Cytotoxicity and apoptotic activities of alpha-, gamma- and delta-tocotrienol isomers on human cancer cells

ABSTRACT

Background: Tocotrienols, especially the gamma isomer was discovered to possess cytotoxic effects associated with the induction of apoptosis in numerous cancers. Individual tocotrienol isomers are believed to induce dissimilar apoptotic mechanisms in different cancer types. This study was aimed to compare the cytotoxic potency of alpha-, gamma- and delta-tocotrienols, and to explore their resultant apoptotic mechanisms in human lung adenocarcinoma A549 and glioblastoma U87MG cells which are scarcely researched.

Methods: The cytotoxic effects of alpha-, gamma- and delta-tocotrienols in both A549 and U87MG cancer cells were first determined at the cell viability and morphological aspects. DNA damage types were then identified by comet assay and flow cytometric study was carried out to support the incidence of apoptosis. The involvements of caspase-8, Bid, Bax and mitochondrial membrane permeability (MMP) in the execution of apoptosis were further expounded.

Results: All tocotrienols inhibited the growth of A549 and U87MG cancer cells in a concentration- and time-dependent manner. These treated cancer cells demonstrated some hallmarks of apoptotic morphologies, apoptosis was further confirmed by cell accumulation at the pre-G1 stage. All tocotrienols induced only double strand DNA breaks (DSBs) and no single strand DNA breaks (SSBs) in both treated cancer cells. Activation of caspase-8 leading to increased levels of Bid and Bax as well as cytochrome c release attributed by the disruption of mitochondrial membrane permeability in both A549 and U87MG cells were evident.

Conclusions: This study has shown that delta-tocotrienol, in all experimental approaches, possessed a higher efficacy (shorter induction period) and effectiveness (higher induction rate) in the execution of apoptosis in both A549 and U87MG cancer cells as compared to alpha- and gamma-tocotrienols. Tocotrienols in particular the delta isomer can be an alternative chemotherapeutic agent for treating lung and brain cancers.

Keyword: Tocotrienol isomers; Cytotoxicity; Apoptosis; DNA damage; Caspase-8; Bid; Bax; Mitochondrial membrane permeability; Cytochrome c