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Biflavonoids from Selaginellaceae as Epidermal Growth Factor Receptor Inhibitors and Their Anticancer Properties

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Abstract : The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein involved in cellular signalling processes and, its aberrant activity is crucial in the development of many cancers such as lung cancer. Selaginellaceae are fern allies that have long been used in Chinese traditional medicine to treat various cancer types, especially lung cancer. Biflavonoids, the major secondary metabolites in Selaginellaceae, have numerous pharmacological activities, including anti-cancer and anti-inflammatory. For instance, amentoflavone induces a cytotoxic effect in the human NSCLC cell line via the inhibition of PARP-1. However, to the best of our knowledge, there are no studies on biflavonoids as EGFR inhibitors. Thus, this study aims to investigate the EGFR inhibitory activities of biflavonoids isolated from Selaginella siamensis and Selaginella bryopteris. Amentoflavone, tetrahydroamentoflavone, sciadopitysin, robustaflavone, robustaflavone-4-methylether, delicaflavone, and chrysocauloflavone were isolated from the ethyl-acetate extract of the whole plants. The structures were determined using NMR spectroscopy and mass spectrometry. In vitro study was conducted to evaluate their cytotoxicity against A549, HEPG2, and T47D human cancer cell lines using the MTT assay. In addition, a target-based assay was performed to investigate their EGFR inhibitory activity using the kinase inhibition assay. Finally, a molecular docking study was conducted to predict the binding modes of the compounds. Robustaflavone-4-methylether and delicaflavone showed the best cytotoxic activity on all the cell lines with IC50 (μM) values of 18.9 ± 2.1 and 22.7 ± 3.3 on A549, respectively. Of these biflavonoids, delicaflavone showed the most potent EGFR inhibitory activity with an 84% relative inhibition at 0.02 nM using erlotinib as a positive control. Robustaflavone-4-methylether showed a 78% inhibition at 0.15 nM. The docking scores obtained from the molecular docking study correlated with the kinase inhibition assay. Robustaflavone-4-methylether and delicaflavone had a docking score of 72.0 and 86.5, respectively. The inhibitory activity of delicaflavone seemed to be linked with the C2”=C3” and 3-O-4”’ linkage pattern. Thus, this study suggests that the structural features of these compounds could serve as a basis for developing new EGFR-TK inhibitors.

Keywords : anticancer, biflavonoids, EGFR, molecular docking, Selaginellaceae
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