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Cellular mechanisms mediating the anticancer activity of a novel polyherbal formulation.

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Abstract Disclosures

Abstract

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Cellular mechanisms mediating the anticancer activity of a novel polyherbal formulation Background: There is an increased interest in understanding the molecular mechanisms by which herbal mixtures elicit their effects with the hope that they can be translated into new anticancer therapies. A novel herbal decoction 3HX was formulated that exerted excellent anticancer activity in preclinical models, specifically AML and melanoma. The present study explored the anticancer mechanism of 3HX. **Methods:** Cell lines SK-MEL-2 and THP-1 were treated with 3HX followed by analysis of apoptotic markers. Angiogenesis was evaluated by proliferation, migration and VEGF estimation in human endothelial cells EA.hy926. Kinase inhibition was assessed by Z' Lyte assays. Topoisomerase II activity was determined by Kinetoplast DNA Cleavage assay. NFkB signaling assay was done using NFkB-bla THP-1. Immunostimulatory assays were done by estimation of MIP-1-α, TNF-α and IL-1-β in murine splenocytes. Anti-metastatic activity was assessed by lung colonization assay. **Results:** 3HX induced strong apoptotic signaling in tumor cell lines mediated by ROS generation, PS externalization, mitochondrial membrane depolarization, caspase-3 activation, DNA fragmentation and cell cycle arrest. Considerable inhibition of proliferation, migration and VEGF release was recorded in treated endothelial cells. Further inhibitory effect was observed on all the 8 kinases - AKT1 (PKB alpha), ERBB2 (HER2), FLT3, MAPK1 (ERK2), PRKCA (PKC alpha), BRAF, BRAF V599E and MAP2K1 (MEK1) with > 50% inhibition at 1:10 dilution in all except MAPK1 (ERK2). Inhibition of Topoisomerase II and NFkB signaling was also observed. 3HX also increased the levels of cytokines especially MIP-1-α and TNF-α. Metastatic assays revealed inhibition of melanoma nodule count and decrease in melanin content at 2 doses of 500 mg/kg and 250 mg/kg respectively administered orally. **Conclusions:** 3HX exerts anticancer action by multi-target and multi-signal pathways involving apoptosis; anti-angiogenesis; anti-metastasis; inhibition of

signaling kinases, topoisomerase II and modulation of tumor microenvironment by enhancement of immune function and suppression of inflammation.

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