Title: In silico evaluation of anti-colorectal cancer inhibitors by Resveratrol derivatives targeting Armadillo repeats domain of APC: molecular docking and molecular dynamics simulation

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Abstract: Colorectal cancer is the second leading cause of cancer-related deaths. In 2018, there were an estimated 1.8 million cases, and this number is expected to increase to 2.2 million by 2030. Despite its prevalence, the current therapeutic option has a lot of side effects and limitations. Therefore, this study was designed to employ a computational approach for the identification of anti-cancer inhibitors against colorectal cancer using Resveratrol derivatives. Initially, the pass prediction spectrum of 50 derivatives was conducted and selected top seven compounds based on the maximum pass prediction score. After that, a comprehensive analysis, including Lipinski Rule, pharmacokinetics, ADMET profile study, molecular orbitals analysis, molecular docking, molecular dynamic simulations, and MM-PBSA binding free energy calculations. The reported binding affinity ranges of Resveratrol derivatives from molecular docking were -6.1 kcal/mol to -7.9 kcal/mol against the targeted receptor of human armadillo repeats domain of adenomatous polyposis coli (APC) (PDB ID: 3NMW). Specifically, our findings reported that two compounds [(03) Resveratrol 3-beta-mono-D-glucoside, and (29) Resveratrol 3-Glucoside] displayed the highest level of effectiveness compared to all other derivatives (-7.7 kcal/mol and -7.9 kcal/mol), and favorable drug-likeness, and exceptional safety profiles. Importantly, almost all the molecules were reported as free from toxic effects. Subsequently, molecular dynamic simulations conducted over 100ns confirmed the stability of the top two ligand-protein complexes. These findings suggest that Resveratrol derivatives may be effective drug candidate to manage the colorectal cancer. However, further experimental research, such as in vitro/in vivo studies, is essential to validate these computational findings and confirm their practical value.

Keywords: Drug design, Resveratrol derivatives, Colorectal cancer, Molecular docking, Molecular dynamics simulation

DOI: https://doi.org/10.3389/fonc.2024.1360745

https://pmc.ncbi.nlm.nih.gov/articles/PMC11091374/