The American Journal of Applied Sciences
ISSN 2689-0992 Volume 08 - 2026

**Proceedings of Women in Academia, Research and Management for Work-life Initiatives for Sustainable Health & Empowering Safety (WARM-WISHES 2026)**

# Discovery of Potential Multi-Target Therapeutics for Alzheimer's Disease Through in Silico Drug Repurposing and Molecular Docking: Identification of Withaferin A and Sorafenib as Promising Candidates

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Received: 19 Apr 2026 | Received Revised Version: 26 Apr 2026 | Accepted: 22 May 2026 | Published: 18 June 2026

DOI: 10.37547/tajas/warm-28

## Abstract

*Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, neuronal degeneration, and memory impairment. Despite extensive research, effective disease-modifying therapies remain limited. Drug repurposing combined with computational approaches has emerged as a promising strategy for identifying potential therapeutic candidates with reduced development time and cost. The present study employed molecular docking to evaluate the interaction of ten bioactive compounds, Apigenin, Berberine, Curcumin, Huperzine A, Kaempferol, L-Theanine, Quercetin, Resveratrol, Withaferin A, and Sorafenib, with three proteins implicated in AD pathogenesis: Nicastrin, TREM2, and Cystatin C. Protein structures were generated using homology modelling through SWISS-MODEL, and docking simulations were conducted using AutoDock Vina. Binding affinities were evaluated using docking scores (kcal/mol). Among the evaluated compounds, Sorafenib and Withaferin A exhibited the strongest interactions across all targets, particularly with Cystatin C, showing binding energies of -7.7 kcal/mol and -7.6 kcal/mol respectively. Other phytochemicals such as Curcumin, Berberine, and Huperzine A demonstrated moderate binding affinities. These findings indicate that Sorafenib and Withaferin A may act as promising multi-target therapeutic candidates for Alzheimer's disease. Further experimental validation through in vitro and in vivo studies is necessary to confirm their therapeutic potential.*

Keywords: Alzheimer's disease, drug repurposing, molecular docking, phytochemicals, Nicastrin.



**Cite This Article:** Shukla, A., Awasthi, G., & Nigam, M. (2026). Discovery of Potential Multi-Target Therapeutics for Alzheimer's Disease Through in Silico Drug Repurposing and Molecular Docking: Identification of Withaferin A and Sorafenib as Promising Candidates. The American Journal of Applied Sciences, 327–344. https://doi.org/10.37547/tajas/warm-28

## 1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and represents a major global health challenge affecting millions of individuals worldwide. It is characterized by progressive cognitive decline, memory impairment, and behavioural disturbances resulting from neuronal degeneration in the brain. The pathological hallmarks of AD include extracellular amyloid-beta (Aβ) plaque deposition, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, oxidative stress, neuroinflammation, and synaptic dysfunction (Tripathi et al., 2024; Selkoe & Hardy, 2016).

Globally, Alzheimer's disease affects more than 55 million individuals, and this number is expected to increase dramatically as life expectancy rises. The disease not only causes severe impairment in cognitive functions but also imposes significant social and economic burdens on patients, families, and healthcare systems. Despite decades of research, the precise mechanisms underlying the onset and progression of Alzheimer's disease remain incompletely understood.

Current therapeutic options for AD are limited and largely symptomatic. Drugs such as donepezil, rivastigmine, galantamine, and memantine are widely used to improve cognitive function by modulating cholinergic neurotransmission or glutamatergic signaling. However, these treatments do not prevent neuronal degeneration or halt disease progression (Cummings et al., 2019). The development of disease-modifying therapies has proven challenging due to the complex and multifactorial nature of AD pathology.

Traditional drug discovery approaches are costly and time-consuming, often requiring more than a decade of research and billions of dollars in investment. Furthermore, a large proportion of candidate drugs fail during clinical trials due to inadequate efficacy or unexpected toxicity. These challenges highlight the need for alternative strategies that can accelerate the identification of effective therapeutic candidates (Ashburn & Thor, 2004).

Drug repurposing has emerged as a promising strategy for overcoming these limitations and continues to gain attention as an efficient approach for identifying clinically viable therapeutic candidates for diseases. Drug repurposing involves identifying new therapeutic uses for existing drugs or bioactive compounds with known pharmacological profiles and established safety data. This approach significantly reduces the time, cost, and risk associated with traditional drug discovery processes (Phemphunananchai et al., 2026).

Recent advances in computational biology have further enhanced drug repurposing efforts. In silico methods such as molecular docking, virtual screening, and molecular dynamics simulations allow researchers to evaluate potential drug-target interactions rapidly and efficiently. Molecular docking, in particular, is widely used to predict the binding orientation and affinity of small molecules within the active sites of target proteins (Lionta et al., 2014).

