Chapter I

INTRODUCTION
Chapter I
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The human body is known to expose to oxidative stress on daily basis. To combat the oxidative stress, the threat by reactive oxygen species (ROS), the antioxidant defense systems (ADS) plays an important role (Saumya et al., 2006). Natural antioxidants that are present in our body are catalase, superoxide dismutase, glutathione, while synthetic antioxidants like butylated hydroxy toluene and butylated hydroxy anisole are suspected to be carcinogenic and hence, are no more in use. Therefore, the need for the search of antioxidants from natural origin has been greatly felt in the present years (Jayaprakash et al., 2001). Superoxide dismutase, an oxido-reductase enzyme that dismutases superoxide radicals to hydrogen peroxide, which, in turn, is decomposed by catalase, a ubiquitous enzyme of peroxysomal origin and by glutathione peroxidase (GPx). Glutathione-dependant enzyme system plays a vital role in the antioxidant defense mechanism (Rady, 1993; Oommen et al., 1999; Saumya et al., 2006).

'Oxidative stress' is a term denoting an imbalance between the production of oxidants and the respective defense systems of an organism. Oxidants encompass oxygen free radicals, reactive nitrogen species, sulphurcentred radicals and various others (Abuja and Albertini, 2001). Reactive oxygen species (ROS) are biologically important, damaging molecules, such as lipids, DNA or proteins, and are involved in the pathobiochemistry of degenerative diseases (Snook et al., 2008). Under normal healthy conditions, the oxidant–antioxidant system is in equilibrium. When there is an imbalance in this system, tissue injury can be seen (Yilmaz et al., 2006). Because of this, oxidative stress has been implicated in a growing list of human diseases (Vendemiale et al., 1999).

An abundance of ROS engenders oxidative stress, which is thought to play a role in a number of pathologies, including neurodegenerative diseases (Rao and Balachandaran, 2002; Ischiropoulos and Beckman, 2003), inflammation (Dedon and Tannenbaum, 2004; Korhonen et al., 2005), cancer (Ames et al., 1993) and a wide range of cardiovascular diseases (Rojas et al., 2006), including hypertension, Type II diabetes, hypercholesterolemia, atherosclerosis and heart failure (Hamilton et al., 2004).
Among the many health predictions, the most alarming is that of cardiovascular diseases (CVD). Principally, heart diseases and stroke are the Nation's leading killer for both men and women among all the racial and ethnic groups. By 2020, India could bear the heaviest CVD burden in the world, with the number of fatalities projected to increase to more than 20 million a year, and to more than 24 million a year by 2030 (Mackay and Mensah, 2004). Ischemic heart disease is a leading cause of death in India, with an estimated 3 million deaths per year accounting for 25% of all mortality (Mukherjee, 1995). The World Health Organization predicts that deaths due to circulatory system diseases are projected to double by 2015 (Bulatao and Stephens, 1990; Reddy, 1993).

Myocardial Infarction (MI), one of the major causes of mortality is associated with the ischemic necrosis of cardiac muscles due to compromised supply of blood to a portion of myocardium for proper physiological function.

In an animal model, the induced disorder should closely resemble the disorder in human with respect to structural and functional characteristics. The most important clues how to create an animal model fulfilling this condition as far as possible can be obtained from the etiology of the disease. The surgical induction of MI or ischemia in an animal model by left anterior descending coronary artery ligation (LAD) has the advantage to facilitate a precise timing, location and extent of the coronary event, leading to more reproducible results. Therefore, this approach is indispensable in cardiovascular research (Bimbaum et al., 2005). Therefore, in the present study, LAD model was used to induce MI.

