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Molecular Docking of Resveratrol Against Potential Molecular Targets in Alzheimer's Disease

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Abstract. Alzheimer's disease is a neurological anomaly characterized by the production of neurotoxic proteins which interact adversely with neurons, leading to degeneration. The literature shows that acetylcholinesterase, butyryl cholinesterase, amyloid precursor protein, beta-secretase, presenilin-I, glycogen synthase-kinase, muscarinic-acetylcholine receptor and gamma-secretase are fundamental molecular drug targets implicated in neurodegeneration. The role of a novel phytochemical, resveratrol is widely explored as a cure for AD. However, its exact molecular drug-target specificity within this disease still needs to be elucidated. The present study was designed to evaluate resveratrol computationally, using PatchDock against alzheimer's molecular drug targets in comparison with commonly prescribed drugs. The results revealed a remarkable activity for resveratrol against all drug targets: hydrogen and covalent bonds were formed with slight hydrophobic interactions in the active site residues, whereas the influence of anti-alzheimer drugs was recorded to be attenuate towards these targets. LigRMSD of resveratrol docked complexes showed an adequate level of stability from the reference ligand structure. Our findings indicate that resveratrol is a stable and versatile drug molecule, and should be subjected to further *in vitro* analysis and possible drug development.

Keywords: resveratrol, PatchDock, alzheimer's disease, neurodegeneration, anti-alzheimer's drugs

Introduction

Alzheimer's disease (AD) is an important mental health concern in both developed and developing countries, affecting more than 40 million individuals worldwide (Lei *et al*., 2021). This disease was named after a German psychiatrist and neuropathologist, Alois alzheimer, who described the disease pathology. It is an accretion of neurotoxic amyloid proteins and neurofibrillary tangles in the brain which affect neurons and synapses, hence, instigating neurodegeneration leading to progressive neurological dysfunction. From a clinical perspective, it is a deleterious form of dementia causing memory loss and cognitive deficits in about 50-75% of cases (Veitch *et al*., 2019; Young *et al*., 2018). Studies have indicated that acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), amyloid precursor protein (APP), beta secretase (BACE1), glycogen synthase kinase-3 beta (GSK-3β), presenilin-1 (PSEN1), muscarinic acetylcholine receptor (mAChR) and gamma secretase (GSI), all play a pivotal role in neurodegeneration (Kumar *et al*., 2016).

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Over the last two decades, numerous therapeutic interventions are focused on inhibiting those pivotal factors which contribute to the pathogenesis of this disease. Acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonist are medicines which are currently employed with alzheimer's patients' (Hsu *et al*., 2018). They have a negligible effect on the disease, and cause several adverse effects, including the inhibition of DNA polymerase (Vyjayanti *et al*., 2008). Failures in drug therapies have been observed as mostly due to a lack of understanding of disease pathogenesis, and drug resistance. Novel information is continually provided by experimental and clinical research which aims to bring forth different ligands directing multiple targets to reduce amyloid plaques. Moreover, numerous in-silico approaches, have recently explored the role of compounds of natural origins as powerful therapeutic molecules in AD.

The neuroprotective functions of resveratrol have led to it being widely studied for its effect on a wide range of neurodegenerative disorders (Gomes *et al*., 2018). Resveratrol has shown remarkable neuroprotective potential in numerous clinical trials and studies of *in vitro* models of AD (Tomé-Carneiro *et al*., 2013). This

is due to its antioxidant properties and ability to prevent amyloid plaques, neuroinflammation and mitochondrial impairment. However, resveratrol's exact binding affinity and specificity with a particular drug target is still needs to be elucidated. This is one of the main reasons why resveratrol is not being used clinically. Therefore, the present study is designed to computationally evaluate the nature of resveratrol binding with alzheimer's molecular drug targets to develop targeted therapeutics for the future.

Materials and Methods

Procurement of 3D structures of receptors and ligands. Receptors considered for this study were acetylcholinesterase (PDB ID: 1GQR), amyloid precursor protein (PDB ID: 1OWT), beta secretase-1 (PDB ID: 1W51), butyrylcholinesterase (PDB ID: 4BDS), glycogen synthase kinase-3 beta (PDB ID: 4ACG), muscarinic acetylcholine receptor (PDB ID: 5CXV) and presenilin-I (PDB ID: 2KR6). These receptor structures were downloaded from the RCSB protein data bank (Berman *et al*., 2000). 3D structures of ligands such as trans-resveratrol (CID: 445154), donepezil (CID: 3152), galantamine (CID: 77991) and rivastigmine (CID: 9651) were obtained from Pub Chem (Kim *et al*., 2015).

