

## Antiproliferation and induction of caspase-8-dependent mitochondria-mediated apoptosis by $\beta$ -tocotrienol in human lung and brain cancer cell lines

### ABSTRACT

The pure vitamin isomer,  $\beta$ -tocotrienol has the least abundance among the other vitamin E isomers that are present in numerous plants. Hence, it is very scarcely studied for its bioactivity. In this study, the antiproliferative effects and primary apoptotic mechanisms of  $\beta$ -tocotrienol on human lung adenocarcinoma A549 and glioblastoma U87MG cells were investigated. It was evidenced that  $\beta$ -tocotrienol had inhibited the growth of both A549 ( $GI_{50}=1.38\pm 0.334\mu M$ ) and U87MG ( $GI_{50}=2.53\pm 0.604\mu M$ ) cells at rather low concentrations. Cancer cells incubated with  $\beta$ -tocotrienol were also found to exhibit hallmarks of apoptotic morphologies including membrane blebbing, chromatin condensation and formation of apoptotic bodies. The apoptotic properties of  $\beta$ -tocotrienol in both A549 and U87MG cells were the results of its capability to induce significant ( $P<0.05$ ) double-strand DNA breaks (DSBs) without involving single-strand DNA breaks (SSBs).  $\beta$ -Tocotrienol is said to induce activation of caspase-8 in both A549 and U87MG cells guided by no activation when caspase-8 inhibitor, z-IETD-fmk was added. Besides, disruption on the mitochondrial membrane permeability of the cells in a concentration- and time-dependent manner had occurred. The induction of apoptosis by  $\beta$ -tocotrienol in A549 and U87MG cells was confirmed to involve both the death-receptor mediated and mitochondria-dependent apoptotic pathways. These findings could potentiate the palm oil derived  $\beta$ -tocotrienol to serve as a new anticancer agent for treating human lung and brain cancers.

**Keyword:**  $\beta$ -tocotrienol; Antiproliferation; Apoptosis; DNA damage; Caspase-8; Cytochrome c