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RESEARCH ARTICLE

Ligand and Structure-Based Hybrid Screening for Anti-Parkinson Agents and their Pharmacological Evaluation

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ABSTRACT

The behavioral and biochemical antiparkinson effect of 7-hydroxyflavone (7-HF) was evaluated by using virtual screening with an e-pharmacophore and shape-based screening approach, and the compound was screened by using the Sigma Aldrich compound library. Screened hits were filtered based on Lipinski's rule, absorption, distribution,me tabolism,elimination, (software for evaluation) (ADME), and toxicity parameters. The best scoring hit, 7-hydroxy 2 phenyl-4H-chromen-4-one, i.e., 7-HF was selected based on shape similarity (> 0.7), g-score, and conserved interactions. Toxicity assessment of retrieved hits was carried out by Osiris and Lazar programs. This study aims to obtain some potential hits, against various antiparkinson category from reported literature and available online resources, and validate their potency by *in vivo*, *in vitro* methods. Reserpine 5 mg/kg produces Parkinson's like condition by depleting presynaptic catecholamines, particularly dopamine through the process of degranulation of storage vesicles. 7-HF 25, 50, and 100 mg/kg was used as a test compound. Syndopa 275 mg/kg was used as a standard drug. The results demonstrate that treatment with 7-HF improved the total locomotor activity and muscular coordination in the rotarod test. In the open field test, enhanced rearing, grooming duration of mobility, and gripping strength in the chimney test, while a decrease in cataleptic scores in the bar test. 7-HF significantly increases catalase, superoxide dismutase, and reduces glutathione level, while reduced the Malondialdehyde (MDA) level. The total protein concentration was also increased in 7-HF treated groups. The behavioral and biochemical results obtained from this study disclosed a definite neuroprotective role of 7-HF in a dose-dependent manner. It is also clear that 7-HF showed potent and effective antiparkinson activity in a similar way as standard. Interestingly, in behavioral and biochemical studies, 7-HF showed approximately equivalent effects as compared to syndopa.

Keywords: 7-hydroxyflavone, Catecholamine, Parkinson, Reserpine, Superoxide dismutase, Syndopa.

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INTRODUCTION

Parkinson disease (PD) is a common, slowly progressive, and neurodegenerative disorder resulting from the degeneration of dopaminergic neurons in the substantia nigra (SN), a region of the brain that controls the movement.[1] It was described by James Parkinson in 1817 as "shaking palsy."[2] The initial symptoms of PD, include tremor at rest, muscular rigidity, bradykinesia, postural abnormalities, and instability.[3] The clinical manifestation of PD occurs when about 50% of nigral dopaminergic neurons and about 70% of straital dopamine fibers are lost.[4] Recently, rivastigmine also useful in PD by inhibiting the breakdown of acetylcholine (ACh), improve regularity in walking, maintaining speed, and balance.[5] Oxidative stress is known to damage lipids, proteins, and DNA, along with decreased superoxide dismutase (SOD), catalase, and glutathione levels. The etiology of PD results from a defect in mitochondrial function, dysregulation of brain iron, inflammatory responses, and abnormalities of energy metabolism.[6] Without treatment, PD progresses over 5 to 10 years to a rigid akinetic state, in which patients are incapable of caring themselves. Brain-derived neurotrophic factor (BDNF) initiates plastic changes and modulation of synaptic activity, having a role in the etiopathogenesis of PD.[7] The PD can be treated with various drugs, including levodopa, carbidopa, orphenadrine, benztropine, selegiline, pergola, and many more, which act by reversing the symptoms, but these drugs possess various side effects, like nausea and vomiting, respiratory disturbances, hallucinations, orange discoloration of saliva and urine, mania, dyskinesia convulsions, etc.[8,9] Neural apoptosis is normally prevented by neuronal growth factors, including nerve growth factor and brain-derived neurotrophic factor. These growth factors regulate the expression of the two gene products *Bax* and *Bcl-2*, *Bax* being proapoptotic and *Bcl-2* being antiapoptotic. Blocking apoptosis by interfering at specific points on these pathways, represents an attractive strategy for developing neuroprotective drugs.[10] Recent studies have suggested some contribution of the glycogen synthase kinase-3 (GSK-3) to the degeneration of dopaminergic neurons.[11] Evidence shows that oxidative damage