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Review

Unraveling potential neuroprotective mechanisms of herbal medicine for Alzheimer's diseases through comprehensive molecular docking analyses

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ABSTRACT

Alzheimer's disease (AD) continues to be a worldwide health concern, demanding innovative therapeutic approaches. This study investigates the neuroprotective potential of herbal compounds by scrutinizing their interactions with Beta-Secretase-1 (BACE1). Through comprehensive molecular docking analyses, three compounds, Masticadienonic acid (ΔG: −9.6 kcal/mol), Hederagenin (ΔG: −9.3 kcal/mol), and Anthocyanins (ΔG: −8.1 kcal/mol), emerge as promising BACE1 ligands, displaying low binding energies and strong affinities. ADME parameter predictions, drug-likeness assessments, and toxicity analyses reveal favorable pharmacokinetic profiles for these compounds. Notably, Masticadienonic Acid exhibits optimal drug-likeness (−3.3736) and negligible toxicity concerns. Hederagenin (drug-likeness: −5.3272) and Anthocyanins (drug-likeness: −6.2041) also demonstrate promising safety profiles. Furthermore, pharmacophore modeling elucidates the compounds' unique interaction landscapes within BACE1′s active site. Masticadienonic acid showcases seven hydrophobic interactions and a hydrogen bond acceptor interaction with Thr232. Hederagenin exhibits a specific hydrogen bond acceptor interaction with Trp76, emphasizing its selective binding. Anthocyanins reveal a multifaceted engagement, combining hydrophobic contacts and hydrogen bond interactions with key residues. In conclusion, Masticadienonic acid, Hederagenin, and Anthocyanins stand out as promising candidates for further experimental validation, presenting a synergistic balance of efficacy and safety in combating AD through BACE1 inhibition.

1. Introduction

Alzheimer's disease (AD) continues to be a serious worldwide health concern, standing as the fifth-leading cause of death in the United States and demanding urgent attention due to its escalating prevalence and profound societal impact (Association, 2020). As the demographic ages, the burden of AD is expected to intensify, necessitating effective therapeutic strategies to address this complex neurodegenerative disorder. Despite substantial research endeavors, the intricate etiology of AD persists as a conundrum, with genetic factors accounting for a subset of cases and the majority presenting as sporadic with no clear genetic basis (Musiek and Schindler, 2013). The pathological features of AD involve neurodegeneration and synaptic loss, primarily affecting crucial brain regions, including the cortex, subcortical structures, and hippocampus. This leads to symptomatic manifestations, including memory loss, impaired learning, mood swings, executive dysfunction, and an inability to perform daily activities (DeTure and Dickson, 2019; Serrano-Pozo et al., 2011). The advanced stages of AD result in a complete loss of memory, necessitating comprehensive care (Dharmarajan and Gunturu, 2009).

Genetic factors contribute to AD, with the ApoE ε4 allele significantly increasing the risk of developing the disease. Pathologically, extracellular β-amyloid (Aβ) deposits and intracellular neurofibrillary tangles (NFTs) are hallmark features of AD (Raulin et al., 2022; Sadigh-Eteghad et al., 2015). Aβ deposits contribute to neurodegeneration, while NFTs, composed of aberrantly folded tau proteins, destabilize the microtubule network, a hallmark of AD (Gulisano et al., 2018). Tau protein plays a crucial role in stabilizing microtubules, which are structures within neurons that help maintain the cell's shape and provide tracks for transporting various substances throughout the cell. Microtubules are composed of tubulin subunits, and tau protein binds to these subunits, promoting their assembly into stable microtubules (Spillantini and Goedert, 2013). Despite the focus on Aβ and tau, therapeutic interventions targeting these pathways have faced setbacks, highlighting the necessity of taking into account other pathophysiological entities that underlie AD. A paradigm shift toward personalized

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Table 1
Selected herbal medicines with their main active molecule and neuroprotective effects.

No	Herbal medicine	Main active molecule	Neuroprotective effects	Ref
1	*Allium sativum L.*	Allicin	Decreased inflammatory response through decreased IL-1 and microglial activation; decreased psychological stress through regulation of stress hormones and the brain's oxidative stress response.	(Mathew & Biju, 2008; Nillert et al., 2017; Sripanidkulchai, 2020)
2	*Alpinia oxyphylla-Schisandra chinensis* herb pair	Schisandrin	Regaining the ability to function as GST, COX-2, SOD, iNOS, and overall antioxidant capacity; inhibiting the TLR4/NF-kB/NLRP3 pathway; and increasing malondialdehyde, NO, and GSH levelsR	(Qi et al., 2019)
3	*Bacopa monnieri L.*	Bacosides	Reduced damage caused by β-amyloid, safeguarded neuronal cells by lowering ROS levels, and exhibited cognition-enhancing effects through the inhibition of acetylcholinesterase (AChE), thereby preventing cholinergic degeneration.	(Dhanasekaran et al., 2007; Russo & Borrelli, 2005; Uabundit et al., 2010)
4	*Benincasa hispida L.*	Triterpenoid	Inhibited the creation of senile plaques; exhibited antioxidant scavenging effects; safeguarded dentate granule cells in the hippocampus by averting the deposition of extracellular senile plaques.	(Veerendra Kumar & Gupta, 2002)
5	*Bojungikgi-tang*	Ginsenosides	Suppressed the accumulation of Ab, boosted BACE activity within a living organism, and elevated antioxidant capabilities; thwarted the clustering and Aβ peptides, NeuN, and BDNF expression in the hippocampal tissues.	(Lim et al., 2018)
6	*Buchanania axillaris D*	Quercetin	Suppress α- and β-glucosidase, AChE, and BuChE activities to produce neuroprotective effects against oxidative stress-induced cell death.	(Penumala et al., 2018)
7	*Centella asiatica L.*	Asiaticoside	Reduced levels of oxidative stress and β-amyloid disease in the brain; shielded neurons from Aβ1–40′s neurodegenerative effects, decreased ROS production, and triggered the antioxidant defense system by boosting glutathione and glutathione disulfide levels and the activity of several related enzymes.	(Chen et al., 2016; Shinomol et al., 2011; Veerendra Kumar & Gupta, 2003)
8	*Convolvulus pluricaulis C.*	Scopoletin	Diminished brain expression of tau and amyloid-beta precursor protein (AβPP), suggesting a decrease in the accumulation of pathological proteins associated with neurodegenerative processes.	(Bihaqi et al., 2012; Nahata et al., 2008)
9	*Coriandrum sativum L.*	Apigenin	Demonstrated neuroprotective effects were observed in response to the neurotoxicity induced by Aβ42.	(Liu et al., 2015)
10	*Corylus avellana*	Kaempferol	Improved cognitive function, diminished feelings of unease, and mitigated both neuroinflammation and programmed cell death processes in the nervous system.	(Bahaeddin et al., 2017; Gorji et al., 2018)
11	*Curcuma longa L.*	Curcumin	Alleviated oxidative stress induced by $CeCl_3$, boosted the performance of antioxidant enzymes, and reduced AChE activity.	(Hamaguchi et al., 2010; Hishikawa et al., 2012; Yuliani et al., 2019)
12	*Eisenia bicyclis*	Polyphenols	Diminished the generation of ROS within PC12 cells prompted by the introduction of Aβ25–35	(Ahn et al., 2012)
13	*Fuzhisan (FZS)*	Baicalein	Promoting resistance against cell death and reducing the accumulation of Aβ, while simultaneously boosting acetylcholine levels and fostering neurotrophic effects in the nervous system.	(Bi et al., 2011; Li et al., 2008)
14	*Ginkgo biloba L.*	Ginkgolide	Neutralized harmful free radicals, safeguarded against disruptions in mitochondrial function, triggered the JNK and ERK signaling pathways, and impeded the process of programmed cell death in neurons.	(Singh et al., 2019; Zhao et al., 2021)
15	*Glycyrrhiza inflata B.*	Glycyrrhizic acid	Decreased levels of ROS and prevention of abnormal tau folding, coupled with strong capabilities to inhibit the aggregation of amyloid-beta (Aβ) and effectively scavenge radicals and inhibit the production of ionized calcium-binding adapter molecule 1 (Iba1), prostaglandin E2, TNFα, IL-1β, and/or NO.	(Chang et al., 2016; Chen et al., 2014; Chiu et al., 2018)
16	*Hedera nepalensis K.*	Hederagenin	Increased the amounts of catalase and superoxide dismutase (SOD) while lowering glutathione (GSH) levels in the process.	(Hashmi et al., 2018)
17	*Hibiscus sabdariffa L.*	Anthocyanins	Prevented deficits in memory by improving neuroinflammation and reducing the production of amyloid plaques induced by STZ.	(El-Shiekh et al., 2020)
18	*Ishige foliacea*	Phlorotannins	When AChE activity in the brain was reduced, oxidative stress was inhibited, and the ERK-BDNF-CREB signaling pathway was activated simultaneously.	(Um et al., 2018)
19	*Juglans regia*	Juglone	Suppressed the production of inflammation-inducing proteins, lowered AChE levels, and significantly restored the activity of antioxidant enzymes while reducing the activity of NF-κB, an important inflammatory process regulator.	(Li et al., 2017; Muthaiyah et al., 2011; Pribis et al., 2012)
20	*Momordica charantia L.*	Charantin	Diminished inflammatory responses in the form of gliosis, lowered oligomeric Aβ levels, reduced tau hyperphosphorylation, and prevented neuronal loss. Furthermore, it enhanced the expression of proteins associated with synapses and increased the levels of pS9-GSK3b.	(Huang et al., 2018; Sepehri et al., 2019)
21	*Nardostachys jatamansi D.*	Nardosinone	Prevented cellular demise triggered by Aβ. This intervention acted as a safeguard against the detrimental effects induced by amyloid-β, preserving cell viability and thwarting potential damage.	(Liu et al., 2018; Liu et al., 2015)
22	*Oryza sativa*	Ferulic acid	Reduced enzymatic activity of AChE in the hippocampus and lowered the production of lipid peroxidation byproducts.	(Pannangrong et al., 2011)
23	*Panax ginseng*	Ginsenosides	Diminished the production of Aβ, impeded the activity of AChE, reinstated the diminished levels of synaptophysin and choline acetyltransferase (ChAT) activity, and attenuated both the formation and aggregation of Aβ.	(Choi et al., 2017; Heo et al., 2016; Kim et al., 2013)
24	*Phyllanthus acidus*	Hypophyllanthin	The concentration of antioxidant enzymes in the brain is increased to improve cognitive functioning and mitigate oxidative stress. Lipid peroxidation and AChE activity are both declining at the same time.	(Uddin et al., 2016)
25	*Phyllanthus amarus*	Phyllanthin	Increased levels of catalase, NADH dehydrogenase, and superoxide dismutase, which provide a stronger antioxidant defense mechanism in the biological environment.	(Alagan et al., 2019)
26	*Phyllanthus emblica*	Gallic acid	Enhanced cognitive functions such as learning and memory, boosted antioxidant capabilities and reduced the activity of AChE.	(Uddin et al., 2016)