Several proteins are implicated in the pathogenesis of Alzheimer's disease. Recent advances in precision medicine have further emphasized the importance of identifying and targeting multiple molecular pathways involved in Alzheimer's disease progression, supporting the development of multi-target therapeutic strategies (De Strooper & Karran, 2026). Among these, Nicastrin, TREM2, and Cystatin C have been identified as important molecular targets involved in amyloid processing, immune regulation, and neuroprotection. Nicastrin is an essential component of the gamma-

secretase complex responsible for cleaving amyloid precursor protein (APP) into amyloid-beta peptides (De Strooper & Karran, 2024). TREM2 is a receptor expressed on microglial cells that regulates immune responses and phagocytosis of amyloid plaques (Guerreiro et al., 2013). Cystatin C is a cysteine protease inhibitor that has been reported to prevent amyloid-beta aggregation and provide neuroprotective effects (Grant, 2024).

Natural phytochemicals have attracted increasing attention in neurodegenerative disease research due to their antioxidant, anti-inflammatory, and neuroprotective properties. Compounds such as curcumin, quercetin, and resveratrol have demonstrated promising effects in experimental models of Alzheimer's disease by reducing oxidative stress and amyloid toxicity (Wang et al., 2022; Poortalebi et al., 2024).

In addition to natural compounds, repurposing FDA-approved drugs with multi-target pharmacological effects may provide novel therapeutic opportunities. Therefore, the present study aimed to perform a computational drug repurposing analysis using molecular docking to evaluate the interaction of selected phytochemicals and an FDA-approved drug with three key proteins involved in Alzheimer's disease pathology: Nicastrin, TREM2, and Cystatin C.

## 2. Materials and Methods

### *2.1 Selection of Target Proteins*

Three proteins associated with Alzheimer's disease pathogenesis were selected as molecular targets:

- Nicastrin (NCSTN): Component of the gamma-secretase complex involved in amyloid-beta generation
- TREM2: Receptor regulating microglial activation and neuroinflammation
- Cystatin C (CST3): Cysteine protease inhibitor involved in amyloid aggregation regulation

The gene sequences corresponding to these proteins were retrieved from the NCBI GenBank database, a comprehensive repository of publicly available nucleotide and protein sequences (Sayers et al., 2023).

### *2.2 Protein Structure Modeling*

The nucleotide sequences of the selected genes were translated into protein sequences using the ExPASy Translate Tool, a widely used bioinformatics resource for converting nucleotide sequences into amino acid sequences.

As experimentally determined crystal structures were not available for all selected proteins, three-dimensional models were generated using SWISS-MODEL, an automated homology modelling server that predicts protein structures based on sequence similarity with known template structures (Daina & Zoete, 2019).

The quality of the predicted models was assessed using Global Model Quality Estimation (GMQE) and QMEAN scores, which provide estimates of structural reliability before further computational analysis.

### *2.3 Ligand Selection*

Ten ligands were selected based on literature evidence demonstrating neuroprotective, antioxidant, or anti-inflammatory properties. These ligands included both natural phytochemicals and an FDA-approved drug:

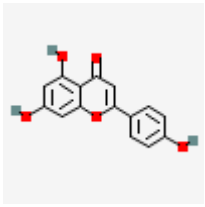
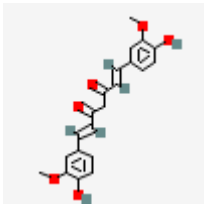
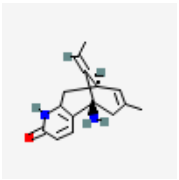
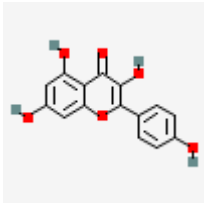
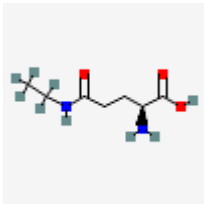
- Apigenin
- Berberine
- Curcumin
- Huperzine-A
- Kaempferol
- L-Theanine
- Quercetin
- Resveratrol
- Withaferin-A
- Sorafenib

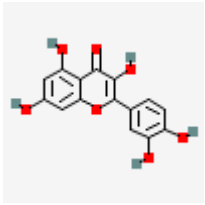
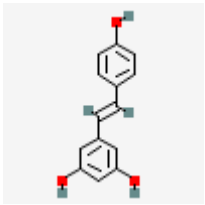
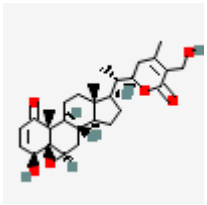
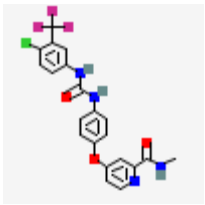
### *2.4 Ligand Structure Retrieval*

Three-dimensional structures of the selected ligands were retrieved from the PubChem database in SDF format. PubChem is a publicly accessible database that provides chemical structures, biological activities, and physicochemical properties of small molecules (Kim et al., 2025).