Preparation of receptors and ligands. The 3D structure of receptors were prepared by removing pre-exiting ligands and water molecules, whereas ligand molecules were hydrogenated on the polar ends. All of these procedures were carried out with Discovery Studio 2017 R2 software. The receptor structures were subjected to MoD Refiner for structure refinement and bonds relaxation (Xu and Zhang, 2011) to make them suitable for ligand interactions. The ligands refinement and energy minimization was carried out by the PRODRG SERVER (Schüttelkopf *et al*., 2004).

Receptors active site prediction. The metapocket 2.0 database was used to identify potential ligand binding sites in the receptors (Zhang *et al*., 2011). This was carried out by uploading receptor's structure in PDB to the data base, to predict potential binding sites. These predicted active sites of receptors acted as a reference to evaluate the interaction of ligands during the docking analysis.

Molecular docking procedure. Prepared receptors and ligands were obtained with the afore mentioned procedure and their mutual interaction was investigated using the online molecular docking data base PatchDock (Schneidman-Duhovny *et al*., 2005). Docking parameters were optimized by keeping the cluster RMSD value at 2.0 Å and using a complex type as an enzyme inhibitor to carry out interaction studies.

Docking results interpretation and visualization. After docking process, results were generated and top 10 docked pose were selected, based on high score, and adequate atomic contact energy. These results were downloaded, along with solution table and subjected to further pharmacophoric visualization of receptor-ligand interaction, using Discovery Studio R2 2017. LigRMSD (Velázquez-Libera *et al*., 2020) was used to calculate the root mean square deviation (RMSD) of docked complexes with the reference ligand (galantamine and rivastigmine). The methodology of this study is summarized in (Fig.1).

Results and Discussion

Comparative molecular docking studies. The PatchDock algorithm generated 1000 docked conformers of ligand-receptor complexes. The top 10 solutions were downloaded and analyzed for atomic contact energy (ACE), chemical bonding between ligands and receptors, and hydrogen-bond length. Resveratrol exploited hydroxyl groups in the formation of hydrogen bonds with all the receptors whereas benzene rings created hydrophobic interactions. The ACE of resveratrol docked complexes were between 38.25-285.61 Kcal/mol, whereas the H-bond length between receptor's residues remained at 1.00-4.91 Å. The anti-alzheimer's drugs

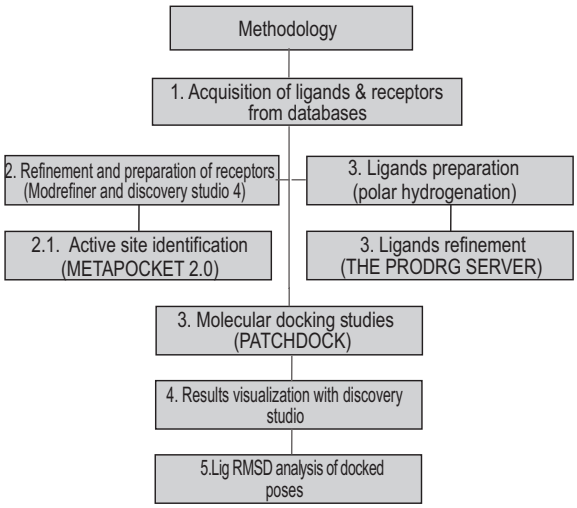

Fig. 1. Schematics of study methodology design

such as donepezil and galantamine used oxygen and benzene rings to form hydrogen and hydrophobic interactions, whereas carbonyl and oxo groups of rivastigmine established hydrogen bonds and benzene rings created hydrophobic interactions. The ACE and H-bond length was -46.96 to -354.63 Kcal/mol and 2.37-7.30 Å respectively. The LigRMSD analysis showed the docked orientation of all ligands was 2.13 to 3.27 Å. The results of ligands interaction with the receptors are depicted in Table 1 and also elaborated in the following headings:

***Acetylcholinesterase*.** Insilico analysis showed that resveratrol formed three hydrogen bonds with the active residues of GLN69, GLU199, and HIS440 and a hydrophobic interaction with TRP84 of AChE. Single hydrogen bonds were made by donepezil, and rivastigmine with TYR130 and TYR334 whereas galantamine established two hydrogen interactions with ASP72 and ASN85 respectively. Unfavourable interactions made by donepezil, galantamine and rivastigmine with AChE residues are TYR70, TYR121, PHE330, and TYR384 respectively.

***Amyloid precursor protein*.** Resveratrol established two hydrogen bonds with LYS155 and LEU165 and a single covalent bond with THR135. It also formed a π-alkyl interaction with LEU148 and ASN164. Donepezil made single hydrogen bonds with GLU139 and had five unfavourable interactions with SER124, ASP125, ALA126 and LEU127. Galantamine interacted with GLU 138 through hydrogen bonding and also created two π-alkyl and unfavourable interactions with VAL129, LEU136, LEU128 and ARG140. Rivastigmine formed π-alkyl interactions with LEU30 and a single hydrogen bond with THR232.

