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## Chemotherapeutic activity of ellagic acid combined with doxorubicin nanoliposomes in 4T1 breast cancer cells and NIH3T3 normal breast fibroblast cells

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Nowadays, there is an increasing emphasis on combination chemotherapy using cytotoxic and naturally occurring chemopreventive agents, having different mechanisms of action with non-overlapping toxicity. The fruit of the *Punica granatum* (pomegranate) contains a lot of phytochemicals with antioxidant properties, thought to be due to the action of ellagic acid (ELG), the main polyphenol in pomegranate. ELG is also seen at high concentrations in grapes and many berries including strawberries, raspberries and cranberries. Some studies reported that it can induce G1 cell cycle arrest, induction of apoptosis and inhibition of overall tumor cells growth. In the present study we investigated the cytotoxic effects of combined Doxil, nanoliposomal doxorubicin (DXL), and ELG on 4T1 breast cancer cells compared with NIH3T3 normal mouse fibroblast cells. The results showed that the cytotoxic effects of ELG on viability of 4T1 cancer cells were higher than NIH3T3 normal cells, respectively). Furthermore, the results showed that depending on the molar ratio of ELG to DXL in combination therapy, the effect of ELG on therapeutic efficacy of DXL could be synergistic, additive or antagonistic in both 4T1 cancer cells and NIH3T3 normal cells. In conclusion, these findings confirm that ELG, as an antiproliferative agent can increase the chemotherapeutic efficacy of DXL in 4T1 cancer cells.

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