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Structural insights into the interactions of repositioning and known drugs for Alzheimer's disease with hen egg white lysozyme by MM-GBSA

Amit Kumar Halder[a,b]*, Puja Mishra[a], Souvik Basak[a]*, Debjani Roy[c], Anurag Das[a], Sucheta Karmakar[a], Ritam Mondal[a], Shrestha Banerjee[a], Prakarsha De[a], Ankit Chatterjee[a], Susmita Mallick[a] and Abhijit Hazra[d]

[a]Dr. B. C. Roy College of Pharmacy & Allied Health Sciences, Durgapur, India; [b]LAQV@REQUIMTE/Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto, Porto, Portugal; [c]Department of Biological Sciences, Bose Institute, Kolkata, India; [d]National Institute of Pharmaceutical Education and Research, Kolkata, India

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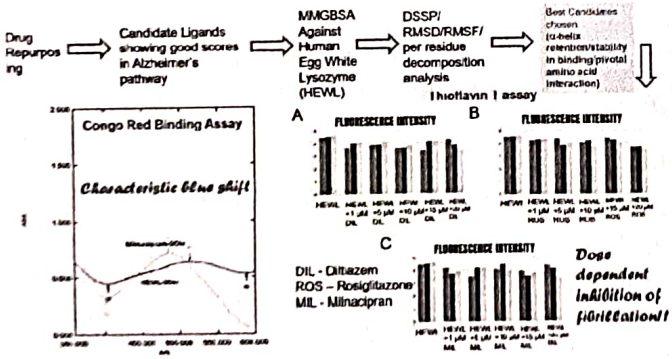
ABSTRACT

Six drugs (dapsone, diltiazem, timolol, rosiglitazone, mesalazine, and milnacipran) that were predicted by network-based polypharmacology approaches as potential anti-Alzheimer's drugs, have been subjected in this study for *in silico* and *in vitro* evaluation to check their potential against protein fibrillation, which is a causative factor for multiple diseases such as Alzheimer's disease, Parkinson's disease, Huntington disease, cardiac myopathy, type-II diabetes mellitus and many others. Molecular docking and thereafter molecular dynamics (MD) simulations revealed that diltiazem, rosiglitazone, and milnacipran interact with the binding residues such as Asp52, Glu35, Trp62, and Asp101, which lie within the fibrillating region of HEWL. The MM-GBSA analysis revealed −7.86, −5.05, and −10.29 kcal/mol as the binding energy of diltiazem, rosiglitazone, and milnacipran. The RMSD and RMSF calculations revealed significant stabilities of these ligands within the binding pocket of HEWL. While compared with two reported ligands inhibiting HEWL fibrillation, milnacipran depicted almost similar binding potential with one of the known ligands (Ligand binding affinity −10.66 kcal/mol) of HEWL. Furthermore, secondary structure analyses revealed notable inhibition of the secondary structural changes with our candidate ligand; especially regarding retention of the 3/10 α-helix both by DSSP simulation, Circular dichroism, and FESEM-based microscopic image analyses. Taking further into experimental validation, all three ligands inhibited fibrillation in HEWL in simulated conditions as revealed by blue shift in Congo red assay and later expressing percentage inhibition in ThioflavinT assay as well. However, dose-dependent kinetics revealed that the antifibrillatory effects of drugs are more pronounced at low protein concentrations.



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1. Introduction

Protein fibrillation is a process characterized by the structural integration of a series of unfolded or misfolded proteins resulting in the formation of fibril-like structures. This fibril-like structure is often mediated by the formation of β-sheet as the core protein monomer, which by end to joining, forms fibril-like oligomers leading to protein aggregation and plaque formation (Arnaudov & de Vries, 2015; Athar et al., 2021; Ban et al., 2018; Borana et al., 2014; Chiti & Dobson, 2006; Dobson, 2003; Faramarzian et al., 2020; Harada et al., 2008). This process, known as amyloidogenesis, often results in tissue dysfunction by

CONTACT Amit Kumar Halder amit.halder@bcrcp.org, amitcsir2011@gmail.com; Debjani Roy roydebjani13@gmail.com
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