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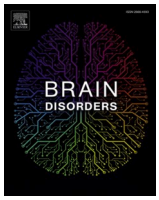

Computational discovery of plant-derived flavonoids as potential amyloid-β fibril disaggregating agents for alzheimer's disease

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ABSTRACT

The neurological hallmark of Alzheimer's disease (AD) is a pathogenic deposition of amyloid-β peptide in the brain. Amyloid-β aggregation is neurotoxic and ultimately results in dysfunction of the nervous system. The present study aims to find potential amyloid-β fibrils disaggregating molecules from plant sources through molecular modeling techniques, which seems to be a promising and attractive therapeutic approach. Here, 500 flavonoids from various plants were considered, initially undergoing ADME studies to screen molecules that could cross the blood-brain barrier. Later, potential Amyloid-β-disaggregating molecules were predicted by molecular docking and molecular dynamics studies. Five molecules, prenylmethoxy flavonol (-7.3 kcal × mol^{-1}), isopentenyl flavonol (-7.3 kcal × mol^{-1}), 7,3′-Dihydroxyflavone (-7.2 kcal × mol^{-1}), 7-Hydroxy-5-methyl-4′-methoxyflavone (-7.2 kcal × mol^{-1}), 8-hydroxy-7-methoxyflavone (-7 kcal × mol^{-1}) exhibited top binding score against Alzheimer's Aβ (1–42) fibrils, and these are very close to the standard drug (Donepezil) (-7.90 kcal × mol^{-1}). Further, the MD simulation studies confirmed the stability of the five selected ligands-Amyloid-β oligomer protein complex. Based on these findings, the selected five compounds might be used as potential Amyloid-β fibril disaggregating agents, and *in vitro* and *in vivo* studies are necessary to confirm the promising therapeutic capability.

Introduction

Alzheimer's disease (AD) is a progressive neurological illness associated with verbal, behavioural, and cognitive problems that eventually interfere with day-to-day functioning [1]. Sadly, there is no known treatment for AD, and each person's experience with the disease is unique [2]. Aberrant protein accumulation within and around brain cells is believed to be the root cause of AD [3]. Amyloid-beta (Amyloid-β) is a naturally occurring protein that accumulates in the Alzheimer's brain in abnormal proportions to form plaques that damage cell function [4]. Amyloid-β plaques are the main factor behind neuritic plaques in AD, a condition that gradually deteriorates cognitive abilities [5]. The enzymatic cleavage of APP (Amyloid Precursor Protein) leads to the release of Amyloid-β monomers (37–42 residue long), which, upon aggregation, form neurotoxic Amyloid-β fibrils [6]. The early formation of Amyloid-β plaques mostly depends on the monomeric Amyloid-β42 peptide [7]. Misfolded Amyloid-β42 peptides self-assemble to form oligomers, which aggregate to form fibrils [8]. The Amyloid-β42 monomer is a crucial indicator of AD and has been extensively utilized in preventing and managing AD [9].

There are two possible approaches to avoid the misfolding and aggregation of the Amyloid-β42 peptide. The first is limiting the Amyloid-β monomer's conformational change using inhibitors targeting this process. The second approach is to destabilize/disaggregate the native state of the Amyloid-β42 monomer by refolding it from its misfolded configuration [10]. Researchers initiated destabilization/disaggregation as a

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therapeutic method due to the clinical failure of medicines using an anti-aggregation technique [11]. Amyloid-β fibril destabilization has a double effect: the distorted fibrils stop being neurotoxic in and of themselves and prevent the production of additional higher-order aggregates [12]. Natural chemicals have been the go-to option for breaking up preformed Amyloid-β fibrils because of their minimal toxicity to humans and biocompatibility [13]. Plant-based phytochemicals are the safest option among all-natural compound sources because of their greater potency, fair availability, extractability, and broad-spectrum applicability. Natural polyphenolic molecules, especially flavonoids, are gaining much attention because they inhibit the formation and aggregation of Amyloid-β fibrils [14]. Soluble monomers of amyloid-β (Aβ) peptides, specifically Aβ42, initiate the formation process when they undergo structural changes from genetic or environmental stressors and cellular elements [15]. Cytokines first misfold and then link into oligomeric forms, which scientists agree are poisonous because they destroy synaptic signals and cellular barriers. Oligomers evolve into insoluble protofibrils and mature amyloid fibrils that produce the extracellular plaques which characterize Alzheimer's disease [16]. The pathological cascade in Alzheimer's disease begins because of oxidative stress together with metal ion dysregulation, mitochondrial dysfunction, and abnormal cleavage of amyloid precursor protein (APP). The protein-folding instability caused by these factors leads to the beginning of the amyloidogenic pathway while simultaneously causing neurodegeneration [17].

Flavonoids are a class of secondary metabolites that have garnered interest from the pharmaceutical sector due to their diverse medicinal applications. A benzopyrone ring with several positions for phenolic or polyphenolic groups is the main structural element of flavonoids [18]. These are produced spontaneously via the phenylpropanoid pathway, and their bioactivity relies on their bioavailability and mode of absorption. Most plants, fruits, herbs, stems, cereals, nuts, vegetables, flowers, and seeds contain flavonoids [19]. To date, over 10,000 distinct flavonoid molecules have been identified and extracted. Most flavonoids are widely acknowledged to be helpful therapeutic agents, including neuroprotection [20,21]. The pathogenesis of AD is considered to be the result of an excessive generation of ROS causing neurofibrillary tangles as aggregates of tau, in addition to amyloid-β plaque aggregation of Amyloid-β [22]. This can also lead to higher metabolic demand and mitochondrial dysfunction [23]. Some studies have suggested flavonoids may offer protective effects for brain cells [24]. Some early-stage animal studies have shown that flavonoids can block amyloid-β plaque buildup in the brain, a trademark of Alzheimer's [25]. These naturally occurring flavonoids were suggested as possible therapeutic candidates, but their molecular mechanism remains unclear; thus, it would be ideal to increase *in silico* research [26].

The technique of using *in silico* molecular modeling research to discover new drug candidates from plant-derived flavonoids for AD treatment is outstanding and continually changing [27]. There is an increasing agreement that plant-derived flavonoids with aromatic rings are suitable for treating AD. Flavonoids have been found to possess antioxidant and neuroprotective properties, which have been shown to slow down the onset of Alzheimer's disease [28]. Molecular dynamics simulation modeling provides atomistic insights into the mechanism of disaggregating Amyloid-β fibrils, which can aid in discovering drugs for treating AD [9,29]. In this work, five hundred diverse flavonoid compounds derived from plants were randomly chosen from drug libraries. The objective was to anticipate probable molecules that can disaggregate amyloid-β fibrils. The molecules were picked randomly, and their ability to penetrate the blood-brain barrier was determined using *in silico* ADME tests. Additionally, these flavonoids were docked with Amyloid-β oligomer to identify possible binders of Amyloid-β oligomer. The docked complexes were further subjected to molecular dynamics (MD) modeling to identify the most promising compounds for the disaggregation of Amyloid-β fibrils.

Experimental section

Amyloid-β protein preparation

The three-dimensional architecture of Alzheimer's amyloid beta (1–42) fibrils (PDB entry id: 2BEG, *Homo sapiens*) was acquired from the RCSB Protein Data Bank (https://www.rcsb.org/structure/2BEG). Before molecular docking studies, the retrieved amyloid-β (1–42) fibrils underwent preprocessing steps, which involved removing water molecules and adding polar hydrogens and Kollmann charges. This was done using Swiss-PDB Viewer v4.1.0. Later, the file was designated as target . pdb and stored for subsequent examination. A grid box was created based on the results of the ligand binding site prediction tool of PrankWeb (https://prankweb.cz/). The active sites' protein structure and amino acid locations were calculated using BIOVIA Discovery Studio Visualizer version 4.0 software (Accelry's Software Inc., San Diego, *CA*). This program was then utilized to conduct molecular docking studies.

Ligands selection

Five hundred flavonoid molecules were chosen from different plant sources from IMPPAT 2.0 (Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0) [30] and Dr. Duke's databases [31]. The molecular structures of chosen bioactive molecules and standard drug (Donepezil) were drawn using Chemsketch software and exported as Structure Data Format (SDF). Subsequently, they were translated to mol2 chemical format using Open Babel. Atoms were allocated Gasteiger-type polar hydrogen charges, whereas non-polar hydrogen molecules were combined with carbons. The internal degrees of freedom and torsions were then adjusted to zero. The ligand molecules were subsequently transformed into the dockable PDBQT format using AutoDock Tools.

