1. Introduction

Cardiovascular disease, particularly ischemic heart disease (IHD), has become a worldwide health problem. IHD is the leading cause of morbidity and mortality globally, reaching to the pandemic proportion (Goyal and Yusuf, 2006; Backer, 2009; Subhashini et al., 2011; El-Sayed et al., 2011). It is predicted that IHD will be the most important cause of mortality in India by 2020 (Rajdurani and Prince, 2007).

Myocardial infarction (MI) is the most lethal manifestation and is a subject of intense investigation for clinicians and basic medical scientists. It is caused by an imbalance between myocardial oxygen supply and demand, resulting in myocardial hypoxia and accumulation of waste metabolites, which occurs often due to atherosclerotic disease of the coronary arteries (Buja and Entman, 1998; Mallika et al., 2007).

Myocardial infarction (MI), the most dreaded sequel among IHD, invariably followed by several biochemical alterations, such as lipid peroxidation, free radical damage, hyperglycemia, hyperlipidemia, elevation in cardiac markers and pro-inflammatory cytokines leading to qualitative and quantitative alterations of myocardium (Kumar et al., 1992). The pathogenesis of MI involves a complex process including several mechanisms such as oxidative stress due to oxygen free radical formation, calcium overload, neutrophil-mediated myocardial and endothelial injury, contractile dysfunction, metabolic changes and cell death either by necrosis or apoptosis or both (Majno and Joris, 1995; Buja and Entman, 1998; Logue et al., 2005; Rupinder et al., 2007).

Isoproterenol (ISP) is a synthetic catecholamine, nonselective β-adrenoreceptor agonist, which causes severe stress in the myocardium and produces infarct like lesions, when injected in rats (Rona et al., 1959; Goyal et al., 2010;
Shukla et al., 2012). ISP model is a well standardized and most reliable for assessing the cardioprotective activity of several drugs (Dwivedi et al., 1988; Bhindi et al., 2006; Anandan et al., 2007; Panda and Naik, 2008; Zhou et al., 2008). The generation of highly cytotoxic free radicals through the auto oxidation of catecholamine create disturbances in the physiological balance between production of free radical and anti oxidative defence system (Srivastava et al., 2007) referred as an important risk factor in the loss of integrity and function of myocardial membrane. The pathophysiological and morphological alterations in the heart of ISP-induced myocardial infarcted rats mimic the resemblance with that of human myocardial infarction (Anandan et al., 2007; Panda and Naik, 2008; Zhou et al., 2008). Apoptosis is found to coexist with oxidative stress in myocardial ischemic injury (Buja, 1998; Piper and Garcia-Dorado, 1999; Kumar et al., 2002). Necrosis and apoptosis differ in several morphological and cellular regulatory features (Reed, 2000). The apoptotic mode of cell death has pathological as well as therapeutic implications. The pharmacological treatments for myocardial ischemia aimed at re-establishing the balance between oxygen delivery to oxygen demand by the myocardial tissue. This equilibrium is maintained by decreasing the mechanical power consumption of the myocardial tissue through a reduction in heart rate, blood pressure and contractibility or coronary vasodilation (Dhalla et al., 2000; Wang et al., 2002; Bolli et al., 2004).

Now a days, there are number of pharmacological interventions available to counteract the ill effect of myocardial ischemic injury, such as beta-blockers, ACE inhibitors, antiplatelet agents, thrombolitics, calcium antagonist, nitrates, antioxidants and free radical scavengers which delays myocardial necrosis and decreases ischemic injury. They have been shown to possess cardioprotective activities against
myocardial ischemia and found to reduce morbidity and mortality in patients with IHD (Verma et al., 2002; Moens et al., 2005). However, their chronic usage is often associated with adverse effects. Therefore, development of new and safer drugs for the treatment and prevention of IHD is still a major concern.

As such, novel therapeutic strategies for protecting the heart against ischemic injury are urgently needed to reduce myocardial injury, preserve cardiac function, prevent the development of heart failure and improve clinical outcomes in patients with IHD (Yellon and Hausenloy, 2007; Ovize et al., 2010). There is increasing trend towards the application of herbal medicines to treat the cardiovascular diseases (Nandave et al., 2007; Hina et al., 2010; Ojha et al., 2011). 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). Herbal plants have been observed to possess various medicinal properties, such as antioxidant, anti hyperglycemic, hypolipidemic, antithrombotic, anticoagulant and cardioprotective activities with regards to cardiovascular disorder. The role of plant based drugs in the prophylaxis and treatment of IHD have been investigated for long and shown to have promising results in experimental as well as clinical studies (Chen, 1996; Dwivedi et al., 1996; Zapfe et al., 2001; Mckenna et al., 2001; Sun et al., 2002; Degenring et al., 2003; Stys et al., 2004; Herrera-Arellano et al., 2004; Wu et al., 2007; Cheng, 2007; Basu et al., 2007; Han et al., 2008; Hina et al., 2010; Ojha et al., 2011). Currently, a scientific appraisal of the de novo actions of the medicinal plants suggests that these could be better source for the development of safe, effective and acceptable therapeutic agents. The beneficial effects of many plant food and
herbal medicines in reducing cardiovascular diseases and promoting heart health are known (Davidson et al., 2003; Ernst, 2003; Mamtani and Mamtani, 2005; Ho and Jie, 2007; Wang et al., 2007; Shukla et al., 2010; Govind and Sahni, 2011). The first effective treatment for hypertension (HTN) and congestive heart failure (CHF) was derived from plants. Previous studies have demonstrated cardioprotective effects of several herbs against ISP-induced myocardial infarction (Sharma et al., 2001; Gupta et al., 2004; Mohanty et al., 2004; Prabhu et al., 2006; Gauthman et al., 2006; Bansal et al., 2006; Arya et al., 2006).

