10H-3,6-Diazaphenothiazines triggered the mitochondrial-dependent and cell death receptor-dependent apoptosis pathways and further increased the chemosensitivity of MCF-7 breast cancer cells via inhibition of AKT1 pathways

ABSTRACT

Breast cancer is one of the leading causes of death in cancer categories, followed by lung, colorectal, and ovarian among the female gender across the world. 10H-3,6-diazaphenothiazine (PTZ) is a thiazine derivative compound that exhibits many pharmacological activities. Herein, we proceed to investigate the pharmacological activities of PTZ toward breast cancer MCF-7 cells as a representative in vitro breast cancer cell model. The PTZ exhibited a proliferation inhibition ($IC50 = 0.895\ \mu M$) toward MCF-7 cells. Further, cell cycle analysis illustrated that the S-phase checkpoint was activated to achieve proliferation inhibition. In vitro cytotoxicity test on three normal cell lines (HEK293 normal kidney cells, MCF-10A normal breast cells, and H9C2 normal heart cells) demonstrated that PTZ was more potent toward cancer cells. Increase in the levels of reactive oxygen species results in polarization of mitochondrial membrane potential ($\Delta\Psi m$), together with suppression of mitochondrial thioredoxin reductase enzymatic activity suggested that PTZ induced oxidative damages toward mitochondria and contributed to improved drug efficacy toward treatment. The RT2 PCR Profiler Array (human apoptosis pathways) proved that PTZ induced cell death via mitochondria-dependent and cell death receptor-dependent pathways, through a series of modulation of caspases, and the respective morphology of apoptosis was observed. Mechanistic studies of apoptosis suggested that PTZ inhibited AKT1 pathways resulting in enhanced drug efficacy despite it preventing invasion of cancer cells. These results showed the effectiveness of PTZ in initiation of apoptosis, programmed cell death, toward highly chemoresistant MCF-7 cells, thus suggesting its potential as a chemotherapeutic drug.

Keyword: 10H-3,6-Diazaphenothiazine; AKT1 pathways; Apoptosis; Breast cancer; Mitochondrialthioredoxin reductase