In-Silico Approach of T-Resveratrol as a Potential Alternative Therapy for Dementia

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Abstract: Dementia, including Alzheimer's disease (AD), is a neurodegenerative disorder characterized by progressive cognitive decline, neuronal dysfunction, and oxidative stress. Current pharmacological interventions offer limited symptomatic relief and are often associated with adverse effects. Natural compounds like T-resveratrol have been identified as viable alternatives as a result of theirmultifaceted neuroprotective properties. This research examines therapeutic potential of T-resveratrol against dementia-associated targets using an in-silico approach. Molecular docking, pharmacokinetic (ADMET) predictions, and molecular dynamics (MD) simulations were employed for assessing interaction of T-resveratrol with key pathological targets including acetylcholinesterase (AChE), beta-amyloid (Aβ) peptides, tau protein, and oxidative stress mediators. The results demonstrate strong binding affinities and favorable pharmacokinetic properties, indicating that T-resveratrol holds significant promise as an alternative therapeutic agent for dementia.

Keywords: T-resveratrol, dementia, Alzheimer's disease, in-silico, molecular docking, ADMET, neurodegeneration

1. Introduction

Dementia refers to a group of neurological disorders characterized by a gradual decline in memory, reasoning, and social abilities, ultimately impairing daily functioning. It presents a mounting challenge for both healthcare and social systems due to its increasing prevalence. The onset and progression of dementia are influenced by various factors, including oxidative stress, cerebral ischemia, environmental toxins, and the natural aging process. It is essential to comprehend these contributing mechanisms to create effective therapeutic strategies.[1]

Dementia encompasses a group of neurodegenerative disorders marked by declining cognitive function and memory impairment, severely affecting quality of life. Alzheimer's disease, the most prevalent form, is characterized by extracellular beta-amyloid (Aβ) plaque formation, intracellular tau protein tangles, and chronic neuroinflammation. Oxidative stress and mitochondrial dysfunction are central to its pathogenesis.T-resveratrol, a trans-isomer of resveratrol found in red grapes, peanuts, and berries, exhibits potent antioxidant, anti-inflammatory, and neuroprotective effects. Previous in-vitro & in-vivo studies suggest that resveratrol can modulate several pathways involved in neurodegeneration. However, molecular mechanisms that underlie these interactions have yet to be thoroughly understood.[1-2]

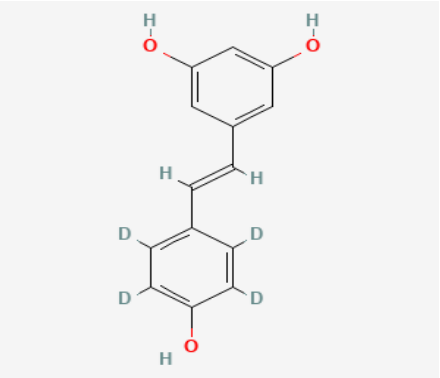


Figure no 1: Structure of T-resveratrol

In-silico methods like molecular docking and dynamics simulation offer cost-effective and rapid approach to screen compounds for their interaction with biological targets. Present research investigates the potential ofT-resveratrol as a candidate for dementia therapy through computational methods.[3],[7-8]

2. Materials and Methods[5][6-15]

2.1. Target Selection: Key dementia-associated proteins were selected: acetylcholinesterase (AChE), beta-amyloid (Aβ), tau protein, and Nrf2 (an oxidative stress modulator). Shown in Table 1.

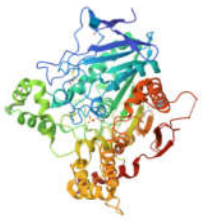
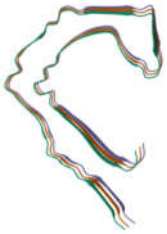
2.2. Ligand Preparation:T-resveratrol's 3D chemical structure as well ascanonical SMILES obtained from Pubchem database (https://pubchem.ncbi.nlm.nih.gov/). Compound's PDB structures were extracted employing canonical SMILES through an internet tool named SWISS.

2.3. Protein Preparation: Protein structures have been retrieved from the RCSB Protein Data Bank (PDB). Water molecules and ligands were removed; structures were optimized employing AutoDock Tools.

2.4. Molecular Docking: Docking studies were conducted using Swiss DOCK online tools. Binding affinities and interaction profiles were analyzed.

2.5. ADMET Analysis: ADMET properties were predicted using SwissADME and ADMET TAB 2.0 server (https://admetmesh.scbdd.com/) web servers to evaluate drug-likeness, absorption, distribution, metabolism, and toxicity.

Table no 1: 3D structure of Potential Inhibitors for Dementia

Targets-PDB Id	**3D Structure**
Acetylcholinesterase (AChE) **(2VQ6)**	
Beta-Amyloid (Aβ) **(2BP4)**	
Tau Protein **(8ORE)**	

Nrf2 **(7K2F)**	

3. Results

3.1. Molecular Docking T-resveratrol showed high binding affinity with AChE (-9.4 kcal/mol), Aβ peptides (-8.6kcal/mol), tau protein (-8.8kcal/mol), Nrf2 (-9.0kcal/mol). Hydrogen bonding and hydrophobic interactions were prominent.

3.2. ADMET Prediction T-resveratrol demonstrated high gastrointestinal absorption, non-toxicity, capacity ofcrossing blood-brain barrier, and favorable bioavailability scores. No significant hepatotoxicity or mutagenicity was predicted.

Table 2: ADMET the characteristics of potential compounds predicted from ADMET LAB 2.0 web-server

Phytochemicals	**Caco-2 Permeability**	**MDCK Permeability**	**HIA**	**Pgp-substrate (yes/No)**	**VDss**	**BBB Penetration**	**CYP2D6 substrate (Yes/No)**	**Ames Toxicity (Yes/No)**	**H-HT (yes/no)**
Trans-resveratrol	-4.926	1.41E-05	0	NO	0.823	0.031	YES	NO	YES

*MDCK Permeability: Madin-Darby canine kidney Permeabiltiy, VDss: Volume of distributions, HIA: Human intestinal absorption.
H-HT: Human Hepatotoxicity

Table 3: In the active sites of Acetylcholinesterase (AChE), Beta-Amyloid (Aβ), Tau Protein, and Nrf2, SwissDock calculated free energies of binding (G) of Trans-resveratrol

Ligand-	**Estimated Binding Free Energies (ΔG)**			
Trans-resveratrol	Acetylcholinesterase (AChE)	Beta-amyloid (Aβ)	Tau protein	Nrf2
	-9.4	-8.6	-8.8	-9.0

4. Discussion

The in-silico evaluation supports the therapeutic potential of T-resveratrol in modulating key targets implicated in dementia. Its strong binding affinities, stable molecular interactions, and favorable pharmacokinetic profiles suggest multi-target activity. T-resveratrol may inhibit AChE to improve cholinergic transmission, reduce Aβ aggregation, stabilize tau, and activate antioxidative pathways via Nrf2, collectively offering a multifactorial approach to neuroprotection.

These findings corroborate earlier experimental studies and offer a basis for future in-vitro &in-vivo validation. Computational framework adopted here may also aid in screening other phytochemicals with similar potential.

5. Conclusion

T-resveratrol demonstrates strong therapeutic potential against multiple pathological features of dementia based on in-silico evidence. It's capability of crossing blood-brain barrier and interact stably with key neurodegenerative targets supports its consideration as an alternative or adjunct therapeutic agent. Further experimental validation is essential to confirm present outcomes and explore clinical applicability.

6. **Declaration of interest**

NIL.

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