Proteomic analysis of a diarylpentanoid, MS13 (1,5-bis(4-Hydroxy-3-Methyoxyphenyl)-1,4-Pentadiene-3-One), in lung adenocarcinoma cells

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Track: Research
Theme: Treatment

ABSTRACT

Introduction: Lung cancer is the main cause of cancer incidence and mortality globally. Non-small-cell lung cancer (NSCLC), the more common lung cancer subtype is treated with a combination of targeted, chemo- and radiotherapy. Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor commonly used in NSCLC treatment, faces widespread resistance including in Malaysian EGFR-mutated NSCLC patients. Phytocompounds have gained attention in cancer research due to their therapeutic effects which may increase efficacy while overcoming resistance and toxicity. Curcumin, derived from turmeric (Curcuma longa), is an attractive anti-cancer compound however, poor bioavailability hindered its efficacy. This led to development of curcumin analogues possessing improved bioavailability such as MS13, a diarylpentanoid exhibiting potent inhibitory activity against various cancers. **Aim:** To investigate the anti-cancer mechanisms of MS13 in NCI-H1650, an EGFR-mutated lung adenocarcinoma (LUAD) cell line. Methods: Cytotoxic effects of MS13 were assessed using MTT with gefitinib as a standard drug control while apoptotic induction was analysed using flow cytometry. The proteomic profile of MS13-treated NCI-H1650 was obtained using shotgun proteomics (LC-MS/MS), followed by protein classification and pathway analysis. **Results:** MS13 exhibited significant cytotoxic effects that were greater than gefitinib, in a time- and dose-dependent manner in NCI-H1650 (IC50: 24h: 10.4µM, 48h: 5.4µM, 72h: 4.7µM). MS13 demonstrated significant apoptotic induction, further evidenced by significant induction of caspase-3/7 activity ($p<0.0001$) in NCI-H1650 compared to control. LC-MS/MS identified differentially expressed proteins (DEPs) which were downregulated in MS13-treated NCI-H1650 and subsequent pathway analysis revealed their significant association with the "RHO GTPase effectors" pathway. These DEPs include translational (RPS27), scaffold/adaptor (YWHAB, YWHAE, YWHAZ), cytoskeletal (NUDC, ACTB, PFN1, ARPC3, CFL1), protein-binding activity modulator (IQGAP1, CDC42) and chromatin/chromatin-binding, or -regulatory proteins (H2AZ2). **Conclusion:** The present findings suggest that MS13 induces cytotoxic and apoptotic effects in EGFR-mutated LUAD cells possibly via downregulation of proteins associated with RHO GTPase effectors.

Keywords: Curcumin, NSCLC, EGFR, gefitinib, curcumin analogues