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Targeting beta-Catenin signaling in gugulipid-induced apoptosis

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Abstract

Introduction: Gugulipid (GL), extract of Indian Ayurvedic medicinal plant *Commiphora mukul*, has been used to treat a variety of ailments. We now report anti-cancer effect and mechanism of GL against human breast cancer cells.

Methods: Using the human estrogen receptor-positive (MCF-7) and triple-negative (MDA-MB-231) breast cancer cells as well as the normal human mammary epithelial cell line (HMEC), we evaluated the anti-breast-cancer efficacy of GL. We measured the activity of GL on apoptosis inducing. Finally, we determined the cellular and molecular mechanism of GL-inhibited breast cancer cell growth.

Results: Treatment with GL significantly inhibited viability of human breast cancer cell line MCF-7 and MDA-MB-231 cells with an IC_{50} ~ 2 μM (24 h treatment) at pharmacologically relevant concentrations standardized to its major active constituent z-guggulsterone. The GL-induced growth inhibition correlated with apoptosis induction as evidenced by an increase in cytoplasmic histone-associated DNA fragmentation and caspase 3 activity. Interestingly, a normal human mammary epithelial cell line HMEC is significantly more resistant to growth inhibition and apoptosis induction by GL. The GL-induced apoptosis was associated with down-regulation of β-Catenin signaling pathway. The decrease of Wnt/β-Catenin targeting genes, such as cyclin D1, C-myc and inhibition of transcription factor (T-cell factor4, TCF4) was observed in GL-treated breast cancer cells. The GL treatment caused apoptotic cell death was significantly enhanced by RNA Interference of β-Catenin and TCF-4.

Conclusion: the present study indicates that β-Catenin signaling pathway is the target for GL-induced the growth inhibition and apoptosis induction in human breast cancer.