Oxidative stress is a well established etiopathogenic factor of ischemic heart disease (IHD) and its consequences (Banerjee et al., 2002). Reperfusion of the ischemic myocardium is the only logical approach for the successful management of patients with acute obstruction of coronary arteries. Morphologic observations of the ischemic myocardial tissue undergoing reperfusion suggest that reperfusion injury is a true pathologic phenomenon and a distinct entity from the preceding ischemic injury. Generation of ROS immediately upon reperfusion has been documented in experimental conditions, as well as in patients with acute myocardial infarction undergoing
thrombolysis, coronary angioplasty or open heart surgery (Bolli, 1998). Upon reperfusion, molecular oxygen undergoes sequential reduction to form ROS, including superoxide anion and hydroxyl radical, in addition to hydrogen peroxide. The interaction of oxygen-derived free radicals with cell membrane lipids and essential proteins contribute to myocardial cell damage, leading to depressed cardiac function, arrhythmias, and irreversible tissue injury with concomitant depletion of certain key endogenous antioxidant compounds, e.g., superoxide dismutase (SOD), catalase, reduced glutathione (GSH) and glutathione peroxidase (GPx) (Ferrari et al., 1991). These oxygen free radicals (OFR) may result in membrane permeability changes resulting in an increase in myocardial malondialdehyde (MDA) content (Curello et al., 1986). It has been suggested that the beneficial effects of reperfusing the myocardium might be, in part, reversed by the occurrence of reperfusion injury (Ferrari et al., 1990).

Results from several studies have implicated depressed activity of Na-K-ATPase in the development of cardiovascular disease (Blaustein and Hamlyn, 1991; Blaustein, 1996). Sarcolemmal Na-K-ATPase activity has been reported to be decreased in patients with idiopathic dilated cardiomyopathy (Norgaard et al., 1988). Na-K-ATPase is a crucial enzyme responsible for the active transport of sodium and potassium ions in the cardiovascular system (CVS) necessary to maintain the ionic gradient for cardiac excitability (Smith, 1988; Clausen, 1998). Myocardial ischemia results in an increase in intracellular sodium concentration ([Na⁺]), which secondarily increases intracellular calcium via Na/Ca exchange, resulting in cellular injury (Steenbergen et al., 1990; Miyata et al., 1992). Theoretically, the rise in [Na⁺] could also be limited by increasing sodium efflux during ischemia via the sodium potassium pump (Na-K-ATPase). Because the Na-K-ATPase is the primary mechanism for sodium efflux, stimulation of this enzyme would be expected to limit the rise in [Na⁺] during ischemia. Since it has been shown that inhibition of Na-K-ATPase activity can be prevented by antioxidants in vitro (Avrova et al., 1999; Streck et al., 2001), therefore, the present study was planned to investigate the effects of Embelia ribes on the Na-K-ATPase activity in LAD- induced myocardial infarction in rats.
Chapter I

Introduction

Vigorous global research is underway in an effort to develop pharmacological means to control morbidity and mortality arising from ischemic heart disease (Seth et al., 1998). Oxidative reperfusion injury was suggested to be a central mechanism of the cellular damage affecting all organs and tissues after ischemia; however, the mechanisms, which trigger and modulate this damage, have been partially characterized (Xia and Zweier, 1995). Since reperfusion injury is associated with an imbalance of oxidative stress and antioxidant defense system, then, theoretically, it would be possible to limit oxidative damage and ameliorate disease progression by supplementing antioxidants. Indeed, many antioxidative plants and their isolated active components have been reported to be cardioprotective in ischemia reperfusion- induced myocardial infarction (Banerjee et al., 2002; Mohanty et al., 2004; Rao et al., 2005).

Apart from the traditional risk factor of MI, recently many reports have suggested that hyperhomocysteinemia plays an important role in MI (Angeline et al., 2005). Hyperhomocysteinemia has emerged as an independent risk factor for development of coronary, cerebrovascular and peripheral arterial occlusive diseases (Omenn et al., 1998). It is one of the main factors that cause various diseases, such as atherosclerosis (Refsum et al., 2001; Merkel, 2004), diabetes (Luis et al., 2004), cancer (Poirier et al., 2001), and some other aged-related illnesses including Alzheimer’s disease (Clarke et al., 1998; Nilsson et al., 2002). Although severe hyperhomocysteinemia is rare, mild elevations in homocysteine concentration have been found in nearly 7% of the general population and in 20 to 30% of patients with coronary and peripheral vascular disease (Clarke et al., 1991; McCully, 1996; Folsom et al., 1998). A mere increase of 12% over the normal level of homocysteine has been associated with a 3-folds increase in risk for myocardial infarction (Naygard et al., 1998).

