**Probing the interactions between Ipragliflozin with RAGE for treating Alzheimer’s disease: An *in-silico* drug repurposing approach**

Bhogal Inderjeet1, Pankaj Vaishali1, and Roy Sudeep1

1 Department of Biomedical Engineering, Faculty of Electrical Engineering and Communication, Brno University of Technology, Brno, 616 00, Czech Republic

Alzheimer’s disease (AD), a progressive neurodegenerative condition, is characterized by the accumulation of amyloid beta peptides and neurofibrillary tangles. The receptor for advanced glycation end products (RAGE) is a multiligand receptor of the immunoglobulin superfamily that has emerged as a crucial target for various complex diseases, including AD. Repurposing existing drugs offers a reliable and cost-effective approach in drug discovery. The current study aims to investigate the possibility of repurposed drugs for treating AD via targeting RAGE. A library of 4,541 repurposed molecules from ChemDiv was used for structure-based virtual screening. Compounds were then filtered using molecular docking, molecular dynamics (MD) simulations, molecular mechanics generalized born surface area (MM/GBSA) binding free energy calculations, principal component analysis (PCA), and absorption, distribution, metabolism, excretion, and toxicity (ADMET) to assess binding affinity and stability of the top-ranked compounds. Five repurposed drugs were predicted as potential RAGE inhibitors based on docking scores ranging from -5.79 to -8.61 kcal/mol. The MD simulation and MM/GBSA studies elucidated the conformational dynamics and stability of predicted repurposed drugs, and Ipragliflozin emerged as a significant binder of RAGE. These findings suggest that Ipragliflozin may offer therapeutic potential for treating neurodegenerative diseases, especially Alzheimer’s disease, after further validation through *in vivo* and *in vitro* studies.

**Keywords**

RAGE, Drug repurposing, Alzheimer’s disease, Ipragliflozin, Virtual screening, Molecular dynamics simulation