(*continued on next page*)

Table 1 (*continued*)

No	Herbal medicine	Main active molecule	Neuroprotective effects	Ref
27	*Pistacia atlantica*	Piscidic acid	Inhibition of AChE enzymatic function was observed, indicating the ability to modulate the breakdown of acetylcholine, a neurotransmitter crucial for cognitive functions.	(Moeini et al., 2019)
28	*Pistacia integerrima*	Gallic acid	Engaging in neutralizing free radicals and inhibiting the activity of cholinesterase enzymes, contributes to enhanced antioxidant effects and potential modulation of neurotransmitter functions.	(Zahoor et al., 2018)
29	*Pistacia lentiscus*	Masticadienonic acid	lessened the lipopolysaccharide-induced memory impairment, which in turn caused the brain tissue's oxidative stress indicators and AChE activity to drop.	(Ammari et al., 2018)
30	*Pistacia vera*	β-sitosterol	Prevented cognitive and motor deficits induced by cisplatin or vincristine, showcasing a protective effect against the adverse impacts on cognitive and motor functions caused by these substances.	(Golchin et al., 2015)
31	*Prunus dulcis*	Amygdalin	Reduced levels of AChE activity, cholesterol, and triglycerides; increased serotonergic turnover and brain tryptophan monoamine levels to enhance memory and learning.	(Batool et al., 2016; Haider et al., 2012; Kulkarni et al., 2010)
32	*Punica granatum*	Ellagic acid	Mitigated oxidative stress, alleviated inflammation in the brain, diminished the build-up of soluble Aβ42, and lowered the deposition of amyloid in the hippocampus.	(Hartman et al., 2006; Rojanathammanee et al., 2013; Yuan et al., 2016)
33	*Salvia miltiorrhiza B.*	Salvianolic acid	Suppressed oxidative stress and the apoptotic pathway dependent on mitochondria. Hindered the expression of iNOS and the production of NO. Stimulated the differentiation of neuron cells derived from rat mesenchymal stem cells	(Jiang et al., 2013; Yu et al., 2014)
34	*Spirulina maxima*	β-carotene	Lowered the expression of APP, BACE1, and Aβ1-42 in the hippocampus, blocked AChE activity, lessened oxidative stress in the hippocampus, increased BDNF levels, and started the BDNF/PI3K/Akt signaling pathways for improved neural signaling and defense.	(Koh et al., 2018; Koh et al., 2017; Lee et al., 2013)
35	*Spirulina platensis*	γ-linolenic acid	Prevented the production of inflammatory genes including COX-2, TNF-α, IL-6, and iNOS, reduced cellular toxicity, and neutralized dangerous free radicals to prevent them from killing cells. This suggests a defense system against inflammation and oxidative damage.	(Bermejo-Bescós et al., 2008; Mohd Sairazi & Sirajudeen, 2020)
36	*Thalassospira profundimaris*	Eicosapentaenoic acid	Maintained the integrity of synaptic structures, preventing neuron death associated with cell cycle dysregulation. This safeguarding of synaptic architecture contributes to the overall preservation of neuronal health and function by averting cell cycle-induced neuronal demise.	(Zhu et al., 2020)
37	*Uncaria rhynchophylla M.*	Rhynchophylline	Exhibited antioxidative properties by disassembling pre-existing Aβ fibrils and scavenging free radicals, thereby preventing lipid peroxidation and reducing microglial activation.	(Hsieh et al., 1999; Shi et al., 2003; Tang et al., 2010)
38	*Viscum album L.*	Isorhamnetin	Significant decrease in the neurotoxic effects of AlCl3 due to significantly higher blood levels of brain-derived neurotrophic factor (BDNF).	(Szurpnicka et al., 2020)
39	*Vitis vinifera L.*	Resveratrol	Prevented the clustering of Aβ; exhibited antioxidant, anti-neuroinflammatory, and anti-amnesic properties by countering oxidative stress, reducing neuroinflammation, and mitigating memory-related impairments.	(Lian et al., 2016; Loureiro et al., 2017; Siahmard et al., 2012)
40	*Zingiber officinale R.*	Gingerol	Suppressed AChE activity and lipid peroxidation; mitigated excessive stimulation of NMDA receptors and thwarted the generation of free radicals.	(Ali et al., 2008; Oboh et al., 2012)

precision therapeutics has emerged as a response to the complex nature of AD. A report on cases of cognitive decline reversal is achieved by using a thorough, customized strategy that pinpoints and resolves the causes of cognitive decline. This paradigm incorporates exceptional herbs and their bioactive ingredients., demonstrating effectiveness as part of the overall protocol (Bredesen, 2014).

Herbs and herbal remedies, with their extensive historical use, represent an intriguing avenue for AD treatment. Herbal remedies for cognitive impairments are frequently recommended by traditional medical systems, such as Ayurveda, traditional Chinese medicine (TCM), and Native American medicine (Julie Gregory et al., 2021; Halder et al., 2021). The synergistic and modulatory actions of bioactive principles in herbs are emphasized, contributing to their historical efficacy. While herbs possess a rich history of traditional use, scientific exploration of their potential in AD remains an untapped resource. It is said that a variety of plants and the components they contain that are advised in traditional medicine might improve cognitive function and reduce symptoms of AD. The rational selection of herbs is grounded in their historical use, identification of phytochemicals with potential therapeutic benefits, neuropharmacological activities, and preclinical or clinical evidence supporting their cognitive-enhancing and anti-dementia effects (Ballard et al., 2011; Gregory et al., 2021; Perry et al., 1999).

Recent advancements in understanding Aβ production have identified Beta-Secretase-1 (BACE1) as the rate-limiting enzyme. Inhibition of BACE1 represents a promising mechanism for treating AD. Importantly, BACE1 cleaves the amyloid precursor protein (APP), initiating the cascade leading to Aβ formation. Given its pivotal role, targeting BACE1 is considered a significant avenue for therapeutic intervention, aiming to reduce Aβ levels and mitigate downstream neurodegenerative processes (Hampel et al., 2018; Vassar, 2014). β-secretase, specifically BACE1, has garnered attention as a crucial enzyme in the amyloidogenic pathway. It cleaves the transmembrane domain of APP, initiating the generation of Aβ peptides. This step is considered the rate-limiting and initiating factor in Aβ production (Cole and Vassar, 2007; Selkoe and Hardy, 2016). As such, inhibiting BACE1 has become a focal point for therapeutic strategies aiming to curtail Aβ accumulation. Several BACE1 inhibitors have been developed and investigated as potential AD treatments in preclinical and clinical studies. However, challenges and setbacks in clinical trials, including efficacy, safety, and tolerability issues, have tempered initial enthusiasm (Egan et al., 2018; Vassar, 2014). The complexity of the BACE1 function, coupled with the intricate regulatory mechanisms governing Aβ production, underscores the need for a comprehensive understanding of these processes to develop effective BACE1-targeted therapies (Zhou et al., 2011). In light of the evolving landscape of AD research and therapeutic strategies, the exploration of herbs and their bioactive compounds gains significance. The intricate interplay of multiple pathophysiological entities in AD necessitates a holistic approach, and herbs represent a promising avenue for multi-targeted interventions with their diverse pharmacological profiles.