Homocysteine is toxic to neuronal cells (Lipton et al., 1997) and animals exposed to homocysteine accumulate this compound in the brain (Algaidi et al., 2005). Homocysteine is rapidly taken up by neurons through a specific membrane transporter, leading to high intracellular levels of homocysteine (Grieve et al., 1992). Concentrations of homocysteine in the brain and cerebrospinal fluid (CSF) are elevated in several
neurological diseases (Yamai et al., 1983; Regland et al., 1997). Hyperhomocysteinemia has been implicated as a risk factor for vascular disease as well as brain atrophy (den Heijer et al., 2003) and therefore, may be related to the development of dementia and possibly, Alzheimer's disease.

Although its pathophysiological mechanisms are complex and not fully understood, much evidence suggests that hyperhomocysteinemia induces vascular and brain damage because of the highly reactive thiol group in homocysteine that is readily oxidized leading to the formation of homocysteine, homocysteine mixed disulfides and homocysteine thiolactone. During these oxidative processes, several reactive species are generated (Loscalzo, 1996). The methionine cycle is responsible for the creation of all homocysteine in the body (Lipton et al., 1997).

The brain may be particularly vulnerable to high levels of homocysteine in the blood because it lacks two major metabolic pathway for its elimination; betain remethylation and transsulfuration (Finkelstein, 1998). The association between plasma homocysteine and the severity of cerebral atherosclerosis was explored by Yoo et al (1998). The oxidation of homocysteine promotes the oxidation of low density lipoprotein cholesterol (Parthasarathy, 1987), which causes injury to vascular endothelial cells (Harker et al., 1974; Starkebaum and Harlan, 1986) and leads to endothelial dysfunction (Stamler et al., 1993).

Homocysteine is formed by demethylation of the essential amino acid methionine, a potent agent that disrupts endothelial integrity (Hening et al., 1993; Ross, 1993; Toborek and Hening, 1994). Thus, an imbalance in dietary methionine may contribute to the development of atherosclerosis by increasing homocysteine levels (Toborek et al., 1995). Hyperhomocysteinemia in adults may be acquired by an excess dietary intake of methionine or decreased intake of folate (Ubbink et al., 1992).

Animal studies suggest that diets high in methionine, in the presence of B-vitamin deficiencies, may increase the risk for atherosclerosis (hardening of the arteries) by
increasing blood levels of cholesterol and a compound, called homocysteine (Toborek and Hennig, 1994). Excessive methionine intake, together with inadequate intake of folic acid, vitamin B₆, and vitamin B₁₂, can increase the conversion of methionine to homocysteine- a substance linked to heart disease and stroke. Even in the absence of a deficiency of folic acid, B₆, or B₁₂, mega doses of methionine (7 g per day) have been found to cause elevations in blood levels of homocysteine (McAuley et al., 1999). Whether such an increase would create a significant hazard for humans taking supplemental methionine has not been established. Supplementation of up to 2 g of methionine daily for long periods of time has not been reported to cause any serious side effects (Leach and Braganza, 1998).

Reducing homocysteine level by inhibiting its formation or promoting its transformation is becoming an attractive approach in disease prevention. Ramaswami et al (2004) have reported that curcumin from Curcuma longa blocks homocysteine- induced endothelial dysfunction in porcine coronary arteries.

Therefore, the present study was planned to explore the homocysteine lowering potential of standardized extracts (aqueous and ethanolic) of Embelia ribes Burm on methionine-induced hyperhomocysteinemia in albino rats.

One of the complications of MI is cerebral artery embolism, leading to cerebral ischemia and stroke. Stroke is an acute and progressive neurodegenerative disorder and is third leading cause of death throughout the world resulting from the interruption of blood flow (Feigin et al., 2003). A variety of mechanisms are involved in ischemic brain injury. Oxygen Free Radicals (OFR) contributes to brain injury during cerebral ischemia (Traystman et al., 1991; Nakashima et al., 1999). Brain ischemia induces excessive release of excitatory amino acids and subsequent receptor activation leading to calcium influx, metabolic and electrophysiological dysfunction, lipid peroxidation, and other oxidative events (Lipton, 1999). Increasing evidence has indicated that ischemia/reperfusion occurs due to oxidative stress that may potentiate ischemic injury (Traystman et al., 1991). Free radicals generated, initiate lipid peroxidation of the
membrane bound polyunsaturated fatty acids, leading to impairment of the membrane structural and functional integrity (Ajitha and Rajnarayana, 2001). For these reasons, antioxidants have been the focus of studies for developing neuroprotective agents to be used in the stroke therapy. In fact, many antioxidants have been developed in in vitro and in vivo experiments and some of these have been tested in clinical studies of stroke (Margaill et al., 2005).

