DOI: 10.46991/JISEES.2025.SI1.146

Hypericum alpestre Extract and L-NAME Suppress PI3K/Akt Pathway and Enhance Apoptosis in Lung and Breast Cancer Cells

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ABSTRACT

Lung adenocarcinoma and triple-negative breast cancer (TNBC) are aggressive malignancies often resistant to standard therapies. The PI3K/Akt signaling pathway is a critical regulator of tumor cell survival, angiogenesis, inflammation, and apoptosis resistance in both cancer types. Identifying effective inhibitors of this pathway is crucial for the development of novel treatment strategies. Hypericum alpestre (HA), a polyphenol-rich medicinal plant, has shown promising anticancer activity. This study investigates the effects of HA extract, alone and in combination with L-NAME, a nitric oxide synthase (NOS) inhibitor, on PI3K/Akt signaling and related molecular targets in A549 lung adenocarcinoma and MDA-MB-231 TNBC cells. Cytotoxicity was assessed using MTT assays. Western blot and ELISA were used to evaluate PI3K, Akt, TNFα, VEGFα, COX-2, and MMP-2 expression. Apoptosis was confirmed by Caspase-3 activation and Hoechst 33258 nuclear staining. HA significantly suppressed PI3K/Akt signaling in both cell lines, with marked reductions in TNFα and VEGFα levels, indicating decreased inflammation and angiogenesis. The combination of HA with L-NAME led to enhanced inhibition of COX-2 and MMP-2, key factors in tumor progression and metastasis, and significantly increased Caspase-3-mediated apoptosis. Notably, HA+L-NAME demonstrated stronger anticancer efficacy compared to 5-fluorouracil (5-FU), a commonly used chemotherapeutic drug. These findings suggest that Hypericum alpestre extract, particularly in combination with L-NAME, effectively inhibits oncogenic signaling pathways and promotes apoptosis in both lung and breast cancer cells. The results highlight its potential as a complementary therapeutic approach, meriting further investigation in preclinical cancer models.

Keywords: *Hypericum alpestre*, L-NAME, PI3K/Akt, apoptosis, lung adenocarcinoma, triple-negative breast cancer, TNFα, VEGFα, COX-2, MMP-2, inflammation, metastasis

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