Original Article

# Identifying novel compounds against the mutational impact on the PSEN2 protein via molecular docking studies.

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## Abstract

**Aim.**This study aims to identify novel compounds against the mutant structures of PSEN2 protein associated with Alzheimer's disease by molecular docking studies using molecular docking server. **Materials and Methods**.In this study, we retrieved the mutant structures of I149T, L238P and R284G mutations of PSEN2 protein from Dynamut, which predicted these mutations to have destabilizing effects on the PSEN2 protein and performed molecular docking with phytochemicals ; Curcumin and Resveratrol using SWISS-DOCK. **Results.**The docked compounds were analyzed for binding energies. **Conclusion.**Thus, we have performed molecular docking of mutant structures of the PSEN2 protein with potential phytochemicals using the molecular docking web tool used in our study. These docked compounds may serve as an aid to drug development studies and unravel a potential cure for EOAD.

**Keywords:** Alzheimer's disease, EOAD, PSEN2, Mutant structures, Novel compounds, Molecular Docking, SWISS-DOCK.

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## INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder. It is characterized by cognitive impairment by progressive deterioration along with declining daily activities, inability to recollect information occupanied by behavioral changes (Fratiglioni et al., 1999).WHO estimates that more than 55 million people are living with dementia of which 8.1 % of women and 5.4% of men are over 65 years. This number is estimated to rise at an alarming rate to 78 million by 2030 and to 139 million by 2050 (Fratiglioni et al., 1999). According to the Dementia India Report 2010 by the Alzheimer's and Related Disorders Society of India (ARDSI), there were around 3.7 million Indians with dementia in 2010 with the number projected to rise to 7.6 million by 2030.

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) also called as diferuloylmethane, is an important natural polyphenol found in the rhizome of *Curcuma longa* (turmeric) (Aggarwal et al., 2003). Turmeric (*Curcuma longa*) is a rhizomatous herbaceous perennial plant of the ginger family. It is a spice that has great significance in both medical/scientific worlds as well as in the culinary world (Priyadarsini, 2014). Resveratrol (3,4′,5- trihydroxystilbene) is a phytoalexin found in many plants such as grapes, berries and groundnuts (Aggarwal et al., 2004). These compounds are potential phytochemical compounds that can be exploited for molecular docking studies (Miziak et al., 2021). This study helps us gain knowledge about the structural effects of these Phytochemicals on the PSEN2 Protein that is said to be the key cause of familial forms of AD.

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 lack of information on the characterization of the missense mutations that are associated with familial AD. Though novel mutations are being identified, the pathophysiological mechanism of AD (Wan et al., 2021) , effects of mutations associated with the genes APP, PSEN1 and PSEN2 which are linked to the autosomal

dominant familial forms of AD are unknown. With an increasing number of AD cases every year, the quest for a clear picture on this information by considering active research on AD as a priority is inevitable. In this study, we aim to predict the deleterious mutations of PSEN2 protein by adopting in-silico docking web servers to investigate the structural impact of missense mutations on the function of PSEN2 protein.

## Materials and Methods

The research study and experiments were conducted at the Molecular Modeling laboratory at Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences. The specifications of the system used for the study are as follows ; 7th Generation Intel(R) Core(TM) i3-7100U CPU @ 2.40GHz processor was used and the OS of the system is Microsoft Windows 10.0.19042. The graphics used were Intel(R) HD Graphics Family, Intel Corporation compatible and 8 GB memory with a constant power supply between 80-85% 180 W Adapter.There is no ethical approval as human samples are not involved.The sample size used for this study is 3 which are three key mutations of the PSEN2 protein and 2 Phytochemicals which are Cucurmin and Reservatrol.

The list of mutations of PSEN2 gene associated with EOAD was retrieved from Alzforum database Alzforum (https://www.alzforum.org/mutations/psen-2) and the mutations were uploaded for Dynamut predictions which also predicted the mutant structures for particular mutations and three mutations; I149T (Perrone et al., 2020), L238P (Blauwendraat et al., 2016) and R284G (Hsu et al., 2018) were focused as targets for the docking studies. The ligands for docking viz. Cucurmin and Resveratrol were obtained from the Zinc database (Irwin & Shoichet, 2005) that was incorporated into the SwissDock web server.

