PROTECTIVE ROLE OF BETA-CARYOPHYLLENE OXIDE AGAINST HYDROGEN PEROXIDE-INDUCED OXIDATIVE STRESS IN NEURONAL-DIFFERENTIATED SH-SY5Y CELLS

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Introduction: Reactive oxygen species (ROS) are widely acknowledged as relevant mediators of cell survival, proliferation, differentiation, and apoptosis. Antioxidant defense systems scavenge reactive oxygen species in biological systems as a way to prevent build-up of their levels beyond physiologically acceptable limits. Overproduction of ROS is usually linked to the degenerative processes of aging as well as pathogenesis of many diseases. Extensive evidence demonstrate the key role of oxidative stress in etiopathogenesis of neurodegenerative disorders characterized by the progressive loss and dysfunction of nervous cells. Natural compounds have been widely studied as potential neuroprotective agents because of their characteristic properties such as multiple target sites, wider margins of safety, time-tested efficacy, and low cytotoxicity. Among compounds of plant origin, those found in essential oils have received close attention in recent years for their potential role in regulating the pathways involved in oxidative stress promoting the cell survival and preventing the oxidative stress-induced neurodegenerative diseases. The present study evaluated the neuroprotective effect of beta-caryophyllene oxide, a naturally occurring sesquiterpene component of many essential oils, against hydrogen peroxide (H_2O_2)-induced oxidative stress in neuronal-differentiated SHSY5Y cells.
Materials and methods: As an appropriate *in vitro* model, human SH-SY5Y cultures were differentiated in neurons with retinoic acid (three days) and brain derived neurotrophic factor (three days), pretreated with beta-caryophyllene oxide for 24 hours and next, to induce neurotoxicity, treated with H_2O_2 for 24 hours. Moreover, the protective effects of beta-caryophyllene oxide were determined by evaluating some parameters linked to cell viability, cell cycle and apoptosis.
Results: High levels of β-tubulin III, MAP-2, and tyrosine hydroxylase, typical markers of neuronal cells, characterized differentiated cells. Additionally, beta-caryophyllene oxide was found to protect SH-SY5Ycells against H_2O_2-induced neurotoxicity. The mechanistic basis for the neuroprotective

effects of beta-caryophyllene oxide included upregulation of antioxidant genes (SOD 1), downregulation of pro-apoptotic genes (BAX, p21 and caspase-9), and upregulation of anti-apoptotic genes (ERK1/2, AKT1 and NF-Kβ).
Discussion: In this study, beta-caryophyllene oxide protected differentiated SH-SY5Y cells against H_2O_2-induced neurotoxicity through multi-signaling pathways, as evidenced by the reduced cytotoxicity, inhibition of apoptosis and gene expression changes (upregulation of antioxidant genes, downregulation of pro-apoptotic genes, and upregulation of antiapoptotic genes) that tended towards cell survival.
Conclusion: Taken together, these findings suggest that beta-caryophyllene oxide deserve to be deeply investigated for a possible application in the management of neurodegenerative diseases caused by oxidative injury.

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