In Silico Approach for Targeting PDGFR Pathway of Oral Squamous Cell Carcinoma

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is among the top five cancers in Pakistan. Addiction of high-risk content such as tobacco, betel quid, areca nut, etc. contributes to cause malignant condition in oral region. As the malignancy rises, new blood vessels form continuously that lead to the progression of tumor stage. The process of angiogenesis and uncontrolled cell growth are associated with the increased expression of platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor and signal transduction pathways. Inhibition of the signaling pathways is being regulated by advanced targeted therapy using monoclonal antibodies and small molecule inhibitors. Treatment of cancer with small molecule inhibitors is preferred due to easy oral consumption and cost effectiveness. Various indole-based tyrosine kinase inhibitors (TKIs) have been recommended for actively playing role in inhibiting the PDGF/PDGFR signaling mechanism of breast cancer, ovarian cancer, prostate cancer, liver cancer, renal cancer, thyroid cancer, etc. However, PDGF receptor pathway inhibition in OSCC has rarely been studied. Present study focuses to investigate anti PDGR potential of TKIs using in silico approach. Molecular docking studies were conducted using GOLD and PatchDock program to identify the potential anti-PDGFR molecules. Protein ligand interactions was analyzed using visualizing software. The most stable conformation of ligand bound with protein with least energy was suggested as the most active drug candidate. This approach helped in identifying drug candidates that may likely be proposed as a palliative care for OSCC patients.

Keywords: Cancer treatment, In silico approach, Molecular docking, Oral squamous cell carcinoma, PDGFR pathway, TKIs

INTRODUCTION

Oral cancer is a life-threatening disease that impairs lips and its linings and regions of oral cavity. Approximately 90% of oral cancer is related to squamous cells and hence it is also referred as Oral Squamous Cell Carcinoma (OSCC). It ranks 6th among all cancers globally. It is the second most common cancer in Pakistan that put 10,617 lives along with 16,959 new cases in 2020 and 32,646 cases within 5 years. Age-standardized incidence rate of oral cancer is 12.9% in males and 6.2% in females of Pakistan(Anwar et al., 2020).

Geographically, South Asia and Southeast Asia are highly affected from OSCC. The main etiology of OSCC is the addiction of tobacco intake (in the form of smoking, smokeless or chewing) and alcohol; while other risk factors involve betel quid, areca nut, viral infections mainly Human Papilloma Virus (HPV), family background or inheritance, poor diet, weak body defense, UV exposure, etc (Fatima et al., 2015). Chemotherapeutic drugs are toxic and not selective particularly towards tumor cells. They include 5-fluorouracil, and platinum-based drugs such as oxiplatin, carboplatin that damage DNA. Administration of fluorouracil, cisplatin and docetaxel did not improve overall survival in OSCC patients. So far, targeted therapy approach is being employed by use of either monoclonal antibodies or tyrosine kinase inhibitors (TKI).

Extensive studies have been conducted on EGFR, VEGF, mTOR, CDK and PD-1 pathways and their inhibitors. Gefitinib was the first oral kinase inhibitor of EGFR but its toxicity was also reported with the combination of other drugs (Liu et al., 2019). Hence, there is still need to investigate another potential pathway involved in oncogenesis which can be used as potential therapeutic target to expand the horizon of research and treatment for OSCC.

Platelet-derived growth factor (PDGF) is a cell surface receptor that belongs to class III of tyrosine kinase family. It is associated in the progression of various cancers such as gastrointestinal stromal tumor (GIST), thyroid cancer, colorectal cancer, and hepatocellular carcinoma (HCC). mRNA expression of PDGFRA is also found high in case of OSCC which causes secondary tumor. It is reported that PDGFR-b serves as a biomarker for identifying carcinoma associated fibroblasts in OSCC (Kartha et al., 2016). Cierpikowski et al. observed co-expression of PDGFR-a with EGFR/p53 in the study of OSCC samples (Cierpikowski et al., 2019). Till date, it is less explored pathway in the context of OSCC, thus, in-depth association of PDGF pathway with OSCC needs to be exploited.

Computer-aided drug discovery has brought significant revolution in drug discovery process because of its quick performance, time-saving and cost-effectiveness. Using structure-based drug design approach, molecular docking technique is one of the widely adopted methods for the identification of potential drug against the related protein target. It would be a good option to screen tyrosine kinase inhibitors against PDGFR pathway using molecular docking and propose the most potential drug that helps to inhibit PDGF signal transduction pathway. In this way, it could be beneficial therapeutic approach for OSCC.

OBJECTIVES

To explore potential of indole compounds as inhibitors of PDGFR pathway using molecular docking approach.

To study ligand protein complex on the basis of binding energy, hydrogen bonding and molecular interaction.

To suggest best possible indole compound as a possible therapeutic agent in OSCC.

METHODOLOGY

Preparation of receptor

The preliminary step of in silico studies is the selection of crystal structure of protein. Among structures available in PDB, a co-crystallized receptor-ligand complex was preferred having resolution better than ~2Å. Three-dimensional structure of PDGF receptor i.e. 6JOL was taken from RCSB Protein Data Bank. Water molecules and other heteroatoms bound to the both receptors were removed, and polar hydrogens were added in receptor structures.

Preparation of ligands

For current study, indole compounds were downloaded from PubChem database in SDF format. These compounds serve as ligands. OpenBabel tool was used to convert the file format of ligands. File format of ligands was changed according to the need of docking method. Likewise, they were prepared accordingly.

Docking of receptor with ligands

Molecular docking was performed by widely used programs, GOLD and PatchDock. First, the docking method was validated by using a co-crystal ligand. After validation step, binding pocket of receptor was identified followed by the adjustment of grid box. The grid box was centered on the active site of protein within 4 Å of 6JOL. Drug candidates were docked against protein receptor. Energy values were obtained from several runs of docking step and they were analyzed further.

Intermolecular interactions

Discovery Studio Visualizer (DSV) was used for visualization of protein-ligand complex after docking. Intermolecular interactions were observed in terms of non-covalent bonding such as hydrogen bonding, hydrophobic and electrostatic interaction. The ligand was prioritized with respect to the maximum interactions found with the protein target.

CONCLUSION

The current study may provide great understanding for the proposed tyrosine kinase inhibitor and its binding to the active site of platelet derived growth factor receptor. In our study the selected indole compounds were ranked according to the Goldscore fitness function and PatchDock scores. The compound was prioritized which had the maximum interaction with the protein receptor as well as the highest score among both docking software. Therefore, we can conclude that these compounds may serve as possible inhibitors platelet derived growth factor receptor pathway. The current study has potential to suggest putative and promising inhibitors against the drug target of oral squamous cell carcinoma. Hence, our research will be beneficial to provide great understanding for the proposed tyrosine kinase inhibitors for the treatment of OSCC.

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