The downloaded structures were subsequently used in docking simulations without additional structural optimization or energy minimization (Table 1).

**Table 1.** Chemical structures of the selected phytochemical and FDA-approved ligands used in molecular docking studies against Alzheimer's disease-associated target proteins

| Ligand Name | Image |
|---|---|
| **Apigenin** |  |
| **Curcumin** |  |
| **Huperzine A** |  |
| **Kaempferol** |  |
| **L-Theanine** |  |

| | |
|---|---|
| **Quercetin** |  |
| **Resveratrol** |  |
| **Withaferin A** |  |
| **Sorafenib** |  |

### *2.5 Molecular Docking*

Molecular docking simulations were performed using AutoDock Vina, a widely used docking program that predicts ligand-protein interactions and estimates binding affinity using scoring functions (Valdés-Tresanco et al., 2020).

Protein and ligand structures were imported into the docking environment, and grid boxes were defined around predicted binding sites. Multiple docking poses were generated for each ligand-protein combination. The pose with the lowest binding energy value (kcal/mol) was selected as the best binding conformation.

## 3. Biological Significance of Selected Proteins

### *3.1 Nicastrin*

Nicastrin is a transmembrane glycoprotein that forms a critical component of the gamma-secretase complex, which cleaves amyloid precursor protein (APP) to produce amyloid-beta peptides. Accumulation of amyloid-beta peptides leads to plaque formation in the brain, a key pathological feature of Alzheimer's disease (De Strooper & Karran, 2024). The three-dimensional structure of Nicastrin generated through homology modelling is presented in Figure 1 and was used for subsequent molecular docking analyses.

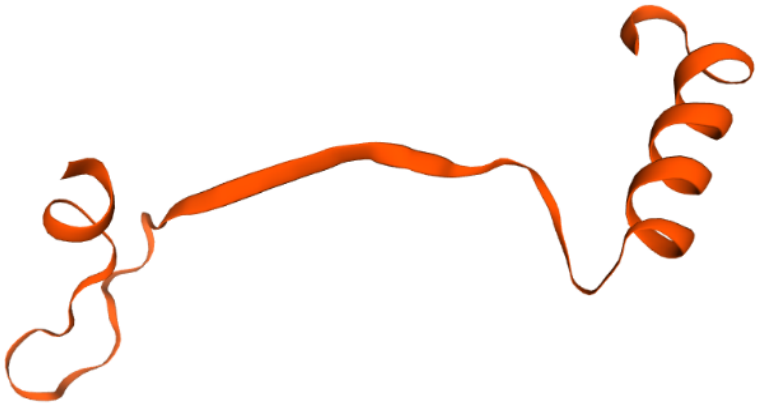


**Figure 1. Nicastrin**

### *3.2 TREM2*

Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) is predominantly expressed on microglial cells in the central nervous system. It regulates microglial activation, phagocytosis of amyloid plaques, and modulates immune responses within the brain. Mutations in the TREM2 gene have been strongly associated with increased risk of Alzheimer's disease, and recent studies further emphasize the central role of TREM2-mediated microglial signalling in disease progression and neuroinflammation (Guerreiro et al., 2013; Abdulkhaliq et al., 2026). The predicted tertiary structure of TREM2 is shown in Figure 2and served as a target for ligand-binding studies.

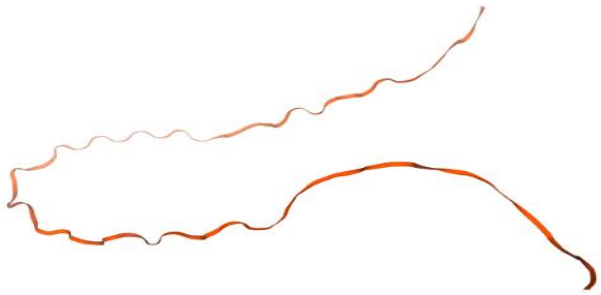


**Figure 2. TREM 2**

### *3.3 Cystatin C*

Cystatin C is a cysteine protease inhibitor found in various tissues and biological fluids. It regulates the activity of lysosomal cathepsins and has been reported to bind amyloid-beta peptides, preventing their aggregation and promoting neuronal protection (Grant, 2024) (Table 2). Figure 3 illustrates the modelled structure of Cystatin C used during docking simulations

