Original Article

Identifying Novel Compound against the Mutational Impact on the Mapt Protein via Molecular Docking Studies

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Abstract

Aim. Molecular docking experiments employing a molecular docking server will be used to find novel drugs against mutant structures of the MAPT protein linked to Alzheimer's disease. **Materials and Methods.** In this study, we used SWISS-Attach to dock phytochemicals Curcumin and Resveratrol with mutant structures of MAPT protein V287I mutation, which were predicted to have destabilizing effects on the MAPT protein by Dynamut.Alzheimer's disease, EOAD, PSEN2, Mutant structures, Novel compounds, Molecular Docking, SWISS-DOCK. Sample size chosen for this study was 1 mutation for the MAPT gene. **Results.** The binding energies of the docked molecules were investigated. **Conclusion.** Using the molecular docking online tool that we employed in our investigation, we performed molecular docking of mutant MAPT protein structures with putative phytochemicals. These docked chemicals could help with medication development investigations and uncover a possible AD treatment.

Keywords: Alzheimer's disease, MAPT, Mutant structures, Novel compounds, Phytochemicals, Molecular Docking, SWISS-DOCK

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INTRODUCTION

Mutations in the microtubule associated protein tau (MAPT) underlie multiple neurodegenerative disorders, yet the pathophysiological mechanisms are unclear (Butler et al., 2019)(Mujahid, 2016). It is distinguished by progressive cognitive deterioration, declining activities of daily living, and behavioral changes. It is the most common form of both pre-senile and senile dementia. According to the World Health Organization (WHO), Alzheimer's type dementia affects 5% of men and 6% of women over the age of 60 in the world(Mujahid, 2016). The microtubule-associated protein tau (MAPT) gene, located on chromosome 17 (17q21), encodes for the protein tau(Gao et al., 2018). Through its microtubule binding, tau impacts multiple cellular functions including microtubule stability, axonal trafficking and development (Butler et al., 2019). Tau, a microtubule-associated protein, is the main component of the intracellular filamentous inclusions involved in tauopathies, which include Alzheimer's disease (AD)(Gao et al., 2018)

Many plants, including grapes, berries, and groundnuts, contain the phytoalexin resveratrol (3, 4′, 5-trihydroxystilbene) (Aggarwal et al., 2004) ; (Vaiserman et al., 2020). Curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also known as diferuloylmethane, is a natural polyphenol found in Curcuma longa (turmeric) rhizome (Vaiserman et al., 2020). Turmeric (Curcuma longa) is a ginger family rhizomatous herbaceous perennial plant. It's a spice that's important in both medical and scientific circles, as well as in the kitchen.These are potential phytochemical substances that can be used in molecular docking experiments (Miziak et al., 2021; Raghuvanshi et al., 2021)(Miziak et al., 2021). This research contributes to our understanding of the structural effects of these phytochemicals on the MAPT Protein, which is thought to be the primary cause of familial forms of Alzheimer's disease.

Our institution is passionate about high quality evidence based research and has excelled in various fields (Devarajan et al., 2021; Dhanraj & Rajeshkumar, 2021; Kamath et al., 2020; Nandhini et al., 2020; Parakh et al., 2020; Perumal et al., 2021; Pham et al., 2021; Sathiyamoorthi et al., 2021; Tesfaye Jule et al., 2021; Uganya et al., 2021). There is a shortage of evidence on the characterization of missense mutations linked to familial Alzheimer's disease. Though new mutations are being discovered, the pathophysiological process of Alzheimer's disease (Li et al., n.d.)and the impact of mutations in the genes MAPT, APP, PSEN1 and PSEN2, which are linked to autosomal dominant familial types of the disease, are unknown. With the number of Alzheimer's disease cases rising every year, the need for a comprehensive picture of the situation through prioritizing active research on the disease is unavoidable. In this study, we use in-silico docking web servers to analyze the structural impact of missense mutations on the function of the MAPT protein in order to anticipate detrimental mutations.

MATERIALS AND METHODS

The research and studies were carried out in the Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences' Computational Biology lab. The following are the details of the system that was employed in the research. We used a 7th Generation Intel(R) Core(TM) i3-7100U CPU running at 2.40GHz and Microsoft Windows 10.0.19042 as the operating system. The graphics parameters are Intel(R) HD Graphics Family, Intel Corporation compliant, and the system memory is up to 8 GB with an 80-85 percent continuous power supply 180 W Adapter.The sample size for this study is one, consisting of three major MAPT protein mutations and two phytochemicals, Cucurmin and Reservatrol.

