Ischemic heart disease (IHD) remains one of the leading cause of deaths despite several advancements in the medical interventions. Among this acute myocardial infarction (AMI) in particular, is one of the most distressing disease which affects large population in the world (Upaganlawar et al., 2011). According to the world health organization (WHO) it will be the major cause of death in the world by the year 2020. (Lopez and Murrau, 1998; Punithavathi and Prince, 2010). The Indian subcontinent accounts for the highest rate of cardiovascular events on global front (Goyal and Yusuf, 2006). Current treatment strategies for protecting the heart from ischemic injury includes: beta-blockers, ACE inhibitors, calcium antagonists, nitrates, antiplatelet agents, thrombolytics, antioxidants and free radical scavengers. These have been shown to be beneficial against MI (Wang et al., 2002; Bolli et al., 2004). However there is still a need for the development of new and safer drug for the treatment of IHD, which remains a major concern and challenge for drug development.

Literature review provides substantial evidence that oxidative stress contributes to myocardial dysfunction, cardiomyocyte apoptosis and myocardial infarction (Ceconi et al., 2003; Griendling and FitzGerald, 2003). The exciting avenue in the treatment of IHD is to target the source of oxidative stress. This approach has been raised the use of antioxidant vitamins and natural products which are demonstrated to posses free radical scavenging properties and exhibit antioxidant activities.

A wide array of plants and its active principles, with minimal side effects, provide an alternate therapy for IHD. Moreover, the plant kingdom represents a largely unexplored reservoir of biologically active compounds. There are wide varieties of experimental models which are used in order to screen drugs for
cardioprotective activity. In the present study isoproteenol model was used to screen cardioprotective, anti-inflammatory, anti-apoptotic and antioxidant activity of herbal extracts.

The herbal extracts, which were studied in the present investigation, are of following:

1. **Terminalia arjuna** (*T. arjuna*)

2. **Eugenia jambolana** (*E. jambolana*)

3. Combination of *T. arjuna* and *E. jambolana*

   In the present study *T. arjuna* and *E. jambolana* were selected considering their traditional use in cardio-metabolic disorders. The ancient medical literature described the preventive potential of *T. arjuna* and *E. jambolana* against various chronic disorders. The chemical contents, biological and pharmacological properties such as antioxidant, free radical scavenging, cardioprotective, anti-inflammatory and anti-apoptotic activities of these plants have been evaluated scientifically in the present study. These medicinal plant were used with an aim to define the role of *T. arjuna* and *E. jambolana* in limiting the deleterious effects of myocardial ischemia by providing scientific data to validate their use as prophylactic approaches or as an adjunct to standard treatment of ischemic heart disease.

   ISP-induced myocardial necrosis results in significant decrease in the activities of antioxidant enzymes suggests the overwhelming oxidative stress. The depletion in GSH level along with elevation in MDA level has been observed during ischemic episode. Consumption of endogenous antioxidant defense mechanism increased during ischemia. Reduced glutathione and superoxide dismutase (GSH & SOD) are the antioxidants which are known to remove the ISP-induced generation of
toxic reactive oxygen species (ROS) by their lipid peroxidative and free radical scavenging activity. ISP-induced myocardial necrosis in rats is reported to attribute the peroxidative damage, as ISP generates lipid peroxides, which may be act as causative factor for irreversible damage to the myocardial membrane (Yates et al., 1980; Singal et al., 1982; Blasig et al., 1984). Reactive oxygen species (ROS) are implicated as mediators of tissue injury in cardiovascular pathology (Kukreja and Hess, 1992). Cytotoxic effects of reactive oxygen species are related in its reaction with membrane lipids (Kuzuya et al., 1991) and subsequent membrane destruction (Burton et al., 1990).