***Presenilin-I*.** Two hydrogen bonds and a single covalent bond were formed by resveratrol with SER438, THR440 and CYS419. Donepezil formed a hydrogen bond with ALA426 and a hydrophobic interaction with PHE445, CYS419, ILE387, 427, 439 and LEU383, 415, 422, 423, 439 respectively. Galantamine established a hydrogen bond with CYS419, hydrophobic interactions with LEU383, 422-423, ALA426 and PHE445 and unfavourable bonds with LEU415 and ILE439. Rivastigmine created single hydrogen and hydrophobic interactions with ILE439 and LEU381, and an unfavourable bond with ILE368.

***Beta secretase-1*.** With the BACE1, resveratrol formed two hydrogen bonds with GLY11 and SER325, at the cost of three unfavourable interactions with GLN73, ARG235 and GLY280. A single hydrogen bond was made by donepezil with LEU213, along with three unfavourable interactions with GLN211, LYS214 and LYS239, and π-sigma and π-alkyl connections with ALA230 and LYS246. Galantamine created two hydrogen bonds with SER10 and GLU339, and unfavourable bonds with ALA168 and GLN303. PRO308 participated in the formation of a π-alkyl interaction. Rivastigmine developed a single hydrogen and hydrophobic interactions with THR232 and LEU30.

***Butyrylcholinesterase*.** BuChE is another variant of the cholinesterase enzyme, belonging to the same class as acetylcholinesterase. Docking results showed that resveratrol formed two hydrogen bonds with SER198 and TRP430, along with π-sigma and π-π interactions with ALA328 and PHE329. Like resveratrol, donepezil also formed two hydrogen bonds with GLY116 and SER198 and π-π interactions with PHE278. Two amino acid residues (THR120, ALA277) participated in an unfavourable clash. Galantamine made a single hydrogen bond with SER198, along with hydrophobic interactions with TRP231, PHE329, ALA328 and HIS438. Rivastigmine created a hydrogen bond with LYS408, a π-alkyl interaction with PRO527 and an unfavourable bond with ASP304.

***Glycogen synthase kinase-3β*.** Resveratrol interacted with this receptor by establishing two hydrogen bonds with LEU88 and GLU97. Similarly, galantamine also formed two hydrogen bonds with ARG141 and GLN185, along with π-sigma and π-alkyl interactions with LEU188, VAL70 and CYS199. Donepezil created a single hydrogen bond with ARG223 and an unfavourable clash with GLY262, PHE291, TYR288, ILE228 and SER215. Rivastigmine made a single hydrogen bond with LYS183, whereas CYS199 and VAL70 participated in π-alkyl interactions and only two residues (PHE67 and ASP200) caused an unfavourable clash.

***Muscarinic acetylcholine receptor*.** ILE119 and ASN422 within this receptor participated in hydrogen bonding with resveratrol, while donepezil, galantamine and rivastigmine formed single hydrogen interactions with TYR408, ASN60 and ASN422. Unfavourable clashes were observed in donepezil and rivastigmine with TRP101, TRP91, GLN177, TYR381 and LYS359. These 3 drugs also participated in the creation of hydrophobic interactions with amino acid residues (TYPR404, TYR179, LEU64, ALA363, LEU367 and ALA363 respectively).

Table 1. Receptor models' active sites depiction and corresponding interaction of ligands

