Inhibition of Endoplasmic Reticulum Stress and Mitochondrial Damage Crosstalk by Gypenoside XVII Protects against Myocardial Ischemia and Reperfusion Injury

Yingli Yu\textsuperscript{1,2}, Guibo Sun\textsuperscript{2}, Min Wang\textsuperscript{2}

\textsuperscript{1}Tianjin University of Traditional Chinese Medicine, China, \textsuperscript{2}Institute of Medicinal Plant Development, Peking Union Medical College and Chinese Academy of Medical Sciences, China

Background: Effective strategies have been developed to prevent or improve recovery from myocardial ischemia and reperfusion injury (MIRI). Direct interactions between mitochondria and endoplasmic reticulum (ER) during heart diseases progression have been extensively investigated. This study aims to explore the cardio-protective effects of gypenoside XVII (GP-17, derived from Panax notoginseng F. H. Chen) against MIRI and illustrate the roles of ER stress, mitochondrial damage and their cross-talk within the progression of MIRI and in GP-17 induced cardio-protection.

Methods: Cardiac contractility function was monitored in the Langendorff perfused rat hearts. H9c2 cells were incubated with GP17 for 24 h and exposed to hypoxia reoxygenation. The effects of GP-17 on mitochondrial functions, particularly opening of the mitochondrial permeability transition pore (mPTP), respiratory function, and reactive oxygen species production, were determined. The protein expression levels of ERS responsive proteins GRP78, PERK, Ire1, ATF6, elf2, and pro-apoptosis proteins CHOP, Caspase-12, JNK, BAD, Bcl-2, Caspase-9 with or without GP-17 were detected by Western blot.

Results: We find that GP-17 reduces cardiac dysfunction, inhibits myocardial apoptosis and improves contractile recovery after MIRI both in isolated rat hearts and in H9c2 cells. MIRI induced apoptosis is predominantly regulated by ER stress as well as mitochondrial damage. The cardio-protective effects of GP-17 are controlled by phosphoinositide 3 kinase protein kinase (PI3K) and P38 signalling pathways.

Conclusion: Our results elucidate the significant protective effects of GP-17 against MIRI injuries both ex vivo and in vitro. GP-17 ameliorates MIRI induced mitochondrial damage and delays the onset of ER stress through PI3K/AKT and P38 signalling pathways.