MAK HILL Publications Research Journal of Pharmacology

Research Article
doi: 10.36478/makrjp.2025.1.12.18

OPEN ACCESS

Key Words
Alzheimer's disease, β-amyloid aggregation, atractylodes macrocephala, molecular docking, in silico analysis

Corresponding Author
Abullah M. Albogami,
Ministry of National Guard-Health Affairs, Saudi Arabia
abullah121@outlook.sa

Author Designation
[1-5]Pharmaceutical Care Department

Received: 15 January 2025
Accepted: 31 January 2025
Published: 04 February 2025

Citation: Ali D. Alshahrani, Abdulmajed A. Alqahtani, Abullah M. Albogami, Ali M. Alamri and Almutairi Abdullah Awadh, 2025. Molecular Docking of Atractylodes Macrocephala Compounds for the Inhibition of β-Amyloid Aggregation in Alzheimer's Disease: A Novel Therapeutic Approach. Res. J. Pharm., 19: 12-18, doi: 10.36478/makrjp.2025.1.12.18

Molecular Docking of Atractylodes Macrocephala Compounds for the Inhibition of β-Amyloid Aggregation in Alzheimer's Disease: A Novel Therapeutic Approach

[1]Ali D. Alshahrani, [2]Abdulmajed A. Alqahtani, [3]Abullah M. Albogami, [4]Ali M. Alamri and [5]Almutairi Abdullah Awadh
[1-5]Ministry of National Guard-Health Affairs, Saudi Arabia

ABSTRACT
Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and the accumulation of β-amyloid (Aβ) plaques in the brain. One of the main pathogenic features of AD is the aggregation of Aβ peptides, which makes it a prime target for treatment. Using molecular docking and in silico drug-likeness screening, this study investigates the potential of bio active compounds from Atractylodes macrocephala to suppress Aβ aggregation. Ten compounds in all were chosen and their binding affinities against the Aβ protein were examined using cromolyn sodium as a control compound. Atractylenolide I, Atractylenolide II, Atractylenolide III, Atractylenolide IV and Quercetin showed strong binding affinities (-5.1 to -5.3 kcal/mol) in comparison to Cromolyn Sodium (-4.9 kcal/mol), according to the molecular docking results. Additionally, Atractylenolide IV showed optimum blood-brain barrier penetration (25.23%) according to ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) predictions, making it an effective option for further studies. According to the study's findings bio active compounds in Atractylodes macrocephala, especially Atractylenolide IV, may operate as natural inhibitors of Aβ aggregation, which might help in the development of therapeutic strategies for AD. To verify their effectiveness and safety, additional in vitro and in vivo validation is required. The article highlights the potential of natural substances in the study of neurodegenerative diseases and offers a foundation for the development of therapeutic drugs derived from plants for Alzheimer's disease.