Serum CPK-MB, SGOT, Trop I and LDH are well known markers of myocardial infarction. When myocardial cells are damaged or destroyed due to deficient oxygen supply or glucose, the cardiac membrane becomes permeable or may rupture which results in leakage of enzymes. These enzymes enter into the blood stream thus increasing their concentration in the serum (Mathew et al., 1985). The enzyme serum oxaloacitate glutamate transaminase (SGOT) is normally present inside the cells. SGOT catalyses the intermolecular transfer of amino groups, which is an important metabolic reaction. The high quantity of enzyme is predominantly present in heart and liver tissues. SGOT released into blood when certain tissues or organ particularly heart and liver are injured. Elevated level of SGOT is an important test for diagnosis of myocardial infarction, but is less specific than CPK-MB. When the cells are damaged these enzymes leaked out and their level is increased in the blood. It has been shown to rise clinically in myocardial infarction. High levels of SGOT may be due to trauma in the myocytes. In the present study, the SGOT level is elevated due to isoproterenol induced myocardial injury. Pre-treatment with extracts at different doses reduces their elevated levels.
The levels of CPK-MB in the serum have an important diagnostic significance, because of the marked abundance of this enzyme in cardiac tissues and virtual absence from most other tissues and its consequent sensitivity. Measurement of CPK-MB is useful as an index of early diagnosis of myocardial injury, which is released from the heart into the blood during myocardial damage due to isoproterenol. When myocardial cells containing CPK-MB is damaged or destroyed, the cell membrane becomes permeable or may rupture, which results in the leakage of this isoenzyme. This is the reason for the increased activity of serum CPK-MB in isoproterenol induced cardio toxic rats (Mathew et al., 1985).

Cardiac troponins T and I are markers of myocardial cell injury (Alpert et al., 2000). These are becoming acknowledged as useful biochemical markers of drug induced cardio toxicity in rats. Troponins are low molecular weight proteins and the components of the myofibrillar contractile apparatus of cardiac muscle. These are not normally present in the blood. As reported earlier, there is an increase in the levels of serum cardiac troponin-I in isoproterenol induced myocardial infarction (Bertinchant et al., 2000). Troponin-I is released into the circulation after onset of damage to myocytes due to deficient of oxygen supply by isoproterenol. Thus, the level of troponin-I was increased in the serum of isoproterenol induced cardio toxic rats. Cardiac troponins can be detected as early as 4-6 h after the onset of ischemia and peaks at approximately 24 h. Troponin levels may remain elevated for 7-10 days after an episode of myocardial infarction (Gupta and de Lemos, 2007).

The process of myocardial tissue necrosis is accompanied by elevation in enzyme serum levels of CPK, SGOT, LDH, and Tropon-I due to myocardial cellular damage. Cardiac troponin (cTn) has established itself firmly as the ‘gold standard’ in the diagnosis of acute coronary syndrome. Elevated troponin levels predict the risk of
both cardiac death and subsequent infarction. In our study, we observed increased levels of cardiac troponin-I (cTnI) in serum of ISP-induced rats.

Previous studies have shown that ISP mediated oxidative stress could lead to myocardial necrosis and finally cardiac dysfunction (Teerlink et al., 1994; Grimm et al., 1998). These deleterious changes and cardiac dysfunction are significantly prevented by medicinal herbs possessing strong antioxidant activities, which were exemplified through various studies (Ayra et al., 2006; Gauthman et al., 2006; Mohanty et al., 2006; Prabhu et al., 2006; Nandave et al., 2007; Kumar et al., 2009; Shukla et al., 2012; Upaganlawar et al., 2012; Ragavendran et al., 2012).

