Unveiling the Multi-Target Therapeutic Potential of Resveratrol Against Alzheimer's Disease: An Integrative Network Pharmacology and Molecular Simulation Approach

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Abstract: This study investigates the multi-target therapeutic potential of Resveratrol against Alzheimer's disease (AD) through an integrative network pharmacology and computational framework. Predicted targets of Resveratrol were identified using multiple databases and cross-referenced with Alzheimer's-associated genes, yielding 11 overlapping targets implicated in apoptosis regulation, mitochondrial function, and neuronal survival. Core proteins, including TP53, BCL2, BAX, and BDNF, formed a tightly connected protein–protein interaction network enriched in apoptotic and neuroinflammatory pathways. Molecular docking revealed strong binding affinities of Resveratrol with key targets, such as 1B8M, BCL2, and TP53, which were further validated by 100-nanosecond molecular dynamics simulations. Key structural metrics, such as RMSD, RMSF, Rg, and SASA, indicated stable protein–ligand complexes with significant hydrogen bonding, particularly in the BCL2 and TP53 systems. Collectively, the findings demonstrate Resveratrol's potential as a multitarget neuroprotective agent in Alzheimer's disease, offering a mechanistic rationale for its repositioning in neurodegenerative therapeutics.

Keywords: resveratrol, Alzheimer's disease, molecular docking, neuroprotection

1. Introduction

Alzheimer's disease (AD) is the most prevalent cause of dementia and a growing global health challenge. It is a complex neurodegenerative disorder marked by progressive deterioration in memory, cognition, and behavior. The neuropathological hallmarks of AD include extracellular amyloid-beta (Aβ) plaque accumulation, intracellular neurofibrillary tangles formed by hyperphosphorylated tau protein, chronic neuroinflammation, synaptic dysfunction, and widespread neuronal death [1]. These multifaceted features contribute to the irreversible loss of neuronal networks and cognitive faculties. Despite decades of research, therapeutic interventions for AD remain

largely symptomatic, with no current treatment effectively halting or reversing disease progression. Given the multifactorial nature of AD, there is a growing consensus that therapeutic agents targeting single pathological features are unlikely to be effective [2]. Therefore, research interest has shifted toward identifying multi-target agents capable of modulating several molecular pathways simultaneously. Resveratrol, a naturally occurring stilbene polyphenol abundant in grapes, peanuts, and various berries, has garnered considerable attention in this context. Its broad spectrum of biological activities, including antioxidative, anti-inflammatory, neuroprotective, and anti-apoptotic effects, renders it a promising candidate for addressing the complex pathogenesis of AD [3]. In this study, we employed an integrative computational pipeline involving ADME/toxicity prediction, multi-database target identification, protein–protein interaction (PPI) network analysis, functional enrichment, molecular docking, and molecular dynamics (MD) simulations. This integrative study reveals the mechanistic underpinnings of Resveratrol's neuroprotective effects and supports its repositioning as a promising multitarget therapeutic candidate for AD.

2. Methodology

SwissTargetPrediction was employed to identify possible protein targets based on Resveratrol's molecular structure. A network pharmacology approach was utilized to screen therapeutic targets, with Resveratrol's 2D structure submitted to multiple target prediction platforms. Functional annotation of these targets was conducted using the PANTHER system, followed by the construction of a protein–protein interaction (PPI) network via the STRING database. Pathway enrichment analysis was performed using the R package clusterProfiler, while molecular docking simulations were carried out with AutoDock Vina to assess binding affinities with selected target proteins. Finally, molecular dynamics simulations using GROMACS evaluated the stability of the protein-ligand complexes.

3. Results and Discussion

3.1 Screening of Targets of Resveratrol Against Alzheimer's Disease

From a compilation of 978 Alzheimer's-related genes sourced from various databases, 11 overlapping targets were identified by intersecting these with 100 predicted targets of Resveratrol, as shown in the Venn diagram (Figure 1). The functional significance of these genes was classified using the PANTHER database, revealing diverse protein classes, with lyases (24%) and cytochrome P450 enzymes (14%) being predominant (Figure 2). Target prediction across multiple platforms yielded over 100 potential protein interactors for Resveratrol, 26 of which overlapped with genes implicated in Alzheimer's disease. Among these, core targets such as TP53, BCL2, BAX, BDNF, and HSPA4

emerged as key regulators based on their topological centrality in the protein–protein interaction (PPI) network [4].

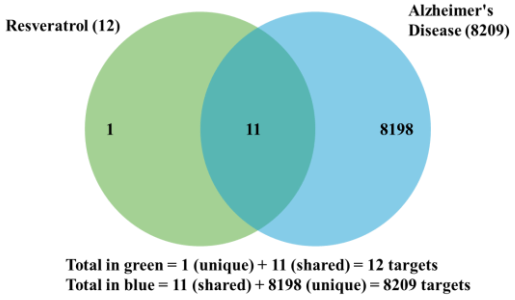

Figure 1: Venn diagram showing overlap between predicted resveratrol targets and Alzheimer's disease-related genes from DisGeNET.

