ORIGINAL ARTICLE

The Discovery of Putative Small Molecules via Ligand-based Pharmacophore Modelling Targeting Human Tau Protein for an Effective Treatment of Parkinson's Disease

Yahaya Sani Najib[1,2], Yusuf Oloruntoyin Ayipo[1,3], Waleed Abdullah Ahmad Alananzeh[1], Mustapha Muhammed[4], Mohd Nizam Mordi[1]

[1] Centre for Drug Research, Universiti Sains Malaysia, USM 11800, Pulau Pinang, Malaysia
[2] Department of Pharmaceutical and Medicinal Chemistry, Bayero University Kano, PMB 3011, Kano Nigeria.
[3] Department of Chemistry, Kwara State University, Malete, PMB 1530, Ilorin, Nigeria
[4] Department of Clinical and Social administrative Pharmacy Universiti Sains Malaysia, USM 11800, Pulau Pinang, Malaysia

ABSTRACT

Introduction: The human tau protein is a key protein involved in various neurodegenerative disease (NDs) including Parkinson's disease (PD). The protein has high tendency to aggregate into oligomers, subsequently generating insoluble mass in the brain. Symptoms of PD include tremor, bradykinesia, rigidity, and postural instability. Currently drugs for PD treatment are only symptom-targeted while effective therapeutic treatment remains a challenge. The objective of this study is to identify novel promising anti-PD drugs using computational techniques. **Method:** ligand-based (LB) receptor modelling was conducted using LigandScout, validated and subjected to Glide XP docking, virtual screening, ADMET, and molecular dynamics predictions. **Results:** The adopted LB modelling generated pharmacophoric features of 5 hydrogen bond donors, 1 aromatic rings, and 7 hydrogen bond acceptors. The validation result indicated GH score of 0.73 and EF of 36.30 as validation protocols, probing it to be an ideal model. Using 3D query of the modelling a total of 192 compounds were retrieved from interbioscreen database containing 70,436 natural compounds. Interestingly, ligands 1, 2, 3, 4 and 5 orderly indicated higher binding affinities to the receptor with Glide XP docking of -7.451, -7.368, -7.101, -6.878, and -6.789 compared to a clinical drug Anle138b with -4.552 kcal/mol respectively. Furthermore, molecular dynamics and pkCSM pharmacokinetics demonstrated ligands 1, 2, & 4 having better stability and low toxicity profiles compared to the reference. **Conclusion:** In summary, the study pave way for discovery of small molecules that could be recommended as adjuvant /single candidate as ant-PD candidates upon further translational study.

Malaysian Journal of Medicine and Health Sciences (2023) 19(6):83-94. doi:10.47836/mjmhs.19.6.12

Keywords: Ligand-based modelling; Human tau protein; Parkinson's disease; aggregation; virtual screening

Corresponding Author:
Sani Yahaya Najib, PhD
Email: najibsani62@student.usm.my,
Tel: +601120988567

INTRODUCTION

A number of neurodegenerative diseases (NDs) share proteopathic characteristics, specifically alpha-synuclein (α-synuclein) protein. Misfolding and aggregation of this soluble protein leads to formation and propagation of toxic soluble debris appearing as insoluble fibrillar structure called β-sheet. Parkinson's disease (PD) is a NDs having symptoms including resting tremor, bradykinesia, appearing at initail stage of the disease while postural instability appears when fibrillar structures of α-synuclein are formed at the terminal stage of the disease (1). Early discovery of α-synuclein protein as a precursor protein for non β-amyloid component of Alzheimer's disease (AD) plaques, makes it an interesting protein in NDs. Recent advance techniques such as immunohistochemistry and immuno electron spectroscopy have identified α-synuclein as the major component of Lewi's body and Lewi's neutriles, indicating it as pathological hallmark in NDs including dementia with Lewi's body and PD (2, 3). Moreover, cyclin dependent kinase enzymes play key role in neuronal development and function. The cyclin dependent kinase 2 (cdk2) is conserved and highly expressed in the neurons, and its activity is increased upon injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a toxin responsible for damaging dopamine neurons and subsequent neurodegeneration causing PD (4).

Mounting evidences suggest that pathogenesis of PD is