Inflammation is a recognized key component of acute coronary syndrome (ACS). Such pathogenetic achievement has led to the use of inflammatory markers and proteins as prognostic tool in ischemic heart disease (IHD). A number of markers have been proposed, including pro-inflammatory cytokines such as interleukin-6, interleukin-1, C-reactive protein and tumor necrosis factor-α. Circulating levels of CRP rise during the acute-phase response to tissue injury, infection and inflammation (Berk et al., 1990; Danesh et al., 1999; Mendall et al., 2000; Biasucci et al., 2004; Sepulveda and Mehta, 2005; Brunetti et al., 2006; Blake and Ridker, 2007). Conversely, CRP, the prototypic acute phase protein has been proven to be reliable and important marker of risk in ischemic heart disease. CRP has been consistently found to be independent from other risk factors and to have an incremental value beyond the common risk factors and biochemical markers of risk, including troponin (Berk et al., 1990; Danesh et al., 1999; Mendall et al., 2000; Biasucci et al., 2004; Sepulveda and Mehta, 2005; Brunetti et al., 2006; Blake and Ridker, 2007). CRP has been shown to exert pro-atherogenic effects on vascular cells exemplified by increasing the secretion of monocyte chemoattractant protein (Pasceri et al., 2001),
reducing nitric oxide bioactivity (Venugopal et al., 2002). Vascular inflammation can be limited by anti-inflammatory counter regulatory mechanisms that maintain the integrity and homeostasis of the vasculature (Tedgui and Mallat, 2001). Since the inflammatory response is associated with cytokine release, cytokines may have an important role in the vascular injury induced by inflammation. The inflammatory process initiated by myocardial tissue necrosis (Neumann et al., 1995) is also related to an increase of nonspecific serum markers such as CRP (Mendall et al., 2000; Blake and Ridker, 2003; Brunetti et al., 2006). Mechanisms underlying the stimulation of vascular inflammatory cytokines during increased catecholamine levels are not yet well established. Prabhu et al (2000) demonstrated that β-adrenergic blockade after myocardial infarction is able to reduce the myocardial expression of TNF-α and IL-1β.

In the present study, expression of pro-inflammatory cytokines CRP, IL-6 and TNF-α are increased during isoproterenol induced myocardial ischemia, which is supported by earlier studies (Lee et al., 2003; Chang et al., 2009; Tang et al., 2010; Chan et al., 2010; Narkhede, 2012).

Apoptosis is a highly regulated biological process that regulates the balance between pro-death and pro-survival cell signals, the outcome of which is key for cell fate. Apoptotic signaling pathways found to play a crucial role in induction of apoptosis in the heart (Vanessa et al., 2005). Although myocardial infarction is long considered to be characterized by non apoptotic (necrotic) cell death due to the breakdown of cellular energy metabolism, there is growing evidence that myocyte loss during the acute stage of myocardial infarction involves both apoptotic and non apoptotic cell death. We have made an attempt to quantify the extent of apoptosis in
our study by means of anti-apoptotic protein Bcl-2, pro-apoptotic protein Bax and TUNEL assay.

Myocardial apoptosis was quantitatively analyzed by detection of DNA fragmentation using the terminal deoxynucleotidyl transferase mediated dUTP nick end labeling (TUNEL) technique (Misao, 1996).

Previous experimental studies in animal model of myocardial infarction suggest that apoptosis may contribute substantially to cell death even within the central infarct area with 5% to 33% of the cardiomyocyte staining positive for DNA fragmentation (Kajstura et al., 1996; Fliss and Gattinger, 1996; Bialik et al., 1997; Yaoita et al., 1998). However, at present the relative importance of apoptotic and non-apoptotic cell death in both the acute and chronic phases of myocardial infarction is not known. Initial evidence for the potential pathophysiological significance of apoptosis has been reported in a rat model of myocardial infarction (Yaoita et al., 1998).

Isoproterenol induced ischemia is associated with multiple alterations in the extracellular and intracellular milieu of cardiomyocytes that may act as inducers of apoptosis. The mechanisms responsible for the phenomenon of apoptosis remain unknown and we are limited to formulating a number of theories. According to one theory, cellular hypoxia causes the onset of apoptosis (Tanaka et al., 1994; Seko et al., 1996), while another theory suspects the oxidative mechanism (stress) as the underlying cause (Bennett and Evan, 1993; Gottlieb et al. 1994). In this study pre-treatment with herbal extracts down regulated the expression of apoptotic markers, which might be useful for isoproterenol-induced myocardial apoptosis and necrosis.
Discussion

Natural products: A promising approach for CVD prevention

Plant derived natural products have received considerable attention in recent years due to their diverse pharmacological properties (Shukla et al., 2010; Govind and Sahni, 2011). The traditional medicine all over the world is currently being revisited and extensive research on different plant species including their therapeutic principles is being undertaken. Traditional herbal drugs have gained lot of acceptance in these days, because they have a relatively higher therapeutic window, less serious side effects and are economical. In recent years, there is considerable interest in investigating anti oxidant, anti-inflammatory and anti-apoptotic effects of herbal drugs from different sources (Gupta et al., 2010). Further herbal drugs containing antiradical constituents are gaining importance in prevention and treatment of oxidative stress linked-diseases (Anand and Shrihari, 2011).

