INTRODUCTION
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Cardiovascular disease (CVD) is one of the leading causes of death worldwide, accounting for 17.3 million deaths per annum, representing 30% of all global deaths. Out of these deaths, 7.3 million were due to coronary heart disease and 6.2 million due to stroke (http://www.who.int/mediacentre/factsheets/fs317/en/index.html). About 2.6 million Indians are expected to die due to coronary heart disease, which will constitute 54.1% of all CVD deaths in India by 2020 (http://www.whoindia.org/LinkFiles/NMH_Resources_burden_cvd__mortality.pdf).

Heart disease has no geographic, gender or socioeconomic boundaries. The CVDs, namely coronary (or ischemic) heart disease and heart failure (HF) are the dominating cause of disability and deaths in all industrialized nations (Gaziano, 2005). The cost of this disease in terms of human suffering is almost incalculable. Most patients with HF have a history of hypertension and/or left ventricular (LV) hypertrophy, which is an important risk factor for subsequent cardiac morbidity and mortality. Hypertrophy is one of the forms of HF which occurs due to excessive cardiac work load leading to an enlargement of the heart in an endeavour to manage the increased hemodynamic demand. Cardiac hypertrophy (CH) is a complex but relatively common form of genetic heart muscle disease that occurs in 1 out of 500 people (Maron, 2002). It is the most common cause of heart related sudden deaths in people under 30 years of age and can also be responsible for exercise disability at almost any age. CH occurs equally in both sexes and has been reported in many races (Maron, 2002).

CH is an adaptive response to pressure or volume stress, mutations of sarcomeric (or other) proteins or loss of contractile mass from prior infarction. Hypertrophic growth accompanies many forms of CVD such as ischemic heart disease (IHD), myocardial infarction (MI), hypertension, HF and valvular disease (Frey et al., 2004). It is a response of myocardium to various physiologic and pathologic stimuli that causes the heart to work harder under condition of increased workload (Carreno et al., 2006). The increased load causes the release and secretion of neurohumoral mediators, growth factors and cytokines that contribute to myocardial mass growth (Selvetella and Lembo, 2005). Various studies reported that chronic administration of a number of chemicals and drugs such as doxorubicin, angiotensin II (Ang II), endothelin 1,
isoproterenol (ISO) and thyroxine (T4), may induce CH (Chen et al., 2001; Kobori et al., 1999; Zhang et al., 2005). Exposure of these chemicals trigger an increase in cardiomyocyte size and protein content with a gene expression profile similar to that observed with in vivo and in vitro models of hypertrophy and hence used as models for hypertrophy (Berry et al., 2007).

Increased sympathetic nerve activity in the myocardium is often implicated in the development of CH and HF (Cohn, 1989; Scheuer, 1999). A correlation between cardiac mass and sympathetic activity was found in young hypertensive human (Fujita et al., 1989) and long term infusion of subpressor doses of norepinephrine led to CH in rats (Ennis et al., 2003). The cardiotoxic effect of catecholamines occurred due to an increased oxidative stress resulting from an increased cardiac reactive oxygen species (ROS) production and reduced antioxidant capacity (Sawyer et al., 2002; Zhang et al., 2005). Various studies reported that chronic β-adrenergic receptors (β-ARs) stimulation by ISO leads to activation of renin-angiotensin system (RAS), overexpression of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), elevation of calcineurin (CaN), expression of inducible nitric oxide synthase (iNOS) and inhibition of Na⁺/K⁺-ATPase (NKA), causing the development of pathological CH and its eventual progression to HF (Baek and Weiss, 2005; Ferreira et al., 2008; Hu et al., 2003; Murray et al., 2000; Rana et al., 2009; Wang and Zweier, 1996).

Thyroid hormone plays a significant role in maintaining cardiovascular function by contributing to myocardial gene expression, contractility and blood pressure (Brent, 1994; Klein and Danzi, 2007). It has profound effects on metabolism, growth and development (Oppenheimer et al., 1987). Numerous studies reported that both experimental and clinical hyperthyroidism alter myocardial function (Piatnek-Leunisseau and Olson, 1967; Symons, 1979). Hyperthyroidism accelerates the basal metabolic rate and oxidative metabolism by induction of specific mitochondrial enzymes that result into increased production of ROS and decreased antioxidant capacity (Asayama and Kato, 1990; Gredilla et al., 2001; Moreno et al., 2005). Several studies demonstrated that sustained administration of T4 leads to increased Ang II level, altered expression of proinflammatory cytokine TNF-α, enhanced activity of CaN and expression of iNOS as well as depressed NKA (sodium pump),
leading to the development of CH (Dixon et al., 1992; Rana et al., 2009; Rodríguez-Gómez et al., 2005; Senzaki et al., 2000; Xia et al., 2006).

