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# Quinacrine and curcumin synergistically increased the breast cancer stem cells death by inhibiting ABCG2 and modulating DNA damage repair pathway

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***Abstract***

Cancer stem cell like cells (CSCs) present a challenge in the management of cancers due to their involvement in the development of resistance against various chemotherapeutic agents. Over expression of ABCG2 transporter gene is one of the factors responsible for drug resistance in CSCs, which causes efflux of therapeutic drugs from these cells. The development of inhibitors against CSCs has not achieved any significant success, till date. In this work, we have evaluated the anti-proliferative activity of curcumin (Cur) and quinacrine (QC) against CSCs using in vitro model system. Cur and QC synergistically inhibited the proliferation, migration and invasion of CSCs enriched side population (SP) cells of cigarette smoke condensate induced breast epithelial transformed (MCF-10A-Tr) generated metastatic cells. Cur + QC combination increased the DNA damage and inhibited the DNA repair pathways in SP cells. Uptake of QC increased in Cur pre-treated SP cells and this combination inhibited the ABCG2 activity by the reduction of ATP hydrolysis in cells. In vitro DNA binding reconstitution system suggests that QC specifically binds to DNA and caused DNA damage inside the cell. Decreased level of ABCG2, representative cell survival and DNA repair proteins were noted after Cur + QC treatment in SP cells. The molecular docking studies were performed to examine the binding behaviour of these drugs with ABCG2, which showed that QC (-53.99 kcal/mol) and Cur (-45.90 kcal/mol) occupy a highly overlapping interaction domain. This suggested that in Cur pre-treated cells, the Cur occupied the ligand-binding site in ABCG2, thus making the ligand binding site unavailable for the QC. This causes an increase in the intracellular concentration of QC. The results indicate that Cur + QC combination causes CSCs death by increasing the concentration of QC in the cells and thus causing the DNA damage and inhibiting the DNA repair pathways through modulating the ABCG2 activity.

The human breast cancer cell lines MCF-7 and MDA-MB-231 were refined in monolayers and kept up in DMEM (Dulbecco's adjusted hawk medium) enhanced with 10% fetal cow-like serum (FBS), 100 U/ml penicillin–streptomycin and 1.5 mM L-glutamine. A control cell line (MCF-10A), which precipitously emerged from refined MCF-10M cells, was gotten from a 36-year-old parous premenopausal lady with broad fibrocystic ailment, with no family ancestry or histological proof of bosom threat. MCF-10A cells are estrogen receptor-negative and have qualities of ordinary cells including development factor reliance, anchorage-dependent development and absence of tumorigenecity in bare mice. Thusly, these cells are considered as a model for ordinary bosom epithelial cells.25 MCF-10A cells were developed in DMEM/F-12, medium enhanced with 5% (v/v) horse serum, 100 U/ml of penicillin, 100 mg/ml of streptomycin, 0.5 mg/ml of hydrocortisone, 100 ng/ml of cholera poison, 10 mg/ml of insulin, 10 ng/ml of epidermal development factor and 1% (w/v) of L-glutamine (Sigma Chemical Co., St., MO). The various cell-culture prerequisites were acquired from HIMEDIA, India. All cells were developed in a humidified air of 5% CO2 at 37°C. After 70–80% intersection, cells were treated with showed groupings of QC (Sigma Chemical Co.) and broke down in sterile DMSO. Medicines were accomplished for different time spans with the expansion of new QC as appeared in individual spots.

***Biography:***

Deepika Nayak is persuing her PhD School of Biotechnology, KIIT, Deemed to be University. She is the ICMR (Indian Council for Medical Research) Senior Research Fellow. She has published 14 in many reputed peer reviewed journals.

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