

Computational screening of repurposed drugs for HMG-CoA synthase 2 in Alzheimer's disease

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Motivation and Aim: HMGCS2 (mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase 2) plays a pivotal role as a control enzyme in ketogenesis, and its association with the β -amyloid precursor protein (APP) in mitochondria implicates a potential involvement in Alzheimer's disease (AD) pathophysiology. Our study aimed at identifying repurposed drugs using the DrugBank database capable of inhibiting HMGCS2 activity.

Methods and Algorithms: Exploiting the power of drug repurposing in conjunction with virtual screening and molecular dynamic (MD) simulations against predefined targets, we present new in-silico insight into structure-based drug repurposing.

Results: The initial molecules were screened for their binding affinity to HMGCS2. Subsequent interaction analyses and extensive 300 ns MD simulations were conducted to explore the conformational dynamics and stability of HMGCS2 in complex with the screened molecules, particularly Penfluridol and Lurasidone.

Conclusion: The study revealed that HMGCS2 forms stable protein-ligand complexes with Penfluridol and Lurasidone. Our findings indicate that Penfluridol and Lurasidone competitively bind to HMGCS2 and warrant their further exploration as potential repurposed molecules for anti-Alzheimer's drug development.

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