Caffeic Acid Phenethyl Ester Augments Docetaxel-Cytotoxicity in PC-3 Cells by Inducing Apoptosis Through Modulation of Estrogen Receptors

Introduction and Objective: Docetaxel (DOC) has been set as a frontline therapy in prostate cancer management. However, the use of high dose DOC is associated with significant toxic reactions. Caffeic acid phenethyl ester (CAPE) is a component of honey bee propolis that possesses a broad-spectrum anticancer activity. The current study aims at investigating the chemomodulatory impact of CAPE on DOC cytotoxicity in PC-3 human androgen-independent prostate cancer cells.
Materials and Methods: Initial studies included cytotoxicity assay and combination index determination. This was followed by mechanistic studies to investigate the effects on the cell cycle and apoptosis. These included flow cytometry and immunocytochemistry for cell cycle regulatory proteins as cyclin D1, p-27 and c-myc. Studies to investigate the influence on apoptosis included caspase-3 activity and protein expression. Estrogen receptor-α (ERα) and ERβ together with their downstreams insulin-like growth factor-1 receptor (IGF-1R) and FOXO-1 protein expression were also assessed.
Results: It was found that CAPE per se has anticancer properties, but with relatively low potency in the tested cells. CAPE significantly increased the potency of DOC in PC-3 cells. The combination index calculations showed synergism. The protein expression of cyclin D1, a cell cycle inducer, was significantly reduced in the combined treatment group with concurrent increase in the cell cycle inhibitor p27. DNA ploidy analysis indicated that combined CAPE/DOC treatment showed a significant increase in the percentage of cells in the pre-G1 phase. Also, caspase-3 activity and protein expression were significantly elevated in the combination-treated cells compared to DOC-alone treated group. This indicates an enhancement of DOC-induced apoptosis. Estrogen receptor-β (ERβ) and its downstream tumor suppressor FOXO-1 levels were significantly elevated in CAPE and combination groups compared to DOC-alone. On the other hand, ERα and insulin like growth factor-1 receptor (IGF-1R) levels were reduced in the same groups in comparison to DOC group.
Conclusions: CAPE enhances the cytotoxic properties of DOC in PC-3 cells through boosting DOC apoptotic activity as evidenced by increase in the percentage of cells in the pre-G1 phase; caspase-3 activity and protein expression; and ERβ and FOXO-1 expression; as well as reduction of ERα and IGF1-R expression.