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EXPLORING THE POTENTIAL OF DRUG REPURPOSING AGAINST ABNORMALLY REGULATED CELL-MATRIX INTERACTIONS IN THE TREATMENT OF PANCREATIC CANCER (A COMPUTATIONAL STUDY)

Shahed Alsawaf
Üsküdar University, Institute of Sciences, Department of Molecular Biology, Istanbul, Türkiye
Shahdsaw@hotmail.com

Tuğba Bal
Üsküdar University, Faculty of Engineering and Natural Sciences, Department of Bioengineering, Istanbul, Türkiye

Zihni Onur Çalışkaner
Biruni University, Faculty of Engineering and Natural Sciences, Department of Molecular Biology and Genetics, Istanbul, Türkiye
zcaliskaner@biruni.edu.tr

ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) represents one of the most aggressive cancers, with a 5-year survival rate of only 8%. The progression of the disease is significantly influenced by the tumor microenvironment, especially by cell-extracellular matrix (ECM) interactions. The aim of this study is to repurpose small molecules as inhibitor candidates to jointly target key receptors for the ECM attachment, specifically discoidin domain receptors (DDR1 and DDR2), which are implicated in promoting tumor growth through cell-collagen

interactions.Using a computational drug repurposing framework, we accomplished ligand docking and virtual screening to identify potential inhibitory agents targeting DDR1 and DDR2. Ligand libraries including 8540 small chemical molecules (neutral charge, molecular weight of 450-500 Da and logP of 2-3 were chosen) were assembled from the Zinc15 database, and 3D structure files of DDR1 (PDB ID: 6BSD) and DDR2 (PDB ID: 2WUH) were processed (removal of water and heteroatoms, polar hydrogen addition, missing atom repair, etc.) using Discovery Studio Software. Following virtual screening by PyRx software, the top 20 ligands were validated by in silico molecular docking using AutoDock4 and PyMOL via parameters such as inhibition constants and affinity scores compared to the known anticancer drugs of Dasatinib, Imatinib, Nilotinip, Ponatinib.Herein, our study has come out with promising candidates, particularly compounds ZINC0000958672 and ZINC000013960048, that can commonly be used for both DDR1 and DDR2 inhibition, with higher efficacy observed for DDR1. These findings suggest that highlighted molecules may be potent to manage PDAC aggressiveness and offer new avenues for therapeutic interventions by targeting ECM receptors and related critical signaling pathways. Consequently, this research bridges the gap between computational drug discovery and clinical applications, aiming to improve treatment outcomes for PDAC patients.

Keywords:

Pancreatic Ductal Adenocarcinoma, Extracellular Matrix, Drug Repurposing, DDR1, DDR2, In Silico Docking.