In silico ADME screening

BBB (blood-brain barrier) selectively allows ions, nutrients, and tiny molecules (<400 Da) into the brain while prohibiting more significant compounds and unwanted cells from entering [32]. Therefore, the prediction of potential BBB crossing compounds from the above-selected five hundred compounds using the SwissADME web tool (https://www.swissadme.ch). In this regard, SMILES (Simplified Molecular Input Line Entry System) was converted from their 3D structure using an online SMILES translator and structure file generator (https://cactus.nci.nih.gov/translate/).

Active site targeted molecular docking of phytochemicals

The molecules screened in the Swiss-ADME research mentioned above have been chosen for molecular docking investigations. The purpose of these studies is to discover molecules that have a high potential for disaggregating amyloid-β fibrils. The docking process was performed with the selected compounds and the standard medicine donepezil against amyloid-β fibrils (PDB id: 2BEG) through the AutoDock Vina program in PyRx 0.8 software, focusing on the active amino acid residues. The molecules and the standard medicine (Donepezil) were imported and subjected to energy minimization using the Open Babel tool. The optimized molecules were then loaded into PyRx 0.8. The Universal Force Field (UFF) was employed as the energy minimization parameter, while conjugate gradient descent was utilized as the optimization algorithm for energy. The docking investigations utilized the active region of the amyloid-β fibrils (2BEG), which was characterized by a grid box size of 30.34 × 25.0 × 18.93 Å and centered at coordinates (x, y, z) of (−5.73, 0.024, 0.247) Å. All the remaining parameters were maintained at their default settings. The intermolecular interactions were observed using Discovery Studio Visualizer version 16.

Molecular dynamics simulation studies

The study used molecular dynamics simulation to examine the stability of binding, conformation, and intermolecular interactions between specific highly ranked bioactive compounds (ligands) and the target protein, amyloid-β fibrils (PDB id: 2BEG). The complexes' time-dependent development was estimated for 100 nanoseconds using the Desmond dynamic package 2017 in Schrodinger (academic version) on a Linux system. The MD simulation (Schrodinger, LLC, Schrodinger Release: QikProp) emphasizes the probable outcomes of protein-ligand complex (PLC) at target binding sites under physiological conditions. The panel for system developers: At first, the panel enables us to construct a cubic container (10 × 10 × 10) that holds water molecules and physiological properties such as pH. If the pH is absent or needs to be adjusted to meet the specific requirements of the study approach, Na+ or Cl- ions can be introduced. The docked protein-ligand complexes were solved using the orthorhombic point-charge (SPC) water model in a direct and uncomplicated manner. The solvated system was rendered electrically neutral by introducing counter ions while maintaining a physiological salt concentration of 0.15 M [33]. The PLC system was exposed to the OPLS AA (Optimal Potentials for Liquid Simulation - All Atom) force field [34]. The system builder panel will significantly reduce the prepared PLC, taking roughly 100 picoseconds. The molecular dynamics simulation utilized a relaxation length of two picoseconds. The Reversible Reference System Propagator Algorithms (RESPA) integrator, the Martyna-Tobias-Klein barostat, and the Nose-Hoover chain thermostat were employed [35]. The system in equilibrium was utilized to generate the final iteration of the molecular dynamics (MD) simulation. The NPT ensemble, which maintains constant temperature, pressure, and number of particles, was employed for the molecular dynamics (MD) simulation [36]. The simulation was conducted for 100 nanoseconds at a temperature of 310.15 Kelvin and a pressure of 1.0 bar, using the default relaxation parameters. An evaluation of the outcomes was performed using a simulated interaction diagram after the completion of the experiment.

Density functionality theory

Density Functional Theory (DFT) is a well-recognized and effective "*ab initio*" method for studying the structure of quantum many-body systems, including atoms, molecules, and solids [37]. The DFT analysis of the top-scored molecules was conducted using the Gauss View molecular visualization software and the Gaussian 03 W package. They were employing a DFT/Becke-3–Lee–Yang–Parr (B3LYP)/6–311 G (d, p) approach to determine the selected bioactive compounds' optimum molecular structure and vibrational frequencies. In addition, the optimal configurations and frontier molecular orbital energies of specific bioactive molecules were calculated. These energies include the lowest unoccupied molecular orbital (ELUMO), highest occupied molecular orbital (EHOMO), and the energy gap between them (Eg). The molecular visualization software Gauss View was utilized to present the molecular orbital energy diagrams of the chosen bioactive molecules.

Results

Binding site identification

Identifying the binding site is accomplished by assessing the physicochemical and shape properties of the protein area. This is a crucial stage in discovering new chemical entities in molecular docking to design new drugs based on the structure of the target protein. Here, the PrankWeb tool identified 10 potential binding sites within the three-dimensional structure of Alzheimer's amyloid-β (1–42) fibrils (PDB entry id: 2BEG). Fig. 1 displays the amino acid residues binding to amyloid-β fibrils. The 10 binding pockets were distinguished by various colours: red, light-yellow, dark-yellow, light green, dark green, light blue, tan, grey, pink, light orange, and dark bluish-green. The molecular docking process was employed to screen the chosen active compounds using the identical binding pockets of the amyloid-β fibrils. Grid generation in molecular docking improved the accuracy of ligand posture grading. To enhance the precision of our ligand posture scoring, we created a receptor grid specifically designed for the selected amyloid-β fibrils. This grid was generated using the binding site residues obtained in prior experiments. To do this, a receptor grid was created with the box dimensions of $X = 67.1909$, $Y = 91.6671$, and $Z = 88.4240$ in angstrom (Å).

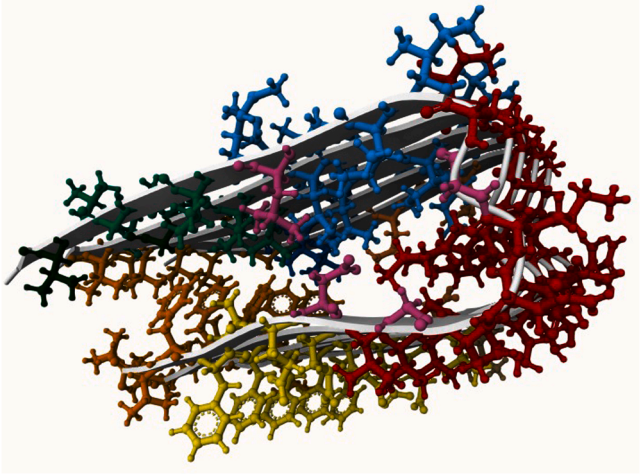

Fig. 1. The PrankWeb tool predicts the binding pockets and correspondence binding sites of the Alzheimer's amyloid-β (1–42) fibrils. The 10 binding pockets were distinguished by various colours: red, light-yellow, dark-yellow, light green, dark green, light blue, tan, grey, pink, light orange, and dark bluish-green.

Active molecules and their structures

The three-dimensional structures of 500 active molecules from various plants were retrieved from the IMPPAT and Dr Dukes databases and optimized with the standard drug, Donepezil. Supplementary Table 1 presents the findings of *in silico* ADME and molecular docking analyses against the Alzheimer's amyloid-β (1–42) fibrils using the optimized structures.

Molecular mechanism of amyloid

The misfolding tendency of amyloid-β (Aβ) peptides, particularly Aβ42, leads to toxic oligomers and fibril formation that cause Alzheimer's disease pathology. The aggregation of these materials disrupts the normal functions of cells and creates oxidative stress, which leads to synaptic problems. The molecular pathway involves ROS production, which creates lipid destruction, mitochondrial breakdown, and neuronal damage. The antioxidant mediators fight ROS while stopping the growth of amyloid fibrils. Natural antioxidants, which include polyphenolic compounds, specifically flavonoids, bond to Aβ peptides in a manner that prevents β-sheet formation and causes disaggregation of the peptides [38].

In silico ADME screening

The blood-brain barrier (BBB) impedes the entry of most medications into the brain. The discovery of drugs for Alzheimer's disease (AD) is hindered by the existence of the blood-brain barrier (BBB). The blood-brain barrier (BBB) prevents over 98 % of small-molecule medications and almost 100 % of large-molecule pharmaceuticals from entering the brain. While most drug candidates for Alzheimer's disease (AD) are

unable to pass through the blood-brain barrier (BBB), the current focus of AD drug development is heavily skewed towards discovering drugs that target the central nervous system (CNS), with <1 % of the effort dedicated to developing drugs that can effectively reach the CNS [32]. Through ADME analysis, this study screened 125 blood-brain barrier crossing ability of flavonoids from 500 molecules. Supplementary Table 2 displays the chosen molecules for subsequent molecular docking investigations.

