Qun Zhou, Pharm Anal Acta 3:1
doi: http://dx.doi.org/10.4172/2153-2435.S1.10

OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference on
Pharmaceutics & Novel Drug Delivery Systems

20-22 February 2012 San Francisco Airport Marriott Waterfront, USA

TITLE

# Targeting Estrogen Signaling in Chemoprevention of Breast Cancer

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Exposure to higher levels of estrogen produces genotoxic metabolites that can stimulate mammary tumorigenesis. Induction of NF-E2-related factor 2 (NRF2)-dependent detoxifying enzymes (e.g., NAD(P)H-quinone oxidoreductase 1 (NQO1)) is considered an important mechanism of protection against estrogen-associated carcinogenesis because they would facilitate removal of toxic estrogens. We found that estrogen-receptor (ER) signaling suppresses NRF2-dependent gene transcription. Inhibition of ERα expression by the novel antiestrogen shikonin reverses the inhibitory effect of estrogen on NQO1 expression. As a consequence, a chemoprevention study was undertaken to monitor the impact of shikonin on DNA lesions and tumor growth. Treatment of MCF-7 breast cancer cells with shikonin inhibits estrogen-induced 8-hydroxy-2-deoxyguanosine (8-OHdG), a marker of DNA damage. NQO1 deficiency promotes estrogen-dependent tumor formation, and shikonin inhibits estrogen-dependent tumor growth in an NQO1-dependent manner in MCF-7 xenografts. These results suggest that estrogen-receptor signaling pathway has an inhibitory effect on NRF2-dependent enzymes. Moreover, shikonin reverses the inhibitory effects of estrogen on this pathway and may contribute to breast cancer prevention.