summary & conclusions
SUMMARY AND CONCLUSIONS

Myocardial ischemia (MI) commonly known as heart attack is one of the leading causes of death in the developed and developing countries. Despite all basic and clinical improvements, MI is still one of the most common and severe health problems in a modern world. MI is caused by critical imbalance between the coronary oxygen supply and the demand of the myocardium which will eventually lead to myocardial necrosis and death. The conventional clinical treatments, such as percutaneous coronary intervention, coronary artery bypass graft surgery and anti or dissolution thrombotic therapy can reduce death rate to a certain extent. Heart transplantation is greatly restricted due to the limited source of donor hearts. Therefore, more effective approaches are urgently needed to treat this disease.

Various clinical ischemic manifestations of myocardial ischemia include angina, myocardial infarction, cardiac sudden death, and heart failure are attributed to the effects of obstruction of coronary blood flow. Pathological alterations underlying myocardial injury begins during ischemia by stoppage of anaerobic metabolism which activates glycolysis, resulting in a decline in intracellular pH and consequently an elevation of sodium and calcium in the cytosol. The ionic disturbances including calcium overload in the cytosol and mitochondria are exacerbated and production of superoxide and other reactive species of oxygen is intensified, leading eventually to structural and functional changes in cellular biomolecules and activation of signaling pathways that result in cell demise.

The rat model of isoproterenol (ISO) induced myocardial ischemia serves as well accepted standardised model to evaluate several myocardial ischemic dysfunctions and to study the efficacy of various natural and synthetic antiischemic agents. Therefore, the study was made using this suitable model system. The
increased production of reactive oxygen species (ROS) is one of the unifying mechanisms in ischemic injury progression, and administration of antioxidants may be protective against ISO induced myocardial ischemia. Recently, there has been a growing interest in establishing the therapeutic potentials of medicinal plants against various diseases. The use of plant extracts for medicinal purposes seems to be more natural, less expensive and without side effects. The biological activities of these plants are due to the presence of various biologically active compounds like flavonoids and polyphenols. Hyperlipidemia and oxidative stress has been implicated in the pathogenesis of myocardial ischemia.

Therefore therapeutic interventions having hypolipidemic and antioxidant activity may exert beneficial effects against ischemic heart diseases. Flavonoids are outstanding antioxidants, at least in vitro and because of their antioxidant activity as well as their abundance in medicinal plants, fruit and vegetables they may partly contribute to the health benefits. There is an ample evidences indicating beneficial effects of flavonoids on ischemic hearts in in vitro applications or administered to blood which could be of use in acute ischemic situations such as heart surgeries and transplants. There is also growing evidence that oral administration of flavonoids could provide protection against myocardial ischemia which would be of benefit to people with chronic conditions such as ischemic heart disease.

Recently flavonoids have been isolated from the leaves of Acalypha indica. The investigation on medicinal potentials of this plant is still in its infancy. Hence, with the aforementioned concept, this plant was selected for the investigations on antiischemic potential. The present study highlights the possible ability of flavonoid rich AIE against ISO induced alterations in myocardial enzymes, antioxidant status, lipid profile alterations and cardiac pathology in rats.

In summary, flavonoid rich AIE pretreatment significantly reduced the concentration of CK-MB, LDH, plasma lipids, plasma lipoproteins, myocardial lipids, blood glucose and the levels of cardiac ischemic markers that are to say IMA, AIP, non-HDL-C. AIE also reduced the hypertrophic index and LDL/HDL ratio in ISO administered rats. Oxidative stress produced by isoproterenol was significantly lowered by the administration of flavonoid rich AIE which was evident from
increased activities of antioxidant enzymes (SOD, CAT, GPx, GR) and reduced concentration of lipid peroxidation products (MDA). Concentration of reduced glutathione (GSH) was also high in AIE pretreated rats. Histopathology of heart of ISO administered rat pretreated with flavonoid rich AIE showed normal myocardium with very little evidence of inflammatory infiltration. These findings provided evidence that flavonoids rich fraction of AIE was found to be protecting the myocardium against ischemic insult and the protective effect could attribute to its antioxidative and antihyperlipidemic activities.

In conclusion, the protective effect of AIE against lipid peroxidation, hyperlipidemia and membrane disintegration could be through its multiple mechanisms antihyperlipidemic and antioxidant potential. Flavonoids of Acalypha indica may prevent production of oxidants (either by inhibition of xanthine oxidase or by chelation of transition metals), inhibit oxidants from attacking cellular targets (by direct scavenging activities), block propagation of oxidative reactions (by chain breaking antioxidant activity), and reinforce cellular antioxidant capacity (through sparing effects on other antioxidants and inducing expression of endogenous antioxidants).

Flavonoids may also facilitate lower oxidant production and better reestablishment of blood in the ischemic zone. Thus, the antiischemic potential of the flavonoid rich fraction of Acalypha indica may be by these multifaceted activities raise their utility as possible therapeutic interventions to ameliorate ischemic injury. Thus there is a possibility to develop this plant as a cardiotonic nutraceutical or functional food. Due to its antioxidant and antihyperlipidemic effects, it will provide an accessible and cheap traditional medicine source for treatment of myocardial ischemia in developing countries.

Collectively, based on our findings we speculate herein that “flavonoids from A.indica may exert its protective effects against the isoproterenol induced MI” stands verified. Further studies are needed to determine the molecular mechanism by which flavonoid rich AIE acts on the myocardium. Studies in this line can open new avenues for novel pharmaceutical compounds in the treatment of ischemic heart diseases.