Target receptors	PDB accession code	Expected receptor's subunits binding site	Reported active sites familiarity with receptor subunits binding sites	Bonding between the receptor and ligands hydrogen = H* covalent = C	Unfavourable interactions between the receptors and ligands	Binding free energy	LigRMSD calculation based on docked poses
Acetylcholinesterase	1GQR	GLN^{69}, TYR^{70}, VAL^{71}, $ASP^{72,}$ GLU^{73}, GLN^{74}, SER^{81}, GLU^{82}, MET^{83}, TRP^{84}, ASN^{85}, PRO^{86}, TYR^{116}, GLY^{117}, GLY^{118}, GLY^{119}, TYR^{121}, SER^{122} GLY^{123}, SER^{124}, LEU^{127}, TYR^{130}, TRP^{279}, LEU^{282}, PHE^{284}, SER^{286}, ILE^{287}, PHE^{288}, ARG^{289}, PHE^{290}, PHE^{330}, PHE^{331}, TYR^{334}, GLY^{335}	TRP^{84}, GLY^{119}, PHE^{330}, HIS^{440}	Ligand1: GLU^{199}*, GLN^{69}*, HIS^{440}* Ligand2:TYR^{130}* Ligand3:GLN^{138}* Ligand4: TYR^{334}*	Ligand1: None, Ligand2: TYR^{70}, TYR^{121}, PHE^{330}, Ligand3: TYR^{121}, TYR^{384}, Ligand4: TYR^{121}	Ligand 1: -199.22 Kcal/mol, Ligand 2: -238.29 Kcal/mol, Ligand 3: -176.21 Kcal/mol, Ligand 4: -174.97 Kcal/mol	Ligand 1: 2. 13 Å, Ligand 2: 3.17 Å, Ligand 3: 3.27 Å, Ligand 4: 2.44 Å
Amyloid Precursor Protein	1OWT	LYS^{134}, PHE^{135}, LEU^{136}, HIS^{137}, $GLN^{138,}$ ARG^{140}, ASP^{142}, VAL^{143}, GLU^{145}, HIS^{149}, TRP^{150}, HIS^{151}, THR^{152}, VAL^{153}, ALA^{154}, THR^{157}, CYS^{158}, SER^{159}, GLU^{160}, LYS^{161}, SER^{162}, THR^{163}, LEU^{165}, VAL^{182}, PHE^{184}, CYS^{186}, CYS^{187}	N/A	Ligand1: THR^{152}*, LYS^{155} LEU^{165}* Ligand2: GLU^{139}* Ligand3: ASP^{72}*, ASN^{85}* Ligand4: N/A	Ligand 1: None Ligand2: SER^{124}, ASP^{125}, ALA^{126}, LEU^{127}. Ligand3: LEU^{128}, ARG^{140}. Ligand4: None	Ligand 1: -38.45 Kcal/mol, Ligand 2: -187.54 Kcal/mol, Ligand 3: -147.34 Kcal/mol, Ligand 4: -138.48 Kcal/mol	

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Target receptors	PDB accession code	Expected receptor's subunits binding site	Reported active sites familiarity with receptor subunits binding sites	Bonding between the receptor and ligands hydrogen = H* covalent = C	Unfavourable interactions between the receptors and ligands	Binding free energy	LigRMSD calculation based on docked poses
Presenilin-I	2KR6	GLU^{339}, TRP^{340}, GLU^{341}, SER^{346}, HIS^{347}, LEU^{348}, GLU^{356}, ALA^{359}, ALA^{360}, GLU^{363}, LEU^{364}, SER^{367}, ILE^{368}, GLY^{378}, VAL^{379}, LYS^{380}, LEU^{381}, GLY^{382}, LEU^{383}, VAL^{393}, GLY^{394}, LYS^{395}, SER^{397}, ALA^{398}, THR^{399}, THR^{440}, ILE^{437}, SER^{438}, ILE^{439}, PHE^{441}, LEU^{443}, VAL^{444}, PHE^{447}, ALA^{448}, TYR^{466}, ILE^{467}	N/A	Ligand1: CYS^{419}, SER^{438}*, THR^{440}* Ligand2: ALA^{426}* Ligand3: CYS^{419}* Ligand4: ILE^{439}*	Ligand1: None, Ligand2: None, Ligand3: LEU^{415}, ILE^{439}. Ligand4: ILE^{368}	Ligand 1: -285.61 Kcal/mol, Ligand 2: -363.71 Kcal/mol, Ligand 3: -354.63 Kcal/mol, Ligand 4: -202.83 Kcal/mol	
Beta Secretase	1W51	LEU^{30}, ASP^{32}, GLY^{34}, SER^{35}, SER^{36}, ASN^{37}, VAL^{69}, PRO^{70}, TYR^{71}, THR^{72} GLN^{73}, GLY^{74}, ILE^{118}, ILE^{126}, ALA^{127}, ARG^{128}, TYR^{198}, LYS^{224}, ILE^{226}, ASP^{228}, SER^{229}, GLY^{230}, THR^{231}, THR^{232}, ASN^{233}, ARG^{235}, LEU^{263}, GLY^{264}, GLN^{304}, LYS^{321}, PHE^{322}, ILE^{324}, SER^{325}, GLN^{326}, SER^{327}, SER^{328}, THR^{329}, GLY^{330}, THR^{331}, VAL^{332}	ASP^{32}, GLY^{34}, TYR^{71}, GLN^{73}, ASP^{228}, GLY^{230},	Ligand1: GLY^{11}*, SER^{325}* Ligand2: LEU^{213}* Ligand3: SER^{10}*, GLU^{339}* Ligand4:THR^{232}*	Ligand1: GLN^{73}, ARG^{235}, GLY^{280}. Ligand2: GLN^{211}, LYS^{214}, LYS^{239}, Ligand3: ALA^{168}, GLN^{303}. Ligand4: None.	Ligand 1: -63.46 Kcal/mol, Ligand 2: -109 Kcal/mol, Ligand 3: -144.39 Kcal/mol, Ligand 4: -61.63 Kcal/mol	