Holistic treatment is the hallmark of Ayurvedic therapy, one of the principle therapeutic approaches in the Indian system of medicine. It demands that one herb or one drug would not cure the imbalance of ‘Dosha’. Therefore, traditionally in most of the diseases, a combination of herbs and plants (which are even part of staple food) are recommended for treatment (Garodia et al., 2007). It is quite possible that a crude herbal formulation has a combination of compounds, where one compound either potentiates the effect of other, or increases the bioavailability or reduces the toxicity (Aggarwal et al., 2011).

Despite the wide usage of herbal plants for several pathological conditions in Ayurveda, only few systemically designed studies are available to assess their cardioprotective potential. However, a major obstacle to this process has been the inability to successfully translate novel cardioprotective strategies discovered in the research laboratory setting directly into the clinical arena (Miura and Miki, 2008).

*Terminalia arjuna* (*T. arjuna*) and their constituents are common ingredients of several herbal formulations used for their potential cardiovascular benefits.
Eugenia jambolana (E. jambolana) has shown hypolipidemic and anti hyperglycemic potential in several studies related to metabolic syndrome. Due to strong medicinal properties these plants viz. T. arjuna and E. jambolana are selected to screen their cardioprotective effects in the present study. These medicinal plants have potential biological significance. Being common ethno medicinal components and major constituents of several phytopharmaceutical formulations, these medicinal plants can be used alone or along with conventional drug as an adjunct therapy for prevention of ischemic heart disease (IHD).

In this context, an attempt has been made to investigate the effect of hydroalcoholic extracts of T. arjuna (HETA) and E. jambolana (HEEJ) on maintaining the myocardial integrity in animals employing a wide array of biochemical, histopathological and immuno-histochemical parameters in ISP-induced myocardial infarction.

Due to a close resemblance to human myocardial ischemia, this model has been adopted to investigate the efficacy of these extracts. Therefore, we have first determined the optimal dose of these plant extracts in ISP-induced myocardial infarction. To establish the antioxidant potential of HETA and HEEJ, the oxidative stress parameters (GSH, SOD & MDA) have been evaluated. In order to assess myocyte injury, cardiac markers viz. creatine phosphokinase-myocardial band (CPK-MB), serum glutamate oxaloacitate transaminase (SGOT) and troponin-I (Trop I) have also been estimated. Inflammatory cascade has been determined by means of pro-inflammatory cytokines viz. interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α). Histopathological studies were incorporated in
the present study to correlate cardiac function and histo-architectural changes in myocardium during myocardial infarction. Immunohistochemical and TUNEL assay were also carried out to study the anti-apoptotic effect of these plant extracts. On the basis of expression of bcl-2 (an anti-apoptotic oncoprotein) and Bax (a pro-apoptotic protein) the extent of myocardial apoptosis was quantified.

The observations of the present study justify the previously reported traditional claims for their synergy and provide a substantial evidence for the clinical application of these medicinal plants for the management of ischemic heart disease.

Recently involvement of apoptotic cell death in MI has been well documented (MacLellan, 1997; Haunstetter et al., 1998; Saraste and Pulkki, 2000; Isodono et al., 2010; Tabas and Ron, 2011; Miyazaki et al., 2011; Velotta et al., 2011). A correlation between Bcl-2 and antioxidant pathways has also been established (MacLellan, 1997). However, no report is available on the anti-apoptotic potential of *T. arjuna* and *E. jambolana*, particularly in isoproterenol induced ischemic injury.

Therefore in the present study the expression of Bax a promoter of apoptosis and Bcl-2 an inhibitor of apoptosis was studied in experimental model of MI. The oxidative stress parameters, cardiac markers, pro-inflammatory cytokines, apoptotic markers and histopathological studies were incorporated in the study design to investigate the underlying mechanism of the myocardial salvaging effects of hydroalcoholic extract of *T. arjuna* and hydroalcoholic extract of *E. jambolana*.

Such an approach may represent a milestone towards the drug development for ischemic heart disease (IHD) and may establish it as an alternative therapy for IHD.