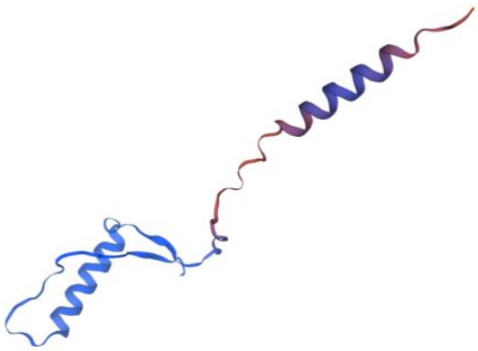


**Figure 3. Cystatin C**

**Table 2.** Selected Alzheimer's disease-associated proteins and their biological functions, along with corresponding PDB identifiers used for molecular docking analysis

| Protein Name | Function in AD | PDB ID |
|---|---|---|
| Nicastrin | Component of the gamma-secretase complex; essential for amyloid-beta generation | 8KCO.1.A |
| TREM 2 | Regulates microglial activation and inflammatory response in AD brain | A0A2K5PSP6.1.A |
| Cystatin C | Involved in neuroprotection; inhibits cysteine proteases that affect amyloid processing | O19093.1.A |

## 4. Biological Relevance of Selected Ligands

Natural compounds such as curcumin, quercetin, and resveratrol possess strong antioxidant properties and have been investigated for their ability to reduce oxidative stress and amyloid toxicity in neuronal cells (Grant, 2024).

- **Huperzine A** acts as a reversible acetylcholinesterase inhibitor and has been used clinically for treating cognitive impairment associated with Alzheimer's disease (Friedli & Inestrosa, 2021).
- **Berberine** has demonstrated neuroprotective effects by reducing amyloid-beta production and tau phosphorylation (Cheng et al., 2022).
- **Withaferin A**, derived from *Withania somnifera*, has shown anti-inflammatory and neuroprotective effects in neurodegenerative disease models (Das et al., 2021).
- **Sorafenib**, an FDA-approved multi-kinase inhibitor used in cancer therapy, has recently been investigated for potential neuroprotective effects due to its ability to regulate signaling pathways involved in inflammation and oxidative stress (Zhou et al., 2021) (Table 3).

**Table 3.** Selected phytochemical and FDA-approved ligands evaluated for their potential therapeutic effects against Alzheimer's disease, including their source, class, and reported biological activities

| Ligand Name | Type | Source/Class | Known/Proposed Activity |
|---|---|---|---|
| Apigenin | Phytochemical | Flavonoid (Parsley, Chamomile) | Antioxidant, anti-inflammatory |
| Berberine | Phytochemical | Alkaloid (Berberis species) | Neuroprotective, anti-amyloid |
| Curcumin | Phytochemical | Curcuminoid (Turmeric) | Anti-amyloid, antioxidant |
| Huperzine A | Phytochemical | Alkaloid (*Huperzia serrata*) | Acetylcholinesterase inhibitor |
| Kaempferol | Phytochemical | Flavonoid (Fruits, Vegetables) | Anti-inflammatory, neuroprotective |
| L-Theanine | Phytochemical | Amino acid (Green tea) | Relaxation, cognitive enhancement |
| Quercetin | Phytochemical | Flavonoid (Apples, Onions) | Antioxidant, anti-amyloid |
| Resveratrol | Phytochemical | Stilbenoid (Red grapes) | Neuroprotective, anti-inflammatory |
| Withaferin | Phytochemical | Steroidal lactone (Ashwagandha) | Anti-inflammatory, anti-tau |
| Sorafenib | FDA-Approved | Multi-kinase inhibitor (Synthetic) | Anti-cancer drug, potential neuroprotection |

## 5. Results

Docking simulations were conducted to evaluate the binding affinity of the selected ligands against the three target proteins. Binding energy values obtained from AutoDock Vina were used to estimate the strength of ligand-protein interactions (Table 4).

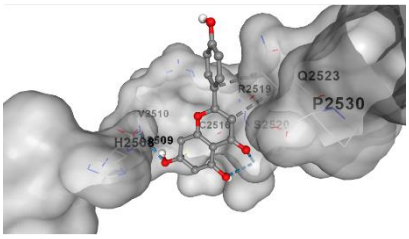
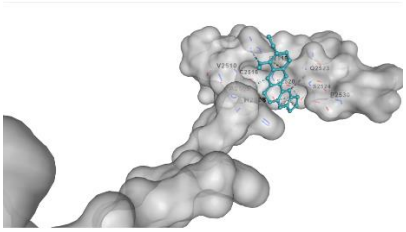
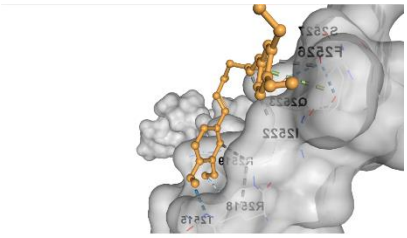
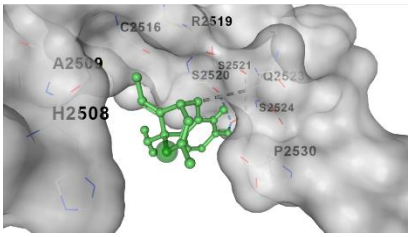
**Table 4.** Molecular docking binding affinities (kcal/mol) of selected ligands against Nicastrin, TREM2, and Cystatin C, indicating their predicted interactions and binding strengths with Alzheimer's disease-related target proteins

