Title: Cardioprotective effect of Ginger in a rat model of myocardial damage and its possible intervention in PERK-ATF 4-CHOP-PUMA apoptotic Pathway.

ABSTRACT

For today the exact mechanisms of myocardial infarction and ischemia/reperfusion injury are still not fully understood. ER stress and integrated stress response pathways are thought to play an essential role in myocardial damage. This includes activation of endoplasmic reticulum kinase (PERK), induction of activating transcription factor 4 (ATF4), expression of pro-apoptotic transcription factor (CHO P) and P53 up-regulated modulator of apoptosis (PUMA) involved in apoptosis control. We used a rat model of isoproterenol-induced myocardial damage to elucidate the possible cardioprotective effect of Ginger through the influence on ER stress-induced apoptotic pathway. We also compared its effect with Captopril, inhibitor of angiotensin-converting enzyme. Male albino Wistar rats received 1.0 or 2.0 ml of Zingiber officinale (Ginger) powder suspension (200 mg/ml) daily by intra-gastric intubation for 28 days. Isoproterenol at a dose of 85 mg/ kg was IP injected on the 27th and 28th days. Serum aspartate transaminase (AST) level was measured using kinetic kit. Heart tissue was used for RNA extraction, evaluation of gene expression by Q-RT-PCR, immunohistochemical determination of caspase-3 expression and histopathological studies. Our results showed that Isoproterenol administration increased CHO P-mRNA expression 4 folds in cardiac muscle tissue compared to normal control. Ginger pretreatment significantly decreased both CHOP and ATF4, and PUMA mRNA expression compared to Isoproterenol-treated groups. A significant reduction in ATF4 mRNA expression in a group pretreated with Captopril and Ginger compared to normal control group was observed. The results showed that Ginger reduced AST serum levels which correlated with results of histopathological studies of heart tissue. Our findings suggest that the protective effects of Ginger against myocardium damage induced by Isoproterenol may be mediated by reducing the endoplasmic reticulum stress by affecting the ATF4-CHOPPUMA pathway**.**

Keywords: myocardial damage, ischemia-reperfusion, ATF4, CHO P, PUMA, AST, Ginger, Captopril, Isoproterenol.

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