Molecular docking

Molecular docking was conducted to evaluate the ability of 125 bioactive molecules to disaggregate Alzheimer's amyloid-β (1–42) fibrils compared to the standard drug Donepezil. Amyloid-β (1–42) fibrils, which are neurotoxic and a hallmark of Alzheimer's disease pathology, are an essential target for therapeutic intervention. The binding affinity of each molecule to the fibrillar protein structure was then assessed using AutoDock Vina. Out of all tested compounds, five molecules had exceptional binding energy of −7.3 kcal × mol^{-1}, close to the reference compound Donepezil, having better binding energy of −7.9 kcal × mol^{-1}. Five of these, prenylmethoxy flavonol, isopentenyl flavonol, 7,3′-Dihydroxyflavone, 7-Hydroxy-5-methyl-4′-methoxyflavone, and 8-hydroxy-7-methoxyflavone, were selected for further study as they exhibited high binding affinities and the ability to destabilize amyloid fibrils [39]. The least binding energy value of Δ_G suggests that it would be an excellent binder to Aβ fibril compared to earlier reports [40]. The protein-ligand interaction profiler web tool (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) was used to visualize the developed residue interactions between the chosen ligands with amyloid-β fibrils.

Base level architecture and energy dispersion

The binding energy values of 125 active molecules ranged from −7.7 to −5.0 kcal × mol^{-1}, showing a wide range of interactions with the amyloid-β fibrils. The lower the binding energy, the more stable the ligand-protein complex, indicating that these compounds might be capable of binding and subsequently interfering with the fibril aggregation process. Notably, the FDA-approved drug Donepezil, used for Alzheimer's treatment, showed the highest binding at −7.9 kcal × mol^{-1}, which validated its confirmed ability to inhibit fibril formation. Five shortlisted compounds displayed relatively lower binding energy than Donepezil but showed competitive binding profiles and are therefore worthy of further investigation.

Analysis of residue interactions and structural docking comparison

The molecular basis of these interactions was deciphered with the aid of the Protein-Ligand Interaction Profiler (PLIP) for mapping the binding interfaces and locating hydrogen bonds and hydrophobic interactions that are essential for ligand affinity. The interactions were visualized in 2D and 3D representations, providing information on binding pocket occupation and stability.

Prenylmethoxy flavonol (−7.3 kcal × mol^{-1})

The compound was bound with a high affinity to amyloid-β fibrils and formed four strong hydrogen bonds with key residues. These attributes possessed three hydrogen bonds with ASN 27B (2.95 Å, 2.79 Å) and ASN 27C (2.07 Å) and one bond with GLY 29C (2.04 Å). The multiple hydrogen bonds with ASN residues-often seen with other docked ligands—show their important role in stabilizing interactions with the fibrillar structure. Such polar contacts may also further provide a mechanism to disrupt the β-sheet stacking necessary for the disaggregation of the fibrils. This mode of action closely mirrors previous studies with flavonoid derivatives that have been shown to destabilize amyloid oligomers.

Isopentenyl flavonol (−7.3 kcal × mol^{-1})

Isopentenyl flavonol had two hydrophobic interactions with ALA 30A (3.84 Å), ALA 30B (3.76 Å) and one hydrogen bond with ASN 27C (1.99 Å) when bound to the amyloid-β fibrils. The interactions with alanine indicate that substantial van der Waals and hydrophobic contact serve as an anchor to stabilize the molecule in the core of the fibril. Although fewer hydrogen bonds were observed compared to prenylmethoxy flavonol, strong nonpolar interactions indicate that a complementary binding mode was employed. This dual engaging mode (polar and hydrophobic) may be responsible for a balanced interaction stabilizing the ligand-protein complex.

7,3′-dihydroxyflavone (−7.2 kcal × mol^{-1})

This compound showed a unique interaction with forming four hydrogen bonds with ASN 27B (2.82 Å), ASN 27C (1.77 Å), ASN 27D (2.32 Å), and ALA 30D (2.61 Å), and one hydrophobic interaction with ALA 30C (3.88 Å). The presence of multiple ASN 27 contacts across three separate chains (B, C, and D) suggests a multivalent binding strategy. It could act this way so that this mechanism can cross-link some other tracts of the fibrillar structure, thereby increasing its disaggregating ability. Both strong hydrogen bonding and a hydrophobic anchor further support its potential to exhibit significant anti-amyloid activity.

7-hydroxy-5-methyl-4′-methoxyflavone (−7.2 kcal × mol^{-1})

This molecule formed three hydrogen bonds with the residues ASN 27B (3.15 Å), ASN 27D (2.14 Å), and ALA 30D (2.58 Å), and two hydrophobic interactions with ALA 30C (3.96 Å) and ALA 30D (3.72 Å). The configuration indicates a stronghold at the binding site through polar and non-polar residues. The affinity and the interaction count are comparable to that of 7,3′-Dihydroxyflavone. Still, the increase in hydrophobic surface engagement indicates this compound could favorably stabilize in the hydrophobic core of the fibril. However, this interaction with several alanine residues is consistent with the exposure of hydrophobic patches commonly recognized in aggregated β-sheet conformations.

8-Hydroxy-7-methoxyflavone (−7.0 kcal × mol^{-1})

This compound formed five hydrogen bonds (an essential number for stable docking) involving ASN 27B (3.03 Å and 2.30 Å), ASN 27C (2.24 Å), ALA 30C (3.11 Å), and ALA 30D (2.13 Å), as well as two hydrophobic interactions with ALA 30B (3.90 Å) and ALA 30C (3.65 Å). The significant inclusion of ASN and ALA residues further supports a balanced interaction profile. With slightly higher binding energy than the top four candidates, it must be a lesser fit, but the quantity of contacts indicates a strong affinity. The presence of both interaction profiles with β-sheet stabilizing residues and flexible loops suggests that it may interfere with fibril elongation.

Donepezil (−7.9 kcal × mol^{-1})

Control drug Donepezil was shown to have the best binding into the proper binding sites by interacting through two hydrogen bonds with ASN27D (3.11 Å) and ALA 30B (2.61 Å) while also forming two hydrophobic interactions with ALA 30B (3.75 Å) and ALA 30D (3.60 Å). Finally, although flotetuzumab and most flavonoids interact less scalability with the target proteins than Donepezil, the latter's strong interactions, optimal binding geometries and more profound accommodation in the protein binding pockets all exam it a strong packing score. A smaller-sized molecule like Donepezil may be better able to be penetrated by the fibrillar groove and be able to disrupt from within. Final analyses, however, indicated common binding sites among all ligands on ASN 27 and ALA 30 residues, implying that amino acids (AAs) ASN 27 and ALA 30 are pivotal anchors for any therapeutic agent targeting amyloid fibrils for disaggregation. Molecules with high hydrogen bonding potential, like 8-hydroxy-7-methoxyflavone and 7,3′-Dihydroxyflavone, produced more stable interactions. Yet, it does not necessarily lower binding energy, suggesting that bond geometry and

total surface contact are essential to binding affinity. Although comparatively fewer, hydrophobic interactions seem to be the driving force in locking the ligands into the non-polar cores of the fibril, where ALA 30 was the constant participant across all of the compounds tested. Interestingly, flavonoids generally utilize a more significant number of hydrogen bonds due to their polyphenolic nature when comparing the binding modes between flavonoids and Donepezil. At the same time, Donepezil uses a much more compact and deep binding mode, which may be the reason for its marginally high binding affinity.

Mechanistic considerations for Amyloid-β disaggregation

Amyloid-β fibrils are stabilized mainly by hydrogen bonding within β-strands and hydrophobic interactions between β-plates. Of these, 51 are also presumed to interact at key interface residues, such as ASN 27 and ALA 30, near β-turns or in β-sheet domains. By binding to such sites, the ligands might destabilize the inter-strand hydrogen bonding or disrupt hydrophobic stacking. Fusion products with more extended non-polar groups, such as prenylmethoxy flavonol and isopentenyl flavonol, could further destabilize fibril integrity by introducing steric hindrance or disrupting planar stacking of β-sheets. In addition, previous research has demonstrated that flavonoid derivatives disrupt the oligomerization and nucleation phases of amyloid fibrillogenesis. This docking analysis corroborates those findings and reveals additional specific flavonols that dock fibrillar interface residues. Metal-binding studies showed that the five selected flavonoid derivatives had a strong binding affinity to metal ions, and molecular docking studies further confirmed that all five compounds interacted strongly with Alzheimer's amyloid-β (1–42) fibrils and specific interactions were observed. These showed *in vitro* interaction profiles closely resembling or complementing the pharmacological action of Donepezil. Prenylmethoxy flavonol and isopentenyl flavonol displayed the most conspicuous binding energy (−7.3 kcal × mol^{-1}), reinforced by significant hydrogen and hydrophobic bonding interactions (Fig. 2 and Supplementary Table 2). The consistent presence of ASN 27 and ALA 30 in all docked poses highlights their role as pharmacophoric hotspots for fibril disaggregation. Induction of molecular dynamics simulations or *in vitro* aggregation inhibition assays followed by cellular toxicity reversal studies can be performed as a biopharmaceutical examination of these docking predictions and kinetic and thermodynamic stabilities of the resultant protein-ligand complexes for further *in vivo* monitoring. These flavonol derivatives are potential scaffolds for developing next-generation anti-Alzheimer's therapeutics should they be validated experimentally.