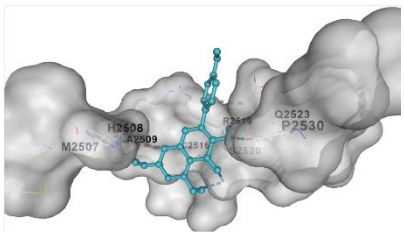
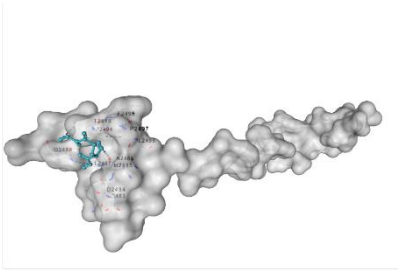
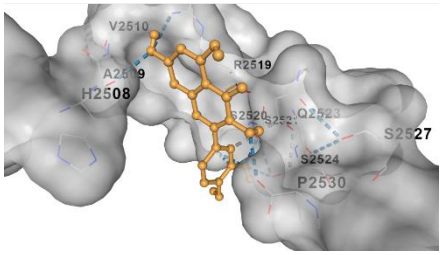
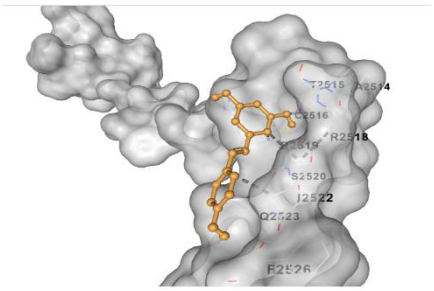
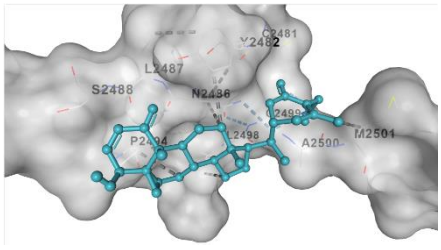
| Ligand | Nicastrin | TREM2 | Cystatin C |
|---|---|---|---|
| Apigenin | -5.0 | -4.4 | -5.9 |
| Berberine | -5.0 | -4.6 | -6.4 |
| Curcumin | -5.1 | -4.5 | -6.6 |
| Huperzine A | -4.9 | -4.7 | -6.2 |
| Kaempferol | -4.9 | -4.3 | -6.0 |
| L-Theanine | -3.7 | -3.1 | -4.3 |
| Quercetin | -4.9 | -4.5 | -6.0 |
| Resveratrol | -4.4 | -4.1 | -5.6 |
| Withaferin A | -6.2 | -5.1 | -7.6 |

| | | | |
|---|---|---|---|
| Sorafenib | -6.2 | -5.8 | -7.7 |

Among the evaluated compounds, Sorafenib and Withaferin A demonstrated the strongest binding affinities, particularly with Cystatin C (Table 5).

**Table 5.** Molecular docking interaction visualizations of selected ligands with Alzheimer's disease-associated target proteins (Nicastrin, TREM2, and Cystatin C), illustrating the predicted binding poses and ligand-protein interactions

| Ligand-Protein Combination | Image |
|---|---|
| Apigenin - Nicastrin |   |
| Berberine - Nicastrin |  |
| Curcumin - Nicastrin |  |
| Huperzine A - Nicastrin |   |

| | |
|---|---|
| Kaempferol - Nicastrin |  |
| L Theanine - Nicastrin |  |
| Quercetin - Nicastrin |  |
| Resveratrol - Nicastrin |  |
| Withaferin A - Nicastrin |  |

