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Identification of Sirtuin 1-targeted anti-Alzheimer agents using structure-based drug design and multi-database screening

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Sirtuin 1 (Sirt1) is a critical enzyme involved in cellular stress responses and neuroprotection, making it a significant target in Alzheimer's disease (AD) research. Dysregulation of Sirt1 contributes to amyloid-beta accumulation, tau hyperphosphorylation, and neuroinflammation—hallmarks of AD pathology. Structure-based drug design (SBDD) aims to develop small molecules that enhance Sirt1 activity, offering a novel therapeutic approach. By targeting Sirt1, these molecules can potentially mitigate AD progression, providing a promising strategy for developing effective treatments. In this present work, a pharmacophore containing six features has been designed using the Sirt1 macromolecule crystal structure using the Discovery Studio 2.0 software and validated by the Gunery-Henery (GH) Scoring method. The GH scores have been found in the acceptable range. Further, validated pharmacophores have been used for exploring the plant-derived database to retrieve the novel hits employing various parameters *viz* fit value, Lipinski rule of five violation, feature mapping, *in silico* pharmacokinetics and toxicological studies. After the virtual screening process, 24-24 molecules from the ZINC and FDA-approved database have been retrieved which have been further subjected to molecular docking to determine the binding interactions with the Sirt1 enzyme's active binding sites using the LibDock module in DS 2.0 software. Based on binding energy and binding interactions 2-2 molecules from the ZINC database and FDA-approved database have been selected for the molecular dynamic simulation. The knowledge obtained in this study may help reveal commercially available compounds that can become potent activators of Sirt1.

Keywords: Sirtuin 1, Alzheimer's disease, Structure-based drug design, Pharmacophore modeling, Molecular docking

Alzheimer's disease (AD) is a devastating stress