INTRODUCTION

Alzheimer's disease (AD), a complicated and varied neurological illness that usually affects older people, is one of the most severe issues facing modern medicine and society. It is the most common type of dementia and it has a lasting impact on people who have it in addition to their families, care givers and healthcare systems. Alzheimer's has extensive emotional and financial effects, underscoring the critical need for thorough investigation of the disease's origin, pathophysiology, available treatments and supportive care techniques[1]. This neurological disorder is characterized by a persistent deterioration in cognitive function, frequently starts slowly with early symptoms including forgetfulness, disorientation, trouble solving problems, or mild behavioral abnormalities[2]. Diagnosis and action may be delayed if these early symptoms are disregarded or dismissed as part of aging. More severe symptoms, such as disorientation, severe memory loss, decreased reasoning and even changes in mood and behavior, appear as the disease progresses. The emotional and financial strain on loved ones and the healthcare system is increased when people with Alzheimer's disease reach a point when they may find it difficult to do everyday duties and need ongoing assistance from family members or paid caretakers[3]. The identification of particular pathology indicators linked to Alzheimer's disease is a fundamental aspect of the research on the disease. Among the most important of these is the buildup of beta-amyloid (Aβ) peptides, which are brief segments of the amyloid precursor protein (APP) and are essential to the development of this disease. Enzymes closely regulate the cleavage of APP under normal physiological settings., in Alzheimer's disease, this process is disturbed. As a result, Aβ production rises, forming oligomers and ultimately insoluble amyloid plaques that build up in the brains of those who are impacted[4]. These amyloid plaques are now considered to be one of the hallmarks of Alzheimer's disease pathogenesis and their existence is a crucial area of study and treatment advancement. It is impossible to overestimate the part Aβ plays in the onset and progression of Alzheimer's disease[5]. For many years, the scientific world has been dominated by the amyloid cascade hypothesis, which holds that the first buildup of Aβ is what triggers the development of Alzheimer's disease. This theory states that tau protein hyper phosphorylation and the development of neuro fibrillary tangles are two downstream processes brought on by the harmful effects of Aβ oligomers, which ultimately result in neuronal death and cognitive impairment. Because of this cascade impact, which implies a straight path from amyloid deposition to neurodegeneration, Aβ is a prime target for therapeutic approaches meant to slow or reverse the course of the illness. Genetic studies that have connected mutations in the APP gene and presenilin proteins, two essential elements of the enzymatic pathways that cause APP cleavage to family cases of Alzheimer's disease provide evidence in favor of the amyloid cascade theory[6]. The fact that people with these genetic mutations frequently have early-onset Alzheimer's disease, usually showing symptoms in their 30s or 40s, highlights the crucial role Aβ plays in the formation of the illness. Furthermore, researchers have been able to see amyloid deposits in vivo thanks to neuroimaging methods like positron emission tomography (PET), which has shown that substantial Aβ buildup takes place long before dementia symptoms manifest. Important information about the window of opportunity for possible therapies is provided by this early detection. Although there is ample evidence linking Aβ to Alzheimer's disease, recent research has questioned the degree to which Aβ deposition is directly linked to cognitive loss. Other pathogenic processes, such as tau protein phosphorylation, neuro inflammation, oxidative stress and vascular dysfunction, are cited by opponents of the amyloid cascade hypothesis as potentially important in the development of AD[7]. One important component of neuronal dysfunction, for example, is tau pathology, which is defined by the accumulation of hyper phosphorylated tau protein into neurofibrillary tangles. Research on the interaction between tau and Aβ is still ongoing since understanding these connections could lead to novel treatment options. As interest in physiotherapy and integrated medicine has grown, so has the investigation of natural plants as possible therapeutic agents in the management and treatment of AD[8]. Numerous herbs have long been utilized in many cultures for their alleged neuroprotective and cognitive-enhancing qualities. Preclinical research and clinical trials have shown promises for compounds derived from plants including Ginkgo biloba[9], turmeric's curcumin[10] and a variety of polyphenol-rich herbs like sage and rosemary. The traditional medicinal herb Atractylodesmacrocephala, which is frequently used in East Asian herbal medicine, has drawn interest due to its many therapeutic uses, especially in the treatment of different illnesses. Known to strengthen the spleen, Atractylodes macrocephala is frequently used to treat gastrointestinal issues, boost immunity, and reduce weariness[11]. In this regard, we employed a computational screening approach encompassing ADMET prediction and molecular docking to find the best active compound in Atractylodes macrocephala extract that has the ability to affect Aβ aggregation for preventing AD.

MATERIALS AND METHODS

Compounds Preparation: The compounds of interest, including Atractylenolide I, Atractylenolide II, Atractylenolide III, Atractylenolide IV, Atractylodin, Caryophyllene, Quercetin, Atractylone, 4'- Hydroxyace to phenone, were sourced from PubChem (https:// pubchem.ncbi.nlm.nih.gov). To establish a baseline for comparison in our investigations, we have chosen Cromolyn Sodium as the control drug for this study identified by its Chemical Identifier(CID: 27503).

Drug-Likness: To evaluate our ligands' drug-likeness we used Swiss ADME(http://www.swissadme.ch/) that provides a variety of parameters and predictive models freely accessible for calculating physicochemistry and calculating pharmacokinetics[12]. Lipinski's Rule of Five, which predicts the oral bioavailability of small compounds by taking into consideration variables including molecular weight, the number of hydrogen bond donors and acceptors, served as the basis for the evaluation. To ascertain each ligand's potential as a workable therapeutic agent, we assessed the extent to which it adhered to these criteria.

Targeted Protein Preparation: The three-dimensional (3D) structure of the targeted protein Aβ (PDB ID: 1IYT) was retrieved from the Protein Data Bank (PDB) (http://www.pdb.org). The protein structure was prepared for docking and energy minimization using the Dock Prep module in UCSF-Chimera software. During preparation, all heteroatoms, including co-crystallized ligands and water molecules, were removed. Hydrogen atoms were added and partial charges were assigned using the Gasteiger charge method. Finally, the structure was energy-minimized using the Amber force field 94 fs (Amberff94fs)[13] to optimize the geometry and reduce steric clashes.