The mutations in the MAPT gene linked to AD were retrieved from the Alzforum database (https://www.alzforum.org/mutations/mapt) and uploaded for Dynamut predictions, which also predicted mutant structures for specific mutations and one mutation V287I. This is chosen as study subjects for docking studies. Cucurmin and Resveratrol were retrieved for docking through the Zinc database(Irwin & Shoichet, 2005), which was integrated into the SwissDock web server.
SwissDock is an online service that predicts molecular interactions between a target protein and a small molecule. This website is built on the EADock DSS engine, which also includes setup scripts that make preparing the target protein and ligand input files as well as curation of frequent problems easier(Gao et al., 2018; Grosdidier et al., 2011; Sim et al., 2012). SwissDock is a web-based technology for fully automated protein docking that uses a programmatic SOAP interface. It also gives you access to a list of ligands from the Zinc database (Irwin & Shoichet, 2005), which you may search using the Zinc Accession number.

RESULTS

Conclude, one mutant structure is used in molecular docking investigations with Cucurmin and Resveratrol, whose skeletal structures are shown in Fig. 1 and fig. 2, respectively. The binding affinities of the MAPT mutant protein with these prospective therapeutic compounds may be seen by seeing the docked novel compounds, such as the V287I mutant protein with Cucurmin in Fig. 3 and Resveratrol in Fig. 4. The docking studies were completed successfully using SwissDock and the Zinc database. Table 1 illustrates the Full Fitness (kcal/mol) and Estimated G (kcal/mol) for a single mutation, V287I, which has been found to destabilize MAPT structure.

DISCUSSION

The structural impact of missense mutations on MAPT protein was investigated in this study utilizing SwissDock and molecular docking experiments with Cucurmin and Resveratrol for V287I mutant structures. From the predictions generated by PROVEAN and Predict SNP, 5 variants were expected to be harmful missense mutations. When the results of Dynamut and I-mutant 2.0 predictions were combined, three mutations were projected to lower the stability of the MAPT protein.
Nowadays, there is no cure for Alzheimer's disease(Chen & Pan, 2014). According to the latest World Health Organization (WHO) estimates, more than 35 million individuals worldwide suffer from dementia. As the world's population ages, this number is predicted to more than triple, approaching 115 million by 2050(Sinha, 2011; Wortmann, 2012).The introduction of high sequencing technology has resulted in significant progress in the sequencing of diseased genomes and the identification of novel mutations linked to diseases, resulting in advances in clinical research(Phillips et al., 2014). Every now and then, new mutations linked to Alzheimer's disease are discovered(Wan et al., 2021).The three single-gene mutations associated with early-onset Alzheimer’s disease are:(i)Amyloid precursor protein (APP) on chromosome 21 (ii)Presenilin 1 (PSEN1) on chromosome 14 (iii)Presenilin 2 (PSEN2) on chromosome 1(Rose, 1998). To date nearly 40 mutations associated with MAPT protein. The pathogenicity and impact of each of these changes, however, remain unknown.

Alzheimer's disease-related mutations are being discovered at a faster rate. However, employing wet lab experiments to determine the pathogenicity and consequences of each of these changes is a monumental task(Bayat, 2002; D'Ascenzo, 2013).The development of bioinformatics tools that use computational algorithms to anticipate the consequences of mutations on proteins is lifesaving. Due to time limits and processing resources, the study was limited to determining the impact of the mutations. In the future, mutant structure modeling, analysis, and molecular docking investigations may be used to enhance medication development studies in the field of Alzheimer's disease research.

CONCLUSION

The mutant structure of V287I was docked with Cucurmin and Resveratrol in our investigation, and novel compounds to combat mutational effects on the MAPT protein were discovered. Drug development and molecular dynamics investigations can be focused on these mutations. This research has important implications for the impact of specific mutations that have detrimental and destabilizing effects on the MAPT protein, resulting in Amyloid Beta protein aggregation, which leads to the production of neural plaques and the autosomal dominant type of Alzheimer's disease. This information on the mutations can be used in genetic testing and counseling for people who are at risk for Alzheimer's disease, as well as in the development of innovative ways to postpone the beginning of the disease.

Declaration:

Conflict of interests

The authors of this paper declare no conflict of interest.

