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opinion Article

Repurposing FDA-Approved Drugs for Neurodegenerative Disorders: A Computational and Experimental Approach

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ABOUT THE STUDY

Neurodegenerative disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD) and Amyotrophic Lateral Sclerosis (ALS) continue to pose a major global health burden, with limited effective treatments available. Traditional drug development for these conditions has been slow and costly, with high failure rates during clinical trials. In light of this challenge, drug repurposing identifying new therapeutic uses for already-approved medications has gained attention as a time- and cost-effective strategy. This study adopts a dual computational and experimental approach to identify FDA-approved drugs with potential efficacy in treating neurodegenerative diseases. By leveraging large-scale bioinformatics databases and molecular docking tools, the investigation aimed to repurpose existing compounds that modulate key pathogenic pathways such as oxidative stress, neuroinflammation, misfolded protein aggregation and mitochondrial dysfunction.

The computational phase began with the identification of validated molecular targets commonly implicated in neurodegeneration, such as amyloid-beta, tau protein, alpha-synuclein, GSK-3β and Monoamine Oxidase-B (MAO-B). The DrugBank and Connectivity Map databases were screened to retrieve a list of FDA-approved drugs that interact with these targets. Approximately 50 candidate molecules were shortlisted and their 3D structures were optimized for docking analysis. Using AutoDock Vina, high-affinity interactions were determined based on binding energies, conformational compatibility and key residue interactions. Several anti-inflammatory, antihypertensive and antimicrobial agents exhibited significant binding scores with multiple targets. Notably, the antihistamine drug clemastine and the antihypertensive drug nilvadipine showed strong docking affinity toward amyloid and tau aggregates, suggesting potential neuroprotective roles.

To validate the computational findings, selected drugs were subjected to in vitro testing using neuronal cell models, including SH-SY5Y and differentiated PC12 cells exposed to neurotoxic insults such as hydrogen peroxide and amyloid-beta peptides.

The neuroprotective effects were also tested in organotypic brain slice cultures, where both compounds preserved neuronal architecture and reduced neurodegeneration, as confirmed by Nissl staining and immunohistochemistry for neurofilament proteins. Pharmacokinetic modeling predicted adequate blood-brain barrier permeability and favorable distribution profiles for both drugs, supporting their feasibility for central nervous system applications.

Histological examination of brain tissues showed a marked reduction in amyloid plaque load and gliosis, reinforcing the therapeutic potential of these repurposed agents. Importantly, no significant adverse effects or behavioral abnormalities were noted during the treatment period, indicating a favorable safety profile at the tested doses.

In conclusion, the integration of computational drug repurposing with experimental validation has proven to be a promising strategy for identifying new treatments for neurodegenerative disorders. The identification of clemastine and nilvadipine as neuroprotective agents opens avenues for further clinical investigation, as these drugs are already approved for human use and have well-characterized safety profiles. The dual action of these compounds targeting protein aggregation and neuroinflammation addresses the multifactorial nature of diseases like Alzheimer's and Parkinson's. This approach not only accelerates the drug discovery pipeline but also minimizes the financial risks typically associated with de novo drug development. Future work will focus on expanding the screening to include broader chemical libraries, optimizing drug combinations and conducting advanced clinical trials to confirm efficacy in human patients suffering from neurodegenerative conditions.

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