In-silico study of 1-methyl-3-phenylindole from *Terminalia bellirica* as an estrogen receptor modulator for breast cancer treatment

Ambiga Chinnathambi[a], Rameshthangam Palanivel[b*], Nalina Viswanathan[c], Vidhyavathi Ramasamy[d]

[a]*Research Scholar, Department of Biotechnology, Alagappa University, Karaikudi – 630003, Tamilnadu, India.*

[b*] *Professor & Head i/c Department of Nutrition and Dietetics, Alagappa University, Karaikudi, Tamilnadu, India.*

[c]*Research Scholar, Department of Bioinformatics, Alagappa University, Karaikudi – 630003, Tamilnadu, India.*

[d]*Assistant Professor, Department of Bioinformatics, Alagappa University, Karaikudi – 630003, Tamilnadu, India.*

***Corresponding author:** rameshthangam@alagappauniversity.ac.in

Abstract

This study aims to examine the evidence regarding the role of the estrogen receptor in human breast cancer development and proliferation, and to evaluate photoactive compounds targeting the estrogen receptor (ER) through molecular docking and pharmacokinetic analyses. For the initial screening, three compounds 1-methyl-3-phenylindole, 4,6-di-tert-butylresorcinol, and 2-ethylacridine were subjected to molecular docking using the PyRx platform. ADME analysis indicated that 1-methyl-3-phenylindole exhibited the highest binding affinity, with a Glide energy of −5.30 kcal/mol and a docking score of −5.29, whereas the other two compounds demonstrated comparatively lower binding affinities based on Swiss ADME predictions. In the present study, human serum albumin (HSA; PDB ID: 1UOR) was further investigated as a tumor-targeted nanocarrier through its interaction with the estrogen receptor DNA-binding domain (ER-DBD; PDB ID: 1D5R). Protein–protein docking using HADDOCK revealed a stable interaction between HSA and ER-DBD, with key interfacial residues including Tyr150, Phe211, Arg257, and Glu380 contributing to the stability of the complex. Apo-state molecular dynamics simulations confirmed the conformational stability of the HSA–1D5R complex. Subsequently, natural compounds, including conjugates of 1-methyl-3-phenylindole, were docked at the protein–protein interface using the Glide XP module. The top three ligands displayed strong binding affinities, supported by hydrogen bonding, salt-bridge formation, and π–π stacking interactions. Prime MM-GBSA free-energy calculations estimated binding energies ranging from −45 to −65 kcal/mol. Furthermore, 100-ns molecular dynamics simulations verified stable ligand binding, with persistent interfacial interactions and enhanced overall stability compared to the apo complex. Overall, these

findings highlight the potential of HSA-conjugated natural indole derivatives as selective, nanocarrier-based therapeutic candidates for breast cancer management.

Keywords: 1-methyl-3-phenylindole, Estrogen receptor, Human serum albumin, Molecular Dynamics Simulation, *Terminalia bellirica*