

Tocotrienol-rich fraction of palm oil activates p53, modulates Bax/Bcl2 ratio and induces apoptosis independent of cell cycle association.

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Anti-cancer properties of palm oil have been attributed to the presence of tocotrienols and carotenoids. Studies from various laboratories have shown that tocotrienol-rich fraction (TRF) of palm oil inhibits cell growth and induces apoptosis in both preneoplastic and neoplastic cells. However, the mechanism by which TRF induces apoptosis remains largely unknown. Since several chemopreventive agents have been shown to utilize p53 pathway in negative regulation of cell growth, using human colon carcinoma RKO cells which express wild type p53, we investigated the effect of TRF on components of p53 signaling network. Treatment of cells with TRF resulted in a dose- and time- dependent inhibition of growth and colony formation. Further, TRF treatment of RKO cells resulted in the induction of WAF1/p21 which appears to be independent of cell cycle regulation and is transcriptionally upregulated in p53 dependent fashion. These results were further confirmed by using cells that express luciferase from a p53 responsive promoter where TRF treatment leads to activation of p53 reporter activity. TRF treatment also resulted in alteration in Bax/Bcl2 ratio in favor of apoptosis, which was associated with the release of cytochrome c and induction of apoptotic protease-activating factor-1. This altered expression of Bcl2 family members triggered the activation of initiator caspase-9 followed by activation of effector caspase-3. These signaling cascades lead to condensed chromatin, DNA fragmentation and shrinkage of cell membrane resulting into apoptosis. Our data suggest that TRF-induced apoptosis in colon carcinoma cells is mediated by p53 signaling network which appears to be independent of cell cycle association.

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