INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Article

In-Silico Characterization, ADMET Prediction, and Molecular Docking Studies of *California Almonds* against Alzheimer's Disease

Swapnil Tirmanwar*, Pratik Dhokane, Shivani Wadichar, Saurabh Kolaskar, Gopal Pondhe, Kajal Prasad

Department of Pharmacognosy, Priyadarshini J. L. College of Pharmacy, Nagpur, Maharashtra, India - 440016.

ARTICLE INFO

Published: 02 Jan. 2025
Keywords:
Alzheimer's disease, molecular docking, phytochemicals, UCSF Chimera, Autodock software, ADMET properties prediction.
DOI:
10.5281/zenodo.14587211

ABSTRACT

A degenerative neurologic condition called Alzheimer's disease results in the death of brain cells and brain shrinkage. The most frequent cause of dementia, which is characterized by a steady deterioration in mental, behavioral, and social abilities that impairs a person's capacity for independent functioning, is Alzheimer's disease. Neurodegenerative diseases like Alzheimer's disease (AD) are marked by difficulties in social identification and learning social cues. We explored whether β1-noradrenergic signaling could be a potential treatment target for AD by examining its impact on cognitive performance. This signaling may also help regulate blood pressure variations in individuals with memory disorders. The bitter almond is used in treatments for Alzheimer's disease. The major chemical constituents of California almonds were studied for molecular docking by using the software. Protein Data Bank (PDB) file of cholinesterase inhibitor with the code 5oug and its co-crystallized ligand rivastigmine (docking score -6.0), donepezil (docking score -9.0) were used for this purpose. The binding affinity and interactions of phytochemicals with amino acids were evaluated. Target protein-protein homology modeling, protein structure validation, and energy minimization were completed. A comparative in silico docking analysis was conducted using phytochemicals documented in the literature for their potential relevance to Alzheimer's disease, alongside a standard drug. These phytochemicals were assessed for their absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, and only those that passed the ADMET filters were included. A preliminary docking study was performed using AutoDock Vina, and the results were validated with AutoDock 4.2.6 and SwissDock.

INTRODUCTION

***Corresponding Author:** Swapnil Tirmanwar
Address: Department of Pharmacognosy, Priyadarshini J. L. College of Pharmacy, Nagpur, Maharashtra, India - 440016.
Email ✉: swapniltirmanwar00@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Alzheimer's disease is a neurological degenerative disorder that leads to the shrinking of the brain and the death of brain cells. It is the most common cause of dementia, which refers to a continuous decline in mental, behavioral, and social skills, ultimately limiting a person's ability to function independently. Treatments for Alzheimer's disease involve the usage of bitter almonds. Using the program, the main chemical components of California almonds were investigated for molecular docking.[1] Alois Alzheimer wrote about a 51-year-old woman who had psychological issues as well as a rather quickly declining memory in 1907 in his book The Case of the Missing Memory. Four years later, she passed away. The early onset of this disorder, along with the discovery of neurofibrillary tangles (NFTs), distinguished it from other well-known progressive and lethal neurological conditions, such as senile dementia.[2],[3] It is still up for dispute why Alzheimer's disease (AD) is being classified as a novel nosological entity and why eminent psychiatrist Emil Kraepelin is advocating for such a novel ailment. The unrelenting neurologic decline caused by the characteristic pathology of AD persists now as it did back then.[4] AD was later split into two clinical groups based on when it first appeared. Following the groundbreaking studies of Tomlinson, Roth, and Blessed, the term "Senile Dementia of the Alzheimer-type" was adopted to describe comparable dementia that affected people over the age of 65. Originally, the term "Alzheimer's disease" was used to describe a form of "presenile" dementia that affected people under the age of 65. History-related significance The possibility that this entity was distinct from "dementia senilis" was questioned by Alzheimer's, even though both age-related classifications are still in use[5]. The existence of a bi-modal age of onset for AD has also never been shown. Above age 65, AD occurs more often and is now generally recognized as a separate entity. Dementias such as vascular dementia, dementia with Lewy bodies, dementia brought on by Parkinson's disease, frontotemporal dementia, and reversible dementias must be separated from Alzheimer's disease (AD).[6] A conclusive diagnosis of AD can only be made on a histological study of the brain during autopsy because there is currently no valid peripheral biochemical marker for the disease.[7] There have been inconsistent results from positron emission tomography (PET) scanning technology employing Pittsburgh Compound B (PiB), a thioflavin T derivative that binds specifically to amyloid- (A).[9],[10] It would seem that asymptomatic controls with amyloid plaques and symptomatic AD may not always be distinguished by PiB binding to A. Additionally, the reported false negative result is explained by the fact that the binding of PiB to A is dependent on the peptide's secondary and tertiary structure[11]. While PiB has made it possible to see brain activity in a way that is pertinent to the development of amyloid plaques, further longitudinal investigations are required to assess its relative value. The clinical diagnostic accuracy has been somewhat enhanced through the refinement of the diagnostic criteria in light of the mild cognitive impairment (MCI) problem, which attempts to identify early neurodegenerative disease but does so in only a subset of patients. However, we might be nearing an endpoint. [12]

