Concurrent Treatment of 5-FU and Luteolin Inhibits The Growth of Prostate Cancer (PC-3) and Colorectal Cancer (HT-29) Cells by Modulating VEGF, PTEN and P38 MAPK

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ABSTRACT

Luteolin, 3’, 4’, 5, 7-tetrahydroxyflavone, is a flavonoid of flavone group. It is known that luteolin activates DNA repair mechanism and is effective against DNA damage and induces apoptosis. Apoptosis is a hallmark of cancer cells and therefore drugs and agents that direct effect apoptosis of cells have great potential for cancer treatment. It has been shown that apoptosis should occur at the center of new anti-cancer therapies. 5-Fluorouracil (5-FU) has a broad spectrum activity and is widely used against many cancer types (colon, pancreas, ovary, liver, brain, breast, etc.) alone or in combination with chemotherapeutic agents. p38 MAPK is a member of mitogen-activating protein kinases. It plays an important role in the regulation of apoptosis, in growth inhibition and differentiation. PTEN has tumor suppressor function and regulates mTOR/AKT pathway negatively. Vascular endothelial growth factor (VEGF) is a significant regulator of angiogenesis and vasculogenesis.

This study is aimed to reveal antiproliferative and apoptotic effects of luteolin, 5-FU and combination of luteolin+5-FU in cancer cell lines. PC-3 human prostate cancer and HT-29 human colorectal adenocarcinoma cell lines were grown in DMEM supplemented with 5 ml of penicillin-streptomycin and 10% fetal bovine serum and in a humidified incubator containing 5% CO₂. Viability of cells was determined by MTT (3-(4,5-dimethylthiazol-2-yi)-2,5-diphenyltetrazolium bromide) assay. Cell Death Detection Elisa Kit was used for determination of apoptotic effects. Human VEGF ELISA method was used to quantitatively measure the amount of VEGF in cell lines. Pure Link RNA Mini Kit was used for total RNA extraction and High Capacity cDNA Reverse Transcription Kit was used for cDNA synthesis. Changes in gene expression levels were measured by RT-qPCR. β-actin was house-keeping gene for optimization. Each assay were performed in triplicate.

When PC-3 and HT-29 cells treated with luteolin+5-FU; inhibition rate was 38% and 90,2%, respectively. In HT-29 cells apoptotic rate increase was found to be significantly ($p<0.05$), also the expression levels of PTEN and p38MAPK significantly changed compared with control group, while VEGF amount significantly decreased ($p<0.05$). In PC-3 cells apoptotic rate was significantly increased ($p<0.05$), however not significant changes observed on PTEN, p38MAPK and VEGF amounts.

As a result, treatment with luteolin inhibits the growth of prostate and colorectal cancer cells and modulate the apoptotic pathway genes. These results when supported by in vivo studies in the future, will allow a better understanding of the mechanism of luteolin in the development of new chemotherapeutic
approaches for cancer.

**Keywords:** HT-29, cancer cell line, MTT, apoptosis, PTEN.