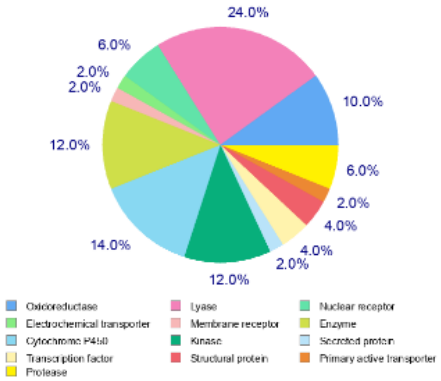

Figure 2: Pie chart of the top 50 targets of Resveratrol by SwissTargetPrediction

3.2 Protein-Protein Interaction (PPI) Network Analysis and Gene Ontology (GO): Using STRING:

nalysis, a densely connected PPI network of Resveratrol-associated targets was constructed (Figure 3). Key proteins such as BCL2, BAX, and TP53 were identified, demonstrating significant interactions and highlighting Resveratrol's multi-target capability in modulating apoptotic signalling pathways. This interconnected network suggests that Resveratrol can modulate both pro- and anti-apoptotic signals, which are crucial for neuronal survival in Alzheimer's disease. GO enrichment analysis revealed significant associations with processes regulating apoptosis, such as the positive regulation of apoptotic processes and cytochrome c release from mitochondria (Figure 4). The analysis highlighted mitochondrial-related components, reinforcing Resveratrol's role in modulating mitochondrial-mediated apoptosis. In the molecular function category, targets were associated with protein binding and regulatory activities, indicating Resveratrol's potential to influence neuroprotective pathways [5].

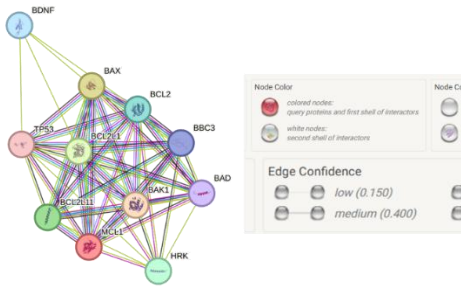

Figure 3: PPI network from STRING database

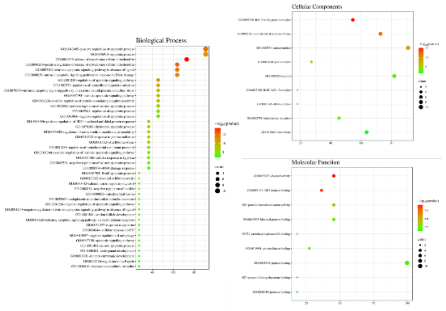

Figure 4: Top pathway GO enrichment analysis of (A) Biological Process BP, (B) Cell Components (C) Molecular Function MF

3.3 Molecular Docking Analysis

Molecular docking studies indicated that Resveratrol exhibits strong binding affinities across various target proteins, with the most favorable interactions observed in the 1B8M complex (−9.5 kcal/mol) (Figure 5). The analysis highlighted stabilizing interactions, including hydrogen bonds and π-alkyl contacts, suggesting solid binding potential for therapeutic applications. These results support Resveratrol's ability to engage diverse binding pockets through multiple non-covalent interactions, enhancing its polypharmacological profile [6].

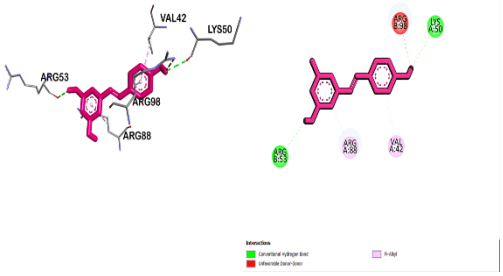

Figure 5. 3D-2D interaction of 1B8M-Resveratrol_CID_445154

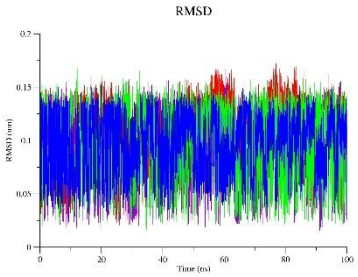

Figure 6: RMSD of BAX1-Resveratrol_CID_445154 (Violet), BCL2-Resveratrol_CID_445154 (Red), BDNF-Resveratrol_CID_445154 (Green), TP53-Resveratrol_CID_445154 (Blue)

3.4 Molecular Dynamics Simulations

The stability of protein-ligand complexes was assessed through molecular dynamics simulations. The Root Mean Square Deviation (RMSD) analysis indicated overall structural stability, with minor fluctuations (Figure 6).²), reflecting more solvent-shielded and stable conformations, which could correlate with improved binding stability and reduced desolvation energy costs [7].

4. Conclusions

Taken together, these findings position BCL2 and TP53 as top candidates for therapeutic modulation by Resveratrol in the context of AD. The integrative computational approach employed here not only elucidates the mechanistic basis of Resveratrol's neuroprotective effects but also supports its repositioning as a multi-target candidate for future therapeutic development in Alzheimer's disease.

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