



Curcumin analogue 1,5-bis(4-hydroxy-3-((4-methylpiperazin-1-yl)methyl)phenyl)penta-1,4-dien-3-one mediates growth arrest and apoptosis by targeting the PI3K/AKT/mTOR and PKC-theta signaling pathways in human breast carcinoma cells

Gamal Badr, Halise Inci Gul, Cem Yamali, Amal A.M. Mohamed, Badr M. Badr, Mustafa Gul, Ahmad Abo Markeb, Nagwa Abo El-Maali

Abstract:

Recent developments in the literature have demonstrated that curcumin exhibit antioxidant properties supporting its anti-inflammatory, chemopreventive and antitumoral activities against aggressive and recurrent cancers. Despite the valuable findings of curcumin against different cancer cells, the clinical use of curcumin in cancer treatment is limited due to its extremely low aqueous solubility and instability, which lead to poor in vivo bioavailability and limited therapeutic effects. We therefore focused in the present study to evaluate the anti-tumor potential of curcumin analogues on the human breast carcinoma cell lines MDA-MB-231 and MCF-7, as well as their effects on non-tumorigenic normal breast epithelial cells (MCF-10). The IC₅₀ values of curcumin analogue J1 in these cancer cell lines were determined to be 5 ng/ml and 10 ng/ml, in MDA-MB-231 and MCF-7 cells respectively. Interestingly, at these concentrations, the J1 did not affect the viability of non-tumorigenic normal breast epithelial cells MCF-10. Furthermore, we found that J1 strongly induced growth arrest of these cancer cells by modulating the mitochondrial membrane potentials without significant effect on normal MCF-10 cells using JC-1 staining and flow cytometry analysis. Using annexin-V/PI double staining assay followed by flow cytometry analysis, we found that J1 robustly enhanced the induction of apoptosis by increasing the activity of caspases in MDA-MB-231 and MCF-7 cancer cells. In addition, treatment of breast cancer cells with J1 revealed that, in contrast to the expression of cyclin B1, this curcumin analogue vigorously decreased the expression of cyclin A, CDK2 and cyclin E and subsequently sensitized tumor cells to cell cycle arrest. Most importantly, the phosphorylation of AKT, mTOR and PKC-theta in J1-treated cancer cells was markedly decreased and hence affecting the survival of these cancer cells. Most interestingly, J1-treated cancer cells exhibited a significant inhibition in the activation of RhoA followed by reduction in actin polymerization and cytoskeletal rearrangement in response to CXCL12. Our data reveal the therapeutic potential of the curcumin analogue J1 and the underlying mechanisms to fight breast cancer cells.

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