Molecular Docking of Compounds Against Aβ: In this study, molecular docking was performed using PyRx, a widely used tool for predicting the binding interactions between small molecules and a receptor with a known 3D structure[14]. Blind docking was conducted to explore potential binding sites across the entire protein surface, ensuring a comprehensive search for ligand-binding regions. The docking process utilized a grid box that encompassed the entire protein structure to allow for unbiased exploration of binding sites. After the docking run, compounds with docking scores (binding energies) lower than those of the control drugs were selected for further analysis. Molecular visualization and interaction analysis were carried out using PyMOL© Molecular Graphics (version 2.4, 2016, Schrödinger LLC, New York, NY, USA) and BIOVIA's Discovery Studio (version 2016). The molecular interaction fingerprints, including hydrogen bonds, hydrophobic interactions and electrostatic connections between the ligand atoms and the protein's amino acids, were examined for each protein-ligand complex to gain insights into the binding mechanisms.

ADMET Prediction in Silico: ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) is essential in the early stages of the drug discovery and design pipeline for analyzing the pharmacokinetics of potential drug candidates. After molecular docking studies, (https://ai-druglab.smu.edu/admet) was used to predict the ADMET characteristics of the compounds with the highest number of hits[15].The server was used for predicting ADMET characteristics after being supplied with the SMILE Strings of the compounds from Pub Chem (https://puchem.ncbi.nlm.nih. gov/compound/) utilizing its search bar.

RESULTS AND DISCUSSIONS

Drug Likeness Screening: We evaluated a total of 10 compounds sourced from Pub Chem using Lipinski's rule of five alongside an analysis of rotatable bonds. Our criteria aimed to identify compounds with the following parameters: molecular weight lower than 300g/mol, hydrogen bond donors (HBD) between 0-5, hydrogen bond acceptors (HBA) between 0-9 and a number of rotatable bonds (nRot) between 2-5 all the compounds pass through these criteria. To further refine our selection, we employed medicinal chemistry parameters to assess these 10 compounds, specifically eliminating those that violated lead likeness criteria, as well as PAINS (Pan Assay Interference Compounds) and Brenk's alerts. This additional scrutiny resulted in a shortlist of 5 compounds (Table 1).

Docking-Derived Binding Affinity: 5 compounds showed they are better binders (between -5.1 and -5.3 kcal/mol) than the control drugs(Cromolyn Sodium= -4.9 kcal/mol) selected in this current in-silico study (Table 2). Essential data regarding the binding affinities and possible drug-like properties of Atractylodes Macrocephala compounds were obtained through molecular docking analysis against Aβ. The ligands' binding energies, as shown in (Table 2), indicate strong interactions with the target protein, Aβ., they ranged from -4.9 to -5.3 kcal/mol, indicating that these compounds have a high potential for therapeutic applications. The docking results revealed that Atractylenolide I, Atractylenolide II and Atractylenolide III all displayed binding energies of -5.3 kcal/mol, indicating strong interactions with Aβ. These compounds share structural characteristics, which are probably responsible for their comparable binding affinities.These ligands' constant binding energies

indicate a stable and advantageous association with the target protein. Atractylenolide IV additionally showed a strong binding affinity, although with a slightly lower binding energy of -5.1 kcal/mol. Despite being slightly <the other Atractylenolide, this compound still has a lot of promises for further research. Quercetin, a well-known flavonoid, confirmed its status as a strong bio active molecule by matching the binding energy of the top Atractylenolide at -5.3 kcal/mol. With a binding energy of -4.9 kcal/mol, Cromolyn Sodium the control in this study had the lowest affinity of all the compounds tested. In molecular interaction of ligands with Aβ (Fig. 1) Cromolyn Sodium's van der Waals interaction is probably less extensive because of its simpler structure. More extensive van der Waals interactions are probably present between quercetin and Atractylenolide. By improving the ligand-protein complex's overall stability, these interactions greatly contribute to their increased binding affinities. Compared to the other ligands, Cromolyn Sodium has less hydrogen bonding. Because hydroxyl and carbonyl groups are present in their molecules, Atractylenolide and quercetin compounds can create multiple and stronger hydrogen bonds with the AB protein. One of the main causes of their improved binding stability and affinity is the forming of these hydrogen bonds. Pt-TI and Pt-Sigma shaped Cromolyn sodium have fewer interactions, which could explain reason its binding energy is lower. Quercetin and Atractylenolide are involved in Pt-Sigma and Pt-TI-shaped interactions, which can considerably stabilize the ligand-protein complex while being less frequent. Their increased binding affinities may be attributed to these interactions, which could be a differentiating characteristic.

