IRSTI 34.15.15 https://doi.org/10.26577/IJBCh2024v17i1-a15

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(Received 23 May 2024; received in revised form 30 May 2024; accepted 1 June 2024)

Targeting beta-amyloid plaques and neurofibrillary tangles: a proteomic approach towards Alzheimer's disease therapy

Abstract. Alzheimer's disease (AD) stands as the most prevalent form of dementia affecting elderly individuals and ranks as the sixth leading cause of death globally. The pathological hallmarks of AD involve the formation of beta-amyloid plaques and neurofibrillary tangles in the brains of affected individuals, contributing to progressive brain degradation. This study aimed to utilize molecular modeling methods as a theoretical approach to explore the inhibition of beta-amyloid plaques and neurofibrillary tangles. Beta-amyloid and tau receptors were employed to carry out molecular docking with the ligands, including curcumin, memantine, nicotine, and caffeine. The selected compounds demonstrated minimum binding affinity and interactions with the active sites of the receptors while docking studies were performed. Notably, molecular interactions of the receptor complexes with curcumin compounds exhibited prominence in number. Curcumin, known for its antioxidant, anti-inflammatory, and lipophilic properties, has shown promise in enhancing cognitive function in AD patients. The findings of this study highlight the potential for further research aimed at developing improved drugs based on curcumin for the treatment of AD.
Key words: Alzheimer's, Dementia, Virulence Factor, Active Site, Docking, Binding affinity.

Introduction

Neurological diseases, characterized by disruptions in regular electrical impulses within the brain or nervous system, pose significant challenges to global health. Among these, Alzheimer's disease (AD) represents a significant and growing public health concern worldwide, particularly among the aging population [1]. As the most common form of dementia, AD poses substantial challenges to both affected individuals and healthcare systems, significantly impacting quality of life and imposing a significant socioeconomic burden [2]. AD is a degenerative condition involving a myriad of symptoms, including motor dysfunction, sensory impairment, cognitive decline, and memory loss Alongside memory deficits, individuals may struggle with language difficulties, including trouble finding words, following conversations, or understanding written text [3].

One of the defining pathological features of AD is the presence of aberrant protein aggregates in the brain, notably beta-amyloid plaques and neurofibrillary tangles [4]. Beta-amyloid plaques consist of extracellular deposits of amyloid-beta peptides, while neurofibrillary tangles comprise intracellular accumulations of hyperphosphorylated tau protein. These proteinaceous aggregates disrupt neuronal function, leading to synaptic dysfunction, neuronal loss, and ultimately, cognitive decline characteristic of AD [5, 6]. These pathological hallmarks, along with genetic predispositions, underscore the intricate interplay between genetic and environmental factors in AD etiology [7].

Various hypotheses have been proposed to elucidate the etiology of AD, including the cholinergic, amyloid, and tau theories. The cholinergic theory implicates reduced acetylcholine synthesis in neuronal degeneration, while the amyloid theory posits extracellular beta-amyloid accumulation as a primary instigator of the disease process [8, 9]. Conversely, the tau hypothesis suggests that abnormalities in tau protein initiate neurofibrillary tangle formation, leading to neuronal collapse (10). Despite extensive research, current treatments for AD are limited to symptomatic management with cholinesterase inhibitors, including tacrine, donepezil, rivastigmine, and galantamine. However, these treatments fail to address the underlying pathology, highlighting the urgent need for novel therapeutic interventions [11].

Given the central role of beta-amyloid plaques and neurofibrillary tangles in AD pathogenesis, targeting these pathological structures represents a promising therapeutic strategy [12, 13]. Molecular modeling methods offer a powerful tool for elucidating the molecular mechanisms underlying disease progression and identifying potential therapeutic interventions. They play a crucial role in drug discovery and development for Alzheimer's disease (AD) [14, 15]. By employing computational techniques, researchers can predict the interactions between target proteins, such as beta-amyloid peptides, tau protein, cholinesterases, and others, and small molecule ligands (potential drugs), facilitating the rational design of novel therapeutics.

The primary aim of this study is to investigate potential therapeutic strategies for Alzheimer's disease (AD) by utilizing molecular modeling methods to target and inhibit beta-amyloid plaques and neurofibrillary tangles, the two abnormal structures implicated in AD pathogenesis.

Materials and methods

In this study, various tools and software were employed to analyze protein structures and assess binding energy properties with active compounds. The Tools and Software employed in this Molecular Docking Analysis are presented on Figure 1.

