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CINOBUFOTALIN AS A NOVEL AGENT TO INHIBIT IN-VITRO EPITHELIAL OVARIAN CANCER CELL PROLIFERATION, MIGRATION AND INVASION

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Objective Cinobufotalin (CINO), a cardiotonic steroid (CTS) or bufadienolide, is extracted from the skin secretions of giant toads and is utilized in traditional Chinese medicine (Chan Su). CINO has been used as a cardiotonic, diuretic and a hemostatic agent. Our lab is familiar with CINO and has shown it to inhibit cytotrophoblast cells function. Recently, it has been shown that CINO also

inhibits the lung cancer cell function, and has been further implicated in other disease processes. In the present study, we propose to pursue this potential application of CINO using ovarian tumor cell line SK-OV-3.

Study Design We evaluated the in-vitro effect of CINO on ovarian cancer cell line SK-OV-3. Cells were treated with 0.1, 1, 5, and 10 μM CINO. Cell proliferation was measured using a CellTiter Assay (Promega), which is a colorimetric method for determining the number of viable cells. Cell migration was measured using a CytoSelect Assay (Cell Biolabs). Cell invasion was measured using a FluoroBlok Assay (BD). Cell viability was measure using a CellTiter Assay (Promega). Cell cycle progression was evaluated by a Cell Cycle Phase Determination Kit (Cayman Chemical) and apoptosis was evaluated by an Apoptotic Blebs Assay Kit (Cayman Chemical). Cell cycle arrest and apoptotic signaling was determined by fluorescence-activated cell sorting (FACS) analysis.

Results CINO at ≥0.5 μM inhibited SKOV-3 cell proliferation, migration, and invasion ($p<0.05$). There was a higher ($p<0.05$) percentage of S phase cells in groups treated with CINO at 0.5 μM. CINO at ≥0.5 μM down regulated expression of PCNA and caused cell death.

Conclusion This data demonstrates that CINO impairs SK-OV-3 cell function via cell cycle arrest and apoptotic signaling. These findings demonstrate the complex nature of this compound. Not only is CINO directly modulating the actions of the Na/K ATPase through classic mechanism of cardiotonic steroids, but is also directly influencing the nuclear expression of proteins involved in cell cycle progression and DNA repair. Additional investigational studies looking into the molecular pathways involved in altering cell cycle and entry into apoptosis are warranted.

In conclusion, we have shown CINO to impair SK-OV3 cell function via cell cycle arrest and apoptotic signaling and suggest that CINO might be further investigated as a novel anti-ovarian cancer agent.