Molecular dynamics (MD) simulation studies

Molecular dynamics simulations were employed to explore the stability of protein-ligand interactions. MD simulations were performed to study the protein-ligand complexes of amyloid-β fibrils-prenyl methoxy flavonol, amyloid-β fibrils-isopentenyl flavonol, amyloid-β fibrils-7,3′-Dihydroxyflavone, amyloid-β fibrils-7-Hydroxy-5-methyl-4′-methoxy-flavone, amyloid-β fibrils-8-hydroxy-7-methoxyflavone and amyloid-β fibrils-donepezil. The RMSD graph and the ligand-protein interactions (2D interaction diagram) were checked to understand the simulated results better. The RMSD graphs approximately demonstrated the evolution of the protein (y-axis on the left) and the ligand (y-axis on the right). The amyloid-β fibrils-prenylmethoxy flavonol complex was stable with RMSD protein values between 4.8 and 7.1 Å and ligand RMSD values between 12.5 and 18.2 Å (Fig. 3(a)). The MD trajectory events of the amyloid-β fibrils-isopentenyl flavonol complex presented that protein RMSD was between 4.2 and 4.8 Å while ligand RMSD was in the range of 24–32 Å, confirming a stable complex (Fig. 3(b)). Based on the MD trajectory events of the amyloid-β fibrils-7,3′-Dihydroxyflavone complex, we found that the RMSD of protein was 8–20 Å, while for ligand and it was 36–42 Å, indicating that protein and ligand complex exhibited non-stability as shown in (Fig. 3(c). RMSD trajectories of the long MD trajectories of amyloid-β fibrils-7-Hydroxy-5-methyl-4′-methoxyflavone complex showed that protein and ligand RMSD at 3.8 to 4.6 Å and 4 to 6 Å, respectively, indicated the stability of the complex (Fig. 3(d)). The MD events for the amyloid-β fibrils-8-hydroxy-7-methoxyflavone complex showed that the protein RMSD was within the range of 4–4.5 Å, whereas the ligand RMSD ranged from 10 to 14 Å (indicating a stable complex) (Fig. 3(e)). The stable complex of amyloid-

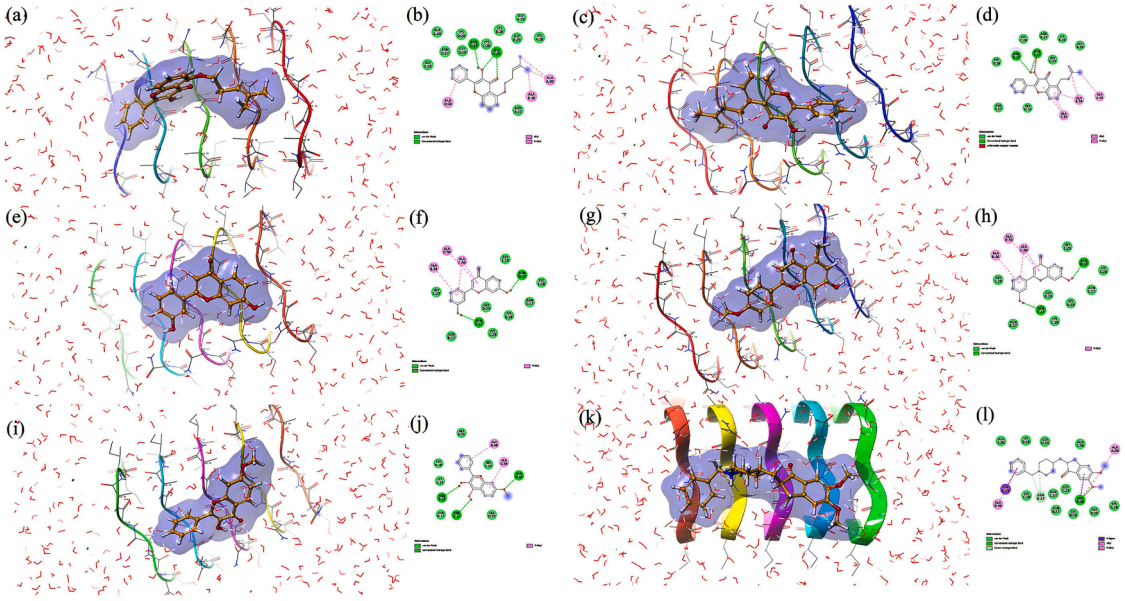

Fig. 2. Interaction between the molecule Prenylmethoxy flavonol and Amyloid-β fibrils. The left side represents 3D (a), and the right represents 2D complex protein-ligand interaction (b), the interaction between the molecule Isopentenyl flavonol and Amyloid-β fibrils. The left side represents 3D (c), the right represents 2D complex protein-ligand interaction (d), and the interaction between molecules 7,3′-Dihydroxyflavone and Amyloid-β fibrils. The left side represents 3D (e), and the right represents 2D complex protein-ligand interaction (f) and the interaction between the molecule 7-Hydroxy-5-methyl-4′-methoxyflavone and Amyloid-β fibrils. The left side represents 3D (g), and the right represents 2D complex protein-ligand interaction (h) and the interaction between the molecule 8-hydroxy-7-methoxy-flavone and Amyloid-β fibrils. The left side represents 3D (i), and the right side represents 2D complex protein-ligand interaction (j) and the interaction between the molecule Donepezil and Amyloid-β fibrils. The left side represents 3D (k), and the right represents 2D complex protein-ligand interaction (l).