The use of various herbal remedies and preparations are described throughout human history representing the origin of modern medicines. Many conventional drugs originating from plant sources such as aspirin, digoxin, quinine and morphine have become mainstays in human pharmacotherapy (Mashour et al., 1998) however, traditional medicines are still the mainstay of about 75-80% of the world population, mainly in developing countries (http://www.who.int/mediacentre/factsheets/fs134/en/). India having a very old and rich tradition of folk medicine has provided very simple but effective remedies to various ailments using plants and plant derived compounds. The use of herbal drugs might be helpful in preventing myocardial injury and oxidative stress related functional abnormalities in myocardium.

*Cissampelos pareira* Linn. (family: Menispermaceae), popularly known as ambastha or laghupatha in Ayurveda, has been extensively used as medicine for the treatment of various disorders (Kiritikar and Basu, 2000). The juice of *C. pareira* leaves has earlier been reported to be used as cardiotonic, diuretic and in heart complaints (Caceres et al., 1987; Kiritikar and Basu, 2000). This plant is frequently prescribed for cough, diarrhoea, dysentery, heart troubles and asthma (Kiritikar and Basu, 2000). It has also been reported that the plant possess antihypertensive (Patnaik et al., 1973), antioxidant (Amresh et al., 2007) and immunomodulatory (Bafna and Mishra, 2005) properties. Roots and aerial parts of this plant contains isoquinoline alkaloids such as hayatin, 1-bebeerine, hayatinin, cissampeline, cissampareine, warifterine, tetradrine, pareirubrines A and B, cissampeloflavone, quercitol, sterol and essential oil (Dwuma-Badu et al., 1975). In vitro study demonstrated that tetradrine has Ca^{2+}-channel blocking properties (Wei-Xing and Ming-Xing, 2002). Bebeerine was reported to reduced blood pressure (Patnaik et al., 1973).

*Acorus calamus* Linn. (Araceae) commonly known as vacha has been widely used in Ayurveda as medicine for treating multitudes of disorders (Kiritikar and Basu, 2000). The root and rhizome is traditionally used to treat general ailments such as emesis, diuresis, dyspepsia, stomachic, colic pain, remittent fever, nervous complaints and bronchitis (Kiritikar and Basu, 2000). Ethanolic rhizome extract of this plant has been
reported to possess sedative, analgesic, respiratory depressant, diuretic and moderately hypotensive properties (Gupta and Tandan, 2004). Recently, ethyl acetate and methanolic extracts of *A. calamus* have shown antioxidant (Manikandan et al., 2005) and aqueous extract has shown anti-inflammatory (Kim et al., 2009) properties. The main constituents of *A. calamus* are monoterpenes, sesquiterpenes, phenylpropanoids, flavonoids, quinine (Patra and Mitra, 1979) and volatile compounds such as α- and β-asarone (Mazza, 1985). The essential oils α- and β-asarone possess antihypercholesterolemic and antioxidative activity, respectively (Ka et al., 2005; Rodriguez-Paez et al., 2003). A clinical study has reported that *A. calamus* reduces the incidence of ischemic heart disease by decreasing serum cholesterol, low density lipoprotein and increasing high density lipoprotein (Mamgain and Singh, 1994).

Calcium channel blockers (CCBs) are widely used in the treatment of hypertension and ischemic heart diseases because of their systemic and coronary vasodilating effects (Black, 2004). Amlodipine, a CCB, appears to have fewer negative inotropic effects than earlier CCBs and improves the prognosis of patients. Numerous studies reported that amlodipine diminishes cardiac remodeling in spontaneously hypertensive rats (Yamazaki et al., 1998) and rats with MIs (Sandmann et al., 2001). Therefore, it has got a potential to be used as standard drug in this study.

Propranolol, a β-blocker and enalapril, an angiotensin converting enzyme (ACE) inhibitor are used in the treatment of hypertension and CH. Various studies reported that the RAS and the adrenergic nervous system (ANS) are involved in CH in hyperthyroid rats (Hu et al., 2003; Kobori et al., 1999). Therefore, these drugs are used as reference drugs in thyroxine-induced hypertrophy.

Although *C. pareira* and *A. calamus* have been a traditional remedy since ancient days, their cardioprotective effect in cardiac damage is not yet well characterized. Thus, the present study was designed with the aim to investigate the effect of ethanolic extract of *C. pareira* root and *A. calamus* rhizome on ISO- and T4-induced CH in rats.