Cytotoxic activity of antitumor compound E-2-Benzo[D]thiazole induces apoptosis and inhibits migration in diffuse type gastric cancer cell line.

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BACKGROUND: It was estimated almost one million new cases of gastric cancer, making it the fifth most common malignancy in the world; however it is the third leading cause of death. Furthermore, it was demonstrated that diffuse type has worst prognosis than intestinal type. Gastric cancer is a combination of several environmental factors, but food intake and smoking have great participation in cancer development. Genetic and epigenetic alterations also have important part of this, contributing in disruption of cell proliferation status. Tumor progression may leads to metastasis, acquiring morphologic changes which promote migration and invasion in adjacent tissues. Therefore, chemotherapy became indispensible for cancer treatment. Several antineoplastic compounds have been selected for their capability to induces cell death and inhibit metastasis features. Benzothiazoles and its analogues have attracted considerable attention because of wide range of pharmacologic activities and represent a potent and highly selective class of antitumor agents.

HYPOTHESIS: Gastric cancer still remains in first places of cancer deaths in the world and searching for new compounds with more affinity and great activity for treatment are constantly required. Benzothiazoles are very well characterized as antitumor agents and it has been tested in several cancer types, such as lung, colon, breast, skin, leukemia and gastric human cancer, but often exhibit high cytotoxic concentrations. Aim of this study was investigated the antineoplastic potential of E-2-Benzo[D]thiazole in different cancer cell lines, reveal what kind of cell death (apoptosis/necrosis) and ability to inhibits cellular migration.

METHODS: Human-derived breast (SKBR-3), myeloid leukemia (K562), diffuse type (ACP02) and intestinal type (ACP03) gastric carcinoma cell line were cultured in optimal temperature and atmosphere. Previously it was performed MTT assay to obtain cytotoxic profile in these cells. Then, cell line with great response was selected to detection and quantification of live, apoptotic and necrotic cells using propidium iodide, fluorescein diacetate and Hoechst 33342. Migratory inhibition was measured by wound healing assay, creating “scratch” in cell monolayer and capturing images in four different times (0, 6, 12, 20 hours). Results were obtained from three independent experiments and statistically evaluated by analysis of variance test (ANOVA) followed by Bonferroni posttest.

RESULTS: E-2-Benzo[D]thiazole in micromolar range elicit potent cytotoxic activity in human-derived breast (IC50 = 5 μM), myeloid leukemia (IC50 = 3.3 μM) and ACP03 (IC50 = 2 μM) cancer cell lines after 72 hours of treatment; however the greatest effect was found in diffuse gastric cancer cell line (ACP02). This compound showed highly cytotoxic effect in ACP02 (IC50 = 1 μM) and significantly induces apoptosis in dose-dependent manner: 0.5 μM ($P<0.01$), 1 μM ($P<0.001$) and 2 μM ($P<0.001$), as well as doxorubicin in 2 μM ($P<0.001$). It was performed wound healing assay to test ability to prevent cell migration and was demonstrated capable to inhibits migration after 20h at 1 μM ($P<0.05$) and 2 μM ($P<0.001$). Therefore, E-2-Benzo[D]thiazole showed cytotoxic activity in gastric cancer cell line (diffuse type), induction to apoptosis and inhibition migratory events, becoming a potential antineoplastic candidate, though is necessary more characterization studies.