This study aims to investigate the potential of herbs in multi-targeted therapeutic strategies for AD, incorporating molecular docking studies to enhance our understanding of the underlying mechanisms. The review aims to shed light on their molecular interactions with key targets implicated in AD pathophysiology by scrutinizing a subset of herbs recognized for historical efficacy and supported by neuropharmacological evidence. We have undertaken a computational exploration to elucidate the affinity of chemical binding and the interactions between particular active substances derived from herbal medicines and the BACE1 receptor, which is identified as a crucial drug target in AD. An extensive literature review was conducted to identify potential inhibitors, sourcing information from various journals focusing on established herbal medicines with therapeutic efficacy against AD. Employing a 3D structure-based pharmacophore molecular docking simulation, we aimed to comprehensively assess the molecular interactions between the ligands derived from herbal sources and the target BACE1 receptor. Subsequently, we conducted an analysis of drug-likeness and Absorption, Distribution, Metabolism, and Excretion (ADME) properties to refine further and select the most promising ligand candidates. The chosen optimal ligand underwent additional scrutiny, evaluating its protein pharmacophore profiles. This approach integrates advanced computational techniques with a thorough understanding of medicinal plant compounds, paving the way for identifying and developing potential herbal-based therapeutic agents for AD treatment.

2. Materials and methods

2.1. Acquisition of data and ligand structure development

In this work, we retrieved the 2.50 Å resolution X-ray crystal structures of human BACE1 docked with cyclohexanecarboxylic acid from the Protein Data Bank (PDB ID: 2WJO (Nicholls et al., 2010)). These crystal structures serve as crucial templates for understanding the molecular interactions between BACE and potential ligands. The data on herbal medicines were meticulously curated through an extensive literature search focused on identifying secondary metabolites with proven inhibitory properties against Alzheimer's disease. PubMed, Scopus, the World Health Organization (WHO) website and Google Scholar were utilized as primary sources, deliberately excluding theses and dissertations. Only scientifically rigorous publications, including journals and WHO-edited case reports, were incorporated into the dataset, culminating in the compilation of medicinal plant information presented in Table 1. The ligands' molecular structures were obtained from the National Library of Medicine (https://pubchem.ncbi.nlm.nih.gov/). In order to guarantee precision, the ligands' three-dimensional (3D) structures were refined through optimization using Chem3D (PerkinElmer Inc.), and additional energy minimization was carried out using MM2 energy minimization in ChemDraw Professional 20.1.1 (PerkinElmer Inc.). This process prepared the ligand structures for ensuing molecular docking simulations and interaction analyses.

2.2. Conducting and validating simulations of molecular docking

In preparation for molecular docking simulations, both receptors and ligands underwent meticulous processing using AutoDockTools 1.5.6 (Morris et al., 2009). T By using cyclohexanecarboxylic acid in a redocking technique, the active site of the BACE1 receptor was accurately determined. The resulting Root Mean Square Deviation (RMSD) was 1.631, which is within the acceptable range. Based on this redocking process, the grid parameter file for the BACE1 receptor was created, consisting of 40 × 40 × 40 points spaced 0.350 Å apart. Next, the receptor's active site (x = 26.289; y = 38.013; z = 39.239) was selected as the grid's center. Both ligands and receptors were protonated, with the ligands receiving Gasteiger charges and the receptor receiving Kollman charges (Weiner et al., 1984). AutoDock 4.2 (The Scripps Research Institute) was used to do the molecular docking simulations that followed. The following settings were specified in the docking parameter file, which was configured using the Lamarckian Genetic Algorithm (LGA): 300 population sizes, 100 runs, 10,000,000 energy assessments, 0.75 crossover, and 0.025 mutation rates per gene. An RMSD tolerance of 2.0 Å was utilized to group the conformation outcomes of the docking simulation (Dermawan et al., 2021). BioVIA Discovery Studio Visualizer 2020 (Dassault Systèmes BIOVIA, 2020) and PyMOL 2.4 (Schrödinger, 2020) were used to view the resultant complexes of receptors and ligands. A crucial part of identifying the characteristics of ligand interaction for every pose inside the receptor's active region was played by LigandScout Advanced 4.5 (Inte: Ligand GmbH, Vienna, Austria) (Wolber and Langer, 2005). All molecular docking simulations were performed using a workspace with specifications: Intel® Core™ i7-12650H 16 CPUs @2.30 GHz, NVIDIA™ RTX 4060 8 GB VRAM, and 16 GB RAM DDR5. This comprehensive approach to molecular docking simulations ensures a detailed understanding of the potential molecular binding modes and interactions between the selected herbal ligands and the BACE1 receptor, contributing valuable insights to the exploration of novel therapeutic avenues for Alzheimer's disease.

2.3. ADME parameter prediction

In the pursuit of a comprehensive understanding of the ligands' potential to inhibit receptors integral to viral replication, an extensive analysis of their toxicological characteristics and oral bioavailability was carried out. This intricate analysis was facilitated through the utilization of the SwissADME tool (https://www.swissadme.ch/) (Daina et al., 2017). By delving into the pharmacokinetic characteristics of the ligands, this computational approach not only aids in identifying candidates with favorable attributes for further investigation but also provides crucial insights into their ADME parameters.

2.4. An examination of drug-likeness and toxicity

The entire ligands underwent a rigorous evaluation encompassing a spectrum of toxicity properties, ranging from tumorigenicity and mutagenicity to irritancy, reproductive effectiveness, and drug similarity. This comprehensive analysis was carried out employing OSIRIS DataWarrior V5.5.0 (Sander et al., 2015). Such a multifaceted examination not only sheds light on potential adverse effects associated with the ligands but also aligns with the fundamental drug-likeness criteria. This scrutiny is paramount in the development of pharmaceutical agents, ensuring that the identified ligands not only exhibit therapeutic potential but also possess attributes conducive to safety and efficacy.

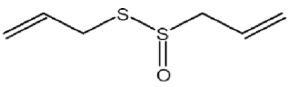
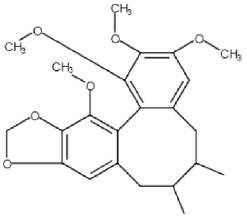
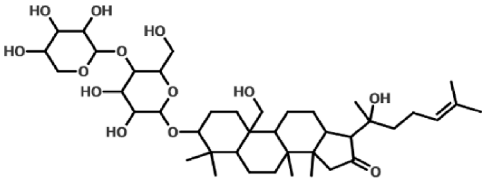
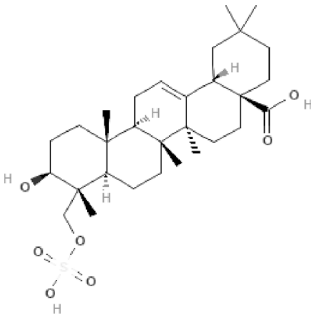
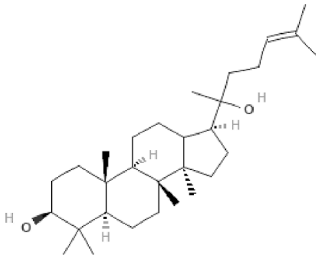
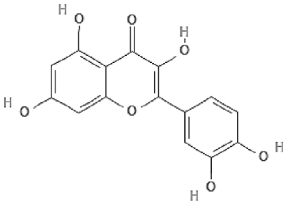
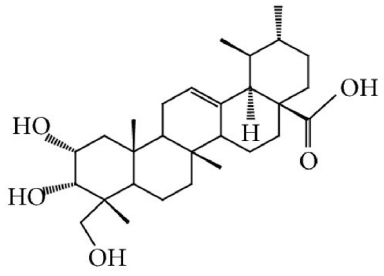
2.5. 3D structural modeling of pharmacophores

An ensemble of steric characteristics known as a pharmacophore is defined as being essential for guaranteeing ideal molecular reactions with a particular target, hence impacting or preventing its biological reactions (Giordano et al., 2022). To thoroughly assess the pharmacophore profile of ligands within the receptor's active pocket, we utilized 3D structure-based pharmacophore modeling in our analysis. For robustness, a previous work was consulted while validating the feature model (Muchtaridi et al., 2018). The rigorously verified 3D pharmacophore modeling approach was used to screen the ligands, executed with LigandScout 4.5 Advanced algorithms (Wolber and Langer, 2005). This methodological approach not only refines our understanding of the ligand-receptor interaction landscape but also establishes a reliable foundation for screening ligands based on their pharmacophoric characteristics, contributing to the identification of potential therapeutically relevant compounds for further exploration in the context of AD.

3. Results

The molecular interactions between various herbal medicines and

Table 2
The results of molecular docking with active molecules in the BACE1 receptor's ligand-binding domain (LBD).