2. MATERIALS AND METHODS:-

A. Software and programs

The ligand compounds were illustrated using Chemsketch., a tool for sketching chemical molecules. [10]. The. mol file was converted to. pdb format using Avogadro software [11]. 4.0 Autodock [12]. The semi-flexible protein-ligand docking investigations were conducted using an early docking tool. The protein database allowed users to download the crystalline structure of the SSRI, which had the pdb code [PDB: 7EOQ]. The

goal of computational studies will be this. The library of derivatives was virtually screened using the Pyrx program. [13] Molecular interaction visualization was conducted using Discovery Studio 3.5. s [14]

B. Preparation of ligand

The ligand structure was created using the clean structure tool in the Chem Sketch program, which helped refine the drawing. An .mol file containing this structure was saved in the working folder. Then, the Avogadro program was utilized to open the .mol file and optimize the structure using its optimization tool. Finally, the optimized structure was saved as a .pdb file in the working directory.

C. Preparation of receptor

The software AutoDock v4.0 was used to refine the crystal structure of the antidepressant, which was obtained in PDB format from an online database. The energy was minimized by evenly distributing the charges across the receptor. Water molecules connected to the receptor were removed, and polar hydrogen atoms were added.

D. Receptor-Ligand Docking

The binding postures and their corresponding binding energies were determined using AutoDock v4.0. A conformation with a higher binding energy is considered less stable due to the inverse relationship between energy and stability. The default settings of the software were applied consistently with standard usage protocols. A grid point spacing of 0.375 angstroms was used, along with 126 grid boxes (x, y, and z) in a ratio of 60:60:60 for energy scoring. The coordinates for the Lamarckian Genetic Algorithm (LGA) were set to X = 50, Y = 26, and Z = 40. The 3D grid box was carefully positioned to surround the receptor's active site, ensuring it was centered on the active ligand binding area.

E. Online chemical property calculator

The properties of the ligand were determined using an online property calculator from Molinspiration and Swiss ADME [15]. Using an internal tool, the ligand's structure was sketched, and various attributes were computed. These attributes were categorized into two main types: structural properties and bioactivity. Acute oral toxicity was predicted using the Protox II web server [15,16,17].

3. RESULTS & DISCUSSION

The molecular docking research findings using AutoDock Vina showed the binding energies of the reference molecules and selected drugs (Table 1). In addition, SwissDock's findings were contrasted with these. The method was divided into many steps, first with the FACTS-based creation of as many binding modes as feasible, then the clustering evaluation. The best full fitness (FF) rating belongs to Cluster "0." Protein and phytochemical samples were provided in separate packages. Each docking run's output cluster was identified, and the individual conformer from each cluster with the most favorable binding mode and the least detrimental force field score was selected for further investigation, as it exhibited the best match.

Table 1. The binding energies of the reference molecules and selected drug

Sr. No.	Ligand	Docking score (kcal/mol)	MW (g/mol)	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA ^{0}A	Follow Lipinski
1.	Donepezil	-8.9	379.210	6	4	0	38.770	Yes
2	Rivastigmine	-6.4	250.170	6	4	0	32.780	Yes
3	Amygdalin	-7.7	457.160	7	12	7	34.780	Yes
4	3hydroxybutanone	-7.3	164.080	3	2	1	37.300	Yes
5	2-ethylpyrazine	-6.2	108.070	1	2	0	25.780	Yes
6	2-pentylfuran	-6.2	138.100	4	1	0	13.140	Yes
7	Trimethylpyrazine	-6.0	122.080	0	2	0	25.780	Yes
8	2,5dimethylpyrazine	-5.1	108.070	0	2	0	25.780	Yes