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Target receptors	PDB accession code	Expected receptor's subunits binding site	Reported active sites familiarity with receptor subunits binding sites	Bonding between the receptor and ligands hydrogen = H* covalent = C	Unfavourable interactions between the receptors and ligands	Binding free energy	LigRMSD calculation based on docked poses
Butyrylcholinesterase	4BDS	GLN[67], ASN[68] ILE[69], ASP[70], GLN[71] SER[72], SER[79], MET[81], TRP[82], ASN[83] PRO[84], TRP[112], GLY[115], GLY[116], THR[120], GLY[121], THR[122], LEU[125], VAL[127], TYR[128], GLU[197], SER[198], TYR[332], ALA[328], PHE[329], TRP[430], MET[437], HIS[438], GLY[439], TYR[440], ILE[442]	TRP[82]	Ligand1: SER[198]*, TRP[430]* Ligand2: GLY[116]*, SER[198]* Ligand3: SER[198]* Ligand4 :LYS[408]*	Ligand1: None, Ligand2: THR[120], ALA[277], Ligand3: None, Ligand4: ASP[304]	Ligand 1: -177.66 Kcal/mol, Ligand 2: -195.14 Kcal/mol, Ligand 3: -179 Kcal/mol, Ligand 4: -46.46 Kcal/mol	
Glycogen Synthase Kinase-3 Beta	4ACG	ILE[62], GLY[63], ASN[64], GLY[65], PHE[67], VAL[70], ALA[83], LYS[85], LEU[88], GLU[97], MET[101], VAL[110], LEU[132], ASP[133], TYR[134], VAL[135], PRO[136], GLU[137] THR[138], ARG[141], ASP[181], LYS[183], ASN[186], LEU[188], CYS[199], ASP[200], PHE[201]	ILE[62], PHE[67,] VAL[70], LYS[85], ASP[133], THR[138], LEU[188]	Ligand1: LEU[88]*, GLU[97]* Ligand2:ARG[223]* Ligand3: ARG[141]*, GLN[185]* Ligand4:LYS[183]*	Ligand1: None, Ligand2: GLY[262], PHE[291], TYR[288], ILE2[28], SER[215] Ligand3: None, Ligand4: PHE[67], ASP[200]	Ligand 1: -103.13 Kcal/mol, Ligand 2: -266.18 Kcal/mol, Ligand 3: -183.22 Kcal/mol, Ligand 4: -84.22 Kcal/mol	

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Target receptors	PDB accession code	Expected receptor's subunits binding site	Reported active sites familiarity with receptor subunits binding sites	Bonding between the receptor and ligands hydrogen = H* covalent = C	Unfavourable interactions between the receptors and ligands	Binding free energy	LigRMSD calculation based on docked poses
Muscarinic Acetylcholine Receptor	5CXV	TYR^{82}, GLN^{110}, VAL^{113}, ILE^{119}, TRP^{157}, LEU^{183}, SER^{184}, GLN^{185}, PRO^{186}, ILE^{188}, THR^{189}, THR^{192}, ALA^{193}, ALA^{195}, ALA^{196}, PHE^{197}, PRO^{200}, PHE^{374}, TRP^{378}, TYR^{381}, ASN^{382}, VAL^{385}, SER^{388}, VAL^{395}, GLU^{397}, THR^{398}, TRP^{400}, GLU^{401}, GLY^{403}, TYR^{404}, CYS^{407}, ASN^{422}	TYR^{106}, SER^{109}, TYR^{381}, ASN^{382}, TYR^{404}	Ligand1: ILE^{119}*, ASN^{422} * Ligand2:TYR^{408}* Ligand3:ASN^{60}* Ligand4:ASN^{422}*	Ligand1: None, Ligand2: TRP^{91}, TRP^{101} GLN^{177}, TYR^{381}, Ligand3: None, Ligand4: LYS^{359}	Ligand 1: - 105.41 Kcal/mol, Ligand 2: - 255.11 Kcal/mol, Ligand 3: - 134.99 Kcal/mol, Ligand 4: - 63.75 Kcal/mol	

Ligand 1 = resveratrol; ligand 2 = donepezil; ligand 3 = galantamine; ligand 4 = rivastigmine

It is clear from clinical and animals studies that AD is a slow, progressive neurodegenerative disorder, affecting not only memory, but also causing behavioural and communication problems (Veitch *et al*., 2019). In this disease, amyloid plaques and neurofibrillary tangles start to accumulate around the neurons, which induces neuroinflammation and disrupting the neuronal metabolism, ultimately, lead to loss of essential neurons and synapses; responsible for memory generation and regulation of brain regions for language and behaviour (Ulep *et al*., 2018). The enzymes which play a crucial role in the formation of amyloid plagues are BACE1 (Wang *et al*., 2018) and GSI (Audagnotto *et al*., 2018). These facilitate the cleavage of large amyloid precursor proteins into smaller protein, whereas the mAChE receptor (Vijayraghavan *et al*., 2018) and AChE (Lushchekina *et al*., 2017) increase the amyloid protein toxicity. Eventually, with BuChE (Gabriel *et al*., 2017) and GSK-3β (Fuster-Matanzo *et al*., 2017) along with other protein factors, these small amyloid subunits form neurofibrillary tangles that adversely interact with neurons and synapses, affecting synaptic transmission and inter-neuronal communication and leading to their degeneration.