SwissDock (http://swissdock.ch/) , a web service to predict the molecular interactions that may occur between a target protein and a small molecule. This webserver is based on EADock DSS engine which also combines setup scripts that makes the preparation of both the target protein and the ligand input files easier as well as facilitates the curation of common problems (Grosdidier et al., 2011). SwissDock is full automated protein docking web-based platform and it employs a programmatic SOAP interface for this purpose. It also provides access to a list of ligands which are sourced from the Zinc database (Irwin & Shoichet, 2005) and can be searched through the Zinc Accession number.

## RESULTS

Overall, 3 mutant structures were used to carry out molecular docking studies with Cucurmin and Resveratrol whose skeletal structures are depicted in Fig. 1. And Fig. 2. respectively. By visualizing the docked compounds viz, I149T mutant protein with Cucurmin which is shown in Fig. 3 and that with Resveratrol in Fig. 4 and docked complex of L238P mutant protein with Cucurmin and Resveratrol depicted by Fig. 5 and Fig. 6; R284G docked complexes shown in Fig. 7 and Fig. 8, provides us with the binding affinities of the PSEN2 mutant protein with these potential drug compounds. SwissDock and Zinc database were successfully used to perform the docking studies. Table 1 shows the Full Fitness (kcal/mol) and Estimated ΔG (kcal/mol) for 3 mutations viz. I149T, L238P and R284G which were found to have destabilizing effects on PSEN2 structure.

## DISCUSSION

In this study, the structural impact of the missense mutations on PSEN2 protein were studied by using SwissDock by performing molecular docking experiments for I149T, L238P and R284G mutant structures with Cucurmin and Resveratrol.From 63 mutations, 10 mutations were predicted to be deleterious missense mutations from the predictions made by PROVEAN and Predict SNP. Among these mutations 3 mutations were predicted to decrease the stability of the PSEN2 protein on combining the results of predictions from Dynamut and I-mutant 2.0.

Currently, AD has no cure and by 2050 it is predicted that the prevalence will increase threefold with the rapid increase in the aging population. This stimulates the urge to discover more effective treatments and raises a need to speeden up AD research (Association & Alzheimer's Association, 2019). Development of high end sequencing methods has made a drastic progress in sequencing of diseased genomes and identification of novel mutations that are associated with diseases leading to advancements in clinical research (Phillips et al., 2014) .Novel Mutations associated with Alzheimer's disease are being identified now and then (Wan et al., 2021). Till date, around 60 mutations of PSEN2 protein have been identified and mentioned in literature (Hsu et al., 2018). However, the pathogenicity and effects of each of these mutations is still unclear.

With the development of Bioinformatics tools, it has become feasible to predict the effects of mutations on the protein by employing computational algorithms compared to conventional wet-lab methods. The limitation of the study is that docking was performed for fewer novel mutations with two potential phytocompounds due to time constraints and computational power. In future, molecular docking studies of these mutated structures with other potential phytochemical compounds can be performed in order to aid the drug development studies related to AD research.

## CONCLUSION

In our study, the mutant structures of I149T, L238P and R284G were docked with Cucurmin and Resveratrol and novel compounds against the mutational impacts on the PSEN2 protein were identified. These mutations can be focused for drug development and molecular dynamics studies.This study provide us with important implications for the impact of particular mutations which have deleterious and destabilizing effects on the PSEN2 protein leading to aggregation of Amyloid Beta protein which in turn leads to formation of neuronal plaques, resulting in autosomal dominant form of EOAD. This information on the mutations serves useful in genetic testing and counseling of individuals at risk and also paves way for the development of new strategies for delaying the onset of AD.

**Declarations:**

**Conflict of Interest**
The authors of this paper declare no conflict of interest.

**Author Contribution**
Author YM was involved in data collection, data analysis, manuscript writing.
Author SE was involved in conceptualization, guidance and critical review of manuscript.

