Pancreatic ductal adenocarcinoma (PDAC) is a fatal disease and is predicted to become the second leading cause of cancer death worldwide. The only treatment option that offers a chance of curing PDAC is a surgical resection, but in many cases, it is not possible due to the advanced stage of the disease. Combination chemotherapy, including FOLFIRINOX and gemcitabine with nab-paclitaxel, is the most commonly used treatment regimen. The complex nature of pancreatic cancer and the lack of an effective treatment option justify the search, study, and implementation of new methods and combination therapies.

This study aimed to identify innovative combination therapeutics based on gemcitabine and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as methods for their delivery to pancreatic cancer cells. The experiments examined combinations of gemcitabine (GEM) with selected NSAIDs (acetylsalicylic acid, ibuprofen, and flurbiprofen) as potential agents that enhance the cytotoxic effects of GEM against selected pancreatic cancer cell lines. Additionally, it was hypothesized that bone marrow mesenchymal stem cells (BM-MSCs), as well as the conditioned medium obtained from these cells (CM) treated with the combination of GEM and NSAIDs, have the potential to enhance the cytotoxic effects of these drugs. Numerous studies have demonstrated that BM-MSCs can inhibit tumor growth by stimulating the immune system, activating apoptosis, and arresting the cell cycle. Furthermore, these cells and their metabolites can serve as carriers for delivering anticancer substances to the tumor microenvironment. Based on observations from in vitro studies, conjugates of gemcitabine and NSAIDs were synthesized, and the physicochemical properties of the new derivatives were investigated. The study provided new data on the potential use of gemcitabine in combination with NSAIDs for the anticancer therapy of pancreatic cancer, utilizing BM-MSCs as drug carriers. Gemcitabine-NSAID conjugates have the potential to become a new class of prodrugs with dual anticancer activity, and their most significant advantage is the ability to combine the cytotoxic effect of gemcitabine with the modulation of the tumor microenvironment and the proapoptotic effects of NSAIDs.