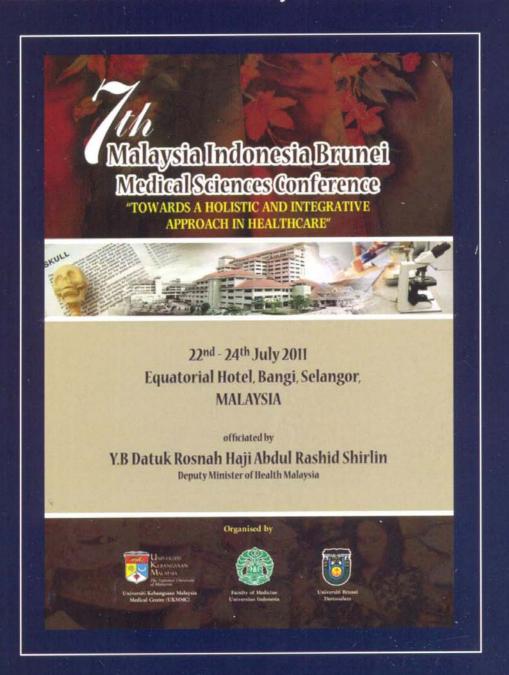


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γ-TOCOTRIENOL PROTECTS AGAINST HYDROGEN PEROXIDE-INDUCED REPLICATIVE SENESCENCE BY REGULATING APOPTOTIC PATHWAY AND MODULATING TELOMERASE ACTIVITY

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Background:

Oxidative stress has been shown to be associated with apoptosis (programmed cell death) in a number of cell systems. Apoptosis is controlled by a diverse range of intracellular signaling that regulates genes and proteins such as apoptotic and antiapoptotic molecules. Besides, oxidative stress also resulted in telomere shortening and progressive reduction of telomerase activity leading to cellular senescence. Vitamin E has revealed many important molecular properties, such as scavenging free radicals, modulating signal transduction in antioxidant and non-antioxidant manners and plays a role in regulating apoptosis. In this study, we developed $\rm H_2O_2\text{-induced}$ premature senescence model of human skin fibroblasts to investigate the protection of γ -tocotrienol against cellular senescence.

Materials and Methods:

Primary human diploid fibroblasts derived from circumcision foreskins were cultured until passage 4 and were treated with 1 μ M γ -tocotrienol. Exposure to 20 μ M H₂O₂ was carried out for two weeks to induce replicative senescence. Real time RT-PCR was performed to determine the expression of pro-apoptotic genes (*Bax* and *Bid*) and antiapoptotic genes (*Bcl-2* and *Bcl-xL*). Proteins expression of Bax and Bcl-2 was determined by Western blotting. Telomerase activity was detected using telomeric repeat amplification protocol (TRAP) while telomere length was determined by Southern Blotting.

Results:

Exposure to H_2O_2 up regulated Bax and increased its protein expression, decreased Bcl-2 protein expression, shortened telomere length and reduced telomerase activity in HDFs (p<0.05). While, treatment with γ -tocotrienol was found to down regulate Bax and increased telomerase activity in H_2O_2 -induced cells (p<0.05).

Conclusion:

Our data suggested that γ -tocotrienol inhibited the progression of apoptosis as evidenced by inhibition of Bax expression. γ -Tocotrienol also showed protection against telomerase activity loss in H_2O_2 -induced cells. This finding revealed the molecular mechanism of γ -tocotrienol in preventing H_2O_2 -induced replicative senescence in human diploid fibroblasts.

Keywords:

γ-Tocotrienol, apoptosis, telomerase, fibroblasts, aging

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