The Indian system of medicine, especially Ayurveda, has several medicinal plants with proven beneficial claims towards these pathological conditions (Tripathi YB, 2009). However, the potential of herbal drugs as defined therapeutic agents is undermined by the difficulty in standardization, pharmacodynamics and pharmacokinetics of these multi component mixtures and also the lack of enough experimental data. Therefore, the potential of medicinal plants in the treatment of cardiovascular disease needs to be further explored. Thus, a major opportunity exists in our natural resources for identifying and selecting efficacious, inexpensive and safer approaches for cardioprotection. Medicinal plants need to be investigated scientifically and rigorously to define their role in prevention and treatment of cardiovascular conditions and to stimulate future pharmaceutical development of therapeutically beneficial herbal drugs. Taking these consideration in our mind, we have planed this study for evaluation of the protective effect of T. arjuna and E.
jambolana, especially with a definite aim of cardioprotection. The potential phytoconstituents of T. arjuna and E. jambolana were quantified by TLC and HPTLC. The quantification revealed the presence of arjunolic acid in T. arjuna, while in E. jambolana gallic acid was found.

Arjunolic acid, a triterpene present in T. arjuna bark, protected against acute ISP induced myocardial changes (Kumar et al., 2009). Gallic acid showed strong antioxidant activity and it inhibits pro-inflammatory reactions by blocking histamine release and pro-inflammatory cytokine expression and suggest its synergetic mechanism of action. Furthermore, in vivo anti-inflammatory action of gallic acid suggests a possible therapeutic application in inflammatory diseases (Kim et al., 2006).

The concept of combination therapy

With the passage of time and enhanced knowledge, it was realized that combination of drugs gives better and faster relief; hence ‘Formulation’ a concept of combining the herbs with similar therapeutic activity came in to existence. There is no doubt that most herbs exhibit their effects owing to a variety of constituents and the idea of synergy within and between them is also gaining acceptance (Jain and Agrawal, 2008). From the above concept it is clear that the mixture or formulation possess greater activity than individual components.

In the present study, pre-treatment with individual extracts of T. arjuna and E. jambolana, contributed a greater extent to the antioxidant, cardioprotective, anti-inflammatory and anti-apoptotic properties during MI. However when they were administered in combination, the contribution of combinatorial extracts points towards their overall synergistic mechanism. Combination of two or three herbs can
make a good formulation for the specific disease and hence combination of HETA and HEEJ could become a novel antioxidant formula for cardiovascular disease associated with free radical generation. However, more detailed pre-clinical and clinical evidences are required to establish its potency.

Herbal extracts or mixtures represent combinatorial chemistry of nature with vast repertoire of chemical entities that have a complex effect on numerous cellular components and functions (Gupta et al., 2010). They have great potential in the multi-target approach to diseases. According to medical practitioners, a combination of drugs exhibits augmented protective efficacy than a single drug (Punithavathi & Prince, 2010). Keeping this view in mind this study was designed to screen the protective effect of two potent herbal extracts of *T. arjuna* and *E. Jambolana* alone and in combination. The results of the present study confirm the potential of combined protective effects of HETA and HEEJ in ISP-induced myocardial infarcted rats.

Isoproterenol (ISP) is a selective β-adrenoreceptor, when isoproterenol is administered to rats, it causes severe stress in myocardium. ISP increased the level of MDA while the antioxidant GSH and SOD are reduced.

