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Coumestrol Induced Apoptosis in Breast Cancer MCF-7 Cells via Redox Cycling of Copper and ROS Generation: Implications of Copper Chelation Strategy in Cancer Treatment

Authors : Atif Zafar Khan, Swarnendra Singh, Imrana Naseem

Abstract : Breast cancer is one of the most frequent malignancies in women worldwide and a leading cause of cancer-related deaths among women. Therefore, there is a need to identify new chemotherapeutic strategies for cancer treatment. Unlike normal cells, cancer cells contain elevated copper levels which play an integral role in angiogenesis. Copper is an important metal ion associated with the chromatin DNA, particularly with guanine. Thus, targeting copper via copper-specific chelators in cancer cells can serve as effective anticancer strategy. Keeping in view these facts, we evaluated the anticancer activity and copper-dependent cytotoxic effect of coumestrol (phytoestrogen in soybean products) in breast cancer MCF-7 cells. Coumestrol inhibited proliferation and induced apoptosis in MCF-7 cells, which was prevented by copper chelator neocuproine and ROS scavengers. Coumestrol treatment induced ROS generation coupled to DNA fragmentation, up-regulation of p53/p21, cell cycle arrest at G1/S phase, mitochondrial membrane depolarization and caspases 9/3 activation. All these effects were suppressed by ROS scavengers and neocuproine. These results suggest that coumestrol targets elevated copper for redox cycling to generate ROS leading to DNA fragmentation. DNA damage leads to p53 up-regulation which directs the cell cycle arrest at G1/S phase and promotes caspase-dependent apoptosis of MCF-7 cells. In conclusion, coumestrol induces pro-oxidant cell death by chelating cellular copper to produce copper-coumestrol complexes that engages in redox cycling in breast cancer cells. Thus, targeting elevated copper levels might be a potential therapeutic strategy for selective cytotoxic action against malignant cells.

Keywords : apoptosis, breast cancer, copper chelation, coumestrol, reactive oxygens species, redox cycling
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