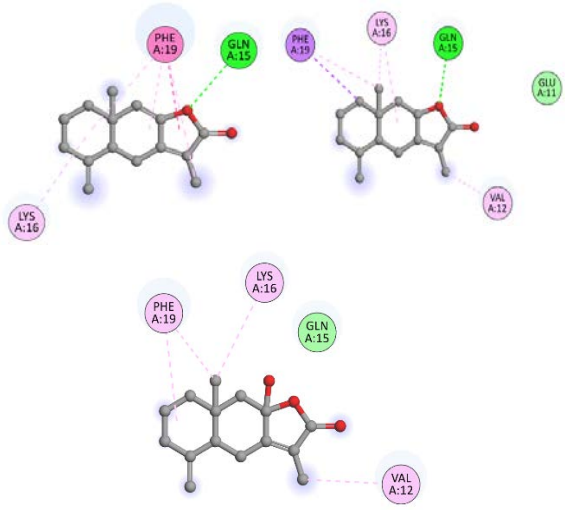

Fig. 1:Molecular Docking of Atractylodes Macrocephala compounds Against Aβ

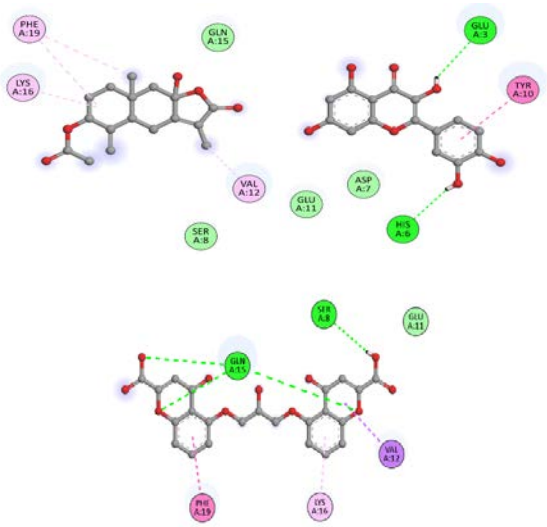

Fig. 2:Atractylenolide I Atractylenolide II Atractylenolide III

Fig. 3: Atractylenolide IV Quercetin Cromolyn Sodium

ADMET Prediction: The ADMET prediction was carried out to ascertain how the 5 hit compounds are absorbed, distributed, metabolized, eliminated and how toxic they can be. The outcome of the evaluation is presented in (Table 3). Caco-2 Permeability scores for the actyleonide compounds are below the optimal threshold (>5.15), indicating potential challenges with absorption. However, actyleonide IV presents the highest permeability at -5.04. Though not optimal, this suggests it could have better absorption compared to other compounds. Human Intestinal Absorption (HIA) actyleonide IV and Quercetin show similar human intestinal absorption rates (72.56%), which are favorable for potential effectiveness in treating Alzheimer's disease, providing adequate bioavailability to reach therapeutic targets in the brain. P-glycoprotein Inhibition, actyleonide IV has a P-glycoprotein inhibition score of 30.12%, which is near the upper limit of acceptable inhibition (≤30%). This supports potential central nervous system (CNS) penetration, crucial for targeting Alzheimer's