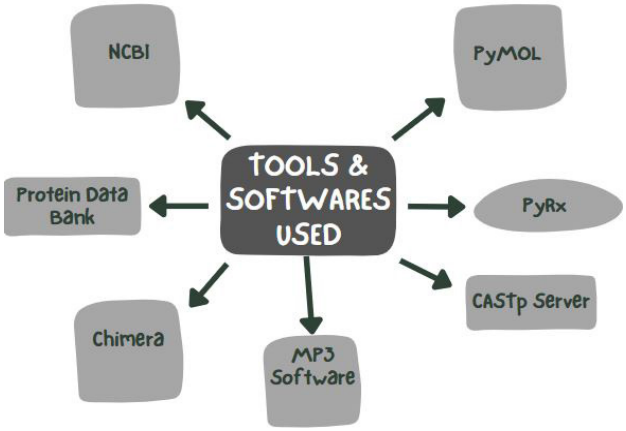


Figure 1 – Schematic representation of tools and software utilized in molecular docking analysis

1. Target identification and retrieval. The study focused on molecular docking analyses of four active compounds against the tau protein (PDB: 2MZ7) and beta-amyloid protein (PDB: 1IYT), both implicated in Alzheimer's disease. Both protein sequences were retrieved from The National Center for Biotechnology Information (NCBI) [16], and the corresponding 3D structures were obtained from the Protein Data Bank (PDB) [17].

2. Choice of ligands. caffeine [18], Curcumin [19], Nicotine [20], and Memantine [21] were selected as ligands based on previous research indicating their potential efficacy against Alzheimer's disease. These ligands were retrieved from NCBI and converted from SDF to PDB format using the Online Smiles Converter.

3. Virulence prediction. MP3 software [22] is used for the prediction of virulent and non-virulent protein properties. In this study, Virulence factor analysis was conducted using MP3 software that predicted the pathogenicity of proteins associated with Alzheimer's disease.

4. Active site analysis. The CASTp Server [23] was utilized for predicting the active sites of the tau protein and beta-amyloid. This online tool identifies and measures pockets and voids within 3D protein structures, providing annotated functional information on specific residues.

5. Chimera visualization. Visualization of the beta-amyloid and tau proteins was performed using UCSF Chimera software [24], enabling interactive visualization and analysis of molecular structures.

6. Molecular docking analysis. Molecular docking was performed using AutoDock Vina software [25] to predict binding modes of protein-ligand complexes. The ligand's rotational bonds were treated as flexible, while those of the protein were kept rigid. Grid boxes were positioned around the active site of the protein to guide the docking process. The resulting poses were ranked based on affinity scores in kcal/mol. PyRx software [26] was utilized for predicting the binding energy of ligands when interacting with receptors.

7. Visualization of docking results. PyMOL software [27] was utilized for visualizing the protein-ligand complexes, generating high-quality 3D images for further analysis. This aided in understanding the active site, binding modes, and interactions between the tau protein and beta-amyloid targets with the ligand molecules.

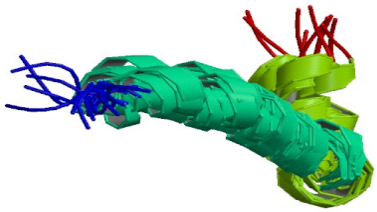
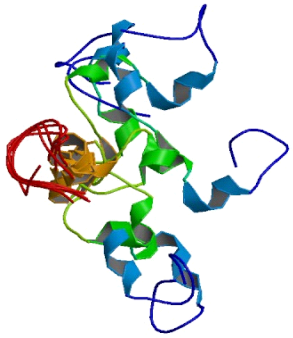
Results and discussion

1. Virulence factor analysis of Alzheimer's protein

Predicting virulence factors is essential for the understanding of infectious diseases, identifying targets for therapeutic intervention, improving diagnostics, assessing disease risk, and elucidating

host-pathogen interactions. The virulence factor was analyzed using MP3 software. The virulence factor prediction indicated the number of pathogenic and non-pathogenic sequences identified for each protein as shown in Table 1. The beta-amyloid protein (PDB code: 1YIT) exhibited 1 non-pathogenic sequence, while the tau protein (PDB code: 2MZ7) displayed 1 pathogenic sequence.

Table 1 – Virulence factor analysis of Alzheimer's protein

Protein	Gene PDB Code	Structure Protein Model	MP3 RESULTS
Beta-Amyloid	1YIT		Total Sequences in File: 1 Total Pathogenic sequences: 0 Total Non-Pathogenic sequences: 1
Tau Protein	2MZ7		Total Sequences in File: 1 Total Pathogenic sequences: 1 Total Non-Pathogenic sequences: 0

2. Active Site Analysis

Predicting the active site of a protein is essential in drug discovery and design processes as it provides crucial insights into the molecular interactions between potential drug candidates and their target proteins. Next, active sites of beta-amyloid and tau protein were identified by using CASTp server. The results obtained from the CASTp server provided valuable structural insights. CASTp identified and characterized the locations and properties of binding sites or pockets on the surface of beta-amyloid and tau proteins. It also calculated the surface area and volume of the identified binding sites. It identified several active pockets within the beta-amyloid protein. Notable active pockets included residues DA, RH, I, D, V, K, II, and M as shown on Figure 2.