Pre-treatment with hydroalcoholic extract of *T. arjuna* (HETA) alone and in combination with *E. jambolana* (HEEJ) at 100, 200 and 400 mg/kg b. w. doses maintained the antioxidant activity as evidenced by increase in the levels of GSH and SOD along with a decrease in the levels of lipid peroxidation product (MDA), which is in accordance to previous reports in this field (Dhuley, 2000; Sharma *et al.*, 2001; Mohanty *et al.*, 2004; Rajadurai and Prince, 2006). The change in these oxidative stress parameters was observed in a dose dependent manner. HETA at a dose of 100
mg/kg b. w. increases the GSH and SOD while MDA level was decreased as compared to ISP control group. There was a statistically significant increase in the antioxidant levels when orally administered with HETA 200 and 400 mg/kg b. w., but highly significant effect was observed with HETA 400 mg/kg b. w.

The cardiac markers SGOT, CPK-MB and Troponin-I were increased in the serum of ISP-induced myocardial infarcted rats. In the present study we observed increased activities of these cardiac markers in the ISP control, which is in agreement with the previous studies (Manjula and Devi, 1993; Fard et al., 2008). The myocardial cells containing these enzymes are damaged or destroyed because of deficient oxygen and glucose supply and the cell membrane becomes permeable or may rupture, which results in the leakage of these enzymes. This accounts for the increased activities of these enzymes in the blood/serum of ISP treated rats. This may be due to the damage caused to the sarcolemma by ISP, rendering it leaky (Mathew et al., 1985). As reported earlier, we have also observed an increase in the levels of serum cardiac troponin-I in isoproterenol induced cardio toxic rats (Bertinchant et al., 2000). The observed increase in the activity of these enzymes is due to ISP-induced cardiac damage. Oral pre-treatment with HETA (200 and 400 mg/kg b. w.) to ISP challenged rats decreased the level of serum SGOT, CPK-MB and Troponin-I significantly, however lower dose of HETA fails to reduce the cardiac markers at significant level. This effect revealed the cardio protective effect of HETA in ISP induced rats.

Pro-inflammatory cytokines CRP, IL-6 and TNF-α were elevated during ischemic episode. Lower doses of HETA have no significant effect in IL-6, CRP and TNF-α level. However, HETA 200 and 400 mg/kg b. w. has reduced the increased levels of pro-inflammatory cytokine in a dose dependent manner. HETA 400 exerted highly significant effect on pro-inflammatory cytokine as compared to ISP control.
and Vit E group. The observation on HETA revealed the better modulation of pro-inflammatory cytokines which is found in accordance to the previous studies (Lee et al., 2003; Chang et al., 2009; Tang et al., 2010; Chan et al., 2010; Narkhede, 2012).

Deleterious effect exerted by isoproterenol was evaluated histopathologically. Isoproterenol produced significant myocardial injury with extensive myonecrosis, edema and infiltration of inflammatory cells in heart as compared to healthy control. HETA 100, 200 and 400 treated groups revealed the improvement in architecture of myocardium, advocated the better mechanistic action produced by HETA. The effect of 400 mg/kg of HETA was highly effective in reducing myocardial infarct size. Apoptosis and necrosis are two important processes occurring during ischemic episode. During ischemia, the expression of Bcl-2 protein was decreased while Bax protein expression was increased, which further leads to apoptosis and/or necrosis. Anti-apoptotic mechanisms are responsible for cell survival.

In this study HETA exerted anti-apoptotic effect and encountered the possibility of myocytes to die due to necrosis. TUNEL is unique technique, which quantifies the apoptotic cells. In the present study, TUNEL assay, Bax (an inducer of apoptosis) and Bcl-2 (inhibitors of apoptosis) were incorporated to know the involvement of apoptosis in ISP-induced myocardial injury. Cardioprotective activity of HETA was confirmed by assessing the severity of pathological changes. Our observation showed that reduction in TUNEL positivity was enhanced with pre-treatment of HETA which receives support from earlier studies (Maulik et al., 1998; Galang et al., 2000). These observations on HETA pre-treatment concluded that HETA is an effective cardioprotective, anti-inflammatory and anti-apoptotic agent. It is predicted that the presence of arjunolic acid and other phytoconstituents may be responsible for their synergetic mechanism of action.
E. jambolana possess strong antioxidant activity due to presence of gallic acid and other phytocomponents. HEEJ alone and in combination with T. arjuna at a dose of 100, 200 and 400 mg/kg b. w. produced significant increase in the antioxidant status (GSH and SOD) while MDA was decreased in a dose dependent manner. Maximum effect on oxidative stress parameter was observed with higher dose of HEEJ (400 mg/kg b. w.). Thus present study receives support from previous reports (Dhuley, 2000; Sharma et al., 2001; Mohanty et al., 2004; Rajadurai and Prince, 2006).