Authors Contributions :

Author YRN was involved in data collection, data analysis, and manuscript writing. Author KA was involved in conceptualization, guidance and critical review of manuscript.

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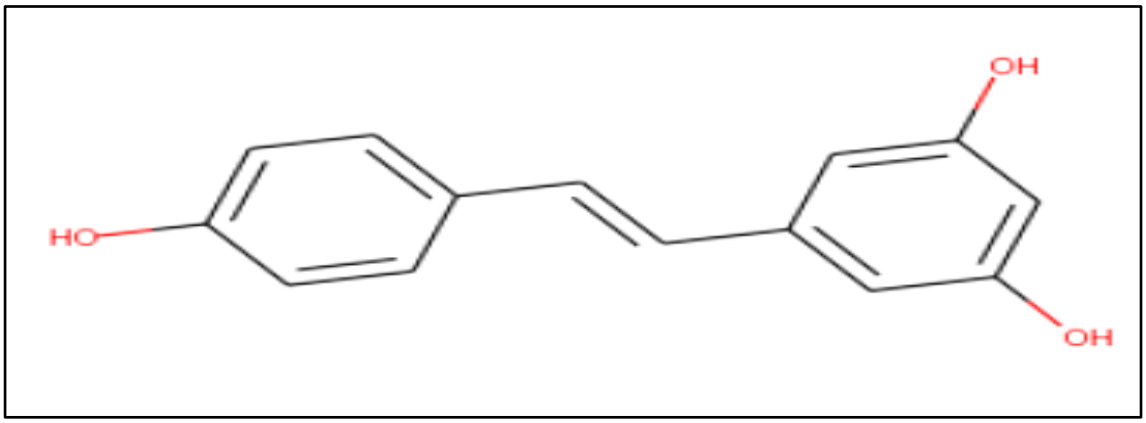

Fig. 1. Skeletal structure of Resveratrol retrieved from ZINC database (ID: ZINC6787)

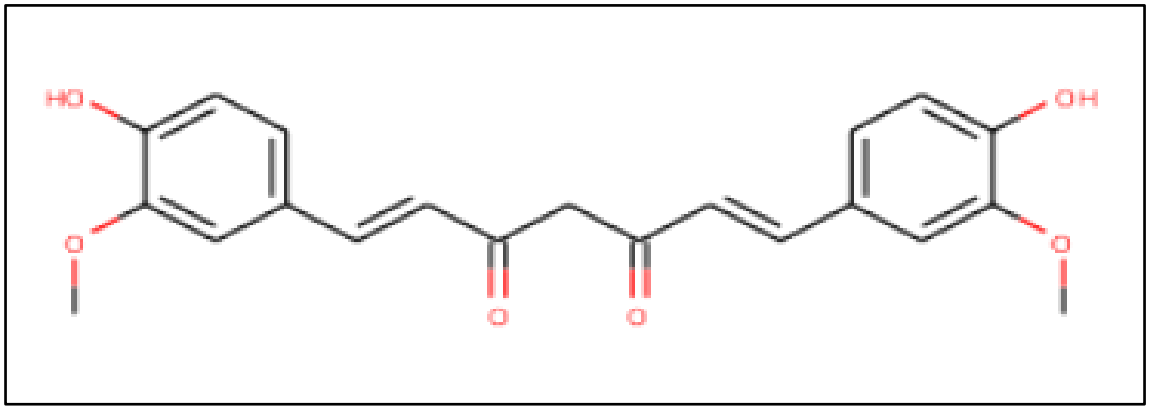

Fig. 2. Skeletal structure of Cucurmin retrieved from ZINC database (ID: ZINC899824)

