

Withanolides Exhibit Dual Activity with Anti-Stromal Effects on Activated Pancreatic Stellate Cells and Cytotoxicity Against BxPC-3 Pancreatic Ductal Adenocarcinoma Cells

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Abstract:

Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy projected to become the second leading cause of cancer-related deaths by 2030. Most patients present with unresectable or metastatic disease. PDAC progression is strongly influenced by its dense stroma, primarily composed of activated pancreatic stellate cells (aPSCs). aPSCs promote tumor growth and chemoresistance, making them an attractive therapeutic target. Withanolides are functional steroidal lactones isolated from *Withania somnifera* (a popular medicinal plant in Asia) with reported anticancer and anti-fibrotic (against other diseases) activities.

Objectives: This study aimed to evaluate the anti-stromal potential of selected withanolides (i.e., withanolide A, withaferin A, and withanone) against aPSCs using *in silico* and *in vitro* approaches, followed by assessing their cytotoxicity in BxPC-3 PDAC cells.

Methods: Molecular docking was performed to predict interactions between withanolides and five aPSC biomarkers: alpha smooth muscle actin (ACTA2), vimentin (VIM), fibronectin (FN1), collagen I (COL1A1), and collagen III (COL3A1). Human primary PSCs were activated with tumor growth factor-