In our current study, receptor models responsible for the progression of AD were considered, in order to assess the activity of resveratrol and conventional drugs which potentially impede the progress of neurodegeneration. However, the exact mechanism of resveratrol activity against various receptors of AD is not yet fully understood. To illustrate their action, PatchDock was exploited to show a comparative interaction between resveratrol and commonly employed drugs such as donepezil, galantamine and rivastigmine with the receptor models. This software utilizes shape complementarity algorithms which divides proteins and ligands into various patches and docks them based on patch complementarity (Schneidman-Duhovny *et al*., 2005). Docking results demonstrated that resveratrol has substantial interaction affinity against all receptor models which have a significant role in disease progression. It forms hydrogen and covalent bonds with the active site residues along with slight hydrophobic bonds. A survey of the literature has shown that hydrogen bonding and covalent bonding of ligands with receptors increases the efficiency of a drug (Chen *et al*., 2016; Kumalo *et al*., 2015). On the other hand, hydrophobic interaction and unfavourable bumps affects drug binding affinity with the receptor, attenuates the therapeutic efficacy, and encourages undesirable effects inside the

host organism (Zhou *et al*., 2015; Patil *et al*., 2010). It was observed that the conventional drugs donepezil, galantamine and rivastigmine also formed hydrogen bonds with considerable hydrophobic and unfavourable bumps (Ali *et al*., 2015). Furthermore, the docked poses of resveratrol with all receptor models were analyzed by LigRMSD and were found to be within the stability range (> 4 Å range results in docked complex instability). (Velázquez-Libera *et al*., 2020).

The insight from our docking analysis encouraged us to propose a novel and relatively safe drug candidate for the treatment of AD. In order to further elaborate the activity of resveratrol against alzheimer's receptor models, Karuppagounder *et al*. (2009) exploited resveratrol against a transgenic rat model carrying two genetic mutations of AD. Their results showed the most significant plaque reduction to be in the hippocampus, followed by the striatum and then the cerebral cortex (Karuppagounder *et al*., 2009). Thus, there is a need to develop such rat models to study the effect of these receptor mutations and to analyze the current study findings of the interaction of resveratrol with considered receptor models. This would allow us to investigate the effectiveness of resveratrol and other drugs against rat models *in vivo* and to use the results as a vehicle to understand the pharmacokinetics of these drugs and their influence on these mutated proteins. These studies could recommend a novel therapeutic agent against this disease which might be a new candidate for comprehensive clinical trials. But the major challenge obstructing resveratrol therapeutic action is low pharmacokinetic solubility inside humans (de Vries *et al*., 2018). To compensate for this, several scientists have attempted to derivatize this molecule by producing resveratrol analogues which significantly improved the bioavailability of resveratrol (Koukoulitsa *et al*., 2016). In addition, resveratrol hybrids, not only increased the solubility of resveratrol but also improved its activity against acetylcholinesterase and monoamine oxidases, both of which are responsible for aggravating AD (Lan *et al*., 2018; Yang *et al*., 2017; Li *et al*., 2014; Pan *et al*., 2014).

Therefore, our study proves that the parent resveratrol molecule is effective for all the receptor models considered except for the BACE1 receptor, which forms a slight unfavourable contact. This might hinder their attachment with the receptor in long-term exposure. These non-favourable interactions and potential side effects inside the host could be rectified by subjecting the molecule to derivatization, further improving its activity against this receptor as described in Koukoulitsa study (Koukoulitsa *et al*., 2016) and other previously described literature for similar models (Lan *et al*., 2018; Yang *et al*., 2017; Li *et al*., 2014; Pan *et al*., 2014).

Conclusion

The docking studies show remarkable results, with resveratrol binding with all receptors of AD. Prominent findings from the present work reveal that resveratrol may be one of the best candidates against AD and can be proposed for lead optimization. It is conclude that resveratrol is a novel drug candidate for the treatment of early onset AD and this generation of resveratrol analogues might further improve its binding with numerous important receptors which help in the progression of this disease. However, further studies are required in order to understand the mechanics of resveratrol against AD *in vitro*.

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Conflict of Interest. The authors declare no conflict of interest.

