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Identification of dual human acetylcholinesterase and butyrylcholinesterase inhibitors through pharmacophore-based virtual screening, molecular docking and molecular dynamics simulation studies

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The concomitant inactivation of both human acetylcholinesterase (hAChE) and butyrylcholinesterase (hBuChE) is a significant factor in the therapeutic approach to AD. The objective of this research is to use *in silico* methodologies namely, pharmacophore-based virtual screening and molecular docking to find potential dual inhibitors targeting both hAChE and hBuChE. Six features' pharmacophores have been developed using structure-based drug design for AChE and BuChE enzymes and the developed pharmacophores have been validated using the Gunery-Henery (GH) Scoring method. The GH scores have been found in the acceptable range; 0.779 for AChE and 0.833 for BuChE-based pharmacophore. Further validated pharmacophores have been used for exploring the ZINC database to retrieve the novel hits employing various parameters *viz* fit value, Lipinski rule of five violation, and feature mapping. After the virtual screening process, 11 molecules have been retrieved which are further subjected to molecular docking to determine the binding interactions with the AChE and BuChE enzymes' active binding sites using the LibDock module in DS 2.0 software. Based on binding energy and binding interactions, three molecules have been selected for the molecular dynamic (MD) simulation and *in silico* pharmacokinetics. Finally, MD simulation and *in silico* pharmacokinetics analysis have exhibited that **ZINC000329492445**, **ZINC000001693021**, and **ZINC000257331938** molecules can be potential dual inhibitors against hAChE and hBuChE.

Keywords: Alzheimer's disease, Structure-based drug design, Virtual screening, Molecular dynamic simulation, *In silico* pharmacokinetics