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Computer-aided anti-cancer drug discovery of EGFR protein based on virtual screening of drug bank, ADMET, docking, DFT and molecular dynamic simulation studies

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ABSTRACT

Numerous malignancies, including breast cancer, non-small cell lung cancer, and chronic myeloid leukemia, are brought on by aberrant tyrosine kinase signaling. Since the current chemotherapeutic medicines are toxic, there is a great need and demand from cancer patients to find novel chemicals that are toxic-free or have low toxicity and that can kill tumor cells and stop their growth. This work describes the in-silico examination of substances from the drug bank as EGFR inhibitors. Firstly, drugbank was screened using the pharmacophore technique to select the ligands and Erlotinib (DB00530) was used as matrix compound. The selected ligands were screened using ADMET and the hit compounds were subjected to docking. The lead compound from the docking was subjected to DFT and MD simulation study. Using the pharmacophore technique, 23 compounds were found through virtual drug bank screening. One hit molecule from the ADMET prediction was the subject of docking study. According to the findings, DB03365 molecule fits to the EGFR active site by several hydrogen bonding interactions with amino acids. Furthermore, DFT analysis revealed high reactivity for DB03365 compound in the binding pocket of the target protein, based on E_{LUMO}, E_{HOMO} and band energy gap. Furthermore, MD simulations for 100 ns revealed that the ligand interactions with the residues of EGFR protein were part of the essential residues for structural stability and functionality. However, DB03365 was a promising lead molecule that outperformed the reference compound in terms of performance and in-vitro and in-vivo experiments needs to validate the study.

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1. Introduction

With 9.6 million fatalities over the previous few decades, cancer is the second biggest cause of mortality worldwide. About one in six deaths worldwide are caused by cancer (Feng et al., 2019). The WHO estimates that during the next two decades, the number of new cases will increase by roughly 70%, or from 14 million to 22 million (Shahzadi et al., 2021). In 2020, cancer was the primary cause of 10 million deaths (Sung et al., 2021). Chemotherapy, surgical procedures, and radiotherapy are currently used to treat cancer. Since the current chemotherapeutic medicines are toxic, there is a great need and demand from cancer patients to find novel chemicals that are toxic-free or have low toxicity and that can kill tumor cells and stop their growth. Therefore, searching for new anti-cancer medications is one of the main objectives of drug research and discovery.

The proliferation, survival, adhesion, migration, and differentiation of cancer cells are all significantly influenced by the epidermal growth factor receptor (EGFR) (Yarden, 2001). The walls of tumor cells contain EGFR. They require this protein to survive and develop. Therefore, in a number of cell phenotypes in the human skin, the EGFR plays a crucial role in regulating immunological responses, cell migration, adhesion, and proliferation (Lacouture, 2006). Additionally, the first receptor to demonstrate a connection between mutation and overexpression in tumor cells is the EGFR (Hynes & Lane, 2005). This receptor has a broad role in signal transduction, oncogenesis, and the development of epithelial malignancies. The tyrosine kinase receptor EGFR belongs to the ErbB/EGFR family and initiates signaling in cells with the help of EGFR ligands like heregulin (Schmidt & Wels, 2002). Additionally, the availability of EGFR ligands is strictly controlled to maintain the homeostatic kinetics of cell growth.

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