Title: Integrative structure-based approach for phytocompound-based dual therapeutics targeting Alzheimer's and Parkinson's disease

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Abstract: Neurodegenerative diseases like Alzheimer's and Parkinson's are growing global health concerns with limited treatment options. In this study, we explored four natural compounds—Baicalein, Vincarubine, Rutin, and Luteolin—for their potential as multi-target drugs using computational methods. These compounds were tested against key proteins involved in disease progression, including LRRK2, APP, and Tau kinase. Molecular docking showed that Vincarubine had the strongest binding with LRRK2 and APP, while Rutin interacted best with Tau kinase. Molecular dynamics simulations further supported Rutin's strong and stable binding, with low fluctuation and deviation values. Although Vincarubine showed high binding affinity, it also displayed greater structural flexibility, suggesting it may need some modifications for better stability. Pharmacokinetic analysis revealed that most of the compounds followed drug-likeness rules, but Rutin and Vincarubine had some limitations in size and brain permeability, meaning advanced delivery systems like nanoparticles may be needed. Toxicity tests showed that Baicalein and Rutin were generally safe, while Vincarubine had potential risks for the kidneys and lungs. When compared to commonly used drugs like Donepezil, Memantine, and Levodopa, these natural compounds showed even better binding strength and stability in simulations. Overall, the results suggest these phytocompounds could be promising candidates for treating neurodegenerative diseases. However, further lab-based studies, both in cells and animals, are essential to confirm their real-world potential. Future research should be focused on improving their structures, delivery methods, and possible combinations to boost their effectiveness.

Keywords: Neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; Molecular docking; Molecular dynamics simulation; Leucine-rich repeat kinase 2 (LRRK2); Amyloid-β precursor protein (APP); Human tau protein kinase; Drug discovery

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