Synergistic Relationship of Cisplatin and Withaferin A in the Treatment of Triple-Negative Breast Cancer

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Triple-negative breast cancer (TNBC) is an aggressive breast cancer subtype associated with a poor prognosis and reduced hormone therapy efficacy. Although the current standard treatment for TNBC is chemotherapy, cisplatin treatment requires a rational selection of effective drug combinations to increase cisplatin's therapeutic efficacy and reduce cisplatin-causing chemoresistance and side effects. Withaferin A (WA) has proven to be a potent chemotherapeutic agent with broad-spectrum anti-cancer activity. Therefore, the combination potential of cisplatin and WA was tested on the SUM159 TNBC cell line using the trypan blue exclusion assay, MTS assay, clonogenic assay, annexin V/PI assay, and western blot analysis to determine cell viability, cell proliferation, cell survival, apoptosis, and protein expression, respectively. Combination treatment of cisplatin and WA displayed synergism in terms of cell growth (viability, proliferation, survival) inhibition. Synergism in inducing apoptosis suggests a mechanistic action for inhibiting cell growth. A western blot analysis on the ATR/Chk1 pathway displayed a downregulation of pATR and pChk1, DNA damage response coordinators. WA may increase the therapeutic index of cisplatin by lowering its effective dose to decrease potential side effects. Downregulation of pATR and pChk1 suggests that treatment may also reduce chemoresistance.