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## List of Figures and Tables

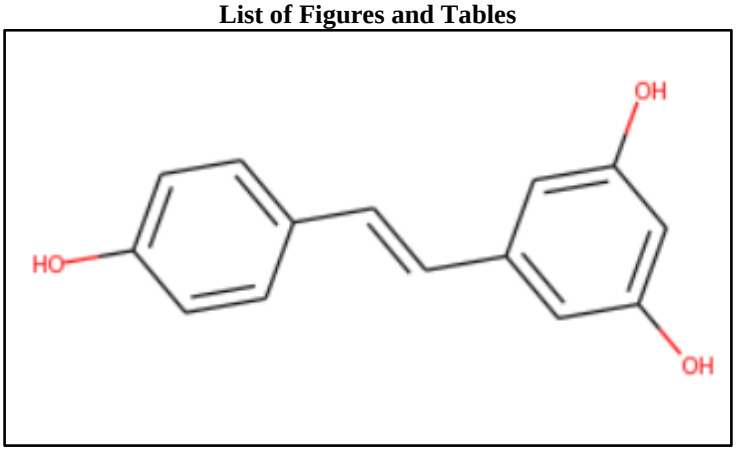


**Fig. 1**. Skeletal structure of Resveratrol retrieved from ZINC database (ID: ZINC6787).

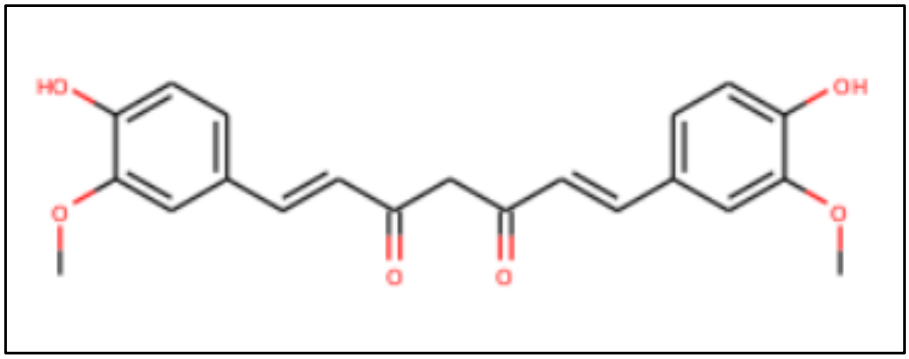


**Fig. 2**. Skeletal structure of Cucurmin retrieved from ZINC database (ID: ZINC899824).

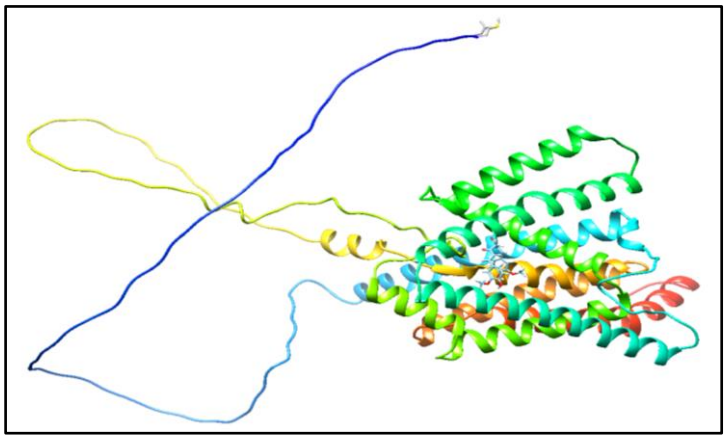

**Fig. 3**. Docked I149T mutant structure of PSEN2 protein with Cucurmin

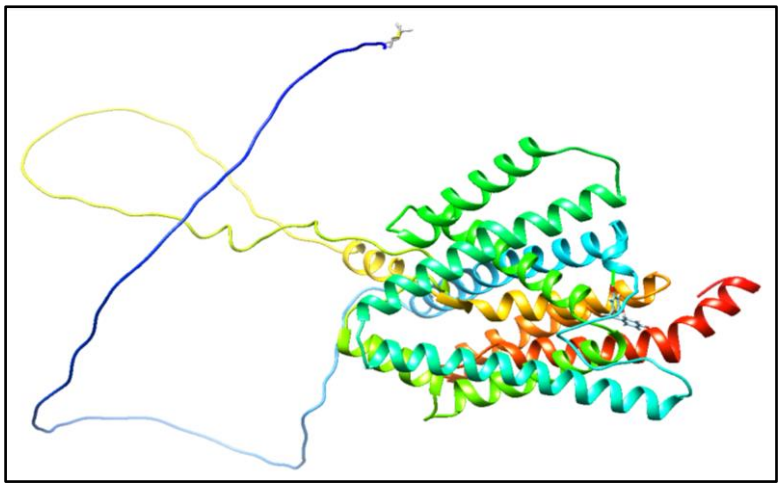