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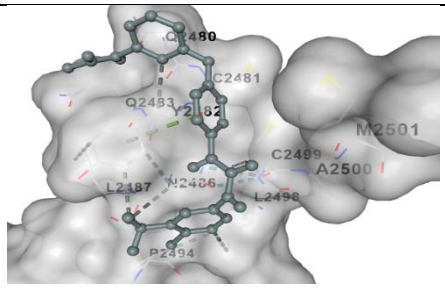
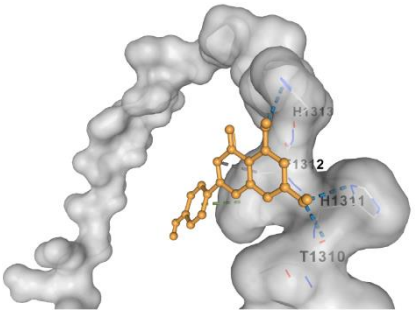
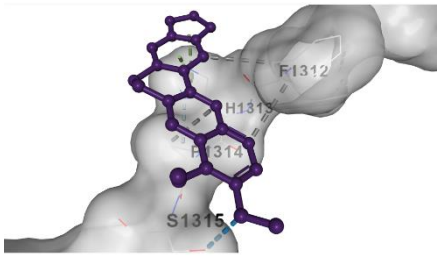
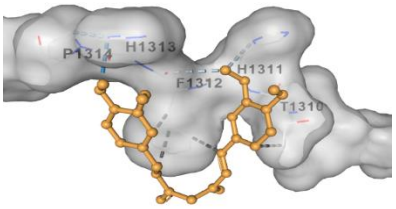
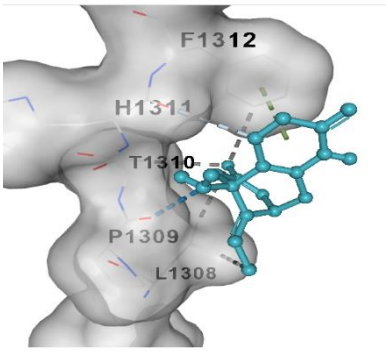
|---|---|
| Sorafenib - Nicastrin |   |
| Apigenin - TREM 2 |   |
| Berberine - TREM 2 |   |
| Curcumin - TREM 2 |   |
| Huperzine A - TREM 2 |   |

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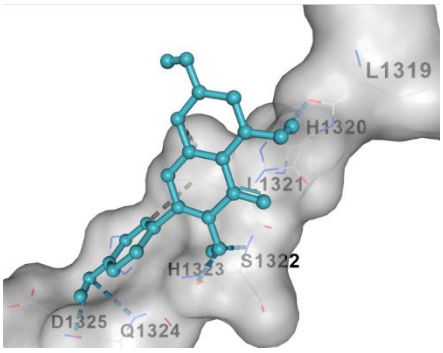
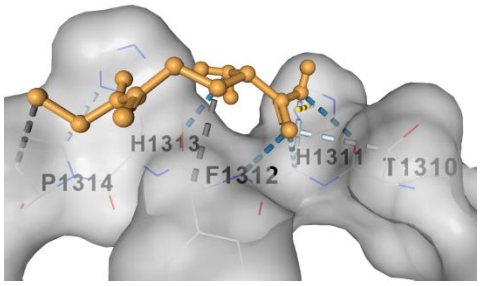
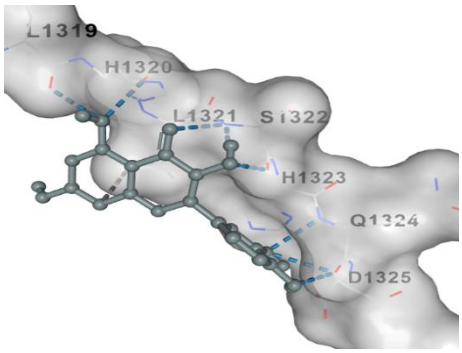
| Kaempferol - TREM 2 |  |
| L Theanine - TREM 2 |  |
| Quercetin - TREM 2 |  |

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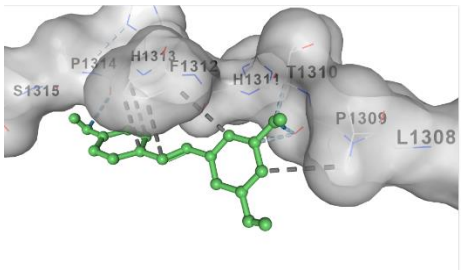
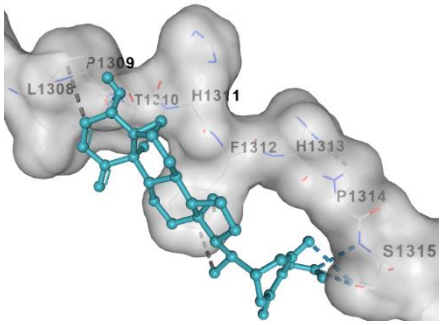
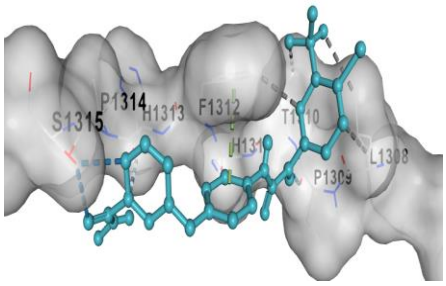
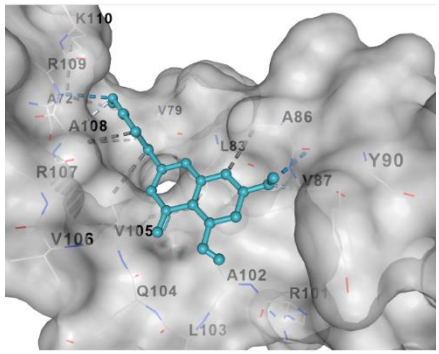
| Resveratrol - TREM 2 |  |
| Withaferin A - TREM 2 |  |
| Sorafenib - TREM 2 |  |
| Apigenin - Cystatin C |  |

