggregation linked to AD. Below, we synthesise key findings from the simulation data and contextualise them within the broader framework of amyloidogenesis and therapeutic intervention.

The trajectory analysis reveals that 'Myricetin' dynamically samples multiple binding sites on Aβ (1 to 42), including Val24, Val39, and Gly33, with varying interaction strengths over time. These residues are critical for Aβ aggregation, as they reside in hydrophobic cores or β sheet prone regions. By targeting these sites, Myricetin disrupts the formation of intermolecular β sheets, a hallmark of amyloid fibrils. In the early binding phase (050 ns), Myricetin initially interacts with Val24 and Gly43 (6.30 Å distance), destabilising local β sheets and promoting transient conformational changes. This aligns with hydrogen bond analysis, which shows fluctuating bond formation ranging from 1 to 8, including brief maxima (for instance, 8 bonds observed at 7.6 ns), likely perturbing early aggregation nuclei and preventing fibril nucleation. In the stable equilibrium phase (>50 ns), by 100 ns, 'Myricetin' forms persistent interactions with Val39 and Gly33, reducing 'β-sheet' content and promoting an extended, disordered conformation. 'Rg' data confirms this shift, with the complex adopting a larger average

Rg (3.5 nm) compared to the free protein (3.2 nm), reflecting steric hindrance that physically impedes the tight packing required for fibril elongation. The dynamic yet sustained hydrogen bonding (mean: 3.5 ± 1.2 bonds) underscores Myricetin's ability to flexibly yet stably associate with 'Aβ (1-42)', with no dissociation observed after 14 ns. RMSD trajectory analysis highlights 3 different phases: initial structural stability (0-40 ns), high fluctuations (40-150 ns), and persistent unfolding beyond 150 ns, where over 90% of RMSD values surpass 2.5 nm, indicating a stabilised, non-aggregating state.

This is supported by secondary structure analysis, showing reduced β sheet content and increased coil/turn elements. SASA calculations further suggest that 'Myricetin' binding increases hydrophobic residue exposure (e.g., Val40), thereby maintaining an extended conformation that prevents hydrophobic collapse contrasting Aβ's native aggregation prone folding. These simulation-based findings are reliable with prior studies, such as those by Scheidt et al. (2019), which demonstrated off-pathway species formation through steric hindrance, and by Nelson et al. (2005), which emphasised the disruption of intermolecular hydrogen bonds to destabilise fibril cores.

Unlike rigid, high-affinity inhibitors, Myricetin's dynamic, adaptive binding suggests a 'chaperone like' mechanism that promotes conformational diversity rather than locking Aβ into a single inactive state, potentially minimising off target effects while preserving efficacy. Biologically, since 'Alzheimer's' disease pathology is driven by Aβ accumulation into toxic oligomers and plaques, Myricetin's ability to stabilise Aβ (1-42) in a non-fibrillar, extended state may inhibit the formation of neurotoxic species. This mechanism aligns with the broader therapeutic strategy of targeting early aggregation intermediates to halt disease progression. Moreover, the observed RMSD shift beyond 2.5 nm after 150 ns positions 'Myricetin' as a 'structure-breaker,' like

compounds like EGCG that redirect Aβ into non-toxic aggregates. Combined with its known 'antioxidant' and 'anti-inflammatory' properties, 'Myricetin' emerges as a promising multifunctional therapeutic candidate for 'Alzheimer's' disease.

CONCLUSION

Myricetin effectively modulates Aβ (1-42) conformational dynamics, shifting it toward a non-aggregating state through dynamic hydrogen bonding and steric hindrance. These findings validate its anti-amyloidogenic potential and suggest that targeting Aβ's early folding intermediates could be a viable strategy for AD intervention. By bridging computational insights with biological relevance, this research provides a base for future experimental investigations and drug development efforts focused on amyloid modulation.

LIMITATIONS

This study is not without limitations. First, the simulation duration of 200 ns, although sufficient to capture early conformational changes, may not be adequate to observe late-stage aggregation or potential dissociation events that typically occur over longer timescales (>1 μs). Second, one key consideration is the reliance on the CHARMM27 force field, which may not fully capture certain non-covalent interactions particularly π-stacking and hydrophobic effects that play a serious role in accurately representing Aβ–ligand binding. Lastly, the results are based solely on computational data and have not yet been validated through experimental techniques such as ThT fluorescence, TEM, or in vitro cellular assays, limiting their immediate translational applicability.

IMPLICATIONS

This research highlights the importance of combining computational modelling with experimental validation to achieve a deeper understanding of the mechanisms driving

amyloid inhibition. 'Myricetin's' dynamic binding mode and dual anti-aggregation/antioxidant activity highlight its potential as a scaffold for AD therapeutics. Furthermore, the methodology described here combining trajectory snapshots, Rg, RMSD, and hydrogen bond analyses provides a robust framework for screening other natural or synthetic compounds targeting neurodegenerative diseases.

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