Name of the molecule	Chemical structure	ΔG (kcal/mol)	Ki (μM)	Interacting hydrogen bonds
Allicin ($C_6H_{10}OS_2$)		−3.7	4.64×10^{6}	Trp76
Schisandrin ($C_{23}H_{28}O_6$)		−7.4	3.56×10^{-6}	None
Bacosides ($C_{41}H_{68}O_{13}$)		−8.9	6.99×10^{-8}	Tyr71, Tyr198, Thr231
Triterpenoid ($C_{30}H_{48}O_7S$)		−9.2	2.13×10^{-8}	Gly34, Tyr198, Gly230
Ginsenosides ($C_{30}H_{52}O_2$)		−7.8	1.55×10^{-6}	Asp32
Quercetin ($C_{15}H_{10}O_7$)		−8.0	9.95×10^{-8}	Asn37, Gln73
Asiaticoside ($C_{48}H_{78}O_{19}$)		−8.9	6.99×10^{-8}	Tyr198

(*continued on next page*)

Table 2 (*continued*)

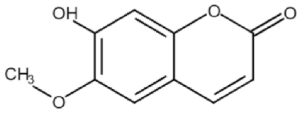
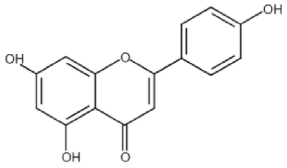
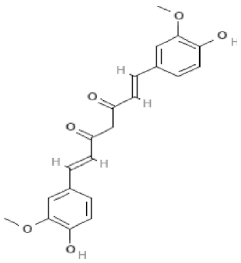
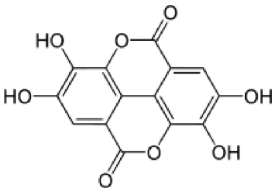
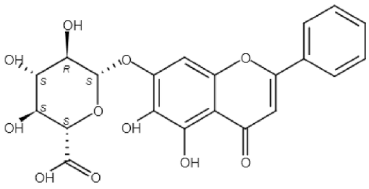
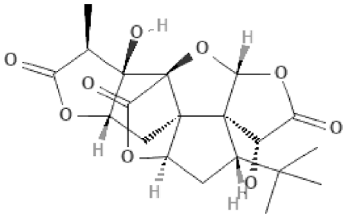
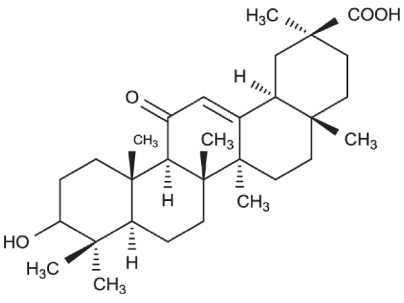
Name of the molecule	Chemical structure	ΔG (kcal/mol)	Ki (μM)	Interacting hydrogen bonds
Scopoletin ($C_{10}H_8O_4$)		−6.1	1.17×10^{-4}	Lys75, Lys107
Apigenin ($C_{15}H_{10}O_5$)		−8.3	3.18×10^{-7}	Lys75, Ile126, Tyr198
Curcumin ($C_{21}H_{20}O_6$)		−7.9	7.92×10^{-7}	Gly34, Lys75, Asp228, Thr231
Polyphenols ($C_{14}H_6O_8$)		−8.0	9.95×10^{-8}	Asp32, Gln73, Lys107
Baicalein ($C_{21}H_{18}O_{11}$)		−8.7	4.05×10^{-8}	Gln12, Thr232
Ginkgolide ($C_{20}H_{24}O_9$)		−7.9	7.92×10^{-7}	None
Glycyrrhizic acid ($C_{42}H_{62}O_{16}$)		−8.6	1.89×10^{-8}	Thr72

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Table 2 (*continued*)

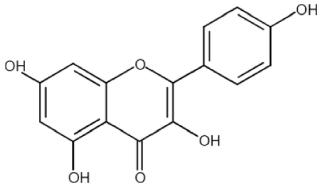
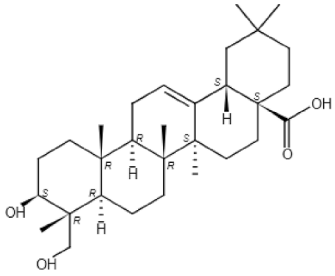
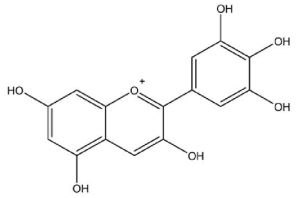
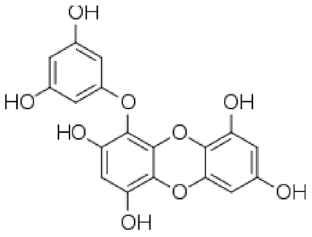
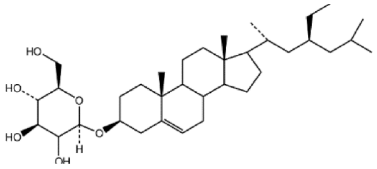
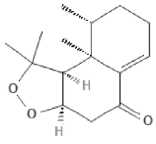
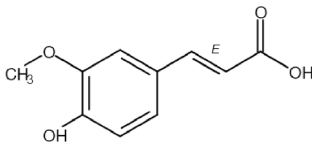
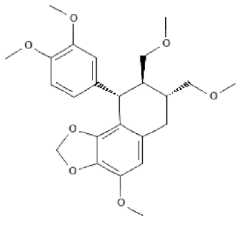
Name of the molecule	Chemical structure	ΔG (kcal/mol)	Ki (μM)	Interacting hydrogen bonds
Kaempferol ($C_{15}H_{10}O_6$)		−8.1	7.34×10^{-8}	Ser35, Ser36, Trp76, Ile126
Hederagenin ($C_{30}H_{48}O_4$)		−9.3	4.08×10^{-9}	Asn37, Gln73, Lys107
Anthocyanins ($C_{15}H_{11}O$)		−8.1	7.34×10^{-8}	Val69, Tyr71, Gln73, Gly230
Phlorotannins ($C_{18}H_{12}O_9$)		−8.2	5.66×10^{-8}	Tyr198
Charantin ($C_{35}H_{60}O_6$)		−8.3	3.18×10^{-7}	Tyr71, Thr231
Nardosinone ($C_{15}H_{22}O_3$)		−6.8	4.54×10^{-5}	None
Ferulic acid ($C_{10}H_{10}O_4$)		−5.8	1.95×10^{-4}	Gln73
Hypophyllanthin ($C_{24}H_{30}O_7$)		−7.8	7.92×10^{-7}	None

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Table 2 (*continued*)

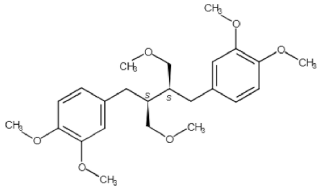
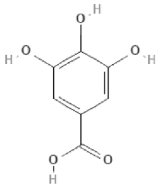
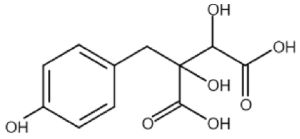
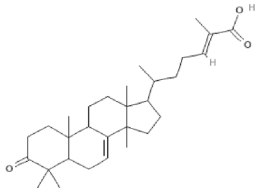
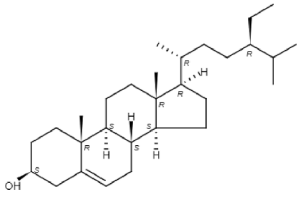
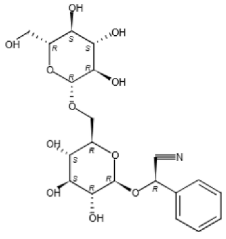
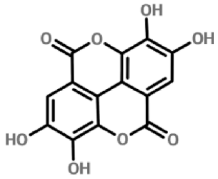
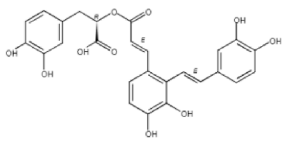
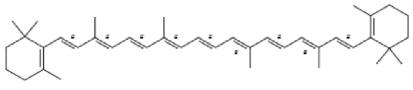
Name of the molecule	Chemical structure	ΔG (kcal/mol)	Ki (μM)	Interacting hydrogen bonds
Phyllanthin ($C_{24}H_{34}O_6$)		−7.4	2.01×10^{-6}	None
Gallic acid ($C_7H_6O_5$)		−5.4	5.37×10^{-4}	Val69, Gln73, Lys107
Piscidic acid ($C_{11}H_{12}O_7$)		−6.0	1.82×10^{-4}	Asp32, Asp106, Gly230
Masticadienonic acid ($C_{30}H_{46}O_3$)		−9.6	1.04×10^{-9}	Ser36, Gly230, Thr232
β-sitosterol ($C_{29}H_{50}O$)		−7.9	7.92×10^{-7}	None
Amygdalin ($C_{20}H_{27}NO_{11}$)		−7.8	2.01×10^{-6}	Asp32, Thr231
Ellagic acid ($C_{14}H_6O_8$)		−8.0	9.95×10^{-8}	Asp32, Asp106
Salvianolic acid ($C_{26}H_{22}O_{10}$)		−8.6	1.89×10^{-8}	Ser35, Tyr71, Gln73, Asp106, Asp228
β-carotene ($C_{40}H_{56}$)		−2.0	1.84×10^{4}	None