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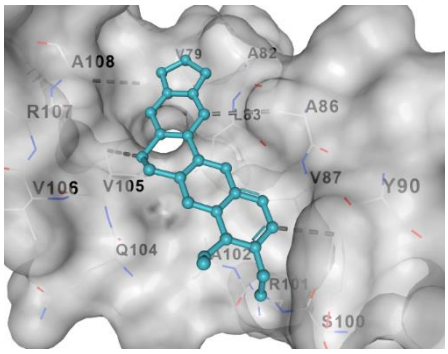
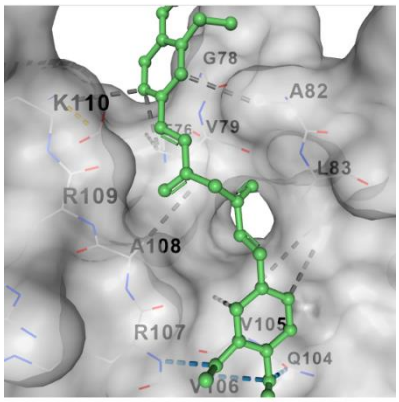
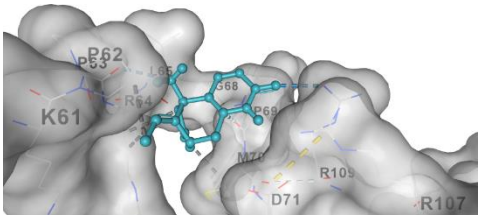
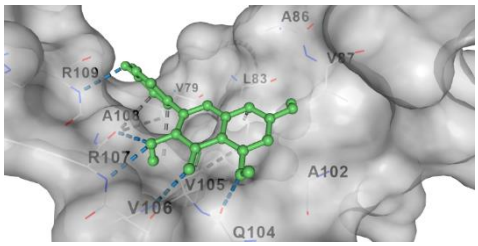
| Berberine - Cystatin C |  |
| Curcumin - Cystatin C |  |
| Huperzine A - Cystatin C |  |
| Kaempferol - Cystatin C |  |

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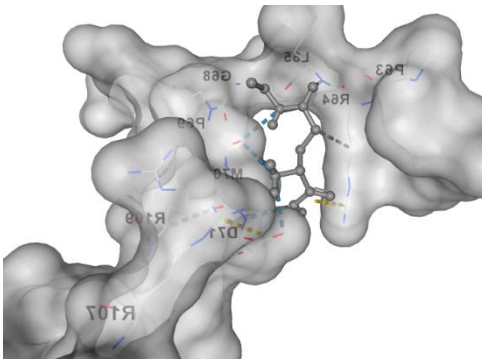
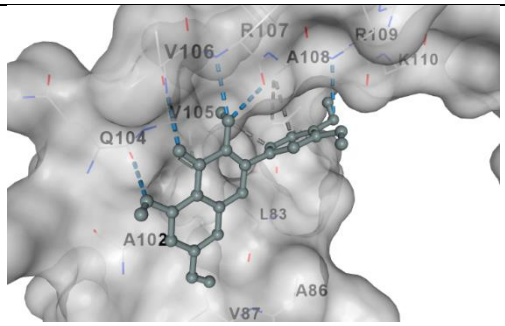
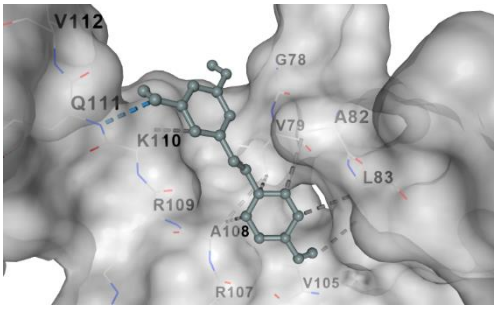
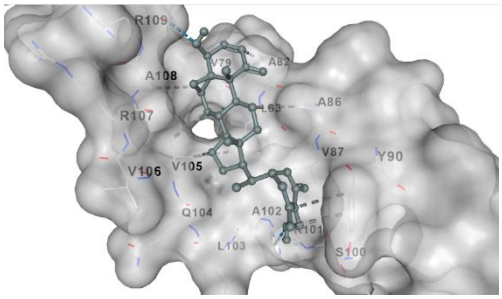
| L Theanine - Cystatin C |  |
| Quercetin - Cystatin C |   |
| Resveratrol - Cystatin C |   |
| Withaferin A - Cystatin C |   |

