Title : Investigation of the biological activities of 2´,4´-Dihydroxy-6´-methoxy-3´,5´-dimethyl chalcone (DMC) derivatives via EGFR inhibition pathway in non-small cell lung cancer

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Major : Biochemistry and Biochemical Innovation

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ABSTRACT

Due to the PM2.5 pollution issue and smoking behavior in Thai society, lung cancer has become the second most diagnosed cancer among the Thai population. Currently, several therapeutic strategies are available for lung cancer treatment, including conventional chemotherapy such as Doxorubicin and targeted therapy using Osimertinib. However, these treatments are often associated with various adverse side effects that significantly affect patients. Therefore, natural products have gained increasing attention as alternative therapeutic agents with the potential to reduce the side effects of conventional chemotherapy. In this study, we focused on the 2´,4´-dihydroxy-6´-methoxy-3´,5´-dimethyl chalcone (DMC) natural compound with anticancer activity that was isolated from the seeds of Syzygium nervosum A. Cunn. Ex. Dc, a local plant is found in northern Thailand. The anticancer activity of DMC derivatives was investigated by conjugating DMC with amino acids, including tyrosine, phenylalanine, and methionine. These modifications were expected to enhance water solubility and cellular uptake, thereby improving anticancer efficacy while reducing the side effects associated with chemotherapy. The cytotoxic effects of the synthesized compounds against human lung cancer H-460 cells were evaluated using the MTT assay and compared with those of Doxorubicin and Osimertinib. The results demonstrated that

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the half maximal inhibitory concentration (IC50) values of DMC, DMC-Tyr, DMC-Phe, DMC-Met, Doxorubicin, and Osimertinib were 13.69 ± 0.32, 12.57 ± 0.44, 15.21 ± 3.62, 7.25 ± 0.54, 0.13 ± 0.04, and 6.33 ± 0.76 μM, respectively. In conclusion, DMC-Met exhibited approximately 2-fold greater inhibitory activity against H-460 lung cancer cells compared with DMC and showed anticancer efficacy comparable to that of currently used anticancer drugs. Furthermore, the expression of epidermal growth factor receptor (EGFR), which is involved in apoptosis-related signaling pathways, was examined using Western blot analysis. After treatment with the compounds at their IC50 concentrations for 48 h. H-460 cells showed a significant reduction in EGFR protein expressions, which were observed after treatment were compared with the control group. These findings suggest that the modified DMC structure with Methionine amino acid can induce apoptosis in lung cancer cells by downregulating EGFR protein expression.

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