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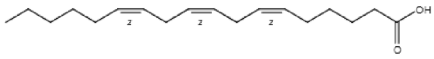
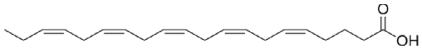
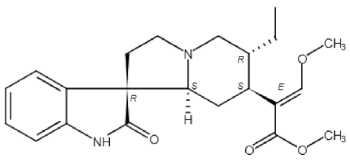
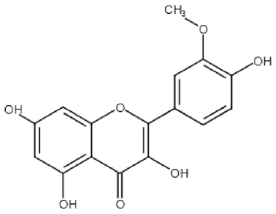
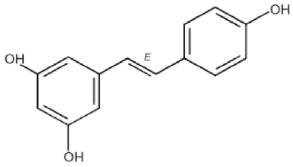
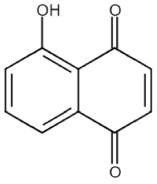
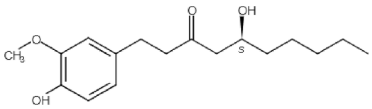
Table 2 (*continued*)

Name of the molecule	Chemical structure	ΔG (kcal/mol)	Ki (μM)	Interacting hydrogen bonds
γ-linolenic acid ($C_{18}H_{30}O_2$)		−5.7	3.32×10^{-4}	None
Eicosapentaenoic acid ($C_{20}H_{30}O_2$)		−6.1	1.17×10^{-4}	Asp106
Rhynchophylline ($C_{22}H_{28}N_2O_4$)		−7.5	5.06×10^{-6}	Gly34
Isorhamnetin ($C_{16}H_{12}O_7$)		−8.0	9.95×10^{-8}	Asp106, Ile126
Resveratrol ($C_{14}H_{12}O_3$)		−7.7	1.67×10^{-6}	Ser35, Asn37, Lys107
Juglone ($C_{10}H_6O_3$)		−6.1	1.17×10^{-4}	Lys107
Gingerol ($C_{17}H_{26}O_4$)		−6.1	1.17×10^{-4}	Lys75, Asp106, Gly230

their respective main active molecules with BACE1, a pivotal receptor associated with AD, were systematically analyzed in this study. The objective was to uncover potential neuroprotective effects against AD-related processes. The diverse array of bioactive compounds found in these herbs showcased promising outcomes in mitigating neurodegenerative mechanisms. Table 1 provides an overview of selected herbal medicines and their main active molecules, illustrating their demonstrated neuroprotective effects through various mechanisms. This comprehensive analysis contributes valuable insights into the potential of herbal medicines as a collective source of compounds with neuroprotective properties. The findings pave the way for future investigations into the therapeutic potential of herbal remedies in addressing the complex pathophysiology of AD.

The outcomes of the molecular docking simulation, as depicted in Table 2, shed light on the potential of selected herbal compounds to act as effective ligands within the ligand-binding domain (LBD) of the BACE1 receptor, a critical target in AD therapy. Among the diverse set of compounds analyzed, several emerged as particularly promising due to their low binding energies (ΔG) and strong binding affinities (Ki). Masticadienonic acid, with its strikingly low value of ΔG by −9.6 kcal/mol and a Ki of 1.04×10^{-9} μM, showcased exceptional potential as a BACE1 inhibitor. The observed hydrogen bonds with Ser36, Gly230, and Thr232 residues suggest a specific and stable interaction. This suggests a strong affinity for the active site of BACE1, indicating a potential inhibitory effect on the enzymatic activity of BACE1. Masticadienonic Acid, a natural compound found in mastic gum, has been linked to several pharmacological actions, including as antioxidant and anti-inflammatory properties (Ottria et al., 2023). In the context of AD, its neuroprotective effects may be attributed to its ability to modulate oxidative stress and inflammation, both of which are implicated in the progression of neurodegenerative diseases. The compound's interaction with BACE1 is crucial, as BACE1 plays a central role in the cleavage of APP, leading to the formation of amyloid-beta (Aβ) peptides, a hallmark of AD pathology (Cole and Vassar, 2008). With a binding energy of −9.3 kcal/mol and a Ki of 4.08×10^{-9} μM, Hederagenin demonstrated robust affinity for the BACE1 receptor. The formed hydrogen bonds with Asn37, Gln73, and Lys107 residues further affirm its potential as an effective BACE1 inhibitor. It has been documented that Hederagenin modulates oxidative stress and inflammatory pathways to have neuroprotective effects (Wu et al., 2017). This dual-action mechanism aligns with the multifactorial nature of AD.

Triterpenoid exhibited a binding energy of −9.2 kcal/mol and a Ki of 2.13×10^{-8} μM. The established hydrogen bonds with Gly34, Tyr198, and Gly230 highlight its robust interaction within the ligand-binding pocket. Triterpenoids have shown anti-amyloidogenic effects and antioxidant properties, suggesting a potential mechanism through the inhibition of Aβ aggregation and reduction of oxidative stress (Park et al., 2023). With a binding energy of −8.9 kcal/mol and a Ki of 6.99×10^{-8}

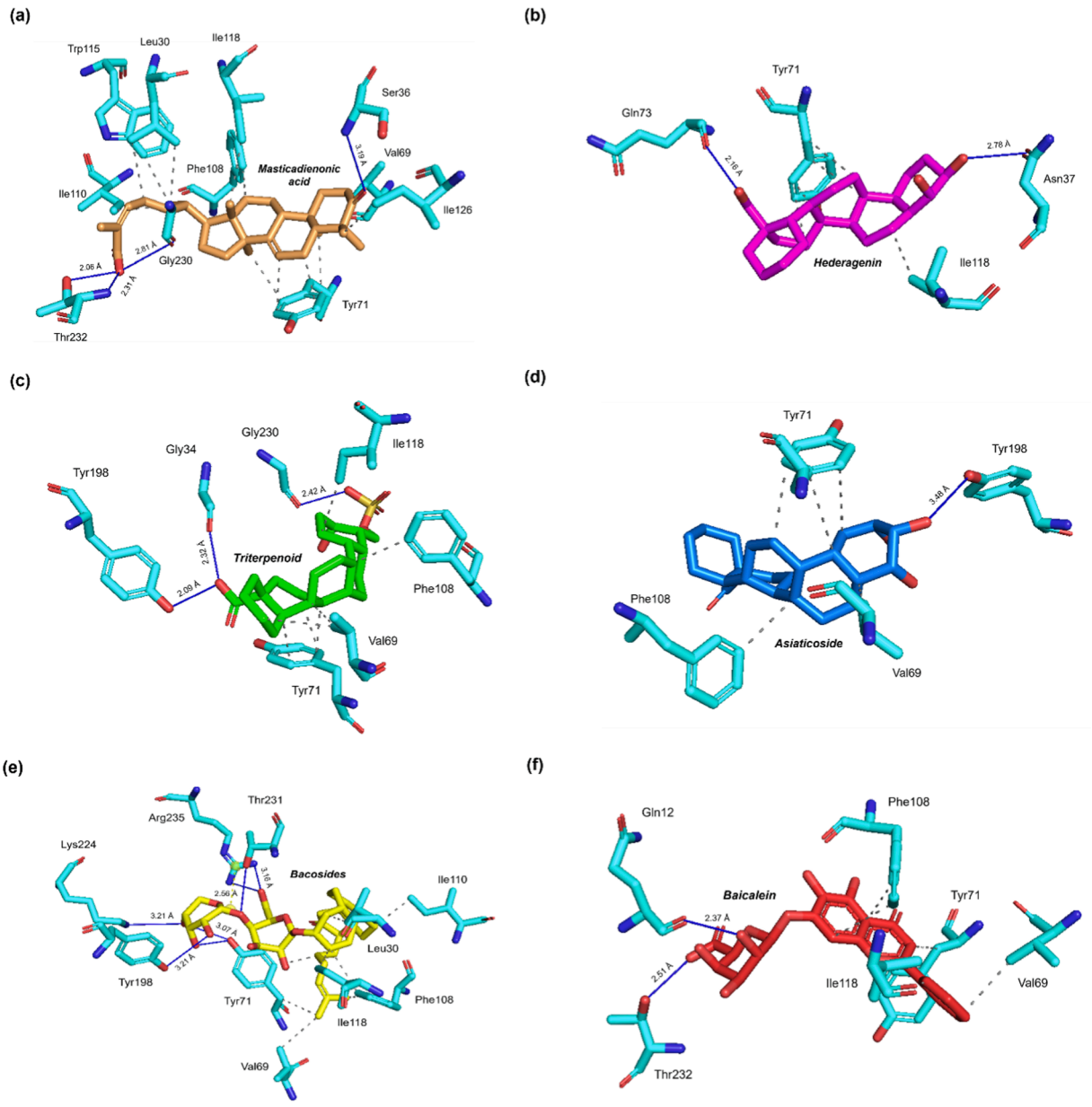


Fig. 1. 3D perspective: The top 6 active molecules (ligands) with their molecular interactions in the ligand binding domain of BACE1 based on the molecular docking simulation. (a) Masticadienonic acid. (b) Hederagenin. (c) Triterpenoid. (d) Asiaticoside. (e) Bacosides. (f) Baicalein.

