Indian Journal of Experimental Biology
Vol. 64, March 2026, pp. 239-253
DOI: 10.56042/ijeb.v64i03.23799

Computational Discovery of an AI-Driven Dexamethasone Derivative for Parkinson's disease: Network Pharmacology, Docking, and MD Simulations

Mohammed M. Alshehri[1,2], Nemat Ali[4]*, Ahmed F. Alanazi[1,2], Abdullah M. Albogami[1,2], Nasser Gazy Almaneia[1,2], Falah Muslat Alsubaie[1,2], Farhan Ali Alanazi[3], Ahmed Salem Alharbi[5], Abdulaziz Adel Alshamsi[5], Musab Saeed Khamisah[5]& Faisal Abdulaziz Alwashmi[5]

[1]Pharmaceutical Care Department, Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia
[2]King Abdullah International Medical Research Center, Ministry of National Guard-Health Affairs, Riyadh 14611, Saudi Arabia
[3]Department of Medical Supply, Rafha Maternity and Children Hospital, Northern Borders Health Cluster, Ministry of Health, Rafha, Saudi Arabia
[4]Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[5]Department of Emergency Medicine, Ministry of National Guard-Health Affairs, Saudi Arabia

Received 17 September 2025; revised 6 December 2025

Parkinson's disease (PD) is a complex neurodegenerative disorder with few treatment options that are responsible for only slowing the disease progression. Several studies observed that dexamethasone exhibits neuroprotective effects; however, its systemic side effects restrict its use for prolonged periods. Our study employed Webserver-Aided Drug Design by Artificial Intelligence and Classical Algorithm (WDDAICA) to generate novel dexamethasone analogues with improved pharmacological properties suitable for PD therapy. Differentially expressed genes (DEGs) from the transcriptome data of PD patients (GSE160299) have been compared with dexamethasone-responsive genes, resulting in the identification of 92 shared targets. Enrichment analysis identified essential molecular functions, including metal ion binding and enzyme regulation, highlighting APOE, ICAM1, GAPDH, and EGF as critical targets. The AI-generated derivatives were evaluated using molecular docking against these targets, with molecule C displaying the best binding affinity to APOE (−7.6 kcal/mol), passing dexamethasone (−7.2 kcal/mol). ADMET profiling shows improved oral bioavailability and blood-brain barrier (BBB) permeability for molecule C; however, it also indicates elevated risk for hepatic damage. Molecular dynamics (MD) simulations validated enhanced structural stability and compactness of the molecule C–APOE complex. Additionally, MM-PBSA free energy assessments indicated a superior binding energy for molecule C (−13.8 kcal/mol) in contrast to dexamethasone (−1.8 kcal/mol), accompanied by more comprehensive per-residue interactions. The data indicates that molecule C may be an acceptable candidate for subsequent in vivo study as a neuroprotective drug in PD.

Keyworks: Parkinson's disease; APOE; Dexamethasone; AI Drug Design; Molecular Dynamics Simulations