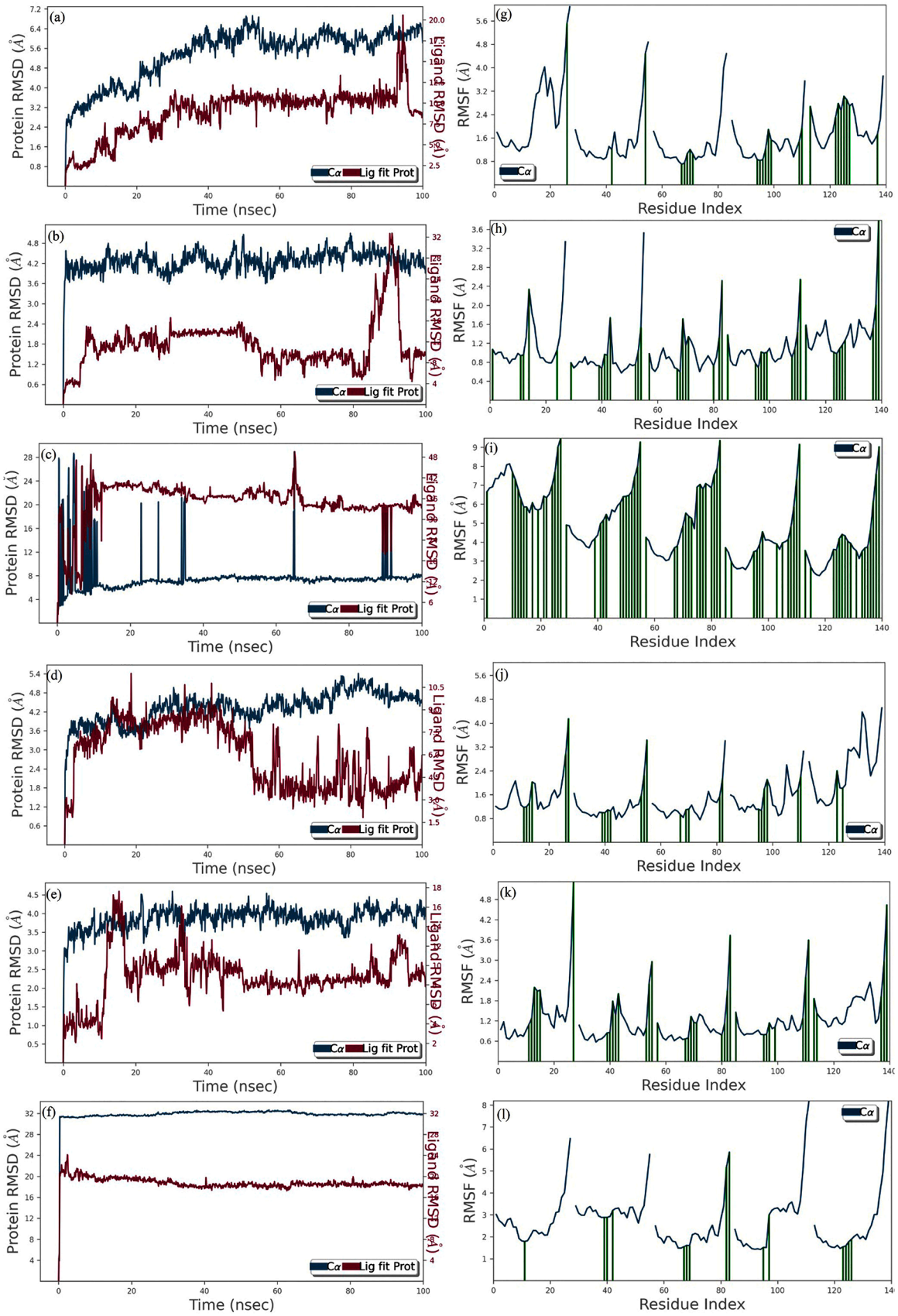

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Fig. 3. RMSD study plot for 100 ns MD simulation of prenylmethoxy flavonol-Amyloid-β fibrils docked complex (a), isopentenyl flavonol-Amyloid-β fibrils docked complex (b), 7,3′-Dihydroxyflavone-Amyloid-β fibrils docked complex (c), 7-Hydroxy-5-methyl-4′-methoxyflavone-Amyloid-β fibrils docked complex (d), 8-hydroxy-7-methoxyflavone-Amyloid-β fibrils docked complex (e), and Donepezil-Amyloid-β fibrils docked complex (f). Root mean square fluctuation (RMSF) of the Prenylmethoxy flavonol for characterizing changes in the ligand atom positions (a), root mean square fluctuation of the isopentenyl flavonol for characterizing changes in the ligand atom positions (b), root mean square fluctuation of the 7,3′-Dihydroxyflavone for characterizing changes in the ligand atom positions (c), root mean square fluctuation of the 7-Hydroxy-5-methyl-4′-methoxyflavone for characterizing changes in the ligand atom positions (d), root mean square fluctuation of the 8-hydroxy-7-methoxyflavone for characterizing changes in the ligand atom positions (e), and root mean square fluctuation of the Donepezil for characterizing changes in the ligand atom positions (f).

β fibrils-donepezil combination, MD trajectory events per (f) protein RMSD of 31–32 Å, (g) compound RMSD of 20–21 Å. Datasets of stable six protein-ligand complexes undergoing RMSF analysis demonstrated no significant differences between the ligands binding to the key functional groups of the amyloid-β fibrils (Figs. 3(g)-3(l)). The MD trajectory of the complex of amyloid-β fibrils- prenylmethoxy flavonol explored interactions with two particular amino acids, ALA30 and GLY29. Thus, these amino acids had the residue index, which did not differ during the MD simulation (Figs. 4(a) and 4(b)). As illustrated by the residue index through the MD trajectory, the connection between the residues was stable, where ALA30 and GLY29 would not mutate during simulation, suggesting a stable connection as seen in the MD trajectory of the amyloid-β fibrils-isopentenyl flavonol complex. The amino acid residues that had the highest interaction with isopentenyl flavonol in this complex were ALA30 and GLY29, according to the protein-ligand interactions of the amyloid-β fibrils-isopentenyl flavonol complex (Figs. 4(d), and 4(e)). The significant contact recovered from protein-ligand interactions of amyloid-β fibril-7,3′-Dimethoxychalcone crowned antagonist (Figs. 4(g) and 4(h)) was caused by residues 27B ASN, 27C ASN, 27D ASN, and 30D ALA: the primary contact made with 7,3′-Dihydroxyflavone. Analyses of the protein-ligand interactions of the amyloid-β fibrils-7-Hydroxy-5-methyl-4′-methoxyflavone complex depicted that amino acid residues 27D ASN and 30D ALA were the most prominent residues that provided vital interactions with 7-Hydroxy-5-methyl-4′-methoxyflavone (Figs. 4(j) and 4(k)). The protein-ligand interactions between the amyloid-β fibril-8-hydroxy-7-methoxyflavone complex showed that the amino acid residues with the most significant contact with 8-hydroxy-7-methoxyflavone were 27B ASN, 27C ASN, and 30C ALA (Figs. 4(m) and 4(n)). Analysis of protein-ligand interactions of the amyloid-β fibrils-donepezil complex showed that residues 30B ALA, 30D ALA, and 27D ASN yielded the most significant interaction with Donepezil (Figs. 4(p) and (q). Figs. 4(c), (f), (i), (l), (o) and (r) represent hydrogen bond contacts and timeline of all amino acids which form H-bonds, hydrophobic, ionic, or water bridges. Thicker lines suggest a constant interaction with the object. These interactions ensured the stability of the protein-ligand complex throughout the molecular docking simulations. Our results indicate that prenylmethoxy classification of flavonol, isopentenyl flavonol, 7,3′-Dihydroxyflavone, 7-Hydroxy-5-methyl-4′-methoxyflavone, and 8-hydroxy-7-methoxyflavone have the potential capacity to disaggregate amyloid-β fibrils, and *in vitro* studies should be performed for this purpose. These compounds may be utilized as the basis for future lead optimization.

DFT studies

The electronic parameters of the chosen flavonoid derivatives, as well as the reference drug Donepezil, were obtained by frontier molecular orbital (FMO) analysis that analyzed the energies of the highest occupied molecular orbital (EHOMO), the lowest unoccupied molecular orbital (ELUMO), and the derived energy gap (Δ_E). These factors are reasonable indications of biological targets' implicit chemical reactivity, stability and functional ability. In this view, 8-hydroxy-7-methoxyflavone reported the smallness of the energy gap (Δ_E = 2.665 eV) in Table 1, confirming high chemical reactivity with better charge transfer properties. A narrow band gap suggests that the compound can quickly transfer electrons from HOMO to LUMO, which contributes to high interaction with biological receptors. Isopentenyl flavonol (Δ_E = 2.687 eV) and Prenylmethoxy flavonol (Δ_E = 2.750 eV) were the next in the reactivity series, further contributing to their favourable reactivity profiles. These results suggest that three of these compounds might bind more firmly with the enzyme or receptor's active site, owing to their increased electron donating and accepting properties. In comparison, 7,3′-Dihydroxyflavone had the highest energy gap (Δ_E = 3.404 eV) among considered molecules, indicating lower reactivity, possibly lower biological activity, but higher chemical stability. The energy gap calculated for this study's standard reference compound, Donepezil, was 3.127 eV. This value is more significant than most analyzed flavonoid derivatives, meaning some selected compounds possess more favourable electronic properties. This means that, for example, 7-Hydroxy-5-methyl-4′-methoxyflavone, which had an Δ_E of 3.117 eV, can also have electronic interactions comparable to those of Donepezil. For the HOMO energies, 7,3′-Dihydroxyflavone showed an EHOMO of −9.285 eV, suggesting that this compound is less probable to donate electrons. On the other hand, 8-hydroxy-7-methoxyflavone possessed a higher EHOMO (−8.515 eV), reflecting stronger electron-donor ability. The ELUMO values of the compounds were reasonably similar, ranging from −5.654 eV to −5.917 eV, with Isopentenyl flavonol having the lowest ELUMO, indicative of increased electron affinity. Dot plots represent the electronic properties calculated for each docked compound, revealing that the bottom rank of certain flavonoids in their cortex compared to Donepezil can likely be attributed to their weaker frontier energies. Similarities in biological activity position these flavonoids as potential drug discovery candidates for neurodegenerative or cholinergic-targeting therapies, but these features may be associated with enhanced biological behaviour.