μM, Asiaticoside demonstrated substantial affinity for the BACE1 receptor. Hydrogen bonds formed with Tyr198 underscore its potential to modulate BACE1 activity. Asiaticoside has been reported to attenuate oxidative stress and reduce Aβ levels, potentially contributing to its neuroprotective effects (Bandopadhyay et al., 2023). Bacosides displayed a binding energy of −8.9 kcal/mol and a Ki of 6.99×10^{-8} μM, forming hydrogen bonds with Tyr71, Tyr198, and Thr231. Bacosides, derived from *Bacopa monnieri*, have demonstrated anti-amyloid and antioxidant properties, suggesting a mechanism involving interference with Aβ aggregation and reduction of oxidative stress-induced neurotoxicity (Abdul Manap et al., 2019). Baicalein, with a molecular binding energy of −8.7 kcal/mol and a Ki of 4.05×10^{-8} μM, engaged in hydrogen bonds with Gln12 and Thr232 residues. Anti-inflammatory and antioxidant properties of Baicalein have been documented, suggesting a mechanism that involves modulation of neuroinflammatory responses and reduction of oxidative stress (Chmiel and Stompor-Gorący, 2023). The 3D and 2D perspective of molecular interactions between top 6 ligands with BACE1 are depicted in Fig. 1 and Fig. 2, respectively.

The discussion of the ADME parameters for specific active molecules, as outlined in Table 3, provides valuable insights into their pharmacokinetic profiles, potential bioavailability, and safety considerations. These parameters, including molecular weight (MW), lipophilicity (MlogP), topological polar surface area (TPSA), hydrogen bond acceptor count (HBA), and hydrogen bond donor count (HBD), are crucial in understanding the drug-likeness and metabolic fate of these compounds. The Lipinski Rule of Five is a widely recognized guideline for drug-like properties, stating that compounds with more than one violation may exhibit poor absorption or permeation (Lipinski, 2004). Observing the Lipinski violations in the table, several compounds, such as Bacosides, Asiaticoside, and Glycyrrhizic acid, show multiple violations. While the rule serves as a useful heuristic, exceptions exist, and additional factors contribute to a compound's pharmacokinetic behavior.

The Cytochrome P450 (CYP) inhibition potential is another critical aspect of drug development, as interactions with these enzymes can affect drug metabolism and clearance (Zhao et al., 2021). Among the

Fig. 2. 2D perspective: Top 6 active molecules (ligands) with their molecular interactions in the ligand binding domain of BACE1 based on the molecular docking simulation. (a) Masticadienonic acid. (b) Hederagenin. (c) Triterpenoid. (d) Asiaticoside. (e) Bacosides. (f) Baicalein. Interactions between ligands are illustrated using distinct colors: traditional hydrogen bonds (depicted in green), carbon-hydrogen bonds (in turquoise), van der Waals forces (in light green), pi-alkyl interactions (in pink), and pi-sigma interactions (in purple).

studied molecules, several exhibit CYP inhibition potential, with Quercetin, Baicalein, Anthocyanins, Phlorotannins, Charantin, β-sitosterol, Amygdalin, Ellagic acid, β-carotene, γ-linolenic acid, Eicosapentaenoic acid, Isorhamnetin, Resveratrol, and Gingerol showing interactions with various CYP isoforms. This information is vital for predicting potential drug-drug interactions and guiding dosage adjustments in co-administration scenarios. One intriguing finding is the Masticadienonic Acid, which exhibits an absence of Lipinski violations and CYP inhibition potential despite its favorable binding energy in the docking simulations with BACE1. This suggests that Masticadienonic Acid may possess desirable drug-like properties, making it a promising candidate for further exploration in drug development for AD.

Table 3
The outcomes of predicting ADME parameters for specific active molecules.

Molecule name	MW (g/mol)	MlogP	HBA	HBD	TPSA(Å^2)	Lipinski violation	CYP inhibitor
Allicin ($C_6H_{10}OS_2$)	162.27	1.18	1	0	61.58	0	None
Schisandrin ($C_{23}H_{28}O_6$)	400.46	2.76	6	0	55.38	0	CYP2C19, CYP2C9, CYP2D6
Bacosides ($C_{41}H_{68}O_{13}$)	768.97	−0.10	13	8	215.83	3	None
Triterpenoid ($C_{30}H_{48}O_7S$)	552.76	4.37	7	3	129.51	2	None
Ginsenosides ($C_{30}H_{52}O_2$)	444.73	6.00	2	2	40.46	1	None
Quercetin ($C_{15}H_{10}O_7$)	302.24	−0.56	7	5	131.36	0	CYP1A2, CYP2D6, CYP3A4
Asiaticoside ($C_{48}H_{78}O_{19}$)	959.12	−2.12	19	12	315.21	3	None
Scopoletin ($C_{10}H_8O_4$)	192.17	0.76	4	1	59.67	0	CYP1A2
Apigenin ($C_{15}H_{10}O_5$)	270.24	0.52	5	3	90.90	0	CYP1A2, CYP2D6, CYP3A4
Curcumin ($C_{21}H_{20}O_6$)	368.38	1.47	6	2	93.06	0	CYP2C9, CYP3A4
Polyphenols ($C_{14}H_6O_8$)	302.19	0.14	8	4	141.34	0	CYP1A2
Baicalein ($C_{21}H_{18}O_{11}$)	446.36	−1.63	11	6	187.12	2	None
Ginkgolide ($C_{20}H_{24}O_9$)	408.40	0.83	9	2	128.59	0	None
Glycyrrhizic acid ($C_{42}H_{62}O_{16}$)	822.93	0.02	16	8	267.04	3	None
Kaempferol ($C_{15}H_{10}O_6$)	286.24	−0.03	6	4	111.13	0	CYP1A2, CYP2D6, CYP3A4
Hederagenin ($C_{30}H_{48}O_4$)	472.70	4.07	4	3	77.76	0	None
Anthocyanins ($C_{15}H_{11}O$)	207.25	3.28	1	0	13.14	0	CYP1A2, CYP2D6
Phlorotannins ($C_{18}H_{12}O_9$)	372.28	0.25	9	6	149.07	1	CYP1A2, CYP2C9, CYP3A4
Charantin ($C_{35}H_{60}O_6$)	576.95	4.06	4	3	77.76	1	None
Nardosinone ($C_{15}H_{22}O_3$)	250.33	2.56	3	0	35.53	0	None
Ferulic acid ($C_{10}H_{10}O_4$)	194.18	1.00	4	2	66.76	0	None
Hypophyllanthin ($C_{24}H_{30}O_7$)	430.49	1.91	7	0	64.61	0	CYP2D6, CYP3A4
Phyllanthin ($C_{24}H_{34}O_6$)	418.52	2.43	6	0	55.38	0	CYP2D6, CYP3A4
Gallic acid ($C_7H_6O_5$)	170.12	−0.16	5	4	97.99	0	CYP3A4
Piscidic acid ($C_{11}H_{12}O_7$)	256.21	−0.60	7	5	135.29	0	None
Masticadienonic acid ($C_{30}H_{46}O_3$)	454.68	4.13	3	1	54.37	0	CYP2C9
β-sitosterol ($C_{29}H_{50}O$)	414.71	6.73	1	1	20.23	1	None
Amygdalin ($C_{20}H_{27}NO_{11}$)	457.43	−3.58	12	7	202.32	2	None
Ellagic acid ($C_{14}H_6O_8$)	302.19	0.14	8	4	141.34	0	CYP1A2
Salvianolic acid ($C_{26}H_{22}O_{10}$)	494.45	1.34	10	7	184.98	1	CYP2C9
β-carotene ($C_{40}H_{56}$)	536.87	8.96	0	0	0	2	None
γ-linolenic acid ($C_{18}H_{30}O_2$)	278.43	4.38	2	1	37.30	1	CYP1A2, CYP2C9
Eicosapentaenoic acid ($C_{20}H_{30}O_2$)	302.45	4.67	2	1	37.30	1	CYP2C9
Rhynchophylline ($C_{22}H_{28}N_2O_4$)	384.47	2.02	5	1	67.87	0	CYP2D6, CYP3A4
Isorhamnetin ($C_{16}H_{12}O_7$)	316.26	−0.31	7	4	120.36	0	CYP1A2, CYP2D6, CYP3A4
Resveratrol ($C_{14}H_{12}O_3$)	228.24	2.26	3	3	60.69	0	CYP1A2, CYP2C9, CYP3A4
Juglone ($C_{10}H_6O_3$)	174.15	0.30	3	1	54.37	0	None
Gingerol ($C_{17}H_{26}O_4$)	294.39	2.14	4	2	66.76	0	CYP1A2, CYP2D6

The assessment of toxicity and drug-likeness properties, as presented in Table 4, sheds light on the safety profiles of the chosen active molecules. The drug-likeness values indicate their similarity to known drugs, while toxicity considerations encompass mutagenicity, tumorigenicity, irritant potential, and reproductive toxicity. Notably, Masticadienonic Acid, Hederagenin, and Anthocyanins emerge as promising candidates based on their favorable drug-likeness scores and minimal toxicity concerns. Masticadienonic Acid, identified as the top ligand in molecular docking simulations (Table 5), exhibits a remarkable ΔG of −9.6 kcal/mol, suggesting a strong binding affinity to the BACE1 receptor. Importantly, it demonstrates a drug-likeness score of −3.3736, indicating favorable drug-like properties. Additionally, it shows no toxicity concerns, making it a promising lead for further investigation.