For the Tau protein, CASTp revealed active pockets including residues QP, NK, D, Q, K, VQSK, GSK, G, K, V, Q, and IP as shown in Figure 3. In addition, the number, area, and circumcircle of the mouth openings for each pocket were also measured.

All measurements were given in two values, one for the solvent-accessible surface (SA) and one for the molecular surface (MS).

3. Visualization using Chimera

The interactive visualizations of the beta-amyloid and tau proteins generated through UCSF Chimera software are shown in Figures 4a & 4b. This visualization helped in analyzing the intricate three-dimensional structures of beta-amyloid and tau proteins, allowing for the identification of key features such as active sites, structural motifs, and binding pockets.

4. Selection of ligands for molecular docking

Following four FDA-approved ligands were selected to determine and compare their binding efficacy with beta-amyloid and tau protein. The selected ligands are shown in Table 2.

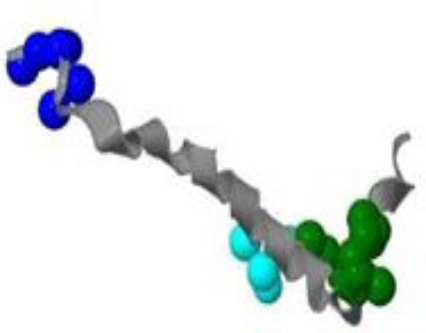
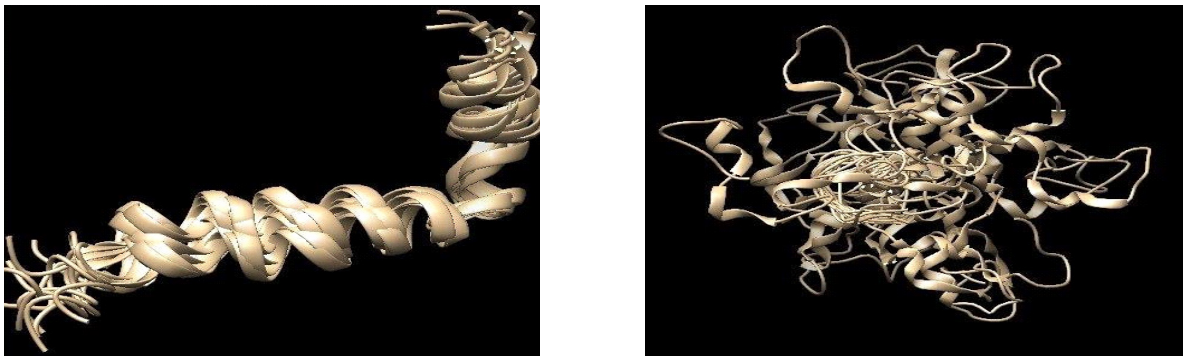


Figure 2 – Visual Representation of Beta-amyloid generated through CASTp Server**.** Blue spheres show DA and RH active pockets of Amino Acid residue. Cyan spheres show I, and D active pockets of amino acid residue. Green spheres show V, K, II, and M active pockets of amino acid residue.

Figure 3 – Visual Representation of Tau protein generated through CASTp Server. Blue spheres show QP, NK, and D active pockets of amino acid residue. Cyan spheres show Q and K active pockets of Amino Acid residue. Green spheres show VQSK and GSK active pockets of amino acid residue. Purple spheres show G, K, V, and Q active pockets of amino acid residue. Yellow spheres show I P active pockets of amino acid residue.



A B

Figure 4 – Visualization of Beta-amyloid chimera (A), Tau protein chimera (B)

Table 2 – Name, Pubchem ID, and structure of selected Ligands

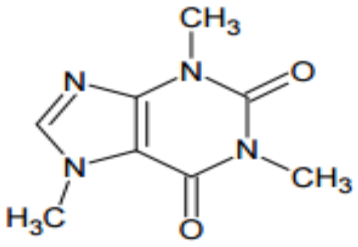
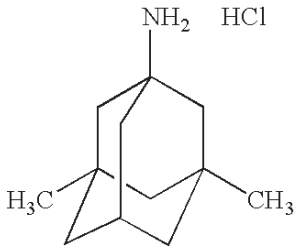
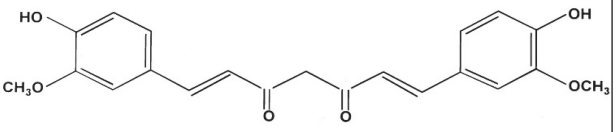
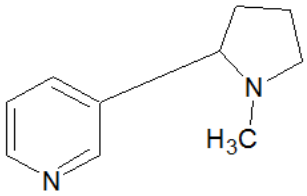
S.No	PubChem ID	Name of compound	Molecular weight (g/mol)	Structure
1	2519	Caffeine	194.1906	

