In the present study, the cardioprotective effects of rosuvastatin, amlodipine and ellagic acid as well as the combination of rosuvastatin with either amlodipine or ellagic acid were investigated on myocardial infarction in hypercholesterolemic rats.

To fulfill the aim of the present study, two types of experimental models were employed in the positive control group. The first model was for induction of hypercholesterolemia. This was accomplished by feeding rats with cholesterol-rich diet for seven weeks. Whereas, the second experimental model comprised of subcutaneous injection of 100 mg/kg isoproterenol in the last two days of experiment for induction of myocardial infarction in rats. Such combined hypercholesterolemic-myocardial infarcted model (HM rats) resembles the clinical condition of myocardial infarction which is usually associated with hypercholesterolemia.

The cardioprotective potentials of the chosen agents were evaluated based on ECG monitoring and assay of serum cardiac biomarkers, namely cardiac troponin I (cTnI), creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST). Also, the oxidative stress markers, including malondialdehyde (MDA) and reduced glutathione (GSH) were assessed in cardiac homogenates. In addition, the lipid profile fractions, namely total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) were estimated in serum. Moreover, western blotting was performed for cardiac tissue to determine the expression levels of various proteins, namely inducible nitric oxide synthase (iNOS), endothelial nitric oxide synthase (eNOS),

Bcl-2-associated X protein (Bax) and B-cell lymphoma 2 (Bcl-2). Finally, histopathological examination of heart sections was conducted.

The main findings of the current study can be summarized as follows:

1. Isoproterenol-induced myocardial infarction was manifested by the marked ST-segment elevation on ECG, as well as the increased serum levels of cardiac biomarkers. These were coupled with myocardial necrosis, granulation tissue formation and inflammatory cells infiltration, which were revealed in cardiac tissues upon histological examination.

2. Both feeding with cholesterol-rich diet and injection of isoproterenol resulted in a state of oxidative stress and extensive alterations in the lipid profile. In addition, they significantly increased the cardiac expression levels of iNOS and Bax proteins, while significantly decreased eNOS expression level.

3. Daily administration of rosuvastatin, amlodipine and ellagic acid for three weeks significantly decreased the ST-segment elevation coupled with a significant decrease in serum levels of cardiac biomarkers of HM rats.

4. Rosuvastatin, amlodipine and ellagic acid significantly decreased the cardiac content of MDA of HM rats.

5. Rosuvastatin and ellagic acid significantly elevated the cardiac content of GSH of HM rats.

6. Rosuvastatin, amlodipine and ellagic acid significantly reduced serum TC, TG and LDL-c levels with a parallel increase in serum

HDL-c level of HM rats. Therefore, the atherogenic index was significantly decreased in the pretreated groups.

7. An additive interaction was noted between rosuvastatin and amlodipine on serum HDL-c level and between rosuvastatin and ellagic acid on serum LDL-c level, when combined together.

8. Rosuvastatin, amlodipine and ellagic acid resulted in a significant decrease in iNOS expression level and a significant increase in eNOS expression level of HM rats.

9. Rosuvastatin and amlodipine significantly protected the cardiomyocytes from apoptosis by lowering Bax expression level; whereas ellagic acid was unable to decrease the level of Bax of HM rats.

10. There was a potentiating interaction between rosuvastatin and ellagic acid on Bax expression level, when administered concurrently.

11. Rosuvastatin, amlodipine and ellagic acid improved isoproterenol-induced cardiac histopathological changes as indicated from alleviation of myocardial necrosis and inflammatory cells infiltration.

Based on the previous findings, the followings could be concluded:

1. Rosuvastatin and amlodipine are effective as cardioprotective agents towards myocardial infarction in presence of hypercholesterolemia via their antioxidant and antihyperlipidemic effects, and also through improvement of coronary endothelial function and protection of heart from apoptosis.

2. Ellagic acid can protect rat hearts from myocardial infarction due to its ability to ameliorate cardiac oxidative stress and to improve the lipid profile and the endothelial function.

3. Further studies are recommended to confirm the antihyperlipidemic activity of amlodipine and ellagic acid, especially when coupled to rosuvastatin. This may open up new avenues for their use in treatment and prevention of hypercholesterolemia in people at high risk for myocardial infarction and other coronary heart diseases.

4. Additional experimental and clinical studies are required to verify the cardioprotective effects of rosuvastatin, amlodipine and ellagic acid.