Hederagenin, another top-performing ligand in docking simulations, also presents a substantial ΔG of −9.3 kcal/mol and a drug-likeness score of −5.3272. Like Masticadienonic Acid, Hederagenin does not raise toxicity concerns, emphasizing its potential as an effective and non-toxic low-binding candidate for Alzheimer's disease treatment. While exhibiting a slightly lower ΔG of −8.1 kcal/mol, Anthocyanins still demonstrate strong binding affinity and favorable drug-likeness (−6.2041). Importantly, Anthocyanins show no toxicity concerns in the assessed categories. The integration of information from Table 4 and Table 5 highlights the importance of considering both efficacy and safety in the selection of lead compounds. Masticadienonic Acid, Hederagenin, and Anthocyanins emerge as promising candidates for further preclinical and clinical studies in the quest for novel Alzheimer's disease therapeutics.

The analysis focused on the top three selected active molecules (ligands), considering results from molecular docking simulations, ADME parameters, drug-likeness, and toxicity assessments. Subsequently, a detailed examination of these molecules was conducted, and their pharmacophore profiles were generated using pharmacophore modeling. Masticadienonic acid demonstrates a notable affinity for the BACE1 receptor, primarily attributed to its intricate pattern of molecular interactions. The hydrophobic nature of Masticadienonic acid is prominently highlighted through the engagement of its benzene rings and methyl groups in a nuanced interplay, establishing a substantial network of seven distinct hydrophobic interactions with specific regions on the BACE1 receptor (Fig. 3). This intricate hydrophobic bonding contributes significantly to the stability and binding strength of Masticadienonic acid within the ligand-binding domain of BACE1. Furthermore, the molecular interactions of Masticadienonic acid extend beyond hydrophobic interactions to encompass hydrogen bond formations. Specifically, Masticadienonic acid serves as a hydrogen bond acceptor, forging a precise interaction with the residue Thr232 on the BACE1 receptor. This hydrogen bond interaction adds an additional layer of specificity to the binding profile, fostering a more comprehensive and targeted association between Masticadienonic acid and BACE1. The dualistic nature of Masticadienonic acid's interactions, combining robust hydrophobic contacts with a discerning hydrogen bond association, underscores its unique structural and chemical attributes. These findings not only shed light on the intricate mechanisms governing the ligand-receptor interaction but also pave the way for a deeper understanding of the potential therapeutic implications of Masticadienonic acid in the context of AD.

The interaction profile of Hederagenin, identified as one of the most promising ligands, manifests a distinctive molecular engagement with the BACE1 receptor. Notably, Hederagenin's interaction repertoire is characterized by a singular yet crucial hydrogen bond acceptor

Table 4
Evaluating the drug-like qualities and toxicity of selected active compounds.

Name of the molecule	Drug-likeness	Mutagenic	Tumorigenic	Reproductive effective	Irritant
Allicin ($C_6H_{10}OS_2$)	−6.1268	None	None	None	None
Schisandrin ($C_{23}H_{28}O_6$)	−2.2777	None	None	None	None
Bacosides ($C_{41}H_{68}O_{13}$)	−17.532	None	None	None	High
Triterpenoid ($C_{30}H_{48}O_7S$)	−1.4148	None	None	None	None
Ginsenosides ($C_{30}H_{52}O_2$)	−1.3000	None	None	None	High
Quercetin ($C_{15}H_{10}O_7$)	−0.0828	High	High	None	None
Asiaticoside ($C_{48}H_{78}O_{19}$)	−12.8380	None	None	None	None
Scopoletin ($C_{10}H_8O_4$)	−3.0612	None	None	Low	None
Apigenin ($C_{15}H_{10}O_5$)	0.2819	High	None	None	None
Curcumin ($C_{21}H_{20}O_6$)	−4.7745	None	None	None	None
Polyphenols ($C_{14}H_6O_8$)	−1.5983	None	None	None	None
Baicalein ($C_{21}H_{18}O_{11}$)	0.3467	None	None	None	None
Ginkgolide ($C_{20}H_{24}O_9$)	−1.7790	None	None	None	None
Glycyrrhizic acid ($C_{42}H_{62}O_{16}$)	−4.2912	None	None	None	None
Kaempferol ($C_{15}H_{10}O_6$)	−0.0828	High	None	None	None
Hederagenin ($C_{30}H_{48}O_4$)	−5.3272	None	None	None	None
Anthocyanins ($C_{15}H_{11}O$)	−6.2041	None	None	None	None
Phlorotannins ($C_{18}H_{12}O_9$)	−2.2054	Low	None	None	None
Charantin ($C_{35}H_{60}O_6$)	−5.3017	None	None	None	None
Nardosinone ($C_{15}H_{22}O_3$)	−7.3344	None	High	None	High
Ferulic acid ($C_{10}H_{10}O_4$)	0.2750	High	High	High	None
Hypophyllanthin ($C_{24}H_{30}O_7$)	−0.8275	None	None	High	None
Phyllanthin ($C_{24}H_{34}O_6$)	−0.8606	None	None	None	None
Gallic acid ($C_7H_6O_5$)	−1.8442	High	None	High	None
Piscidic acid ($C_{11}H_{12}O_7$)	1.7809	None	None	None	None
Masticadienonic acid ($C_{30}H_{46}O_3$)	−3.3736	None	None	None	None
β-sitosterol ($C_{29}H_{50}O$)	−4.4750	None	None	None	None
Amygdalin ($C_{20}H_{27}NO_{11}$)	−10.0190	High	None	High	High
Ellagic acid ($C_{14}H_6O_8$)	−1.5983	None	None	None	None
Salvianolic acid ($C_{26}H_{22}O_{10}$)	−3.8118	None	None	High	None
β-carotene ($C_{40}H_{56}$)	−3.3519	None	None	None	None
γ-linolenic acid ($C_{18}H_{30}O_2$)	−24.3210	None	None	None	None
Eicosapentaenoic acid ($C_{20}H_{30}O_2$)	−14.2910	None	None	None	None
Rhynchophylline ($C_{22}H_{28}N_2O_4$)	3.3474	None	None	None	None
Isorhamnetin ($C_{16}H_{12}O_7$)	0.0563	High	None	None	None
Resveratrol ($C_{14}H_{12}O_3$)	−1.6732	High	None	High	None
Juglone ($C_{10}H_6O_3$)	0.2862	None	High	None	None
Gingerol ($C_{17}H_{26}O_4$)	−9.0620	None	None	None	None

Table 5
Top 3 selected active molecules (ligands) with considerations from results of molecular docking simulation, ADME parameter, drug-likeness, and toxicity.

Molecule name	ΔG (kcal/mol)	Lipinski violation	Drug-likeness	Toxicity
Masticadienonic acid	−9.6	0	−3.3736	None
Hederagenin	−9.3	0	−5.3272	None
Anthocyanins	−8.1	0	−6.2041	None

interaction. This interaction occurs explicitly between the hydroxyl group of Hederagenin and the amino acid residue Trp76 situated within the LBD of BACE1 (Fig. 4). This targeted hydrogen bonds acceptor interaction assumes significance in elucidating the binding mechanism and molecular recognition dynamics between Hederagenin and the BACE1 receptor. The selectivity of Hederagenin for establishing this specific interaction suggests a high degree of precision in its binding orientation within the ligand-binding pocket of BACE1. Moreover, the engagement with Trp76 through a hydrogen bond acceptor interaction underscores the structural complementarity and compatibility between Hederagenin and the targeted binding site on the BACE1 receptor.

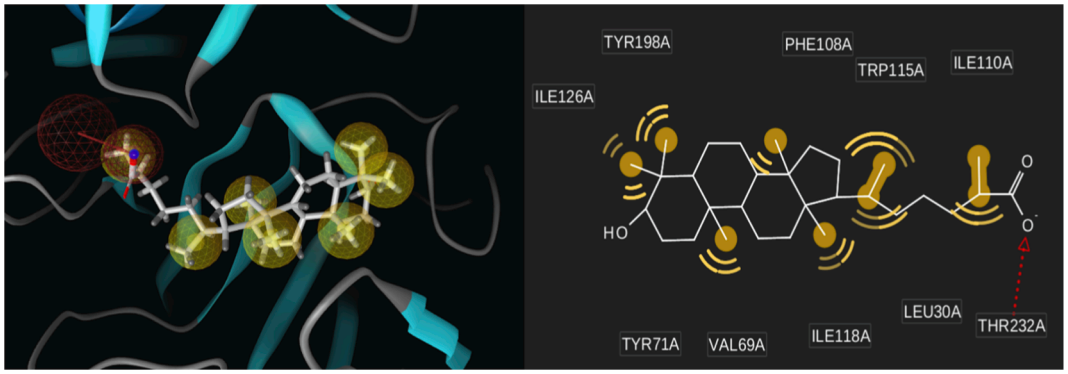


Fig. 3. Utilizing the 3D and 2D structural information, a pharmacophore model was constructed based on the optimal docking conformation of Masticadienonic acid within BACE1 (PDB ID: 2WJO). In this model, hydrophobic interactions and hydrogen bond acceptors are depicted by yellow spheres and red arrows (spheres), respectively.

