DOCTORAL THESIS

The anti-aging effects of ginsenosides on human endothelial cells and dermal fibroblasts

Kwok, Hoi Hin

Date of Award:
2011

The Anti-aging Effects of Ginsenosides on Human Endothelial Cells and Dermal Fibroblasts

KWOK Hoi Hin

A thesis submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

Principal Supervisor: Professor Ricky Ngok Shun WONG

Hong Kong Baptist University

April 2011

ABSTRACT

Ginseng is a precious Chinese traditional herbal medicine used for thousands of years. It is strongly believed that ginseng possess the mysteriously anti-aging effects by improving health quality during aging and increasing longevity. Contemporary scientific research clearly characterized that ginsenosides are the major phytochemical responsible for most pharmacological effects of ginseng. Previous studies reveal diverse activities of ginsenosides, however, the beneficial effects of ginsenosides on aging-related change are still elusive. The present study is performed to provide mechanistic evidences on the anti-aging effects of ginsenosides on human endothelial cells and dermal fibroblasts.

Absence of perfect anti-oxidant system in aerobic life leads to accumulation of reactive oxygen species and produces oxidative stress. Oxidative stress is the main cause of aging and also a variety of age-related cardiovascular diseases. In the first part of this study, it showed that ginsenoside protopanaxatriol (PPT), one of the major ginsenoside metabolites, could prevent H_2O_2-induced human umbilical vein endothelial cells (HUVECs) death. It is demonstrated that hydrogen peroxide (H_2O_2) can cause DNA damage, affect mitochondria function and alter redox states. Ginsenoside PPT could provide protection against redox change and intracellular energy depletion, but only partially against DNA damage induced by H_2O_2. Pretreatment with PPT could improve reduced glutathione / oxidized glutathione ratio by up-regulating glutathione peroxidase and glutathione reductase activities. This suggested that the antioxidative effects of ginsenoside in endothelial cells, and supports the notion that ginsenoside metabolites circulated in our body after the oral consumption of ginseng may provide cardiovascular-protective effect against oxidative stress during aging.

Apart from the challenge by oxidative stress, endothelial cells, which play a key role in regulating angiogenesis, will progressively loss the angiogenic ability during aging. In the second part, we demonstrated that ginsenoside stereoisomers 20(S)-Rg3 and 20(R)-Rg3 differentially induce angiogenesis, in which 20(S)-Rg3 significantly induces HUVECs proliferation, cell migration and tube formation, while 20(R)-Rg3 showed no effects. The underlying mechanisms may be due to the differential activation of peroxisome proliferator-activated receptor gamma (PPARγ) and the downstream ERK/AKT-eNOS signaling. This study not just enhances our understanding on the importance of ginsenoside stereochemistry, but also provides clues for improving delayed angiogenesis by ginseng due to aging.

In addition, skin aging is the most obvious physiological change during aging. Type I collagen is the primary structural component of human skin. We have demonstrated the type I collagen-inducing effect of Rb1 in human dermal fibroblasts. Loss-of-function studies of PPARβ/δ confirmed Rb1 induced type I collagen expression is mediated though PPARβ/δ. Moreover, the non-genomic activation of AKT and JNK signaling, and the suppression of microRNA-25 expression by Rb1 is also PPARβ/δ dependent. This substantiates the beneficial effects of ginseng on skin aging.

Taken together, the current study outlines the beneficial effects and the underlying mechanisms of ginsenosides on endothelial and skin aging.

TABLE OF CONTENTS