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Antitumor Effect of 5-FU+Luteolin Combination Against HT-29 Colorectal Adenocarcinoma Cell Line

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Colorectal cancer (CRC) is the second cause of cancer-related deaths in the world. 5-Fluorouracil (5-FU) is one of the widely used drugs in the clinical treatment of various cancers. However, 5-FU has some adverse effects and this makes it necessary to develop new therapies based on 5-FU. Luteolin, 3',4',5,7-tetrahydroxyflavone, is a flavonoid that is found widely in herbs and has a lot of beneficial properties, such as antibacterial, antiinflammatory, antioxidant and anti-proliferative actions [1].

This study was aimed to elucidate the synergistic effects of the 5-FU+luteolin combination on HT-29 colorectal adenocarcinoma cell line. HT-29 colorectal adenocarcinoma cells were cultured in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 5 ml of penicillin-streptomycin and 10% fetal bovine serum and in a humidified incubator containing 5% CO2. Anti-proliferative activity was evaluated by MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay. IC50 (half maximal inhibitory concentration) values of the 5-FU and luteolin were calculated. According to the IC50 value, luteolin and 5-FU treated to cells alone and with combination. Efficacy of this combination was determined by isobologram analysis. To determine the apoptosis rate Cell death detection Elisa assay was performed. The effects of luteolin with and without 5-FU on p53, Bcl-2 and Bax genes and proteins which have an important role in the apoptotic pathway were analyzed by RT-qPCR (real-time quantitative polymerase chain reaction) and Western blot method. Each assay was performed in triplicate and results are provided as the mean of independent experiments.

Luteolin and 5-FU significantly inhibited the proliferation of HT-29 cells in dose dependent manner (p<0,05). IC50 values were determined as 83,10±2,20 µg/ml and 107,40±3,80 µg/ml for luteolin and 5-FU, respectively. Combination index (CI) of 5-FU+luteolin was calculated as 0,25±0,05 and this result suggested that there was a strong synergism between 5-FU and luteolin. When compared with control, there were 5,2; 4,4 and 10,1-fold increases in apoptosis rate in cells which treated with 5-FU, luteolin and 5-FU+luteolin, respectively (p<0,05). Significant increases in p53 mRNA and protein levels were observed in 5-FU compared with controls (p<0,05), but no significant increase was observed in cells which treated with luteolin and 5-FU+luteolin. Compared with control, significant decreases in Bcl-2 mRNA and protein levels were observed in each treatment group (p<0,05). The increases in Bax mRNA and protein expression levels was not statistically significant in cells which treated with luteolin and combination.

In summary, 5-FU+luteolin treatment decreases proliferation and increases apoptosis in HT-29 human colorectal adenocarcinoma cells. Further study is required to detect the signal pathways regulation mechanism of 5-FU plus luteolin. Luteolin has a fine potential to become a cancer chemotherapy.

References


Keywords: Colorectal cancer, apoptosis, 5-FU, luteolin, western blot