pathology. Blood Brain Barrier (BBB) Penetration is vital for Alzheimer's treatment. Actyleonide IV shows a promising BBB penetration score of 25.23%, suggesting that it is positioned well for CNS access, which is imperative for its therapeutic efficacy in Alzheimer's. Plasma Protein Binding Ratio (PPBR) actyleonide IV has a binding percentage of 53.16%, indicating a favorable pharmacokinetics profile that could sustain drug levels in the body while reaching the brain effectively. CYP Enzyme Inhibition, actyleonide IV exhibits moderate inhibition across key CYP enzymes, particularly CYP2D6 and CYP3A4. Although this indicates potential for drug-drug interactions, it may also signify an active metabolic profile relevant for drugs targeting Alzheimer's symptoms. A thorough examination of its metabolic pathways deserves attention in subsequent studies. Actyleonide half-life IV has a half-life of 55.9 hours, which is advantageous for sustained therapeutic levels in the management of Alzheimer's, potentially reducing dosing frequency. The clearance rates for actyleonide IV are within acceptable limits., good clearance is crucial to avoid accumulation and toxicity while ensuring effective concentrations for pharmacological action. For the toxicity, hERG Blockers, Ames Test and LD50: The toxicity profile for actyleonide IV indicates that it remains within acceptable toxicity ranges. However, there is a need for further assessment regarding its hERG inhibition potential and Ames test results, especially as safety is paramount in any Alzheimer's therapeutic agent. However, considering the specific requirements for treating Alzheimer's disease, actyleonide IV emerges as the most promising candidate for further analysis. Its favorable absorption and distribution characteristics, particularly its potential to penetrate the blood-brain barrier, position it well for targeting Alzheimer's pathology effectively. While some concerns related to CYP enzyme inhibition exist, the overall pharmacokinetics and toxicity profiles support its advancement in research.

AD is a devastating neurological disease characterized by progressive cognitive decline. One of the major pathological features of AD is the accumulation of Aβ, which form insoluble cells in the brain and cause neuronal damage. The study focuses on molecular docking techniques to identify bio active compounds that inhibit Aββ aggregation from Atractylodes macrocephala. Using computational techniques such as molecular docking, ADMET (absorption, distribution, metabolism, excretion and toxicities) predictions and biochemical drug similarity screening, this study provides valuable insight into the therapeutic potential of natural compounds for AD. Molecule docking results revealed that Atractylodesmacrocephala contains several bio active compounds that have promising inhibitory effects on Aβ aggregation. In the tested compounds, Atractylenolide I, Atractylenolide II, Atractylenolide III, Atractylenolide IV and Quercetin have the highest binding affinities, with binding energies ranging from -5.1 to -5.3 kcal/mol. These values indicate that they have strong interactions with target proteins and suggest the potential effectiveness of preventing-amyloid aggregation. The docking results showed that these compounds interact with Aβ by various molecular forces, including hydrogen bonds, hydrogen phobia interactions and electrostatic interactions. In particular, hydrogen bonds play a crucial role in stabilizing the ligand-protein complex and increasing the stability of the binding of compounds. Quercetin is a well-known flavonoid with a strong antioxidant ability, showing one of the strongest binding affinities and its potential for modulating amyloid pathology. Similarly, Atractylenolide compounds, which are sequitur penoid lactones, show comparable binding strength, indicating that their structural characteristics are significant in their interaction with Aβ. With a binding energy of -4.9 kcal/mol, Cromolyn Sodium that employed as the study's control compound. The active compounds from Atractylodesmacrocephala showed higher binding affinities, which implies that these natural products may have better inhibitory effects than the Cromolyn Sodium. The natural molecules created more persistent hydrogen bonds and hydrophobic interactions, which contributed to their higher binding affinities, while Cromolyn Sodium and Aβ mainly interacted through weaker van der Waals forces. ADMET predictions in addition to molecular docking were employed to evaluate the pharmacokinetics characteristics of the targeted compounds. Based on Lipinski's Rule of Five, which considers elements including molecular weight, hydrogen bond donors/ acceptors and lipophilicity, the findings showed that the majority of the hit compounds had advantageous drug-like properties. Atractylenolide IV compared to the other compounds has superior blood-brain barrier (BBB) permeability (25.23%) and human intestine absorption (72.56%) contributed to its standout as a particularly interesting candidate. Since the medication must successfully enter the central nervous system in order to have its neuroprotective benefits, BBB penetration is an essential consideration in Alzheimer's treatment. Additionally, the compound's plasma protein binding ratio (53.16%) was favorable, providing a balanced distribution throughout the body. On the other hand, cytochrome P450 (CYP) enzyme inhibition was identified as a possible cause for drug-drug interactions. To maximize its metabolic profile while preserving therapeutic efficacy, additional study is