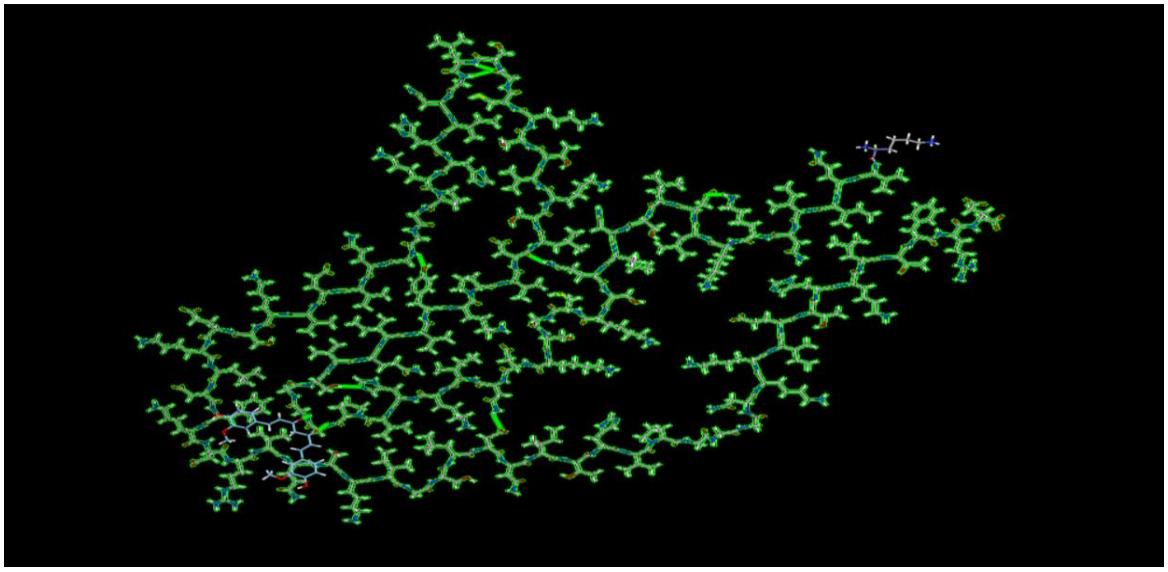

Fig. 3. Docked V287I mutant structure of MAPT protein with Cucurmin

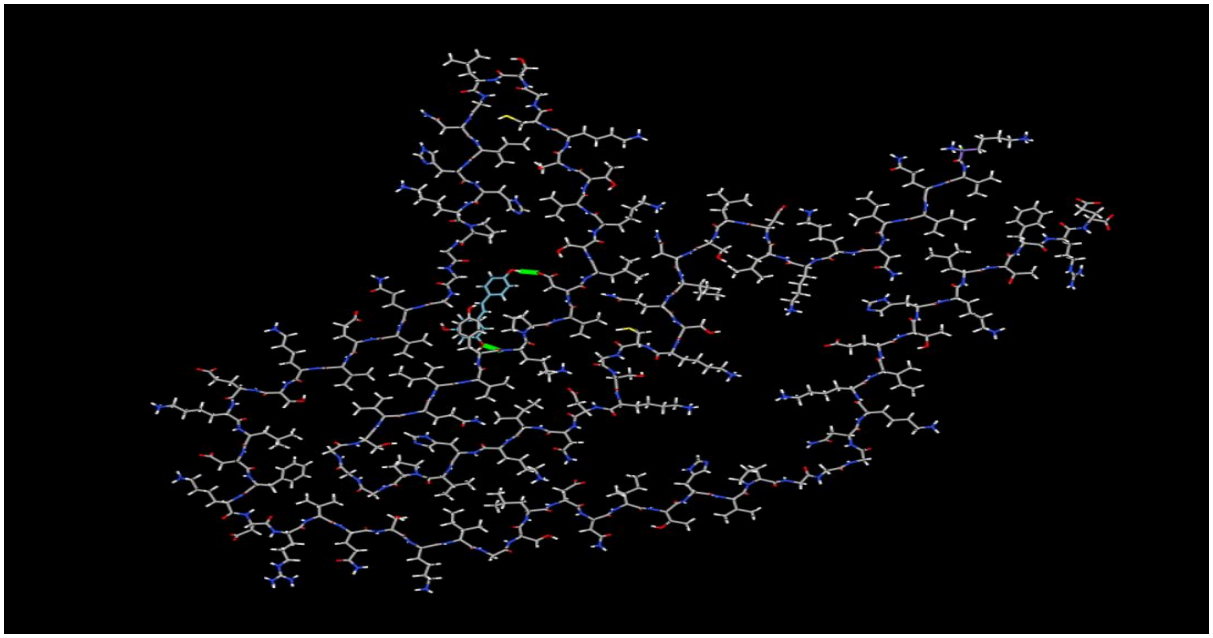

Fig. 4. Docked V287I mutant structure of MAPT protein with Resveratrol

Table 1. Docking scores for V287I mutant structures with Cucurmin and Resveratrol

Target	Ligand	FullFitness (kcal/mol)	Estimated ΔG (kcal/mol)
V287I	Cucurmin	-1143.63	-6.89
V287I	Resveratrol	-1178.01	-6.44