Trop J Nat Prod Res, October 2025; 9(10): ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Molecular Docking and Dynamics Simulation of *Holothuria Scabra* In Non-Small Cell Lung Cancer Through Inhibition of EGFR And KRAS Pathways

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Published online *****

ABSTRACT

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related mortality worldwide, highlighting the urgent need for novel therapeutics to overcome resistance and improve patient outcomes. This study employed an *in silico* pipeline to evaluate the potential of bioactive compounds from *Holothuria scabra* as inhibitors of epidermal growth factor receptor (EGFR) and KRAS, which are key NSCLC drivers. Selected *H. scabra* compounds retrieved from PubChem were screened for toxicity using ProTox 3.0, docked with PyRx/AutoDock Vina against EGFR (PDB: 2ITY) and KRAS (PDB: 7LGI) with Lazertinib as a comparator; the top-ranked complexes were further analyzed through 100 ns molecular dynamics simulations in YASARA (AMBER14/TIP3P) to assess stability. Several *H. scabra* ligands demonstrated stronger docking affinities than Lazertinib (e.g., C3: EGFR ΔG = −9.4 kcal·mol; C4: KRAS ΔG = −8.7 kcal·mol), while toxicity predictions indicated that all compounds were nontoxic. Docking analysis further revealed that compounds C3, C5, and C8 exhibited stronger affinities toward EGFR, with C3 interacting with key binding residues (VAL726, LYS745, and ASP855). Compounds C4, C3, and C7 showed superior affinities for KRAS, with C4 binding to critical residues (LYS117 and LYS147), similar to Lazertinib. Molecular dynamics simulations confirmed that the top ligands, particularly C3 and C4, maintained stable interactions without inducing significant protein unfolding or persistent root mean square deviation fluctuations. These findings indicate that *H. scabra*-derived ligands, especially C3 and C4, represent promising *in silico* candidates for subsequent biochemical and cellular validation as potential NSCLC inhibitors.

Keywords: Non-Small Cell Lung Cancer, Molecular Docking, Molecular Dynamic, Holothuria scabra, Epidermal Growth Factor Receptor, Kirsten Rat Sarcoma Viral Oncogene Homolog

Introduction

Lung cancer is one of the deadliest diseases and has become a major health concern worldwide.[1] According to data from the Global Cancer Observatory (GLOBOCAN) in 2022, lung cancer cases have risen, representing approximately 2.5 million new cases, or 12.4% of all cancers types.[2] In Indonesia, lung cancer is also one of the leading cancers in terms of incidence and mortality, with over 38,904 new cases and 34,339 deaths, making it the leading cause of cancer-related deaths (14.1%) in 2022.[3] Furthermore, a report from BPJS Kesehatan indicates that collected in 2018, the total expenditure on cancer treatment reached IDR 1.4 billion, with the proportion of direct medical costs per patient being 50.3% for males and 49.7% for females.[4] These data show that lung cancer not only affects individual health but also places a significant burden on the national healthcare system.

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Citation: Nugraha IC and Febriza A. Molecular Docking and Dynamics Simulation of *Holothuria Scabra* In Non-Small Cell Lung Cancer Through Inhibition of EGFR And KRAS Pathways. Trop J Nat Prod Res. 2025; 9(10):

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Lung cancer is a malignant disease that begins in the bronchi or lung tissue; it is primarily categorized into two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is the most prevalent, accounting for approximately 85% of all lung cancer cases, whereas SCLC accounts for approximately 15%.[5] Current lung cancer treatments include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. However, these approaches have several limitations, including resistance to therapy, poor prognosis, and high costs. Therapies targeting mutations, such as epidermal growth factor receptor (EGFR), ALK, KRAS, and G12C, have demonstrated improvements in patient outcomes survival.[6] Although effective at extending the life expectancy of patients with advanced-stage cancer, these treatments face challenges, such as drug resistance, which reduces their long-term effectiveness. Therefore, there is an urgent need for new therapeutic agents that are effective and target specific mechanisms of NSCLC.

Mutations in the EGFR are among the most important and commonly seen genetic changes, acting as key driver mutations in NSCLC. EGFR is a transmembrane protein that functions as a tyrosine kinase receptor for various ligands, playing a crucial role in controlling cell growth, differentiation, and survival.[7] Additionally, KRAS mutations are present in approximately 40% of NSCLC cases, with the KRAS G12C variant being the most prevalent subtype, accounting for approximately 10%–13% of all NSCLC cases.[8] With over 17,000 islands, Indonesia is the largest archipelagic country in the world. About 70% of its territory consists of oceans, and its coastline extends more than 81,000 kilometers, making it the country with the second-longest coastline in the world, after Canada.[9] The province of South Sulawesi, for instance, is abundant in marine natural resources. The sea cucumber is a highly nutritious marine resource with medicinal properties. *Holothuria scabra* (commonly known as sandfish) is a species of sea cucumber found around Sulawesi. A study published in SAGE Open Medicine