Table 1: Drug Likeness Screening of Atractylodes Macrocephala Compounds

No.	Compounds	M.W	nRot	HBA	HBD	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations	Bioavailability Score
1	Atractylenolide I	230.3	0	2	0	0	0	0	0	0	0.55
2	Atractylodin	182.2	1	1	0	0	0	0	0	2	0.55
3	4'-Hydroxyacetophenone	136.15	1	2	1	0	3	0	0	1	0.55
4	Atractylenolide II	232.3	0	2	0	0	0	0	0	0	0.55
5	Atractylenolide III	248.3	0	3	1	0	0	0	0	0	0.55
6	Atractylenolide IV	306.3	2	5	1	0	0	0	0	0	0.55
7	Quercetin	302.2	1	7	5	0	0	0	0	0	0.55
8	Atractylone	216.3	0	1	0	0	0	0	0	1	0.55
9	Caryophyllene	204.3	0	0	0	1	0	0	0	1	0.55
10	Cromolyn Sodium*	512.3	8	11	1	2	2	1	1	2	0.17

Table 2: The Docking-Derived Binding Affinity of Atractylodes Macrocephala Compounds with Good Drug-Like Properties Against Aß

S/No	Ligand	PubChemIdentity	Binding Energy
1.	Atractylenolide I	5321018	-5.3
2.	Atractylenolide II	14448070	-5.3
3.	Atractylenolide III	155948	-5.3
4.	Atractylenolide IV	57509416	-5.1
5.	Quercetin	5280343	-5.3
6.	Cromolyn Sodium*	27503	-4.9

Table 3: ADMET Profile of Atractylodes Macrocephala Compounds Using AI Drug Lab

Molecular Property	Optimal Range	Atractylenolide I	Atractylenolide II	Atractylenolide III	Atractylenolide IV	Quercetin	Cromolyn Sodium
Molecular Weight (kg/mol)	100~600	230.13	232.15	248.14	306.15	302.04	512.03
Number of Heteroa-toms	1~15	2	2	3	5	7	13
Number of Rotatable Bonds	<=11	0	0	0	1	1	8
Number of Rings	<=6	3	3	3	3	3	4
Number of HA	<=12	2	2	3	5	7	11
Number of HD	<=7	0	0	1	1	5	1
Absorption							
Caco-2 Permeability (log(cm/s))	>-5.15	-5.02	-5.02	-5.08	-5.04	-5.3	-5.62
HIA (%)	Poor: <=30, Medium: 30~80						
	Optimal: >=80	71.5	72.08	71.5	71.58	72.56	59.4
Pgp Inhibition (%)	Optimal: <=30 Medium: 30~70						
	Poor: >=70	35.33	31.07	30.12	31.64	49.54	45.45
log D7.4	1~3	1.73	1.58	1.38	1.53	1.94	2.06
Aqueous Solubility (log(mol/L))	Soluble:-2~0, Slightly Solu-ble: -4~-2, Insoluble						
	<-4	-4.64	-4.39	-4.64	-4.29	-4.24	-5.3
Oral Bioavailability (%)		45.55	46.06	45.97	42.52	38	48.5
Distribution							
BBB (%)	Optimal: <=30, Medium: 30~70						
	Poor: >=70	28.02	27.95	28.97	25.23	32.22	31.05
PPBR (%)	Optimal: <=90,						
	Poor: >90	43.01	49.19	48.86	53.16	43.33	53.78
Metabolism							
CYP2C9 Inhibition (%)		46.85	53.72	49.61	55.76	67.96	44.38
CYP2D6 Inhibition (%)		81.72	81.92	79.23	84.57	91.79	74.36
CYP3A4 Inhibition (%)		37.57	36.69	36.29	32.33	40.81	28.02
CYP2C9 Substrate (%)		31.45	32.93	31.76	30.71	36.41	32.12
CYP2D6 Substrate (%)		65.91	65.64	56.1	54.98	60.72	52.02
CYP3A4 Substrate (%)		42.26	45.09	42.16	35.01	37.23	27.68
Excretion							
Half-Life (hr.)		41.5	41.1	56.78	55.9	67.42	104.37
CL-Hepa (uL min-1 (106 cells)-1))		40.85	39.42	39.92	43.78	37.59	43.3
CL-Micro (mL min-1 g-1)		38.78	36.57	38.75	37.33	34.8	35.32
Toxicity							
hERG Blockers (%)	Optimal: <=30, Medium: 30~70,						
	Poor: >=70	32.42	35.41	34.58	36.17	37.47	37.3
Ames (%)	Optimal: <=30, Medium: 30~70,						
	Poor: >=70	45.2	48.94	43.38	43.86	43.4	53.08
DILI (%)	Optimal: <=30, Medium: 30~70,						
	Poor: >=70	48.39	51.2	54.23	53.8	56.07	41.08
LD50 [-log(mol/kg)]		2.04	2.26	1.92	2.07	2.23	2.78