References

Ali, T.B., Schleret, T.R., Reilly, B.M., Chen, W.Y., Abagyan, R. 2015. Adverse effects of cholinesterase inhibitors in dementia, according to the pharmacovigilance databases of the United-States and Canada. *PLoS One*, **10:** e0144337.

Audagnotto, M., Lorkowski, A.K., Peraro, M.D. 2018. Recruitment of the amyloid precursor protein by γ-secretase at the synaptic plasma membrane. *Biochemical and Biophysical Research Communications*, **498:** 334-341.

Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., Shindyalov, I.N., Bourne, P.E. 2000. The protein data bank. *Nucleic Acids Research*, **28:** 235-242.

Chen, D., Oezguen, N., Urvil, P., Ferguson, C., Dann, S.M., Savidge, T.C. 2016. Regulation of protein-ligand binding affinity by hydrogen bond pairing. *Science Advances*, **2:** e1501240.

de Vries, K., Strydom, M., Steenkamp, V. 2018. Bioavailability of resveratrol: possibilities for enhancement. *Journal of Herbal Medicine*, **11:** 71-

77.

Fuster-Matanzo, A., Jurado-Arjona, J., Benvegnù, S., García, E., Martín-Maestro, P., Gómez-Sintes, R., Hernández, F., Ávila, J. 2017. Glycogen synthase kinase-3β regulates fractalkine production by altering its trafficking from Golgi to plasma membrane: implications for alzheimer's disease. *Cellular and Molecular Life Sciences*, **74:** 1153-1163.

Gabriel, A.J., Almeida, M.R., Ribeiro, M.H., Durães, J., Tábuas-Pereira, M., Pinheiro, A.C., Pascoal, R., Santana, I., Baldeiras, I. 2017. Association between butyryl cholinesterase and cerebrospinal fluid biomarkers in alzheimer's disease patients. *Neuroscience Letters*, **641:** 101-106.

Gomes, B.A.Q., Silva, J.P.B., Romeiro, C.F.R., dos Santos, S.M., Rodrigues, C.A., Gonçalves, P.R., Sakai, J.T., Mendes, P.F.S., Varela, E.L.P., Monteiro, M.C. 2018. Neuroprotective mechanisms of resveratrol in alzheimer's disease: role of SIRT1. *Oxidative Medicine and Cellular Longevity*, **2018:** 1-15.

Hsu, W.Y., Lane, H.Y., Lin, C.H. 2018. Medications used for cognitive enhancement in patients with schizophrenia, bipolar disorder, alzheimer's disease and Parkinson's disease. *Frontiers in Psychiatry*, **9:** 91.

Karuppagounder, S.S., Pinto, J.T., Xu, H., Chen, H.L., Beal, M.F., Gibson, G.E. 2009. Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of alzheimer's disease. *Neurochemistry International*, **54:** 111-118.

Kim, S., Thiessen, P.A., Bolton, E.E., Chen, J., Fu, G., Gindulyte, A., Han, L., He, J., He, S., Shoemaker, B.A. 2015. PubChem substance and compound databases. *Nucleic Acids Research*, **44:** D1202-D1213.

Koukoulitsa, C., Villalonga-Barber, C., Csonka, R., Alexi, X., Leonis, G., Dellis, D., Hamelink, E., Belda, O., Steele, B.R., Micha-Screttas, M., Alexis, M.N., Papadopoulos, M.G., Mavromoustakos, T. 2016. Biological and computational evaluation of resveratrol inhibitors against alzheimer's disease. *Journal of Enzyme Inhibition and Medicinal Chemistry*, **31:** 67-77.

Kumalo, H., Bhakat, S., Soliman, M. 2015. Theory and applications of covalent docking in drug discovery: merits and pitfalls. *Molecules*, **20:** 1984-2000.

Kumar, A., Nisha, C.M., Silakari, C., Sharma, I., Anusha, K., Gupta, N., Nair, P., Tripathi, T., Kumar, A. 2016. Current and novel therapeutic molecules and targets in alzheimer's disease. *Journal of the Formosan Medical Association*, **115:** 3-10.

Lan, J.S., Liu, Y., Hou, J.W., Yang, J., Zhang, X.Y., Zhao, Y., Xie, S.S., Ding, Y., Zhang, T. 2018. Design, synthesis and evaluation of resveratrol-indazole hybrids as novel monoamine oxidases inhibitors with amyloid-β aggregation inhibition. *Bioorganic Chemistry*, **76:** 130-139.

Lei, P., Ayton, S., Bush, A. I. 2021. The essential elements of alzheimer's disease. *Journal of Biological Chemistry*, **296:** 100105.

