

## Investigation of The Effects of Hydroxytyrosol on Cytotoxicity, Apoptosis, PI3K/Akt, and ERK 1/2 Pathways in Ovarian Cancer Cell Cultures

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**Abstract :** Hydroxytyrosol (HT) is a phenolic phytochemical molecule derived from the hydrolysis of oleuropein, which originates during the maturation of the olives. It has recently received particular attention because of its antioxidant, anti-proliferative, pro-apoptotic and anti-inflammatory activities. In this study, we investigated the cytotoxic and apoptotic effects of hydroxytyrosol and its effects on phosphatidylinositol 3-kinase/Akt (PI3K/Akt) and extracellular signal-regulated kinase 1/2 (ERK 1/2) signaling pathways in human ovarian cancer cell lines OVCAR-3 and MDAH-2774. XTT cell proliferation kit, Cell Death Detection Elisa Plus Kit (Roche) and Human Apoptosis Array (R&D Systems) were used to determine the cytotoxic and apoptotic effects of HT in OVCAR-3 and MDAH-2774 cell lines at 24, 48, 72, and 96 h. Effect of HT on PI3K/Akt and ERK 1/2 signaling pathways were investigated by using specific inhibitors of these pathways. IC50 values of HT were found to be 102.3  $\mu$ M in MDAH-2774 cells at 72 h and 51.5  $\mu$ M in OVCAR-3 cells at 96 h. Apoptotic effect of HT in MDAH-2774 cells was the highest at 50  $\mu$ M at 72 h, and kept decreasing at 100 and 150  $\mu$ M concentrations and was not seen at 200  $\mu$ M and higher concentrations. Highest apoptotic effect was seen at 100  $\mu$ M concentration in OVCAR-3 cells at 96 h, however apoptotic effect was decreased over 100  $\mu$ M concentrations. According to antibody microarray results, HT increased the levels of pro-apoptotic molecules Bad, Bax, active caspase-3, Htra2/Omi by 2.0-, 1.4-, 1.2-, 4.2-fold, respectively and also increased the levels of pro-apoptotic death receptors TRAIL R1/DR4, TRAIL R2/DR5, FAS/TNFRSF6 by 2.1-, 1.7-, 1.6-fold, respectively, however, it decreased the level of Survivin by 1.6-fold which is one of the inhibitor of apoptosis protein (IAP) family in MDAH-2774 cells. In OVCAR-3 cells, HT decreased the levels of anti-apoptotic proteins Bcl-2, pro-caspase 3 by 3.1-, 8.2-fold, respectively and IAP family proteins CIAP-1, CIAP-2, XIAP, Livin, Survivin by 6.5-, 6.0-, 3.2-, 2.2-, 2.7-fold, respectively and increased the level of cytochrome-c by 1.2-fold. We have shown that HT shows its cytotoxic and apoptotic effect through inhibiting ERK 1/2 signaling pathway in both OVCAR-3 and MDAH-2774 cells. Further studies are needed to investigate molecular mechanisms and modulatory effects of hydroxytyrosol.

**Keywords :** apoptosis, cytotoxicity, hydroxytyrosol, ovarian cancer

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