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ABSTRACT BOOK

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New Diagnostic and Therapeutic Tools against Multidrug Resistant Tumours

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Rilmenidine binds to and inhibits the activity of MDR pumps in pancreatic ductal adenocarcinoma

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Abstract:

Pancreatic ductal adenocarcinoma (PDAC) is the sixth leading cause of death worldwide and the fourth in Europe with a 5-year survival rate. The common cause of treatment failure in PDAC patients is multidrug resistance (MDR) due to the increased expression of plasma membrane efflux pumps that limit the intracellular uptake and retention of numerous xeno- and endobiotics. As the 93.3% of pancreatic carcinomas expressed P-glycoprotein (P-gp-MDR1/ABCB1) and 31% co-expressed multidrug resistance protein 1 (MRP1/ABCC1) with MDR1 P-gp, the inhibition of these pumps may be the target for novel anticancer drugs.

We used the FRED 3.2.0.2 software to predict the affinity of I1-imidazoline receptor ligand rilmenidine within the binding site of P-gp-MDR1/ABCB1 and MRP1/ABCC1, and flow cytometry to evaluate the effect of rilmenidine phosphate and rilmenidine fumarate on the efflux pumps in PDAC cells in vitro.

The results of the molecular docking studies indicate that rilmenidine has the binding affinity for both P-gp-MDR1/ABCB1 and MRP1/ABCC1 efflux pumps. While, *in vitro* studies show that rilmenidine fumarate has better potential to inhibit Calcein AM efflux than rilmenidine phosphate, and it did so in a dose-dependent manner.

Our results indicate that rilmenidine has the affinity to bind to MDR efflux pumps and to inhibit their activity. This potential of rilmenidine to overcome multidrug resistance in PDAC should be further investigated in order to develop more effective PDAC therapy.

Keywords: pancreatic ductal adenocarcinoma; multidrug resistance; molecular docking; rilmenidine

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