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Research Article

Identification of 20(*S*)-Ginsenoside Rh2 as a Potential EGFR Tyrosine Kinase Inhibitor

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As the main active ingredients of *Panax ginseng*, ginsenosides possess numerous bioactivities. Epidermal growth factor receptor (EGFR) was widely used as a valid target in anticancer therapy. Herein, the EGFR targeting activities of 20(*S*)-ginsenoside Rh2 (20(*S*)-Rh2) and the relationship of their structure-activity were investigated. Homogeneous time-resolved fluorescence assay showed that 20(*S*)-Rh2 significantly inhibited the activity against EGFR kinase. 20(*S*)-Rh2 was confirmed to effectively inhibited cell proliferation in a dose-dependent manner by MTT assay. Furthermore, quantitative real-time PCR and western blotting analysis revealed that 20(*S*)-Rh2 inhibited A549 cells growth via the EGFR-MAPK pathway. Meanwhile, 20(*S*)-Rh2 could promote cell apoptosis, block cell cycle, and reduce cell migration of A549 cells, respectively. *In silico*, the result suggested that both hydrophobic interactions and hydrogen-bonding interactions could contribute to stabilize their binding. Molecular dynamics simulation showed that the side chain sugar moiety of 20(*S*)-Rh2 was too flexible to be fixed at the active site of EGFR. Collectively, these findings suggested that 20(*S*)-Rh2 might serve as a potential EGFR tyrosine kinase inhibitor.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide. Non-small-cell lung cancer (NSCLC) contributes over 80% of lung cancer cases with a low 5-year survival rate [1]. The development of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) plays a key role in the targeted therapy of NSCLC. Epidermal growth factor receptor (EGFR) is considered a receptor tyrosine kinase with penetrating the cell membrane [2]. EGFR is composed of an extracellular ligand-binding region, a transmembrane region, and an intracellular tyrosine kinase region [3]. Binding to the ligand, EGFR forms a dimer and the phosphate of ATP transfers into the tyrosine residue. Then, different kinds of proteins bind to this phosphorylated tyrosine and signals transmit to downstream pathways, such as mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways [4, 5]. It is well known that EGFR plays a key role in cell proliferation, apoptosis, and migration [6]. Furthermore, EGFR is confirmed to be dysregulated or overexpressed in various solid tumors and used as one of the valid targets in anticancer therapy [7, 8].

As the main active ingredients of *Panax ginseng* (*P. ginseng*), ginsenosides have been widely used in cancer treatment with reduced side effects [9–11]. Ginsenoside Rh2 can be divided into 20(*S*)-ginsenoside Rh2 (20(*S*)-Rh2) and 20(*R*)-ginsenoside Rh2 (20(*R*)-Rh2) according to different orientations of the hydroxyl group at C-20 position [12, 13]. Tumor-associated macrophages (TAMs) are confirmed to play crucial roles in modulating the tumor microenvironment and promoting tumor metastases [14]. Rh2 showed potential to convert TAMs from the alternatively activated M2 macrophages to classically activated M1 macrophages in the microenvironment. Meanwhile, Rh2 prevented NSCLC cell migration, suggesting the therapeutic effects of Rh2 on lung cancer [15]. Rh2 was also demonstrated to inhibit the proliferation and metastasis of NSCLC cells by inducing apoptosis and suppressing epithelial-mesenchymal transition, respectively [16]. In the chemotherapy for NSCLC patients, Rh2 enhanced the antitumor effects of cisplatin through inhibiting the superoxide