Cardiac markers were significantly increased in ISP control. Lower dose of HEEJ exerted no significant change in cardiac markers, however HEEJ 200 and 400 mg/kg b. w., exerted significant decrease in cardiac markers. The results of this study are in agreement with the previous reports (Manjula and Devi, 1993; Fard et al., 2008).

HEEJ administration decreased the level of pro-inflammatory cytokines as compared to ISP control group. IL-6, CRP and TNF-α levels were reduced significantly after treatment with different doses of HEEJ (100, 200 and 400 mg/kg b. w.) in a dose dependent manner. There was no significant change in IL-6, CRP and TNF-α level after treatment with HEEJ 100 mg/kg b. w. dose. HEEJ 200 mg/kg b.w. has significantly reduced CRP as well as IL-6 levels. The modulation of pro-inflammatory cytokine level was found significant with HEEJ 400 mg/kg b.w., which is supported by previous studies (Lee et al., 2003; Chang et al., 2009; Tang et al., 2010; Chan et al., 2010; Narkhede, 2012). Literature survey reveals the presence of gallic acid in HEEJ, which is also quantified in this study. An earlier study has shown that gallic acid has beneficial effect on AST, ALT, lipid peroxidation and GSH in carbon tetrachloride induced damage in albino rats (McCord, 1988). Gallic acid may
be protecting the heart by preventing lipid peroxidation because it scavenges the superoxide and hydroxyl radicals, involved in the production of free radicals as reported earlier (Jadon et al., 2007). Another report showing that binding of the gallate compounds to lipid membranes is a main determining factor of the antioxidant action. The possible mechanism of gallic acid may directly combine with free radicals and lead to inactivate them which may suppress the intracellular concentration of free radicals. This resulted in improved antioxidant status in HEEJ pre-treated cardiotoxic rats. In addition to this, histopathology of HEEJ pretreated rats confirmed the protective nature of gallic acid in ISP-treated rats.

HEEJ 100, 200 and 400 treated groups revealed the improvement in architecture of myocardium, advocated the better mechanistic action produced by HEEJ. Apoptosis and necrosis are counter regulated by anti-apoptotic mechanisms during ischemic episode for cell survival.

In the present study, HEEJ exerted anti-apoptotic effect and encountered the possibility of myocytes to die due to necrosis. Apoptosis is quantified by TUNEL assay, Bax and Bcl-2 to confirm its involvement in ISP-induced myocardial injury. Cardioprotective activity of HEEJ was confirmed by assessing the severity of pathological changes. Our study shows that reduction of TUNEL positivity was enhanced with pre-treatment of HEEJ which receives support from earlier studies (Maulik et al., 1998; Galang et al., 2000). Hence the present study on HEEJ pre-treatment concluded that HEEJ is better and effective cardioprotective, anti-inflammatory and anti-apoptotic agent.

When hydroalcoholic extract of T. arjuna and E. jambolana were taken in combination at a dose of 100, 200 and 400 mg/kg b. w., elevated levels of MDA were decreased, however GSH and SOD were increased in a dose dependent manner.
Maximum effect was seen with the higher dose of HETA+HEEJ (400 mg/kg b. w.), which was verified by the previous reports (Dhuley, 2000; Sharma et al., 2001; Mohanty et al., 2004; Rajadurai and Prince, 2006). Cardiac markers were improved significantly with the combination of HETA and HEEJ in dose dependent manner, which exemplify the traditional approach of combination. HETA and HEEJ combination at 400 mg/kg b. w. produced highly significant effect, which is in accordance to the previous reports (Manjula and Devi, 1993; Fard et al., 2008). Pro-inflammatory cytokines were significantly reduced with the combination dose, more effectively than alone treatment of the HETA and HEEJ.