Table continuation

S.No	PubChem ID	Name of compound	Molecular weight (g/mol)	Structure
2	181458	Memantine	215.765	
3	89594	Nicotine	162.23156	 CURCUMIN
4	969516	Curcumin	368.3799	

5. Molecular Docking of Beta-amyloid and Tau protein

The molecular docking results of Beta Amyloid indicate that Caffeine exhibited a binding affinity of -4.3 kcal/mol, However, Memantine and nicotine displayed -4.8 and -4.1 kcal/mol, and Curcumin demonstrated the highest binding affinity of -5.7 kcal/mol as shown in Table 3. This binding energy makes it the most suitable candidate. Results of Beta-Amyloid Ligand Docking Analysis are shown in Table 3.

Table 3 – Results of Beta-Amyloid Ligand Docking Analysis

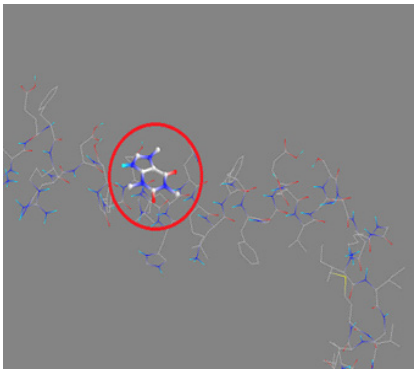
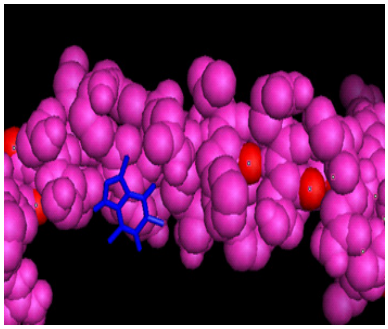
Ligand	PyRx Visualization	Binding Affinity	PyMol Visualization
Caffeine		-4.3 Kcal/Mol	

Table continuation

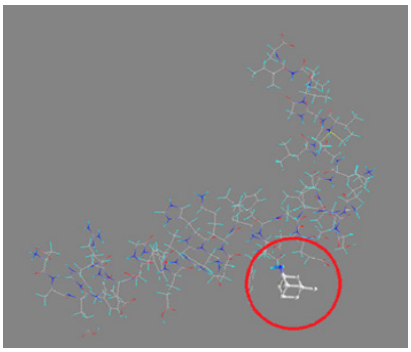
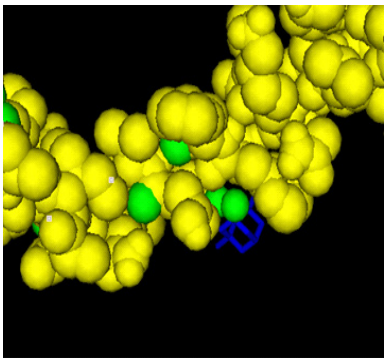
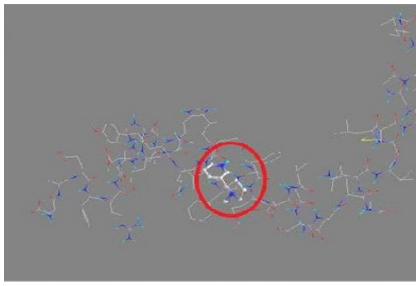
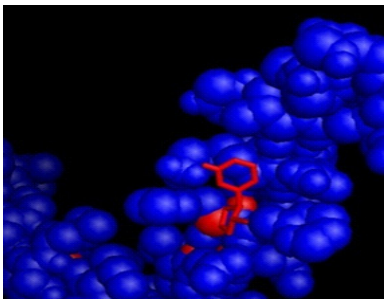
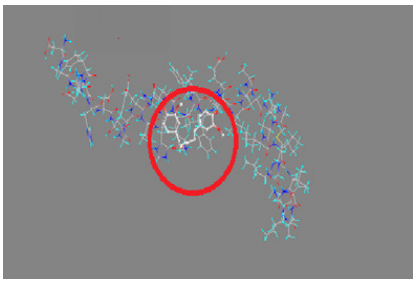
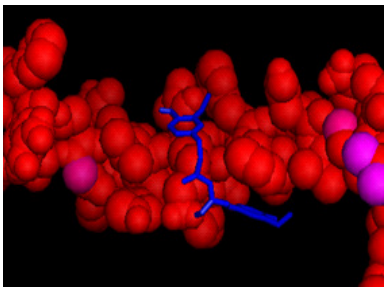
Ligand	PyRx Visualization	Binding Affinity	PyMol Visualization
Memantine		-4.8 Kcal/Mol	
Nicotine		-4.1 Kcal/Mol	
Curcumin		-5.7 Kcal/Mol	

