MASTER'S THESIS

The cyto-protective effect of ginsenosides towards benzo[a]pyrene: induced-DNA damage

Poon, Po Ying

Date of Award:
2010

The Cyto-protective Effect of Ginsenosides towards Benzo[α]pyrene Induced-DNA Damage

POON Po Ying

A thesis submitted in partial fulfillment of requirements

for the degree of

Master of Philosophy

Principal Supervisor: Prof. Ricky Ngok Shun Wong

Hong Kong Baptist University

November 2010

Abstract

Benzo[α]pyrene (BaP) is a well studied polycyclic aromatic hydrocarbon. Humans are exposed to BaP through ingestion or skin contact of cooked food, smoke from incomplete combustion, and soil. Thus, liver and skin are the organs that are mainly exposed to BaP. BaP has been shown to cause genotoxic effects in different tissues and may lead to cancer. *Panax ginseng* C.A. Meyer is a traditional Chinese medicinal herb. Many studies reported that ginseng possesses chemopreventive effects. Ginsenosides are the main active constituent of ginseng and account f or most of the pharmacological effects. In this study, the protective effect of ginsenosides on the BaP-induced DNA damage in human dermal fibroblasts and HepG2 cells was investigated. Results showed that ginsenosides, 20(S)-Rg3, can protect both cell models from BaP-induced DNA damage. 20(S)-Rg3 can activate the phosphorylation of protein kinase B (PKB/Akt) which plays a major role in cell survival signaling. Akt activation can induce nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2), the master regulator of detoxifying enzymes that enhance the elimination of BaP. 20(S)-Rg3 increased gene expression of NQO1, a phase II detoxifying enzyme, probably due to the translocation of Nrf2. Using PI3K inhibitor, the translocation of Nrf2 and furthermore, cytoprotective effect induced by 20(S)-Rg3 was abolished. The results indicated that 20(S)-Rg3 can indeed exert the protective effect against BaP-induced DNA damage through the PI3K/Akt-Nrf2 pathway. On the other hand, pharmacological effects of ginsenosides have been found to relate with nuclear hormone receptor. Among them, pregnane X receptor (PXR) is a sensor of xenobiotics that mediates induction of drug clearance pathways. Activation of PXR can induce gene expression of phase I enzymes, phase II enzymes and phase III transporters. Using competitive binding assay, it was found that 20(S)-Rg3 is a ligand of PXR. Knockdown of PXR by si-RNA eradicates the protective effect of 20(S)-Rg3 towards BaP-induced DNA damage in HepG2 cells. In HepG2, 20(S)-Rg3 can serve as a ligand of PXR and may activate PXR to induce the downstream protective mechanism. In summary, ginsenoside 20(S)-Rg3 can reduce BaP-induced genotoxicity suggesting that ginseng may serve as a natural chemoprotective agent against environmental carcinogens in human.

Table of Contents