Abstract

Breast cancer (BC) remains one of the most common causes of cancer-related death worldwide. Current microtubule-targeting agents are often limited by systemic toxicities resulting from their non-selective interaction with α/β-tubulin. γ-Tubulin is overexpressed in BC, particularly in triple-negative breast cancer (TNBC), making it a promising therapeutic target. This study aimed to screen gatastatin and selected O6-position derivatives in silico to identify compounds with improved γ-tubulin binding affinity, greater selectivity over α/β-tubulin, and reduced predicted cardiotoxicity. TUBG1 expression in breast cancer was analyzed using the TCGA-BRCA dataset through the UALCAN platform. Drug-likeness and pharmacokinetic properties were assessed using SwissADME. Molecular docking was performed against γ-tubulin (3CB2), α/β-tubulin (5JVD), and the hERG potassium channel (8ZYO) using PyRx, followed by interaction analysis using BIOVIA Discovery Studio and PyMOL. TUBG1 expression was significantly elevated in BC tissues compared with normal breast tissue and was highest in TNBC. All screened compounds complied with Lipinski's Rule of Five and Veber's Rule and demonstrated high predicted gastrointestinal absorption. O6-furfuryl exhibited the strongest predicted binding affinity toward γ-tubulin (-9.2 kcal/mol), while gatastatin G2 showed the greatest predicted selectivity due to its weak affinity for α/β-tubulin (-4.7 kcal/mol). Among the novel derivatives, O6-cyanomethyl demonstrated the most favorable balance between γ-tubulin affinity and selectivity. However, all compounds showed strong predicted binding to the hERG channel, suggesting potential cardiotoxicity. Overall, O6-cyanomethyl emerged as the most promising novel derivative for further optimization to reduce its hERG interactions.

Keywords: gatastatin, γ-tubulin, in silico, breast cancer, hERG potassium channel