Table 4 shows the Results of Tau Proteins Ligand Docking Analysis. It was analyzed that Caffeine exhibited a binding affinity of -5.1 kcal/mol, Memantine showed -5.6 kcal/mol, Nicotine displayed -5.0 kcal/mol, and Curcumin demonstrated the highest binding affinity of -5.8 kcal/mol.

Table 4 – Results of Tau Proteins Ligand Docking Analysis

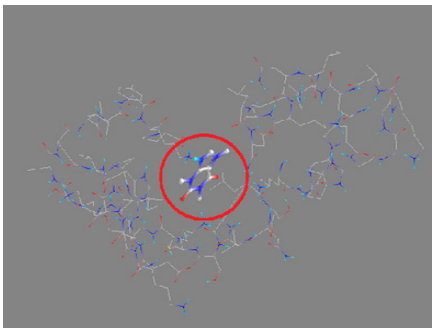
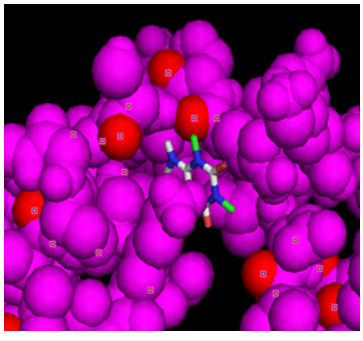
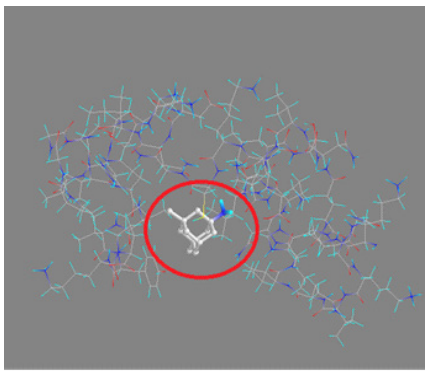
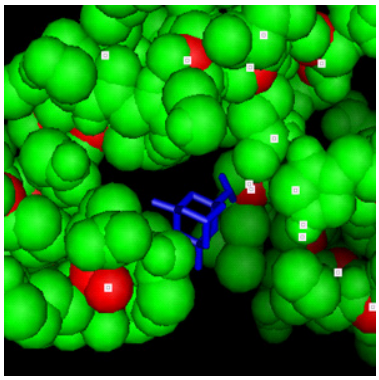
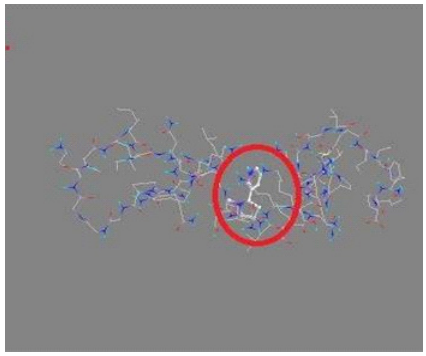
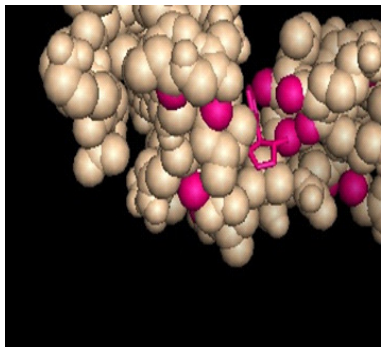
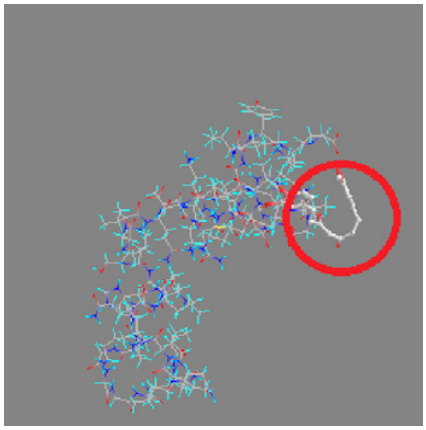
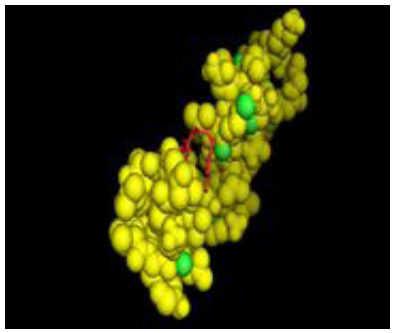
Ligand	PyRx Visualization	Binding Affinity	PyMol Visualization
Caffeine		-5.1 Kcal/Mol	

