

## ***Cytotoxic effects of combined metformin, docetaxel and 5-fluorouracil on the gastric cancer cells***

### ***Abstract***

***Background and objective:*** Until now, many drug combinations have been used against gastric cancer. Despite the use of 5-fluorouracil and docetaxel chemotherapy drugs, drug resistance is increasing in some cancers. Metformin in combination with conventional chemotherapy drugs can be effective in the treatment of gastric cancer. Here, we evaluated the cytotoxic effects of combined metformin, docetaxel and 5-fluorouracil on the gastric cancer cell line, AGS.

***Methods:*** In this experimental study, gastric cancer cells were cultivated in RPMI1640 and 10% FBS. The cells were then exposed to different concentrations of metformin (1–80 mM), docetaxel (0.6–22.5 nM) and 5-fluorouracil (0.045–12 µg / ml). Then, the cell proliferation was evaluated by MTT method. After IC<sub>50</sub> determination, the cell apoptosis was evaluated by acridine orange / ethidium bromide assay. Immunocytochemistry was used to examine the expression of Shh and the ability of colony formation in different groups was evaluated by clonogenic assay.

***Results:*** The results showed that combination therapy by metformin and chemotherapy drugs, docetaxel and 5-fluorouracil significantly reduced gastric cancer cells viability in a concentration- and time-dependent manner. ( $p < 0.05$ ). According to the combination index (CI), metformin/docetaxel and metformin/5-fluorouracil had a synergistic effect on AGS cells apoptosis ( $p < 0.05$ ). In combination therapy, Shh protein expression significantly decreased in comparison to control group. The results also showed that the number of colonies in combination groups, metformin/docetaxel and metformin/5-fluorouracil, was significantly decreased in comparison to docetaxel and 5-fluorouracil alone.

***Conclusion:*** Our results showed that combination of metformin, docetaxel and 5-fluorouracil can be effective in the treatment of patients with gastric cancer.

***Key words:*** Metformin, docetaxel, 5-fluorouracil, gastric cancer, apoptosis, Shh