There is mounting evidence that apoptosis plays an important role at multiple points in the evolution of myocardial infarction and involves not only cardiomyocytes but also inflammatory cells, as well as cells of granulation tissue and fibrous tissue (Ahmad et al., 2010). Apoptosis, being a highly regulated process, is a potential target for therapeutic intervention. Anti-apoptotic therapeutic interventions offer an appealing platform for devising ways to retard the maladaptative growth associated with congestive heart failure. Apoptosis and necrosis is mechanistically counter-regulated with the combination of two potential herbal extracts HETA and HEEJ, which is clearly justified in histopathological findings and TUNEL assay. Moreover, the area of infarction was significantly reduced with combination dose, which further verified the potential of these herbal combinations. Previously the preventive effect of some medicinal plants has been reported in animal tumor models of cancer, possibly by its apoptosis-inducing and anti-proliferative influences (Hanif et al., 1997; Bhaumik et al., 2000; Kirana et al., 2003). However, in the present study, in contrast to earlier reports anti-apoptotic activity of HETA and HEEJ alone and in combination was observed, which was noticed highly significant with the combination.
It has been demonstrated that pre-treatment of these herbals may attenuate apoptosis via a number of mechanisms; upregulation of Bcl-2 may result in formation of heterodimers with Bax, resulting in no/fewer free Bax protein available for homodimerization. If Bax homodimers predominate, cell death will occur, but when Bcl-2 and Bax heterodimerization prevails cell can survive. Substantial evidence indicates that mitochondria play a critical regulatory role in the signal transduction pathway leading to apoptosis (Haunstetter et al., 2000; Saraste and Pulkki, 2000; Isodono et al., 2010; Tabas and Ron, 2011; Miyazaki et al., 2011; Velotta et al., 2011).

Combination of HETA and HEEJ attenuate myocardial injury by reducing lipid peroxidation, improved antioxidant status, preserve mitochondrial function evidenced by inhibition of apoptosis in our study, which is supported by the previous reports (Mohanty et al., 2007). Combination dose also attenuate myocardial apoptosis through prevention of the dephosphorylation of Bad, a proapoptotic protein of Bcl-2 family, by calcenurin (a calcium/calmodulin dependent protein serine/threonine phosphate). Combination of extracts through its highly significant antioxidant and free radical scavenging activity may prevent DNAase activation and reduced myocardial apoptosis.

As outlined above, the results of the present experimental study clearly emphasize the beneficial action of HETA and HEEJ alone and in combination as a potential cardioprotective agent. Several factors are playing contributing role for their synergetic mechanism. Adaptogenic property is one of them. A concept is now emerging of ‘adaptogenic drugs’ that increase non-specific resistance of the users to a variety of stresses through metabolic regulation (Rajak et al., 2004). By virtue of this property, the results of our study demonstrate the myocardial salvaging effects of
HETA and HEEJ. Inhibition of apoptosis and improvement of histological and ultrastructural features suggests the cardioprotective effects of HETA and HEEJ. Thus, it is concluded that hydroalcoholic extract of *T. arjuna* and *E. jambolana* treatment may have indirectly improved the cardiac function and hence potential cardioprotective agent.

It is apparent that experimental evaluation of herbal drugs for the treatment of cardiovascular diseases is rather impressive, but very few have reached clinical trials and still fewer have been marketed. Hence, pharmacologists and researchers need to take more active interest in the evaluation of herbal drugs for potential cardioprotective and anti-apoptotic activity and their standardization to allow them to be clinically effective and globally competitive. Whether the conclusion drawn from our experimental study can be extrapolated to clinical scenario or not, remains to be defined by clinical studies.