Table continuation

Ligand	PyRx Visualization	Binding Affinity	PyMol Visualization
Mamantine		-5.6 Kcal/Mol	
Nicotine		-5.0 Kcal/Mol	
Curcumin		-5.8 Kcal/Mol	

The findings of this study provide valuable insights into potential therapeutic strategies for Alzheimer's disease (AD) targeting beta-amyloid and tau proteins. Through molecular docking analysis, the binding affinities of four active compounds, including Caffeine, Curcumin, Memantine, and Nicotine, were evaluated against beta-amyloid and tau proteins.

The molecular docking results revealed varying degrees of binding affinities among the tested ligands. Curcumin exhibited the highest binding affinity to both beta-amyloid and tau proteins, with binding energies of -5.7 kcal/mol and -5.8 kcal/mol, respectively. The ability of Curcumin to bind effectively to these proteins may impede their aggregation and potentially mitigate neurodegenerative processes associated with AD. Different molecular docking studies have also indicated the potential therapeutic benefits of curcumin and its derivatives for Alzheimer's disease (AD) (20 – 22). This suggests that Curcumin may possess strong inhibitory effects against the aggregation of beta-amyloid and tau proteins, which are characteristic features of AD pathogenesis.

Additionally, Memantine demonstrated notable binding affinity to beta-amyloid protein with a binding energy of -4.8 kcal/mol, suggesting its potential as a therapeutic agent for targeting beta-amyloid aggregation in AD. Some molecular docking studies also provided valuable insights into the therapeutic potential of memantine (23, 24).

Nicotine and Caffeine displayed moderate binding affinities to beta-amyloid protein, indicating their potential as adjunctive therapeutic agents in AD management. While their exact mechanisms of action in AD pathogenesis remain to be elucidated, their ability to interact with beta-amyloid protein suggests potential neuroprotective effects.

The visualization of protein-ligand complexes using PyRx and PyMOL software provided valuable insights into the binding modes and interactions between ligands and target proteins. These visualizations aided in understanding the structural basis of ligand-protein interactions and facilitated the identification of key binding sites and residues involved in ligand binding. Overall, our study underscores the importance of interdisciplinary approaches in drug discovery and highlights the potential of computational techniques in accelerating the development of effective treatments for Alzheimer's disease. These findings contribute to the growing body of research aimed at understanding the molecular mechanisms underlying AD pathogenesis and identifying novel therapeutic targets.

Conclusion

In conclusion, this study highlights the potential of natural compounds such as Curcumin, Memantine, Nicotine, and Caffeine as therapeutic agents for AD by targeting beta-amyloid and tau proteins. The high binding affinity of Curcumin to both proteins suggests its promise as a multifaceted therapeutic agent capable of inhibiting beta-amyloid and tau aggregation, thereby potentially slowing the progression of AD. These findings suggest its potential therapeutic efficacy in preventing the formation of neurofibrillary tangles associated with Alzheimer's disease. The results of this study highlight the need for the exploration of natural compounds as novel treatments for AD and underscore the importance of further research to validate their efficacy and safety profiles in clinical settings. Further experimental validation of the computational predictions presented in this study is warranted to confirm the efficacy of the identified compounds in mitigating AD-associated pathology.

Acknowledgments

The authors acknowledge support from the Department of Biomedical Engineering, NED University of Engineering and Technology for providing us with the platform to accomplish our work.

References

1. Suresh, S., Singh S, A., Rushendran, R., Vellapandian, C., & Prajapati, B. (2023). Alzheimer's disease: the role of extrinsic factors in its development, an investigation of the environmental enigma. Frontiers in neurology, 14, 1303111. https://doi.org/10.3389/fneur.2023.1303111

2. Ding, C., Wu, Y., Chen, X., Chen, Y., Wu, Z., Lin, Z., Kang, D., Fang, W., & Chen, F. (2022). Global, regional, and national burden and attributable risk factors of neurological disorders: The Global Burden of Disease study 1990-2019. *Frontiers in public health*, *10*, 952161. https://doi.org/10.3389/fpubh.2022.952161

3. Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules (Basel, Switzerland), 25(24), 5789. https://doi.org/10.3390/molecules25245789

4. Abubakar, M. B., Sanusi, K. O., Ugusman, A., Mohamed, W., Kamal, H., Ibrahim, N. H., Khoo, C. S., & Kumar, J. (2022). Alzheimer's Disease: An Update and Insights Into Pathophysiology. *Frontiers in aging neuroscience*, *14*, 742408. https://doi.org/10.3389/fnagi.2022.742408

5. Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological alterations in Alzheimer disease. *Cold Spring Harbor perspectives in medicine*, *1*(1), a006189. https://doi.org/10.1101/cshperspect.a006189

6. Jankovska, N., Olejar, T., & Matej, R. (2020). Extracellular Amyloid Deposits in Alzheimer's and Creutzfeldt-Jakob Disease: Similar Behavior of Different Proteins?. International journal of molecular sciences, 22(1), 7. https://doi.org/10.3390/ijms22010007

7. Boyd, R. J., Avramopoulos, D., Jantzie, L. L., & McCallion, A. S. (2022). Neuroinflammation represents a common theme amongst genetic and environmental risk factors for Alzheimer and Parkinson diseases. Journal of neuroinflammation, 19(1), 223. https://doi.org/10.1186/s12974-022-02584-x

8. Chen, Z. R., Huang, J. B., Yang, S. L., & Hong, F. F. (2022). Role of Cholinergic Signaling in Alzheimer's Disease. Molecules (Basel, Switzerland), 27(6), 1816. https://doi.org/10.3390/molecules27061816

9. Ma, C., Hong, F., & Yang, S. (2022). Amyloidosis in Alzheimer's Disease: Pathogeny, Etiology, and Related Therapeutic Directions. Molecules (Basel, Switzerland), 27(4), 1210. https://doi.org/10.3390/molecules27041210

10. Arnsten, A. F. T., Datta, D., Del Tredici, K., & Braak, H. (2021). Hypothesis: Tau pathology is an initiating factor in sporadic Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association, 17(1), 115–124. https://doi.org/10.1002/alz.12192

11. Alhazmi, H. A., & Albratty, M. (2022). An update on the novel and approved drugs for Alzheimer disease. *Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society*, *30*(12), 1755–1764. https://doi.org/10.1016/j.jsps.2022.10.004

12. Sharma, K., Pradhan, S., Duffy, L. K., Yeasmin, S., Bhattarai, N., & Schulte, M. K. (2021). Role of Receptors in Relation to Plaques and Tangles in Alzheimer's Disease Pathology. *International journal of molecular sciences*, *22*(23), 12987. https://doi.org/10.3390/ijms222312987

13. Yin, X., Qiu, Y., Zhao, C., Zhou, Z., Bao, J., & Qian, W. (2021). The Role of Amyloid-Beta and Tau in the Early Pathogenesis of Alzheimer's Disease. Medical science monitor : international medical journal of experimental and clinical research, 27, e933084. https://doi.org/10.12659/MSM.933084

14. Abraham, J. T., Maharifa, H. N. S., & Hemalatha, S. (2022). In Silico Molecular Docking Approach Against Enzymes Causing Alzheimer's Disease Using Borassus flabellifer Linn. *Applied biochemistry and biotechnology*, *194*(4), 1804–1813. https://doi.org/10.1007/s12010-021-03779-3

15. Gnanaraj, C., Sekar, M., Fuloria, S., Swain, S. S., Gan, S. H., Chidambaram, K., Rani, N. N. I. M., Balan, T., Stephenie, S., Lum, P. T., Jeyabalan, S., Begum, M. Y., Chandramohan, V., Thangavelu, L., Subramaniyan, V., & Fuloria, N. K. (2022). In Silico Molecular Docking Analysis of Karanjin against Alzheimer's and Parkinson's Diseases as a Potential Natural Lead Molecule for New Drug Design, Development and Therapy. *Molecules (Basel, Switzerland)*, *27*(9), 2834. https://doi.org/10.3390/molecules27092834

16. Sayers, E. W., Bolton, E. E., Brister, J. R., Canese, K., Chan, J., Comeau, D. C., Connor, R., Funk, K., Kelly, C., Kim, S., Madej, T., Marchler-Bauer, A., Lanczycki, C., Lathrop, S., Lu, Z., Thibaud-Nissen, F., Murphy, T., Phan, L., Skripchenko, Y., Tse, T., … Sherry, S. T. (2022). Database resources of the national center for biotechnology information. Nucleic acids research, 50(D1), D20–D26. https://doi.org/10.1093/nar/gkab1112

17. Burley, S. K., Bhikadiya, C., Bi, C., Bittrich, S., Chao, H., Chen, L., Craig, P. A., Crichlow, G. V., Dalenberg, K., Duarte, J. M., Dutta, S., Fayazi, M., Feng, Z., Flatt, J. W., Ganesan, S., Ghosh, S., Goodsell, D. S., Green, R. K., Guranovic, V., Henry, J., … Zardecki, C. (2023). RCSB Protein Data Bank (RCSB.org): delivery of experimentally-determined PDB structures alongside one million computed structure models of proteins from artificial intelligence/machine learning. Nucleic acids research, 51(D1), D488–D508. https://doi.org/10.1093/nar/gkac1077