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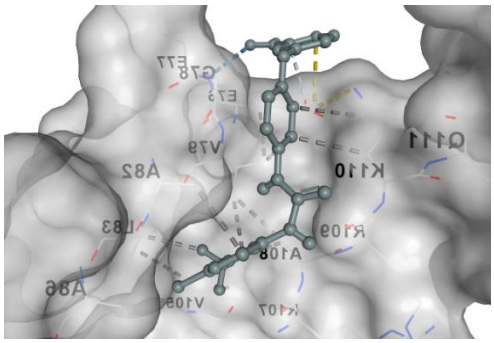
| Sorafenib - Cystatin C |  |

## 6. Discussion

The docking results revealed considerable variation in binding affinity among the evaluated ligands. Sorafenib exhibited the strongest overall binding interactions across all three proteins, with a maximum binding affinity of -7.7 kcal/mol against Cystatin C. This suggests that Sorafenib may influence pathways associated with amyloid aggregation and neuronal protection. Recent computational drug-repurposing studies have similarly highlighted the value of multi-target screening approaches for identifying promising Alzheimer's disease therapeutics from existing drug libraries (Phemphunananchai et al., 2026)

Similarly, Withaferin A demonstrated strong interactions with all targets, particularly Cystatin C (-7.6 kcal/mol) and Nicastrin (-6.2 kcal/mol). These findings are consistent with

previous studies reporting neuroprotective and anti-inflammatory effects of Withaferin A.

Curcumin, Berberine, and Huperzine A also displayed moderate binding affinities. These compounds have previously been reported to reduce amyloid accumulation, oxidative stress, and neuroinflammation in neurodegenerative disease models.

Cystatin C showed the strongest overall binding interactions among the evaluated targets, suggesting that its structural characteristics may provide favorable binding pockets for multiple ligands. Since Cystatin C is known to inhibit amyloid aggregation, compounds interacting strongly with this protein may enhance its neuroprotective role.

The multi-target interaction profile of Sorafenib and Withaferin A indicates their potential as polypharmacological agents, capable of modulating multiple pathways involved in Alzheimer's disease.

## 7. Conclusion

The present study highlights the potential of computational drug repurposing for identifying therapeutic candidates against Alzheimer's disease. Molecular docking analysis revealed that Sorafenib and Withaferin A exhibit strong binding affinity toward key AD-related proteins including Nicastrin, TREM2, and Cystatin C.

These compounds may therefore serve as promising multi-target modulators in Alzheimer's disease. However, molecular docking provides only predictive insights into ligand-protein interactions. Experimental validation through in vitro biochemical assays and in vivo models is necessary to confirm the therapeutic efficacy and safety of these compounds.

Furthermore, the study highlights the importance of targeting multiple proteins involved in Alzheimer's disease rather than focusing on a single pathway. Since AD is a multifactorial neurodegenerative disorder involving amyloid-beta accumulation, neuroinflammation, oxidative stress, and neuronal damage, compounds capable of interacting with several molecular targets may provide improved therapeutic outcomes. The strong binding interactions observed for Sorafenib and Withaferin A against Nicastrin, TREM2, and Cystatin C suggest their potential role in modulating amyloid processing, immune regulation, and neuroprotective mechanisms simultaneously.

The findings also emphasize the usefulness of bioinformatics and molecular docking approaches in accelerating early-stage drug discovery and repurposing studies. Computational screening enables the rapid identification of promising therapeutic candidates while reducing the time, cost, and resource requirements associated with conventional experimental methods. In addition, several phytochemicals evaluated in this study, including Curcumin, Berberine, Quercetin, and Huperzine A, demonstrated moderate but significant interactions, supporting previous evidence regarding their neuroprotective and antioxidant properties.

Overall, the present work provides a theoretical foundation for further investigation of these compounds as potential therapeutic agents against Alzheimer's disease. Recent advances in Alzheimer's disease drug development further support the need for multi-target therapeutic strategies capable of addressing the complex pathology of the disease (Cummings et al., 2026). Future studies involving molecular dynamics simulations, ADMET analysis, cell-line experiments, and animal models will be essential to validate the stability, pharmacokinetics, and biological activity of these ligand-protein interactions before clinical application can be considered.

**Declaration:** The authors hereby declare that the manuscript submitted for consideration is an original work and has not been published or submitted elsewhere for publication. The authors take full responsibility for the integrity, accuracy, and ethical compliance of the work presented in the manuscript, including all revisions made in response to reviewer comments.

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**Conflict of Interest and Ethical Compliance:**

All authors confirm that:

i. Any potential conflicts of interest, whether financial or non-financial, have been fully disclosed. - Not Applicable

ii. All sources of funding and financial support received for the conduct of the study have been appropriately acknowledged, including any updates made during revision. - Not Applicable

iii. Necessary ethical approvals have been obtained from the relevant institutional or regulatory bodies for studies involving human participants, animals, or sensitive data, wherever applicable, and are clearly stated in the manuscript. - Not Applicable

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