required. The results of this study add to the increasing amount of data that suggests using natural compounds as possible anti-Alzheimer's agents. Atractylodes macrocephala compounds may reduce or stop the

progression of disease since they can inhibit Aβ aggregation. Furthermore, these compounds may provide a safer and more natural substitute for synthetic medications because they are derived from traditional medicinal plants. The effectiveness and safety of these medicines must be confirmed by additional experimental validation through in vitro and in vivo research, even though in silico studies provide useful initial data. Future studies should concentrate on assessing their capacity to mitigate neuro inflammation, enhance cognitive abilities and diminish Aβ aggregation in animal models.

CONCLUSION

This study highlights the therapeutic potential of Atractylodesmacrocephala compounds in targeting Aβ aggregation, a key pathological feature of Alzheimer's disease. The docking analysis and ADMET profile demonstrated that Atractylenolide IV possess strong binding affinities and favorable ADMET properties, suggesting potential as drug candidates. Further experimental validation and optimization are required to advance these natural compounds into clinical applications for AD treatment.

REFERENCES

1. Scheltens, P., B.D. Strooper, M. Kivipelto, H. Holstege and G. Chételat *et al.,* 2021. Alzheimer's disease. The Lancet, 397: 1577-1590.
2. Khan, S., K.H. Barve and M.S. Kumar, 2020. Recent Advancements in Pathogenesis, Diagnos-tics and Treatment of Alzheimer's Disease. Curr. Neuropharmacology, 18: 1106-1125.
3. Weller, J. and A. Budson, 2018. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Research, Vol. 7 .10.12688/f1000research.14506.1.
4. Graff-Radford, J., K.X.X. Yong, L.G. Apostolova, F.H. Bouwman and M. Carrillo *et al.,* 2021. New insights into atypical Alzheimer's disease in the era of biomarkers. The Lancet Neurol., 20: 222-234.
5. Mantzavinos, V. and A. Alexiou, 2017. Biomarkers for Alzheimer's Disease Diagnosis. Curr. Alz-heimer Res., 14: 1149-1154.
6. Rostagno, A.A., 2022. Pathogenesis of Alzheimer's Disease. Int. J. Mol. Sci., Vol. 24 .10.3390/ijms 24010107.
7. Gao, Y., L. Tan, J.T. Yu and L. Tan, 2018. Tau in Alzheimer's Disease: Mechanisms and Therapeutic Strategies. Curr. Alzheimer Res., 15: 283-300.
8. Barage, S.H. and K.D. Sonawane, 2015. Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. Neuropeptides, 52: 1-18.
9. Singh, S.K., S. Srivastav, R.J. Castellani, G. Plascencia-Villa and G. Perry, 2019. Neuroprotective and Antioxidant Effect of Ginkgo biloba Extract Against AD and Other Neurological Disor-ders. Neurotherapeutics, 16: 666-674.
10. Chainoglou, E. and D. Hadjipavlou-Litina, 2020. Curcumin in Health and Diseases: Alzheimer's Disease and Curcumin Analogues, Derivatives, and Hybrids. Int. J. Mol. Sci., Vol. 21 .10.3390/ijms 21061975.
11. Zhu, B., Q.L. Zhang, J.W. Hua, W.L. Cheng and L.P. Qin, 2018. The traditional uses, phytochem-istry, and pharmacology of Atractylodes macrocephala Koidz.: A review. J. Ethnopharmacology, 226: 143-167.
12. Daina, A., O. Michielin and V. Zoete, 2017. SwissADME: A free web tool to evaluate pharmaco-kinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci. Rep., Vol. 7 .10.1038/srep42717.
13. Pettersen, E.F., T.D. Goddard, C.C. Huang, G.S. Couch, D.M. Greenblatt, E.C. Meng and T.E. Ferrin, 2004. UCSF Chimera-A visualization system for exploratory research and analysis. J. Comput. Chem., 25: 1605-1612.
14. Dallakyan, S. and A.J. Olson, 2015. Small-Molecule Library Screening by Docking with PyRx. Methods Mol. Biol., 12: 243-250.
15. Tian, H., R. Ketkar and P. Tao, 2022. ADMETboost: A web server for accurate ADMET predic-tion. J. Mol. Model., Vol. 28 .10.1007/s00894-022-05373-8.