Discussion

This study successfully applied molecular modeling tools such as structure-based molecular screening, ADMET, molecular dynamics simulation, and DFT to predict significant amyloid-β fibril disaggregating agents (particularly from flavonoids) from various plant sources. Although molecular modeling tools are widely used in synthetic and medicinal chemistry, there are still few and poorly understood applications in studying molecules produced by plants. Few potential molecules were identified earlier utilizing molecular modeling methods, which were later confirmed by *in vitro* and *in vivo* investigations. The present study selected 500 flavonoids from various plant sources through IMPPAT 2.0, Dr. Duke's phytochemical and ethnobotanical database and other literature. Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0 (IMPPAT 2.0) is the greatest digital library on phytochemicals of Indian medicinal plants to the present date, which is a major improvement and expansion above IMPPAT 1.0. IMPPAT 2.0 is a manually constructed database that digitizes data from over 7000 published research articles, over 100 books on traditional Indian medicine, and other available sources. The current version 2.0, released on June 17, 2022, of the IMPPAT database captures 4010 Indian medicinal plants, 17,967 phytochemicals and 1095 therapeutic uses. The recent version 2.0 of the IMPPAT database includes 4010 Indian medicinal plants, 17,967 phytochemicals, and 1095 therapeutic applications. Another one is that Dr. Duke's database facilitates in-depth plant, chemical, bioactivity, and ethnobotany searches using scientific or common names. These databases were used in several research articles to find significant neuroprotective molecules, which were later

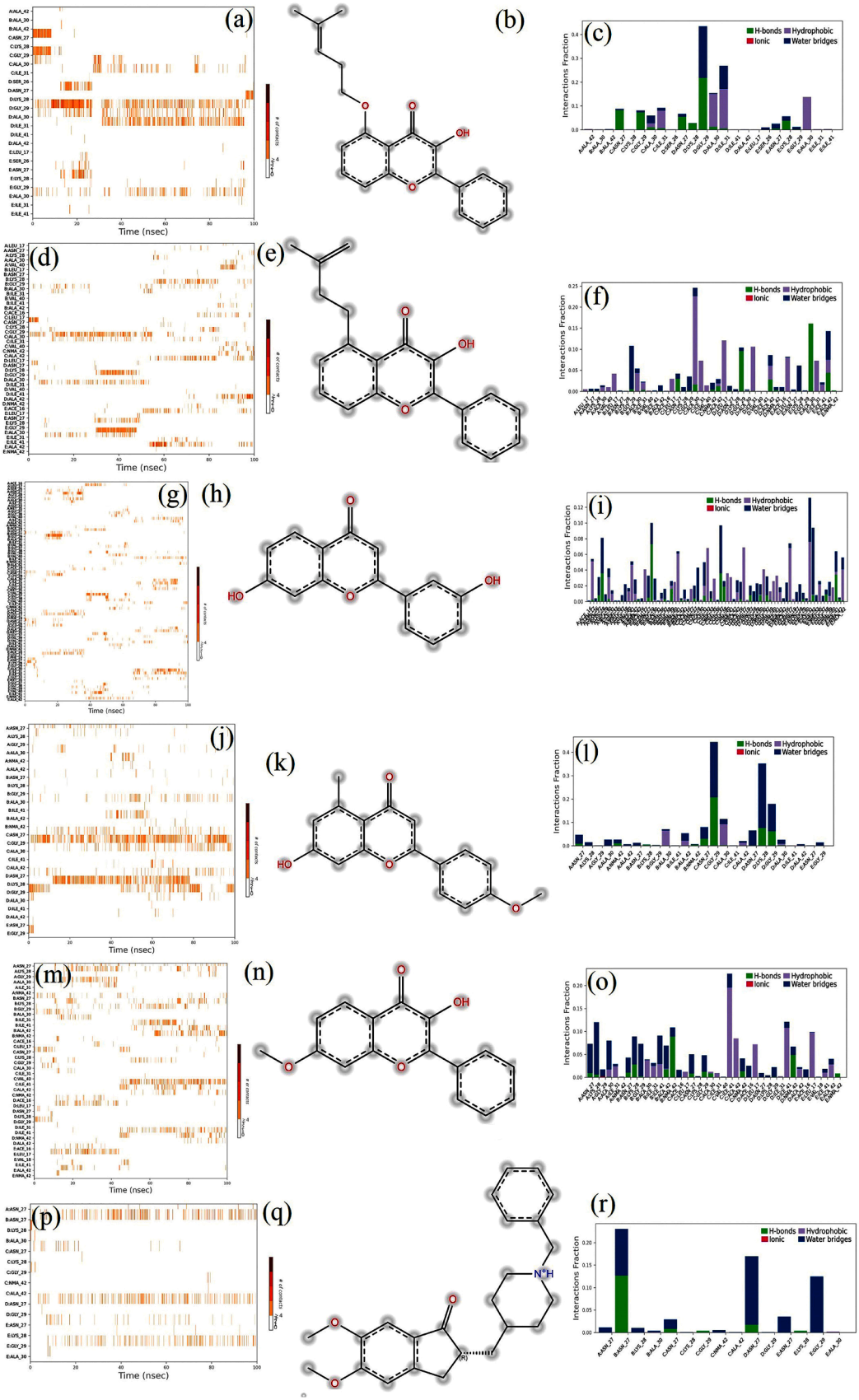

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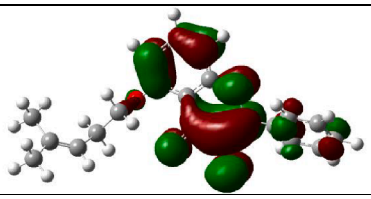
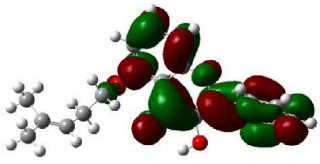
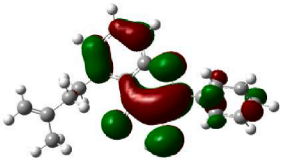
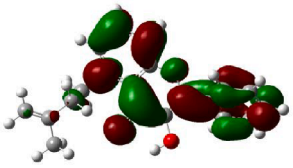
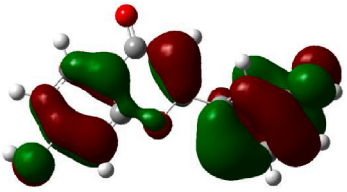
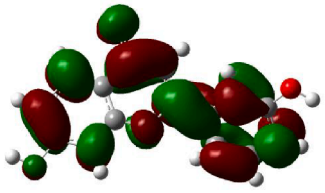
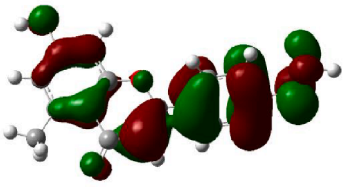
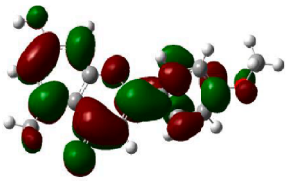
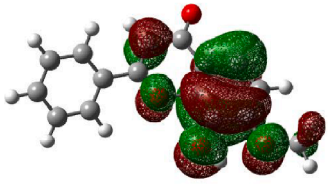
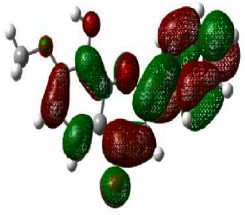
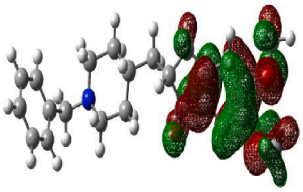
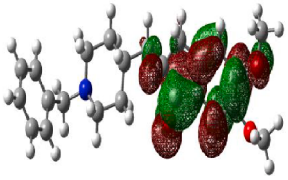
Fig. 4. Prenylmethoxy flavonol-Amyloid-β fibrils docked complex timeline representation of the Prenylmethoxy flavonol (right side) (a), contacts with respect to the amino acids in the target (centre) (a). Percentage of amino acid and water-mediated interactions in MD simulations with Prenylmethoxy flavonol (left side) (c); Isopentenyl flavonol -Amyloid-β fibrils docked complex timeline representation of the isopentenyl flavonol (right side) (d), contacts with respect to the amino acids in the target (centre) (e). Percentage of amino acid and water-mediated interactions in MD simulations with isopentenyl flavonol (left side) (f); 7,3′-Dihydroxyflavone-Amyloid-β fibrils docked complex timeline representation of the 7,3′-Dihydroxyflavone (right side) (g), contacts with respect to the amino acids in the target (centre) (h). Percentage of amino acid and water-mediated interactions in MD simulations with 7,3′-Dihydroxyflavone (left side) (i); 7-Hydroxy-5-methyl-4′-methoxyflavone-Amyloid-β fibrils docked complex timeline representation of the 7-Hydroxy-5-methyl-4′-methoxyflavone (right side) (j), contacts with respect to the amino acids in the target (centre) (k). Percentage of amino acid and water-mediated interactions in MD simulations with 7-Hydroxy-5-methyl-4′-methoxyflavone (left side) (l); 8-hydroxy-7-methoxyflavone-Amyloid-β fibrils docked complex timeline representation of the 8-hydroxy-7-methoxyflavone (right side) (m), contacts with respect to the amino acids in the target (centre) (n). Percentage of amino acid and water-mediated interactions in MD simulations with 8-hydroxy-7-methoxyflavone (left side) (o); Donepezil-Amyloid-β fibrils docked complex timeline representation of the Donepezil (right side) (p), contacts with respect to the amino acids in the target (centre) (q). Percentage of amino acid and water-mediated interactions in MD simulations with Donepezil (left side) (r).

Table 1
E_{HOMO} and E_{LUMO} and Δev values of selected top binding scored compounds and standard drug Donepezil.