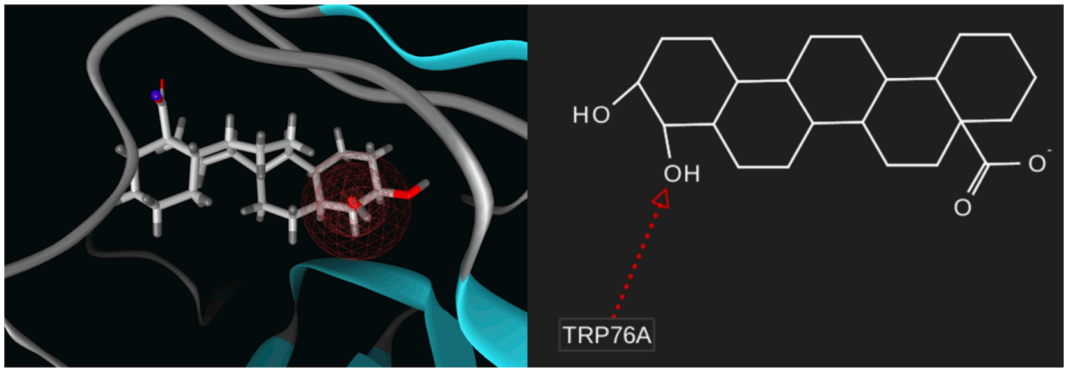


Fig. 4. Pharmacophore modeling based on the 3D and 2D structures was performed using the optimal docking conformation of Hederagenin in BACE1 (PDB ID: 2WJO). The modeling depicted hydrogen bond acceptor interaction as a red arrow (sphere).

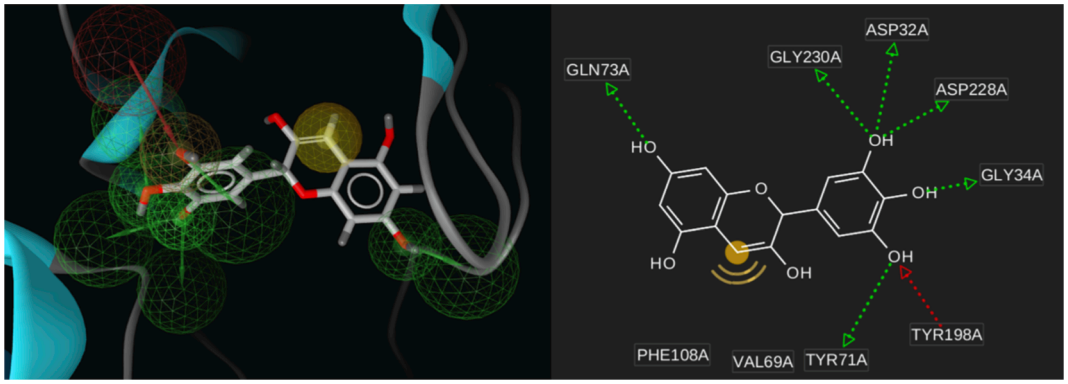


Fig. 5. Pharmacophore modeling was performed based on the optimal docking configuration of Anthocyanins in BACE1 (PDB ID: 2WJO), considering both 3D and 2D structures. In this representation, hydrophobic interactions, hydrogen bond donors, and hydrogen bond acceptors are illustrated as yellow spheres, green arrows, and red arrows (spheres), respectively.

Understanding the nuanced interactions of Hederagenin, particularly the exclusive hydrogen bond acceptor interaction with Trp76, not only contributes valuable insights into the ligand-receptor recognition landscape but also provides a foundation for rational drug design strategies in the context of AD therapeutics. This focused molecular interaction further accentuates Hederagenin's potential as a therapeutic agent through its precise and discerning binding with the BACE1 receptor.

The interaction profile of Anthocyanins, a compelling candidate among the selected ligands, unveils a multifaceted engagement with the BACE1 receptor. Central to this interaction is the establishment of hydrophobic contacts, primarily emanating from the benzene ring of Anthocyanins. This hydrophobic interaction, often indicative of a stable ligand-receptor binding interface, underscores the spatial complementarity between Anthocyanins and the corresponding binding site within the ligand-binding domain of BACE1. Furthermore, Anthocyanins exhibit a noteworthy hydrogen bond acceptor interaction involving its hydroxyl group and the amino acid residue Tyr198 from BACE1 (Fig. 5). This specific interaction adds a layer of selectivity to the binding affinity of Anthocyanins for the BACE1 receptor. Additionally, the intricate network of hydrogen bond donor interactions further enhances the binding specificity, with Anthocyanins contributing six hydrogen bond donors through its hydroxyl groups. Within the ligand-binding pocket, these donors establish connections with key amino acid residues, including Asp32, Gly34, Tyr71, Gln73, Asp228, and Gly230. The combination of hydrophobic contacts, hydrogen bond acceptor specificity, and multiple hydrogen bond donors collectively paints a comprehensive picture of Anthocyanins' molecular interaction landscape with BACE1. This detailed understanding not only sheds light on the structural intricacies governing ligand-receptor recognition but also positions Anthocyanins as a promising therapeutic candidate for AD treatment, given their discerning and versatile binding features.

4. Discussion

The extensive investigation into molecular interactions between herbal compounds and BACE1 offers profound insights into potential avenues for Alzheimer's Disease (AD) therapeutics. Notably, Masticadienonic acid, Hederagenin, and Anthocyanins emerge as promising BACE1 ligands due to their low binding energies and strong affinities. Masticadienonic acid, a triterpenoid, has shown promise in reducing amyloid beta (Aβ) levels, a key factor in Alzheimer's disease (Yan, 2016). Hederagenin, another triterpenoid, has been found to inhibit BACE1, an enzyme involved in Aβ production (Vassar and Kandalepas, 2011). Anthocyanins, a type of flavonoid, have been identified as potent antioxidants that may regulate Aβ generation (Afzal et al., 2019). The molecular docking simulations unveil intricate interactions, such as Masticadienonic acid's hydrogen bonds with Ser36, Gly230, and Thr232, indicating a specific and stable interaction, aligning with its antioxidant and anti-inflammatory properties. Hederagenin, displaying hydrogen bonds with Asn37, Gln73, and Lys107, supports its neuroprotective effects through the modulation of oxidative stress and inflammatory pathways. Anthocyanins showcase hydrophobic interactions and multiple hydrogen bonds, emphasizing their multifaceted binding capabilities. These findings underscore the potential of these compounds as effective BACE1 inhibitors, warranting further exploration in AD drug development.

The comprehensive assessment of ADME parameters, drug-likeness, and toxicity considerations provides a crucial framework for evaluating the translational potential of the identified ligands. While Masticadienonic Acid, Hederagenin, and Anthocyanins exhibit favorable

drug-likeness and minimal toxicity concerns, Lipinski violations and CYP inhibition potential are observed in certain compounds, necessitating nuanced consideration. Masticadienonic Acid stands out with desirable drug-like properties, despite its strong BACE1 binding affinity. The strategic evaluation of both efficacy and safety positions Masticadienonic Acid, Hederagenin, and Anthocyanins as promising candidates for further preclinical and clinical investigations. Additionally, the detailed pharmacophore profiles of these ligands shed light on their specific molecular engagements with BACE1, providing a foundation for rational drug design strategies and emphasizing their potential as targeted and effective therapeutic agents for AD treatment. A range of studies have explored the potential of herbal medicine in treating Alzheimer's disease through molecular docking analyses. A secondary metabolite was identified from the Cannabis plant with a high binding affinity to acetylcholinesterase, a key enzyme in AD (Seniya et al., 2014). Fang et al. (2017) used a network pharmacology approach to decipher the mechanisms of action of various medicinal herbs in AD treatment. Moreover, the therapeutic effects of specific herbs and herbal formulations of *Melissa officinalis*, *Salvia officinalis*, Yi-Gan San, BDW, and Ginkgo biloba might be potentially useful for cognitive impairment in AD (Santos-Neto et al., 2006; Singh et al., 2022).

5. Conclusions

In conclusion, the comprehensive analysis of selected herbal medicines and their main active molecules in relation to BACE1, a receptor associated with Alzheimer's disease (AD), has provided valuable insights into potential candidates for therapeutic intervention. The molecular docking simulations elucidated the binding affinities of various compounds, with Masticadienonic acid, Hederagenin, and Anthocyanins emerging as particularly promising ligands based on their lower binding energies. Masticadienonic acid exhibited robust hydrophobic interactions through its benzene rings and methyl groups, establishing a total of seven hydrophobic contacts with BACE1. Furthermore, the presence of a hydrogen bond acceptor interaction with residue Thr232 showcased its versatile binding profile. Hederagenin, another standout ligand, demonstrated a specific hydrogen bond acceptor interaction with Trp76 from BACE1, highlighting its selective engagement with the receptor. With their intricate network of interactions, Anthocyanins displayed a combination of hydrophobic contacts, a hydrogen bond acceptor interaction with Tyr198, and multiple hydrogen bond donors with key residues, showcasing their multifaceted binding capabilities. Considering additional factors such as ADME parameters, drug-likeness, and toxicity, these ligands, particularly Masticadienonic acid, Hederagenin, and Anthocyanins, present themselves as promising candidates for further investigation. Their favorable binding energies, coupled with favorable pharmacokinetic profiles, underscore their potential as novel drugs for AD. Further experimental trials and in-depth studies are needed to confirm and harness the therapeutic efficacy of these compounds in combating AD. This research paves the way for future drug development endeavors aimed at addressing the complex pathophysiology of AD.

CRediT authorship contribution statement

Faisal Alsenani: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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