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# Identification of Potential Small Molecule Inhibitors Against β-hCG for Cancer Therapy: An In-Silico Study

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**Abstract :** hCG, a heterodimer composed of α and β subunits, is a peptide hormone having numerous biological functions. Although hCG is expressed by placenta during pregnancy, ectopic β-hCG secretion is observed in many non-trophoblastic tumors including that of breast. In-vitro and in-vivo studies done in the lab, have proved that BRCA1 defective cancers express β-hCG and when β-hCG is expressed or supplemented, it promotes tumor progression and exhibits resistance to carboplatin and ABT888, in such cancers but not in BRCA1 wild type cancers. In cancer cells, instead of binding to its regular receptor, LH-CGR, β-hCG binds with Transforming Growth Factor Receptor 2 (TGFβRII) and phosphorylates it resulting in faster tumor progression through the Smad signaling pathway. Targeting β-hCG could be a potential therapeutic strategy for managing BRCA1 defective cancers. Here, molecular docking and dynamic simulation studies were done to identify potential small molecule inhibitors against β-hCG as there are currently no such inhibitors reported. The binding sites of TGFβRII on β-hCG were identified from the top 10 predicted complexes from Z Dock. Virtual screening of selected commercially available small molecules from various libraries such as ZINC, NCI and Life Chemicals amounting to a total of 50,025 molecules were done. Four potential small molecule inhibitors were identified, RgcbPs-1, RgcbPs-2, RgcbPs-3 and RgcbPs-4 with binding affinities -60.778 kcal/mol, -45.447 kcal/mol, -65.2268 kcal/mol and -82.040 kcal/mol respectively. Further, 100ns Molecular Dynamics (MD) simulation showed that these molecules form stable complexes with β-hCG. RgcbPs-1 maintains hydrogen bonds with Q54, L52, Q46, C100, G36, C57, C38 residues, RgcbPs-2 maintains hydrogen bonds with A83 residue, RgcbPs-3 maintains hydrogen bonds with C57, Y58, R94, G101 residues and RgcbPs-4 maintains hydrogen bonds with G36, C38, T40, C57, D99, C100, G101 and L104 residues of β-hCG all of which coincide with the TGFβRII binding site on β-hCG. These results show that these two inhibitors could be used either singly or in combination for inhibiting β-hCG from binding to TGFβRII and thereby directly inhibiting the tumorigenesis pathway.

**Keywords :** β-hCG, breast cancer, dynamic simulations, molecular docking, small molecule inhibitors, virtual screening.
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