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CyPD inhibition for Alzheimer's: *In silico* screening of phytochemicals from Asian medicinal plants

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Cyclophilin D (CypD) is a peptidyl-prolyl isomerase F that resides in the mitochondrial matrix and associates with the inner mitochondrial membrane during the mitochondrial membrane permeability transition. CyPD plays a central role in opening the mitochondrial membrane permeability transition pore (mPTP) leading to cell death and has been linked to Alzheimer's disease (AD). Because CypD interacts with amyloid beta (Aβ) to exacerbate mitochondrial and neuronal stress, it is a potential target for drugs to treat AD. Six features' pharmacophores was developed using structure-based drug design for CyPD enzymes and developed pharmacophores were validated using the Gunery-Henry (GH) Scoring method. The GH scores were found in the acceptable range. Further validated pharmacophores were used for exploring the plant-derived 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 were retrieved which were further subjected to molecular docking to determine the binding interactions with the CyPD enzyme's active binding sites using the LibDock module in DS 2.0 software. Based on binding energy and binding interactions, three molecules were selected for the *in silico* pharmacokinetics. The knowledge obtained in this study may help to reveal natural compounds that can become potent inhibitors of CyPD.

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

Alzheimer's disease (AD) is the prevailing etiology of

include the development of inhibitors that impede the