Compound Name	HOMO	E_{HOMO} (ev)	LUMO	E_{LUMO} (ev)	Energy gap (Δev)
Prenylmethoxy flavonol		-8.578		-5.828	2.750
Isopentenyl flavonol		-8.604		-5.917	2.687
7,3'-Dihydroxyflavone		-9.285		-5.880	3.404
7-Hydroxy-5-methyl-4'-methoxyflavone		-8.771		-5.654	3.117
8-hydroxy-7-methoxyflavone		-8.515		-5.850	2.665
Donepezil		-8.794		-5.667	3.127

confirmed by *in vitro* and *in vivo* studies. Plants possess an array of numerous therapeutic agents, including amyloid-β fibril disintegrating molecules. Flavonoids are a group of polyphenolic compounds that may help with amyloid-β fibril disintegration in Alzheimer's disease. For example, Amentoflavone is a bioflavonoid that encourages the disintegration of amyloid-β fibrils. They attach to amyloid-β fibrils' N-termini, reducing the fibril's β-sheet composition [41]. Another flavonoid, Quercetin, present in the human diet, may prevent the onset of Alzheimer's disease by binding to β-amyloid oligomers at early stages of aggregation [42]. Flavonoids may slow the aging cycle and enhance cognitive abilities [43]. They might accomplish this by modifying their actions and interacting with various signaling pathways.

The neurotoxic Aβ (amyloid-beta) fibrils that collect extra neuronally as senile plaques are the main characteristic of Alzheimer's disease [44]. Although they are less clinically significant, intraneuronal neurofibrillary tangles made of hyperphosphorylated tau proteins are also indirectly linked to the etiology of Alzheimer's disease [45]. Because of their preferential consideration, Amyloid-β fibrils are the perfect target for assessing the therapeutic potential of any medicine in treating Alzheimer's disease. According to multiple studies, oxidative stress and excessive reactive oxygen species (ROS) formation are the primary causes of amyloid-β fibril aggregation. Amyloid-β peptides produce ROS and can harm amyloid-β and nearby molecules like lipids and proteins. Amyloid-β aggregation and neurotoxicity may result from this injury [46–48]. Plant-derived molecules are generally safe, economical, cellularly protective, and capable of reducing or neutralizing adverse effects by preserving the amount of ROS and oxidative stress in cells and tissues [49]. In this view, five hundred bioactive flavonoids were identified from plant molecules repositories All the identified flavonoids were screened against amyloid-β fibril protein, and observed binding energies were between −5 to −7.7 kcal × mol^{-1}. Five flavonoids, namely prenylmethoxy flavonol (−7.3 kcal × mol^{-1}), isopentenyl flavonol (−7.3 kcal × mol^{-1}), 7,3′-Dihydroxyflavone (−7.2 kcal × mol-1), 7-Hydroxy-5-methyl-4′-methoxyflavone (−7.2 kcal × mol^{-1}), and 8-hydroxy-7-methoxyflavone (−7 kcal × mol^{-1}) were found to exhibit potentially binding with the amino acid residues in the active site of amyloid-β (1–42) fibrils.

Conclusion

Traditionally, plant extracts and their secondary metabolites have exhibited numerous chemical constituents which aid in preventing various diseases. These molecules possess high levels of security, exhibit low toxicity levels, and demonstrate economic efficiency, thus enhancing the overall quality of human existence. The aggregation of amyloid-β fibrils in the brain is a characteristic feature of Alzheimer's disease. This work has found five potential molecules, namely prenylmethoxy flavonol, isopentenyl flavonol, 7,3′-Dihydroxyflavone, 7-Hydroxy-5-methyl-4′-methoxyflavone, and 8-hydroxy-7-methoxyflavone, that can disaggregate amyloid-β fibrils. Molecular docking experiments identified these molecules. The stability of the ligand-receptor complex was assessed by molecular dynamics simulation, revealing that all five Aβ oligomer protein complexes remained stable throughout the simulation. The results obtained from density functional theory also indicated that all five compounds exhibit high stability. In conclusion, the five discovered molecules have the potential to serve as lead compounds for further testing as potential neuroprotective agents that can act on Aβ fibril disaggregation. These compounds can be evaluated utilizing both *in vitro* and *in vivo* experiments. The limitation of this research arises from using computational methods are solely conducted. Molecular modeling systems provide predictions yet they fail to reproduce complete biological system intricacies. *In vitro* and *in vivo* testing deficiencies restrict the verification process for the actual fibril-disaggregating properties of flavonoids. The study uses computational predictions as its fundamental approach but establishes a robust basis for identifying possible Aβ fibril disaggregating compounds. Laboratory tests using ThT fluorescence assays and studies with AD mouse models will validate these findings when experimental research starts in the upcoming months.

Informed consent

Not applicable

Ethical approval

Not applicable

Patient consent statement

Not required

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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CRediT authorship contribution statement

Uthirapathi Logeswari Rakesh: Formal analysis, Data curation, Conceptualization. **Golla Anil Kumar:** Funding acquisition, Formal analysis, Data curation, Conceptualization. **Theivendren Panneerselvam:** Investigation, Formal analysis, Data curation, Conceptualization. **Parasuraman Pavadai:** Investigation, Formal analysis, Data curation, Conceptualization. **Suganthan Veerachamy:** Formal analysis, Data curation, Conceptualization. **Ponnusamy Palanisamy:** Formal analysis, Data curation, Conceptualization. **SunilKumar Bandral:** Formal analysis, Data curation, Conceptualization. **Selvaraj Kunjiappan:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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Data availability

Not applicable

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dscb.2025.100233.

