Proposal

On

Computational assessment of tau-protein targeting neuroprotective phytochemicals for the development of therapies to stop and halt the course of Alzheimer's Disease.

Submitted By

MD Foisal Imtiaz

Department Of Pharmacy

B. Pharm Professionals Part-III

Jahangirnagar University

Savar, Dhaka-1342.

Introduction

Mostly affecting people over 65, Alzheimer's disease (AD) is the most prevalent neurodegenerative illness. The pathological manifestations of AD include the formation of senile plaques and neurofibrillary tangles (NFTs) due to the extracellular deposition of β-amyloid (Aβ) and the intracellular accumulation of hyperphosphorylated tau (pTau)[1]. One of the biggest public health concerns is Alzheimer's disease (AD). In 2019, there were an estimated 57.4 million instances of dementia worldwide; by 2050, that number is predicted to rise to 152.8 million cases about 12% to 22%. It is responsible for about two-thirds of these cases[2]. Age, genetic mutations or variations, traumatic brain damage, and co-morbidities including diabetes and infection are among the more than 20 risk factors[1][3][4]. Plant-derived substances that contain pharmacologically active molecules are known as plant bioactive chemicals. In many aspects, these chemicals produced from plants are better than manmade medicine molecules. This is because they possess a multitude of pharmacological activities and can bind to a broad range of target locations in cells and tissues[5]. In healthy settings, tau is a soluble, unfolded protein; in pathological conditions, however, it becomes insoluble and clumps form NFTs and paired helical filaments. Beyond their functions in neurodegeneration, tau proteins are engaged in a number of cellular activities. Their dysregulation can lead to pathological processes in various disorders, and they are involved in signaling pathways, synaptic function, and neural plasticity[6][2]. So, Computational(CADD) assessment of tau protein-targeting neuroprotective phytochemicals for the development of therapies in Alzheimer's disease is greatly considered for study purpose.

Keywords: Alzheimer's disease (AD), Neurofibrillary tangles (NFTs), Tau(pTau), Risk Factors, Phytochemicals, Computer Aided drug Design(CADD)

Methodology

A. Sample of the Phytochemicals:

1. Olive- Olea europaea
2. Lavander- Lavandula angustifolia
3. Green tea- Camellia sinensis
4. Saffron- Crocus sativus
5. Turmeric- Curcuma longa
6. Rose- Rosa damascena

B. Method:

1. Target Identification

a. **Literature** review by Google Scholar, Pub med, Sci-hub, Library Genesis, Sci-space, Elicit, Connected papers, Open Knowledge Map

b. Compound and Ligand search both natural and chemical by IMPAAT, PubChem, ZINC, Drug bank, ChemBL etc. database

- **Protein structure Study** by PDB database and Tau Protein **PDB**
  DOI: https://doi.org/10.2210/pdb6NK4/pdb

2. Protein Preparation

a. Clean up by Swiss PDB Viewer

b. Active site prediction by Biovia Discovery Stdio

3. Ligand Selection by open bibel via file formatting

4. Virtual screening

a. Ligand based via MOE Tools

b. Featured based via LIGAND SCOUT Tools

c. Docking score via PyRx Tools

5. Molecular Docking

a. Blind Docking for single-ligand or multiple-ligand protein by Autodock Vina

b. Site specific Docking for single-ligand or multiple-ligand protein by PyRx

6. ADMET Analysis by Swiss ADME and ProTox II

7. **Molecular Dynamic Simulation** by Yaasara(Windows), Desmond/Gromace(Linux), Simlab(Web server) with 200ns.

8. PCA Analysis by Rstdio and Minitab18

Objectives

1. **CADD modeling** of multi targeted ligands in Alzheimer's disease (AD)

2. **Target Strategy and experimental potentials** of Alzheimer's disease (AD) treatment

3. **Finding and Improving Protein Degraders** Targeted by neurofibrillary tangles (NFTs) of Tau protein

4. **Protective properties** against the neurological dysfunctions associated with NFTs of Alzheimer's illness

5. **Progression and potential** contributions to pathogenesis of AD

References

[1] E. Liu, Y. Zhang, and J. Z. Wang, "Updates in Alzheimer's disease: from basic research to diagnosis and therapies," *Transl. Neurodegener.*, vol. 13, no. 1, pp. 1–48, 2024, doi: 10.1186/s40035-024-00432-x.

[2] M. Abyadeh *et al.*, "Amyloid-beta and tau protein beyond Alzheimer's disease," *Neural Regen. Res.*, vol. 19, no. 6, pp. 1262–1276, 2024, doi: 10.4103/1673-5374.386406.

[3] N. Villain and R. Michalon, "What is Alzheimer's disease? An analysis of nosological perspectives from the 20th and 21st centuries," *Eur. J. Neurol.*, no. March, pp. 1–10, 2024, doi: 10.1111/ene.16302.

[4] X. Zheng, S. Wang, J. Huang, C. Li, and H. Shang, "Predictors for survival in patients with Alzheimer's disease: a large comprehensive meta-analysis," *Transl. Psychiatry*, vol. 14, no. 1, pp. 1–9, 2024, doi: 10.1038/s41398-024-02897-w.

[5] N. Campano, "The Epidemiology of Alzheimer ' s Disease and It ' s Phyto-Therapeutic Approaches," vol. 28, no. 1, pp. 3225–3231, 2024.

[6] M. C. Silva *et al.*, "Discovery and Optimization of Tau Targeted Protein Degraders Enabled by Patient Induced Pluripotent Stem Cells-Derived Neuronal Models of Tauopathy," *Front. Cell. Neurosci.*, vol. 16, no. March, pp. 1–14, 2022, doi: 10.3389/fncel.2022.801179.