18. Schreiner, T. G., & Popescu, B. O. (2022). Impact of Caffeine on Alzheimer's Disease Pathogenesis-Protective or Risk Factor?. Life (Basel, Switzerland), 12(3), 330. https://doi.org/10.3390/life12030330

19. Shabbir, Umair, Momna Rubab, Akanksha Tyagi, and Deog-Hwan Oh. (2021). Curcumin and Its Derivatives as Theranostic Agents in Alzheimer's Disease: The Implication of Nanotechnology. *International Journal of Molecular Sciences* 22, no. 1: 196. https://doi.org/10.3390/ijms22010196

20. Newhouse, P.A., Raman, R., Saykin, A.J., Dumas, J., Levin, E., Kellar, K. and Aisen, P.S. (2023), Long-term nicotine treatment of mild cognitive impairment (The MIND Study): Baseline characteristics and study progress. Alzheimer's Dement., 19: e064697. https://doi.org/10.1002/alz.064697

21. Tang B-C, Wang Y-T, Ren J. (2023). Basic information about memantine and its treatment of Alzheimer's disease and other clinical applications. ibrain.; 9: 340-348. doi:10.1002/ibra.12098

22. Gupta, A., Kapil, R., Dhakan, D. B., & Sharma, V. K. (2014). MP3: a software tool for the prediction of pathogenic proteins in genomic and metagenomic data. PloS one, 9(4), e93907. https://doi.org/10.1371/journal.pone.0093907

23. Binkowski, T. A., Naghibzadeh, S., & Liang, J. (2003). CASTp: Computed Atlas of Surface Topography of proteins. Nucleic acids research, 31(13), 3352–3355. https://doi.org/10.1093/nar/gkg512

24. Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C., & Ferrin, T. E. (2004). UCSF Chimera--a visualization system for exploratory research and analysis. Journal of computational chemistry, 25(13), 1605–1612. https://doi.org/10.1002/jcc.20084

25. Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of computational chemistry, 31(2), 455–461. https://doi.org/10.1002/jcc.21334

26. Dallakyan, S., & Olson, A. J. (2015). Small-molecule library screening by docking with PyRx. Methods in molecular biology (Clifton, N.J.), 1263, 243–250. https://doi.org/10.1007/978-1-4939-2269-7_19

27. Rigsby, R. E., & Parker, A. B. (2016). Using the PyMOL application to reinforce visual understanding of protein structure. Biochemistry and molecular biology education: a bimonthly publication of the International Union of Biochemistry and Molecular Biology, 44(5), 433–437. https://doi.org/10.1002/bmb.20966

28. Mokhamad Fahmi Rizki Syaban, Rislan Faiz Muhammad, Basyar Adnani, Gumilar Fardhani Ami Putra, Nabila Erina Erwan, Safira Dita Arviana, Agung Dwi Krisnayana, Dedy Budi Kurniawan.(2022). Molecular Docking Studies of Interaction Curcumin against Beta-secretase 1, Amyloid A4 Protein, Gamma-secretase and Glycogen Synthase Kinase-3β as Target Therapy for Alzheimer Disease. Research Journal of Pharmacy and Technology. 15(7):3069-4. https://doi.org/10.52711/0974-360X.2022.00513

29. Dai, R., Sun, Y., Su, R., & Gao, H. (2022). Anti-Alzheimer's disease potential of traditional chinese medicinal herbs as inhibitors of BACE1 and AChE enzymes. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 154, 113576. https://doi.org/10.1016/j.biopha.2022.113576

30. Waseem, R., Shamsi, A., Khan, T., Hassan, M. I., Kazim, S. N., Shahid, M., & Islam, A. (2022). Unraveling the Binding Mechanism of Alzheimer's Drugs with Irisin: Spectroscopic, Calorimetric, and Computational Approaches. *International journal of molecular sciences*, *23*(11), 5965. https://doi.org/10.3390/ijms23115965

31. Siddiqui AJ, Badraoui R, Jahan S, Alshahrani MM, Siddiqui MA, Khan A and Adnan M (2023) Targeting NMDA receptor in Alzheimer's disease: identifying novel inhibitors using computational approaches. *Front. Pharmacol.* 14:1208968. https://doi.org/10.3389/fphar.2023.1208968

32. Marotta, Giambattista, Filippo Basagni, Michela Rosini, and Anna Minarini. (2020). "Memantine Derivatives as Multitarget Agents in Alzheimer's Disease" Molecules 25, no. 17: 4005. https://doi.org/10.3390/molecules25174005

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