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Ivermectin And Gemcitabine Combination Treatment Enhances Antitumor Effect In Pancreatic Cancer Through Mitochondria Dysfunction.

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Background : Pancreatic cancer is the fourth leading cause of cancer death and the 5-year survival rate is less than 8% due to late diagnosis, frequent metastases, and limited treatment options. Currently, gemcitabine is the standard first-line chemotherapy for patients with pancreatic cancer, but still does not contribute to improving overall survival. Therefore, it is necessary to identify new chemotherapeutic agents or therapeutic strategies to enhance the effect of tumor susceptibility to gemcitabine and reduce tumor growth.

Methods : To investigate the effect of ivermectin, gemcitabine, and ivermectin-gemcitabine combination treatment on human pancreatic cancer cells. We performed WST assay for 72 hours to measure the cell viability. We evaluated cell cycle arrest and apoptosis using FACS analysis. Also, we confirmed ROS levels to characterize the mechanism of apoptosis using redox sensitive dye DCFDA and evaluated MMP by JC-10 staining. Moreover, we checked OCR level using Seahorse assay. With pancreatic cancer xenograft model, we confirmed that combination treatment effectively suppresses tumor growth than gemcitabine or ivermectin alone .

Results : The present study represents the first study evaluating the anticancer efficacy of ivermectin in pancreatic cancer. We found that the anticancer effect of ivermectin in combination with gemcitabine on pancreatic cancer is more effective than gemcitabine alone. Ivermectin-gemcitabine combination inhibited cell proliferation via G1 arrest of the cell cycle, as evidenced by down-regulated cyclin D1 expression through mTOR/STAT3 signaling pathway. In addition, ivermectin-gemcitabine induced apoptosis by ROS generation and reduction of mitochondrial membrane potential (MMP), and blocked mitophagy. In vivo experiments also confirmed that ivermectin-gemcitabine groups significantly suppressed the tumor growth of pancreatic cancer compared with gemcitabine alone groups.

Conclusions : Our results indicate that ivermectin has a synergistic effect with gemcitabine in preventing cancer progression and could be a potential antitumor drug for the treatment of pancreatic cancer.

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