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Investigation on the effects of hydroalcoholic extract of *Levisticum officinale* on cGMP levels and *PDE5* gene expression in breast cancer cell lines MCF-7 and MDA-Mb-468Ali Shaharki¹, Marzieh Lotfian Sargazi² and Ramin Saravani²¹University of Sistan and Baluchestan, Iran²Zahedan University of Medical Sciences, Iran

Increased expression of cyclic guanosine 3', 5' monophosphate phosphodiesterase-5 (cGMP-PDEs) mRNAs has been demonstrated in several human carcinomas, including breast carcinoma, pancreatic cancer, bladder cancer, squamous cell carcinoma and prostate cancer, in comparison to adjacent normal tissues. Studies have elucidated that an increase in intracellular cGMP induces apoptosis and decreases cell population growth. Therefore, selective inhibitors of these PDEs might be potential anticancer agents. Previous investigations have demonstrated that *Levisticum officinale* contains flavonoids and alkaloids compound that are known as antitumoral components. The purpose of this study was to investigate the effect of *Levisticum officinale* hydroalcoholic extract on phosphodiesterase 5 gene expression, cGMP signaling pathway and its role in inducing apoptosis in the MCF-7(ER+) and in MDA-Mb-468 (triple-negative) cell lines. The mean inhibitory concentration (IC₅₀) of extract was determined in both cell lines using of MTT assay, and the type of cell death was detected by flow cytometry. The expression of *PDE5* and cGMP levels was measured by real-time polymerase chain reaction and colorimetric assay, respectively. Treatment with hydroalcoholic extract of *Levisticum officinale* showed that 200 µg/ml to be the IC₅₀ for both cell lines. 12 hour treatment with IC₅₀ dosage showed a maximum decrease in the *PDE5* expression and maximum increase in intracellular cGMP level, although, these effects were more significant in MDA-MB-468. In conclusion, our results showed that hydroalcoholic extract of *Levisticum officinale* had an anti-proliferative and apoptotic effect in MCF-7 and MDA-Mb-468 targeting *PDE5* and cGMP signaling pathway.



Figure 1: Effect of hydroalcoholic extract of *L. officinale* in inhibition of cell growth of breast cancer MCF-7 and MDA-Mb-468 cell lines. Cells were treated with different concentration of extract for 24, 48 and 72h. Proliferation was measured with MTT assay. Extract reduced cell proliferation in a time and dose-dependent manner. Results are presented as Mean±SD of three experiment. **P<0.01 compared to untreated control group.

Recent Publications

1. Saravani R Galavi H R and Shahraki A (2017) Inhibition of phosphodiesterase 5 and increasing the level of cyclic guanosine 3', 5' monophosphate by hydroalcoholic *Achillea wilhelmsii* C. Koch extract in human breast cancer cell lines MCF-7 and MDA-Mb-468. Breast Cancer: Basic and Clinical Res. 1-7.
2. Afarnegan H, Shahraki A and Shahraki J (2017) The hepatoprotective effects of aquatic extract of *L. officinale* against paraquat hepatocyte toxicity. Pak J Pharm Sci 30:2363-2368.
3. Lagzian M, Shahraki A, Besharatian M and Asoodeh A (2017) A thermostable alkaliphilic protein-disulfide isomerase from bacillus subtilis DR8806: cloning, expression, biochemical characterization and molecular dynamics simulation. Int J Biol Macromol. 09:033.
4. Sargazi S, Saravani R, Galavi H R, et al. (2017) Effect of *Levisticum officinale* hydroalcoholic extract on DU-145 and PC-3 prostate cancer cell lines. Gene Cell Tissue 4(4):e66094.

5. Galavi H R, Saravani R, Shahraki A and Ashtiani M (2016) Anti-proliferative and apoptosis inducing potential of hydroalcoholic *Achillea wilhelmsii* C. Koch extract on human breast adenocarcinoma cell lines MCF-7 and MDA-Mb-468. Pak J Pharm Sci 29: 2397–2403.

Biography

Ali Shahraki has his expertise in Teaching and Research at the University of Sistan and Baluchestan, Zahedan, Iran. He supervised more than 25 theses of Biochemistry for Master's Degree of Science students. He works in the fields of neuroscience, herbal medicine and signal pathways for inducing anti-proliferative and apoptosis in cancer cell lines through medicinal plants. He has built this model after years of experience in research, evaluation, teaching and administration in universities and education institutions.

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