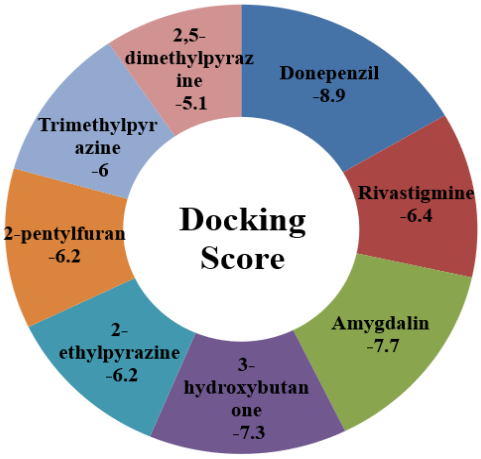

Fig 1. Docking Score

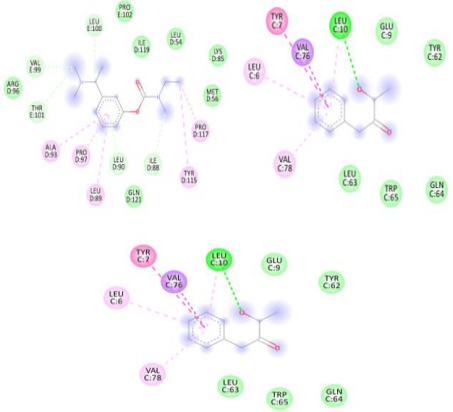

Fig 2. Rivastigmine, 3-hydroxybutanone and 2-pentylfuran

Table 2. The toxicity studies the reference molecules and selected drugs

Sr. No	Compound	Absorption		Distribution (PPB)	Metabolism	Excretion	Toxicity	
		Caco-2 permeability	MDCK permeability				Organ toxicity	Carcinogenicity
1.	Donepezil	-4.793	2.1e-05	87.743%	+	10.635	0.98	0.50
2.	Rivastigmine	-4.873	1.4e-05	42.943%	+	13.812	0.93	0.74
3.	Amygdalin	-5.895	9.8e-05	28.922%	-	0.999	0.86	0.89
4.	3hydroxybutanone	-4.321	3e-05	57.718%	-	11.782	0.61	0.71
5.	2-ethylpyrazine	-4.177	3.5e-05	18.232%	+	9.375	0.64	0.57
6.	2-pentylfuran	-4.272	2.1e-05	95.481%	+ + +	9.353	0.80	0.61
7.	Trimethylpyrazine	-4.632	2.8e-05	49.115%	-	7.265	0.74	0.50

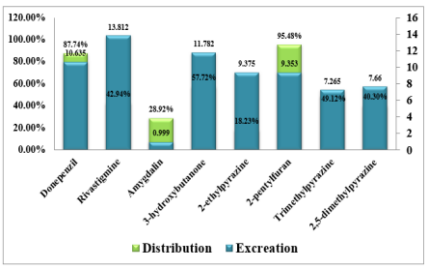

Fig 3. Distribution and Excreation the reference molecules and selected drugs

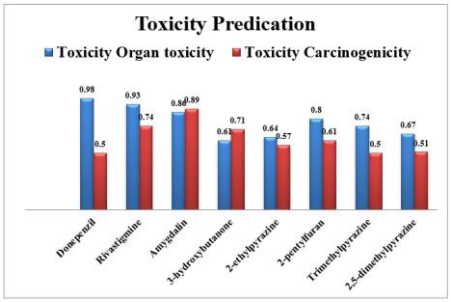

Fig 4. Toxicity prediction the reference molecules and selected drugs

4. CONCLUSION: -

The evaluation of libraries of *California Almonds* revealed that amgydalin and 3-hydroxybutanone bind the target efficiently, as it may hold significant value as an agonist of 5oug acetylcholine. As a result, we have concluded that these phytochemicals can be used to improve memory and treat AD. We also recommend that more in vitro and in vivo research be done to achieve a clearer understanding of the best California almond structure for memory improvement and Alzheimer's disease prevention and treatment. The overall comparison of the standard drug and naturally obtained drug (*California Almonds)* of this drug docking score is a comparison of rivastigmine (docking score -6.4), donepezil (docking score -8.9), and amygdalin (Docking score -7.7) and3-hydroxybutananone

