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The Cancer Control Challenge:
Better Understanding It to Better Face It

ANTINEOPLASTIC EVALUATION OF PIPERINE IN GASTRIC CANCER CELL LINES

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Introduction: Malignant neoplasms currently represent a significant and persistent challenge for global public health systems. Within the diverse spectrum of malignancies, gastric cancer is particularly noteworthy, ranking as the fourth leading cause of cancer-related mortality worldwide and the fifth most frequently diagnosed cancer in Brazil. Notably, mortality rates for this disease are particularly elevated in the Northern region of the country. While conventional therapies have demonstrated efficacy, their clinical utility is limited by the occurrence of adverse effects, including significant toxicity and the rapid emergence of chemoresistance. In this context, natural products are prominent due to their diverse bioactive properties, with piperine, an alkaloid derived from the specie *Piper nigrum L.*, which belongs to be family *Piperaceae,* being particularly noteworthy for its mechanisms of action, specifically in mitigating adverse effects and enhancing drug bioavailability. **Objectives:** The present study aimed to investigate the *in vitro* antineoplastic activity of isolated piperine on models of primary and metastatic gastric cancer **Methods:** Piperine crystals were isolated from dried seeds of *Piper nigrum L.* (black pepper) using a heat-independent method. The analysis was conducted through the assessment of cytotoxicity using the MTT assay, a colorimetric test that evaluates mitochondrial function, and the analysis of the cell death patterns through staining with annexin V and propidium iodide, which allows the differentiation, by fluorescence, between viable cells and those undergoing apoptosis or necrosis, in the AGP-01 (malignant ascites), AGP-01 *PIWIL1 KO* (with the PIWIL1 gene inactivated), ACP-02 (primary diffuse-type cancer), and ACP-03 (primary intestinal-type cancer) cell lines. **Results:** Based on the MTT assay data, piperine exhibited cytotoxicity against all tested models, resulting in half-maximal inhibitory concentration (IC50) values of 12,06 µg/mL, 44,32 µg/mL, 26,28 µg/mL and 47,10 µg/mL for the AGP-01, AGP-01 *PIWIL1 KO*, ACP-02 and ACP-03 cell lines, respectively. These results demonstrate that piperine's IC50 values varied considerably, with AGP-01 being the most sensitive cell line, presenting the lowest IC50 value. Furthermore, piperine

exhibited a selectivity index of 3,6, suggesting the presence of specific mechanisms targeting tumor cells. A concentration-dependent reduction in cell viability was observed across all tested cell lines, starting at 12,5 µg/mL. Despite its cytotoxic activity in all models, piperine was more active against cells with a more aggressive phenotype, which are characteristic of tumors with higher malignancy. Moreover, due to the higher sensitivity observed in AGP-01, the cell death pattern analysis was performed exclusively on this lineage and indicated that cell death occurred predominantly through apoptosis, with significant differences among the tested concentrations in a concentration-dependent manner. **Conclusion:** The data obtained highlight the potential of piperine as a therapeutic agent, particularly in the treatment of aggressive gastric cancer, which often exhibits high resistance to conventional therapies. These findings underscore the importance of exploring natural products for the development of novel therapeutic approaches against cancer.

Keywords: Gastric cancer; *Piperine;* Natural products.