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Survival rate for pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC) is poor, with about 80% of patients succumbing to the disease within 10 years of diagnosis, attributed to innate/acquired resistance and activation of pro-survival pathways. The Mnk1/2-eIF4E and NF-κB signaling pathways are implicated in PDAC disease progression/metastasis and also associated with gemcitabine-induced cell-death. Previous studies have shown effects on the aforementioned pathways. We show for the first time, that gal/analogs (VNPT55, VNPP414 and VNPP433-3b) profoundly inhibited cell viability of gemcitabine-naive/resistance PDAC cell lines and strongly synergized with gemcitabine-induced caspase 3-mediated cell-death of PDAC cells. Gal/analog also caused profound downregulation of Mnk1/2, peIF4E and NF-κB (p-p65), metastatic inducing factors (N-cadherin, MMP-1/-2/-9, Slug, Snail and CXCR4) and putative stem cell factors, (β-Catenin, Nanog, BMI-1 and Oct-4). Gal/analog also depleted EZH2 and upregulated E-Cadherin. These effects resulted in significant reduction of PDAC cell migration/invasion and proliferation. These promising findings strongly support further development of gal/analogs as novel therapeutics for PDAC.

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Abstract

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