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Tumour active plant derived compounds in combination with targeted therapy towards overcoming drug resistance in ovarian cancer

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Whereas platinum resistance is associated with increased expression of anti-apoptotic factors such as NF-kB and AKT, a number of phytochemicals serve to dampen their expressions so that they may act synergistically in combination. In this study we investigated synergism from combination of platinum drugs and a number of tumour active phytochemicals including curcumin, EGCG, thymoquinone, resveratrol and genistein in human ovarian tumour models. Generally sequenced combinations with 2 to 4 h time gap are found to be synergistic whereas the bolus is often antagonistic. The variation in nature of the combined drug action with change in sequence of administration clearly indicates that the action of one drug modulates that of the other. Proteomic studies have identified over thirty proteins that are believed to be associated with platinum resistance in ovarian cancer. They belong to six major groups including cytoskeletal proteins, molecular chaperone and stress related proteins, proteins involved in detoxification and drug resistance, proteins involved in metabolic processes and mRNA processing proteins. Synergistic outcome from combinations of cisplatin with phytochemicals is found to be associated with down-regulation of mRNA processing proteins that play a variety of roles in tumour development and progression, and up-regulate molecular chaperones that are needed for constant surveillance to ensure normal protein homeostasis. Detoxification and drug resistance proteins are found to be up-regulated after treatment with synergistic combinations of Cis with other phytochemicals, indicating that the phytochemicals have served to sensitize resistant A2780cisR cancer cells towards platinum action by targeting various cellular pathways.

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