Li, S.Y., Wang, X.B., Kong, L.Y. 2014. Design, synthesis and biological evaluation of imine resveratrol derivatives as multi-targeted agents against alzheimer's disease. *European Journal of Medicinal Chemistry*, **71:** 36-45.

Lushchekina, S.V., Kots, E.D., Novichkova, D.A., Petrov, K.A., Masson, P. 2017. Role of acetylcholinesterase in β-amyloid aggregation studied by accelerated molecular dynamics. *Bionanoscience*, **7:** 396-402.

Pan, L.F., Wang, X.B., Xie, S.S., Li, S.Y., Kong, L.Y. 2014. Multitarget-directed resveratrol derivatives: anti-cholinesterases, anti-β-amyloid aggregation and monoamine oxidase inhibition properties against alzheimer's disease. *Medicinal Chemistry Communication*, **5:** 609-616.

Patil, R., Das, S., Stanley, A., Yadav, L., Sudhakar, A., Varma, A.K. 2010. Optimized hydrophobic interactions and hydrogen bonding at the target-ligand interface leads the pathways of drug-designing. *PloS One*, **5:** e12029.

Schneidman-Duhovny, D., Inbar, Y., Nussinov, R., Wolfson, H.J. 2005. PatchDock and SymmDock: servers for rigid and symmetric docking. *Nucleic Acids Research*, **33:** W363-W367.

Schüttelkopf, A.W., Van Aalten, D.M.F. 2004. PRODRG: a tool for high throughput crystallography of protein–ligand complexes. *Acta Crystallographica Section D: Biological Crystallography*, **60:** 1355-1363.

Tomé-Carneiro, J., Larrosa, M., González-Sarrías, A., Tomás-Barberán, F.A., García-Conesa, M.T., Espín, J.C. 2013. Resveratrol and clinical trials: the crossroad from *in vitro* studies to human evidence. *Current Pharmaceutical Design*, **19:** 6064-6093.

Ulep, M.G., Saraon, S.K., McLea, S. 2018. Alzheimer Disease. *The Journal for Nurse Practitioners*, **14:**

129-135.

Veitch, D.P., Weiner, M.W., Aisen, P.S., Beckett, L.A., Cairns, N.J., Green, R.C., Harvey, D., Jack, C.R., Jagust, W., Morris, J.C., Petersen, R.C., Saykin, A.J., Shaw, L.M., Toga, A.W., Trojanowski, J.Q. 2019. Understanding disease progression and improving alzheimer's disease clinical trials: recent highlights from the alzheimer's disease neuroimaging initiative. *Alzheimer's and Dementia*, **15:** 106-152.

Velázquez-Libera, J.L., Durán-Verdugo, F., Valdés-Jiménez, A., Núñez-Vivanco, G., Caballero, J. 2020. LigRMSD: a web server for automatic structure matching and RMSD calculations among identical and similar compounds in protein-ligand docking. *Bioinformatics*, **36:** 2912-2914.

Vijayraghavan, S., Major, A.J., Everling, S. 2018. Muscarinic M1 receptor over stimulation disrupts working memory activity for rules in primate prefrontal cortex. *Neuron*, **98:** 1256-1268.

Vyjayanti, V.N., Chary, N.S., Rao, K.S. 2008. On the inhibitory affect of some dementia drugs on DNA polymerase β activity. *Neurochemical Research*, **33:** 2187-2196.

Wang, M., Jing, T., Wang, X., Yao, D. 2018. Beta-secretase/BACE1 promotes APP endocytosis and processing in the endosomes and on cell membrane. *Neuroscience Letters*, **685:** 63-67.

Xu, D., Zhang, Y. 2011. Improving the physical realism and structural accuracy of protein models by a two step atomic level energy minimization. *Biophysical Journal*, **101:** 2525-2534.

Yang, X., Qiang, X., Li, Y., Luo, L., Xu, R., Zheng, Y., Cao, Z., Tan, Z., Deng, Y. 2017. Pyridoxine-resveratrol hybrids Mannich base derivatives as novel dual inhibitors of AChE and MAO-B with antioxidant and metal-chelating properties for the treatment of alzheimer's disease. *Bioorganic Chemistry*, **71:** 305-314.

Young, A.L., Scelsi, M.A., Marinescu, R.V., Schott, J.M., Ourselin, S., Alexander, D.C., Altmann, A. 2018. Genome wide association study of data-driven alzheimer's disease subtypes. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, **14:** P1042-P1043.

Zhang, Z., Li, Y., Lin, B., Schroeder, M., Huang, B. 2011. Identification of cavities on protein surface using multiple computational approaches for drug binding site prediction. *Bioinformatics*, **27:** 2083-2088.

Zhou, H., Gao, M., Skolnick, J. 2015. Comprehensive prediction of drug-protein interactions and side effects for the human proteome. *Scientific Reports*, **5:** 11090.