References

[1] A. Atri, The Alzheimer's disease clinical spectrum: diagnosis and management, Med. Clinics 103 (2) (2019) 263–293.
[2] P.B. Harris, The person with Alzheimer's disease: Pathways to understanding the experience, JHU Press, 2002.
[3] R.R. Rajeshkumar, B.K. Kumar, P. Parasuraman, T. Panneerselvam, K. Sundar, D. N. Ammunje, et al., Graph theoretical network analysis, in silico exploration, and validation of bioactive compounds from Cynodon dactylon as potential neuroprotective agents against α-synuclein, BioImpacts 12 (6) (2022) 487.
[4] R. Rajmohan, P.H. Reddy, Amyloid-beta and phosphorylated tau accumulations cause abnormalities at synapses of Alzheimer's disease neurons, J. Alzheimer's Disease 57 (4) (2017) 975–999.
[5] R. van der Kant, L.S. Goldstein, R. Ossenkoppele, Amyloid-β-independent regulators of tau pathology in Alzheimer disease, Nat. Rev. Neurosci 21 (1) (2020) 21–35.
[6] E.A. Bignante, F. Heredia, G. Morfini, A. Lorenzo, Amyloid β precursor protein as a molecular target for amyloid β–induced neuronal degeneration in Alzheimer's disease, Neurobiol. Aging 34 (11) (2013) 2525–2537.
[7] D.A. Butterfield, A.M. Swomley, R. Sultana, Amyloid β-peptide (1–42)-induced oxidative stress in Alzheimer disease: importance in disease pathogenesis and progression, Antioxid. Redox Signal 19 (8) (2013) 823–835.
[8] T.C. Michaels, A. Šarić, S. Curk, K. Bernfur, P. Arosio, G. Meisl, et al., Dynamics of oligomer populations formed during the aggregation of Alzheimer's Aβ42 peptide, Nat. Chem 12 (5) (2020) 445–451.
[9] A. Rustamzadeh, A. Tafakhori, A. Ariaei, M. Heydari, M.E. Shah-Abadi, F. Seif, Targeting caspases 3/6 and cathepsins L/B may decrease laminopathy-induced apoptosis in Alzheimer's Disease, J. Alzheimer's Disease 101 (1) (2024) 211–221.
[10] C. Barucker, H.J. Bittner, P.K.-Y. Chang, S. Cameron, M.A. Hancock, F. Liebsch, et al., Aβ42-oligomer interacting peptide (AIP) neutralizes toxic amyloid-β42 species and protects synaptic structure and function, Sci. Rep 5 (1) (2015) 15410.
[11] P. Salahuddin, R.H. Khan, M. Furkan, V.N. Uversky, Z. Islam, M.T. Fatima, Mechanisms of amyloid proteins aggregation and their inhibition by antibodies, small molecule inhibitors, nano-particles and nano-bodies, Int. J. Biol. Macromol 186 (2021) 580–590.
[12] T.C. Jakhria, Amyloid fibrils are nanoparticles that target lysosomes, University of Leeds, 2014.
[13] S. Gupta, A.K. Dasmahapatra, Lycopene destabilizes preformed aβ fibrils: mechanistic insights from all-atom molecular dynamics simulation, Comput. Biol. Chem 105 (2023) 107903.
[14] M. Stefani, S. Rigacci, Protein folding and aggregation into amyloid: the interference by natural phenolic compounds, Int. J. Mol. Sci 14 (6) (2013) 12411–12457.
[15] G. Šneiderienė, A. González Díaz, S.D. Adhikari, J. Wei, T. Michaels, T. Šneideris, et al., Lipid-induced condensate formation from the Alzheimer's aβ peptide triggers amyloid aggregation, Proceed. Nat. Acad. Sci 122 (4) (2025) e2401307122.
[16] Y. Yu, S. Yu, G. Battaglia, X. Tian, Amyloid-β in Alzheimer's disease: structure, toxicity, distribution, treatment, and prospects, ibrain 10 (3) (2024) 266–289.
[17] Alkhalifa A., Alkhalifa O., Durdanovic I., Ibrahim D.R. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease: insights into pathophysiology and treatment. 2024.
[18] S. Kunjiappan, S.R.K. Pandian, T. Panneerselvam, P. Pavadai, S.J. Kabilan, M. Sankaranarayanan, Exploring the Role of Plant Secondary Metabolites for Aphrodisiacs. Plant Specialized Metabolites: Phytochemistry, Ecology and Biotechnology, Springer, 2023, pp. 1–19.
[19] B. Sawicka, P. Ziarati, M. Messaoudi, J. Agarpanah, D. Skiba, B. Bienia, et al., Role of Herbal Bioactive Compounds as a Potential Bioavailability Enhancer for Active Pharmaceutical Ingredients. Handbook of Research on Advanced Phytochemicals and Plant-Based Drug Discovery, IGI Global, 2022, pp. 450–495.
[20] A. Ullah, S. Munir, S.L. Badshah, N. Khan, L. Ghani, B.G. Poulson, et al., Important flavonoids and their role as a therapeutic agent, Molecules 25 (22) (2020) 5243.
[21] M.E. Shah-Abadi, A. Ariaei, F. Moradi, A. Rustamzadeh, R.R. Tanha, N. Sadigh, et al., In silico interactions of natural and synthetic compounds with key proteins involved in Alzheimer's disease: prospects for designing new therapeutics compound, Neurotox Res 41 (5) (2023) 408–430.
[22] X. Sun, W.-D. Chen, Y.-D. Wang, β-amyloid: the key peptide in the pathogenesis of Alzheimer's disease, Front Pharmacol 6 (2015) 221.
[23] X. Wang, B. Su, G. Perry, M.A. Smith, X. Zhu, Insights into amyloid-β-induced mitochondrial dysfunction in Alzheimer disease, Free Radic. Biol. Med. 43 (12) (2007) 1569–1573.
[24] F. Dajas, F. Rivera-Megret, F. Blasina, F. Arredondo, J. Abin-Carriquiry, G. Costa, et al., Neuroprotection by flavonoids, Brazil. J. Med. Biologic. Res 36 (2003) 1613–1620.
[25] P. Pritam, R. Deka, A. Bhardwaj, R. Srivastava, D. Kumar, A.K. Jha, et al., Antioxidants in Alzheimer's disease: current therapeutic significance and future prospects, Biology 11 (2) (2022) 212.
[26] R. Islam, D.K. Dhaked, Exploring natural phenolic compounds as amyloid-beta fibril inhibitors: computational insights for Alzheimer's disease, J. Biomolecul. Struct. Dynamics (2024) 1–18.
[27] A. Tiwari, R. Singh, S. Kumar, A. Sunkaria, A. Jain, From plant to pathway: molecular mechanisms of ruscogenin in preventing amyloid-beta aggregation through computational and experimental approaches, ACS Chem. Neurosci (2025).
[28] A. Calderaro, G.T. Patanè, E. Tellone, D. Barreca, S. Ficarra, F. Misiti, et al., The neuroprotective potentiality of flavonoids on Alzheimer's disease, Int. J. Mol. Sci 23 (23) (2022) 14835.
[29] C. Palanichamy, P. Pavadai, T. Panneerselvam, S. Arunachalam, E. Babkiewicz, S. Ram Kumar Pandian, et al., Aphrodisiac performance of bioactive compounds from Mimosa pudica Linn.: in silico molecular docking and dynamics simulation approach, Molecules 27 (12) (2022) 3799.
[30] K. Mohanraj, B.S. Karthikeyan, R. Vivek-Ananth, R.B. Chand, S. Aparna, P. Mangalapandi, et al., IMPPAT: a curated database of I ndian M edicinal P lants, P Hytochem. A Nd T Herapeutics. Scient. Reports. 8 (1) (2018) 4329.
[31] Duke J.A. Dr. Duke's phytochemical and ethnobotanical databases. 1994.
[32] D. Wu, Q. Chen, X. Chen, F. Han, Z. Chen, Y. Wang, The blood–brain barrier: structure, regulation, and drug delivery, Signal Transduct. Targeted Therapy 8 (1) (2023) 217.
[33] C.P. Kuntz, Molecular Mechanisms of Ligand Recognition by the Human Serotonin Transporter: A Molecular Modeling Approach, Purdue University, 2015.
[34] J.R. Espinosa, C.R. Wand, C. Vega, E. Sanz, D. Frenkel, Calculation of the water-octanol partition coefficient of cholesterol for SPC, TIP3P, and TIP4P water, J. Chem. Phys 149 (22) (2018).
[35] Y. Liu, Novel theoretical analysis methods and algorithms for classical and ab initio molecular dynamics, New York University, 2002.
[36] M. Kim, E. Kim, S. Lee, J.S. Kim, S. Lee, New method for constant-NPT molecular dynamics, J. Physic. Chem. A 123 (8) (2019) 1689–1699.
[37] Ghosal A., Roy A.K. DFT calculations of atoms and molecules in cartesian grids. 2016.
[38] H. Hampel, J. Hardy, K. Blennow, C. Chen, G. Perry, S.H. Kim, et al., The amyloid-β pathway in Alzheimer's disease, Mol. Psychiatry 26 (10) (2021) 5481–5503.
[39] A. Kumar, S. Srivastava, S. Tripathi, S.K. Singh, S. Srikrishna, A. Sharma, Molecular insight into amyloid oligomer destabilizing mechanism of flavonoid derivative 2-(4′ benzyloxyphenyl)-3-hydroxy-chromen-4-one through docking and molecular dynamics simulations, J. Biomolecul. Struct. Dynamics 34 (6) (2016) 1252–1263.
[40] S. Gupta, A.K. Dasmahapatra, Destabilization potential of phenolics on aβ fibrils: mechanistic insights from molecular dynamics simulation, Physic. Chem. Chem. Phys 22 (35) (2020) 19643–19658.
[41] B.H. Han, B. Cofell, E. Everhart, C. Humpal, S.-S. Kang, S.K. Lee, et al., Amentoflavone promotes cellular uptake and degradation of amyloid-beta in neuronal cells, Int. J. Mol. Sci 23 (11) (2022) 5885.
[42] A. Alghamdi, D.J. Birch, V. Vyshemirsky, O.J. Rolinski, Impact of the flavonoid quercetin on β-amyloid aggregation revealed by intrinsic fluorescence, J. Phys. Chem. B 126 (38) (2022) 7229–7237.
[43] S.L. Gardener, S.R. Rainey-Smith, M. Weinborn, C.P. Bondonno, R.N. Martins, Intake of products containing anthocyanins, flavanols, and flavanones, and cognitive function: a narrative review, Front Aging Neurosci 13 (2021) 640381.
[44] U. Sehar, P. Rawat, A.P. Reddy, J. Kopel, P.H. Reddy, Amyloid beta in aging and Alzheimer's disease, Int. J. Mol. Sci. 23 (21) (2022) 12924.
[45] L.C. Walker, Aβ plaques, Free Neuropathol 1 (2020) 1–31.
[46] Cheignon Cm, M. Tomas, D. Bonnefont-Rousselot, P. Faller, C. Hureau, F. Collin, Oxidative stress and the amyloid beta peptide in Alzheimer's disease, Redox Biol 14 (2018) 450–464.
[47] H. Fanlo-Ucar, P. Picón-Pagès, V. Herrera-Fernández, G. Ill-Raga, F.J. Muñoz, The dual role of amyloid beta-peptide in oxidative stress and inflammation: unveiling their connections in Alzheimer's disease etiopathology, Antioxidants 13 (10) (2024) 1208.
[48] S. Miranda, C. Opazo, L.F. Larrondo, F.J. Muñoz, F. Ruiz, F. Leighton, et al., The role of oxidative stress in the toxicity induced by amyloid β-peptide in Alzheimer's disease, Prog. Neurobiol 62 (6) (2000) 633–648.
[49] S. Shoaib, M.A. Ansari, A.A. Fatease, A.Y. Safhi, U. Hani, R. Jahan, et al., Plant-derived bioactive compounds in the management of neurodegenerative disorders: challenges, future directions and molecular mechanisms involved in neuroprotection, Pharmaceutics 15 (3) (2023) 749.