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Novel Isosteviol Derivatives Induced Apoptosis In Human Lung Cancer

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Ahmed Malki, Phd; Stephen Bergmeier, Phd

Corresponding author :
ahmed.malki@qu.edu.qa
College Of Arts And Sciences, Qatar University, Doha, Qatar

Abstract

Background. Cancer metastasis is the major cause of cancer death. We previously reported novel isosteviols derivatives which induced cytotoxicity in lung cancer cells. The understanding of mechanisms which regulate lung cancer sensitivity to our novel isosteviol derivatives is necessary for development of novel set of anticancer derivatives.
Aims. Investigate the molecular mechanisms of the optimized ring novel isosteviol derivatives on inhibition of proliferation, migration and tumor growth in lung cancer in vitro and in vivo.
Results. Our data showed that novel MOM-ether analogs of isosteviol 8c and 9d decreased cell proliferation and induced apoptosis in H1299 lung cancer cells more than p53 stably transfected H1299 cells. Flow cytometric analysis showed that both isosteviol derivatives 8c and 9d arrested the H1299 cells in G1 phase which is further confirmed by increased expression level of p21. Moreover, both isosteviol derivatives 8c and 9d increased caspase-9 activity in H1299 cells and the induction of apoptosis was significantly reduced after treating cells with caspase-9 inhibitor LEHD-CHO. Both isosteviol derivatives 8c and 9d increased Caspase 3 activities and induced Parp-1 cleavage in H1299 cells. Both derivative 8c and 9d reduced expression levels of AKT and Bcl-2 and increased expression levels of Bax and Bad in H1299cells. Induction of apoptosis was significantly reduced after treating H1299 with AKT inhibitor LY294002. In mice, oral administration of isosteviol derivative 9d inhibited the growth of xenograft tumors, invasion, migration, and anchorage-independent growth in tumor tissues without affecting body weight and it decreased the expression levels of VEGF, MMP-9, MEK and MAPK in tumor tissues.
Conclusion. Based on previous results, our data support the development of isosteviols derivatives as potential agent for lung cancer treatment via targeting MEK/MAPK pathways.