REFERENCES

1. Alzheimer A. Uber eine eigenartige Erkrankung der Hirnrinde. Allgemeine Zeits Psychiat PsychischYGerichtlich Med. 1907;64:146–148. [Google Scholar]
2. Roth M, Tomlinson BE, Blessed G. Correlation between scores for dementia and counts of 'senile plaques' in cerebral grey matter of elderly subjects. Nature. 1966;209:109–110. [PubMed] [Google Scholar]
3. Roth M, Tomlinson BE, Blessed G. The relationship between quantitative measures of dementia and degenerative changes in the cerebral grey matter of elderly subjects. Proc R Soc Med. 1967;60:254–260. [PMC free article] [PubMed] [Google Scholar]
4. Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. J Neurol Sci. 1970;11:205–242. [PubMed] [Google Scholar
5. Berrios G. Alzheimer's disease: A conceptual history. International Journal of Geriatric Psychiatry. 1990;5:355–365. [Google Scholar]
6. Wiley CA, Lopresti BJ, Venneti S, Price J, Klunk WE, DeKosky ST, et al. Carbon 11-labeled Pittsburgh Compound B and carbon 11-labeled (R)-PK11195 positron emission tomographic imaging in Alzheimer's disease. Arch Neurol. 2009;66:60–67. [PMC free article] [PubMed] [Google Scholar]
7. Roe CM, Mintun MA, D'Angelo G, Xiong C, Grant EA, Morris JC. Alzheimer disease and cognitive reserve: variation of education effect with carbon 11-labeled Pittsburgh Compound B uptake. Arch Neurol. 2008;65:1467–1471. [PMC free article] [PubMed] [Google Scholar]
8. Klunk WE. Biopsy support for the validity of Pittsburgh compound B positron emission tomography with a twist. Arch Neurol. 2008;65:1281–1283. [PMC free article] [PubMed] [Google Scholar]
9. Cairns NJ, Ikonomovic MD, Benzinger T, Storandt M, Fagan AM, Shah AR, et al. Absence of Pittsburgh compound B detection of cerebral amyloid beta in a patient with clinical, cognitive, and cerebrospinal fluid

markers of Alzheimer disease: a case report. Arch Neurol. 2009;66:1557–1562. [PMC free article] [PubMed] [Google Scholar]
10. Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol. 2008;65:1509–1517. [PMC free article] [PubMed] [Google Scholar]
11. Leinonen V, Alafuzoff I, Aalto S, Suotunen T, Savolainen S, Nagren K, et al. Assessment of beta-amyloid in a frontal cortical brain biopsy specimen and by positron emission tomography with carbon 11-labeled Pittsburgh Compound B. Arch Neurol. 2008;65:1304–1309. [PubMed] [Google Scholar]
12. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256:183–194. [PubMed] [Google Scholar]
13. Chemsketch : http://www.acdlabs.com(Web server issue 2014)
14. Avogadro: http://avogadro.cc (Web server issue 2010)
15. Autodock v4.0 : http://autodock.scripps.edu(Web server issue 2014)
16. Molinspiration online property calculator: https://www.molinspiration.com(Web server issue 2018)
17. pyrex : http://www.pyrex.cc(Web server issue 2010)
18. Ouassaf, Mebarka, et al. "Combined molecular docking and dynamics simulations studies of natural compounds as potent inhibitors against SARS-CoV-2 main protease." Journal of Biomolecular Structure and Dynamics 40.21 (2022): 11264-11273. Discovery Studio 3.5 http://www.3dsbiovia.com(Web server issue 2011)
19. Banerjee P., Eckert O.A., Schrey A.K., Preissner R.: ProTox-II: a web server for the prediction of toxicity of chemicals. Nucleic Acids Res (Web server issue 2018); NAR
20. Kumar. P, Asnani. A, (2019), Docking of 3,5-diphenyl- pyrazoline with monoamine oxidase A receptor and In-Silico structural property calculation, Journal of Drug Delivery & Therapeutics.; 9(3-s):43-45. [cross reference]

HOW TO CITE: Swapnil Tirmanwar*, Pratik Dhokane, Shivani Wadichar, Saurabh Kolaskar, Gopal Pondhe, Kajal Prasad, In-Silico Characterization, ADMET Prediction, and Molecular Docking Studies of California Almonds against Alzheimer's Disease, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 01, 131-136. https://doi.org/10.5281/zenodo.14587211