**Fig. 4**. Docked I149T mutant structure of PSEN2 protein with Resveratrol

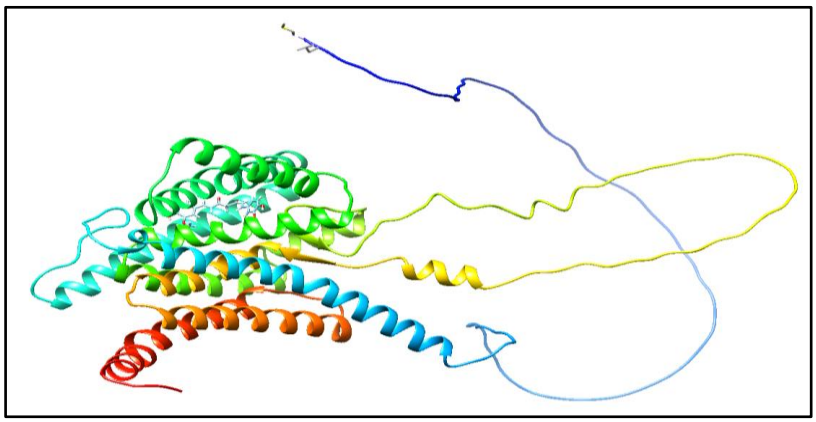

**Fig. 5**. Docked L238P mutant structure of PSEN2 protein with Cucurmin

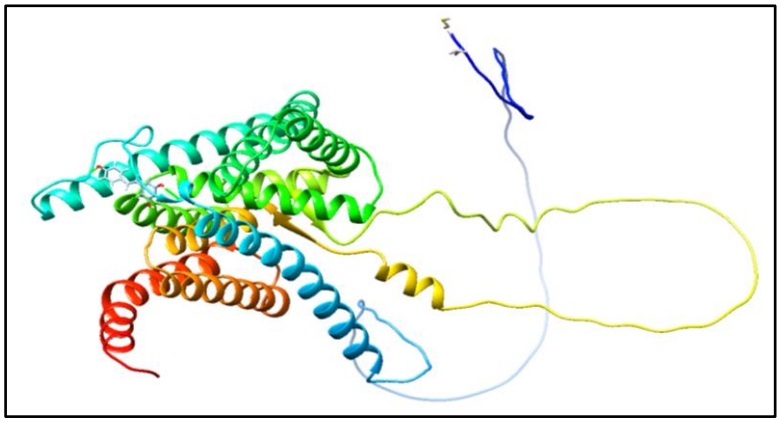

**Fig. 6**. Docked L238P mutant structure of PSEN2 protein with Resveratrol

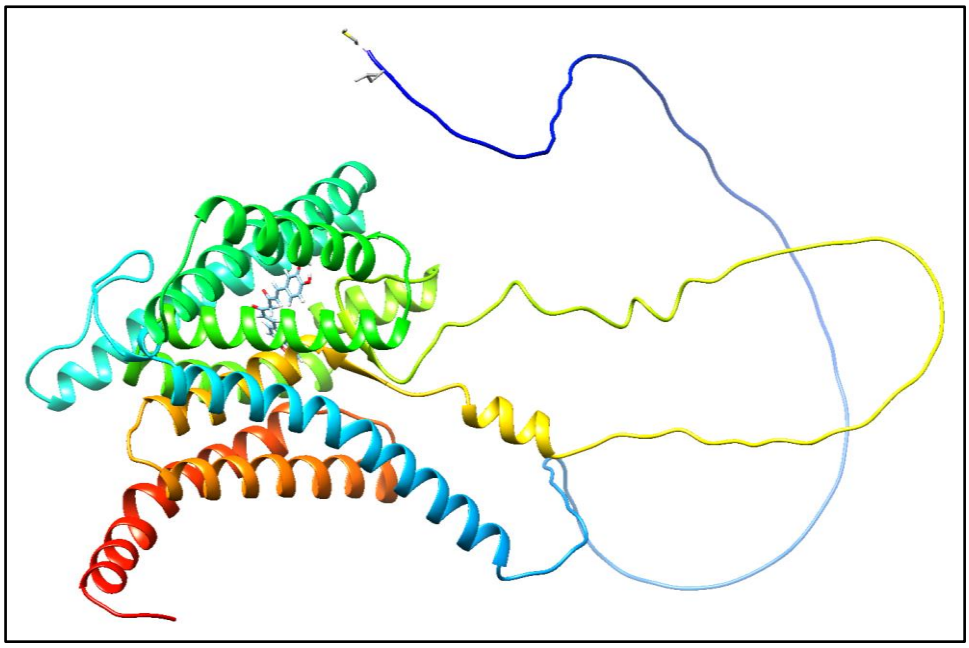

**Fig. 7**. Docked R284G mutant structure of PSEN2 protein with Cucurmin

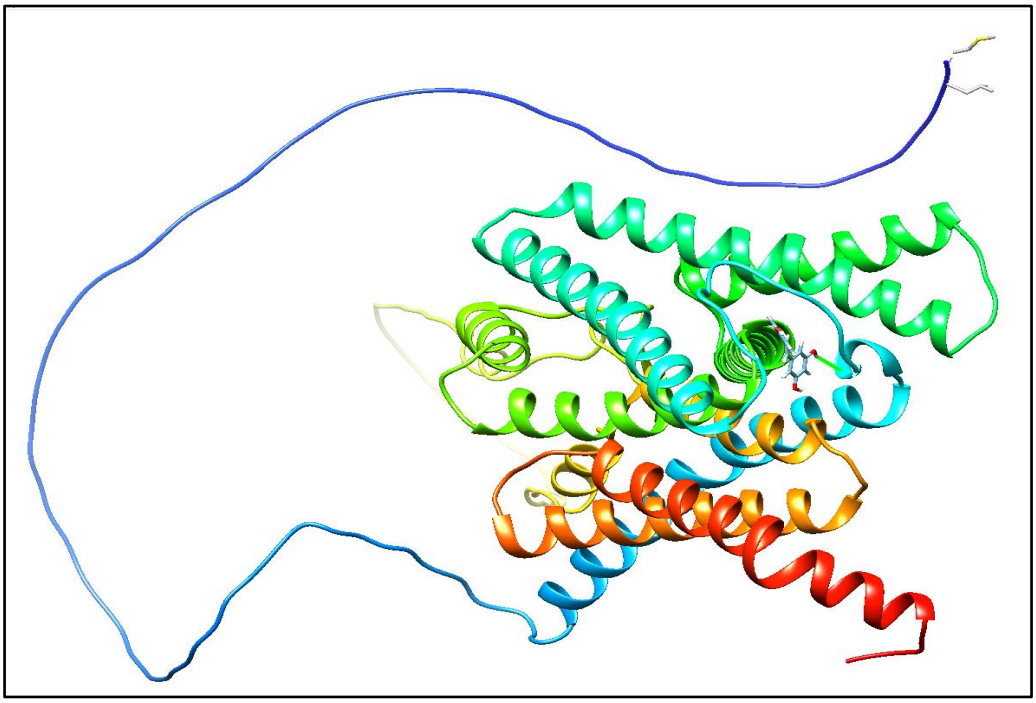

**Fig. 6**. Docked R284G mutant structure of PSEN2 protein with Resveratrol

**Table 1.** Docking scores for I149T , L238P and R284G mutant structures with Cucurmin and Resveratrol

| Target | Ligand | FullFitness (kcal/mol) | Estimated ΔG (kcal/mol) |
|---|---|---|---|
| I149T | Cucurmin | -2514.82 | -7.94 |
| I149T | Resveratrol | -2544.35 | -6.80 |
| L238P | Cucurmin | -2513.43 | -7.88 |

| | | | |
|---|---|---|---|
| L238P | Resveratrol | -2543.01 | -7.39 |
| R284G | Cucurmin | -2509.14 | -7.62 |
| R284G | Resveratrol | -2540.14 | -7.41 |