The pathophysiology of cerebral ischemia has been studied extensively in rats with various methods, including multiple vessel occlusion, hypotension, and hypovolemia, to produce global alteration in cerebral blood flow and metabolism (Brown and Brierley, 1972; Salford et al., 1973; Dienel et al., 1980; Furlow et al., 1983; Laas et al., 1983; Lear et al., 1984). The search for a reliable, less invasive rat stroke model of temporary regional ischemia has been prompted by the extensive neurochemical data already available in rats, the rising cost of experiments with larger animals, and the limitations of other rodent models of focal cerebral ischemia, such as occlusion of the common carotid artery (CCA) (Yanagihara, 1978) or middle cerebral artery (MCA) (Yoshimine and Yanagihara, 1983) in gerbils.

The lack of effective and widely applicable pharmacological treatments for ischemic stroke patients may explain a growing interest in traditional medicines, for which extensive observational and anecdotal experience has accumulated over the past thousand years. It has been suggested that some herbal medicines, or their products, may improve microcirculation in the brain (Gong and Sucher, 2002; Wang et al., 2005), protect against ischemic reperfusion injury (Lee et al., 2005; Wang et al., 2005), possess neuroprotective properties (Gong and Sucher, 2002; Kim, 2005) and inhibit apoptosis (Bei et al., 2004), thus, justifying their use in ischemic stroke patients.

The present study was planned to investigate the neuroprotective effect of standardized extracts (aqueous and ethanolic) of Embelia ribes Burm in middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia in albino rats.
Plant infusions and decoctions have been used as popular medicine in several under
developed and developing countries as an alternative treatment for various
pathophysiological conditions (Elisabetsky, 1987). The local communities residing in the
biodiversity-rich areas of the North Eastern Region of India have traditionally used and
relied on herbs for treating various ailments (Kayang et al., 2005). This practice has
continued even today where the low cost and less availability, coupled with the poorly
equipped government health facility and rising cost of drugs, has left the rural community
with hardly any options but to rely on traditional health care practices. These increasing
trends in the use of plants as medicines locally and globally necessitate scientific
investigations especially where information regarding toxicity is lacking on such plants or
their extracts.

*Embelia ribes* Burn (family, Myrsinaceae) is commonly known as *Vidanga, Vayavidang,
Babrang* (Hindi), *Bavding* (Gujrat), *Vaya vilanga* (Kannada), *Vivilangam* (Tamil),
*Vavidungalu* (Telugu), *False Black Pepper* (English) and *Krimighna, Tamhda* (Sanskrit).
It is a large woody climbing shrub, which is sparsely distributed in India, Sri Lanka,
Malaysia and South China (Guhabakshi et al., 2001). Ayurveda describes *vidanga* as
pungent, causing increase in digestive fire, easily digestible, cures colic and flatulence,
mitigate kapha and vata, removes worm and constipation. The plant is used as anti-
inflammatory agent to relieve rheumatism and fever (Kapoor et al., 1983). Seeds are used
as antibiotic, anthelmintic, antituberculosis, alterative and stimulative (Guhabakshi et al.,
2001). The fruit is bitter in taste, good appetizer, cures tumors, ascites, bronchitis,
jaundice and mental disorders (Kirthikar and Basu, 1987). Fruits contain a quinone
derivative, embelin (3-undecyl 2, 5-dihydroxy, 1,4-benzoquinone), an alkaloid
christembine (Tyagi et al., 1978) and a volatile oil vilangin; its chemical constituent is
2,5-dihydroxy-4-undecyl-3, 6-benzoquinone (Rao and Venkateswaralu, 1961). It is
highly esteemed in Ayurveda, as a powerful anthelmintic (Hordegen et al., 2006).

In a preliminary study, Tripathi (1979) has reported the antihyperglycemic activity of
have reported diabetic dyslipidemic activity of ethanolic *Embelia ribes* extract (200

Hence, the present research work is designed to study the effects of the standardized *Embelia ribes* extracts (aqueous and ethanolic) against oxidative stress induced by myocardial ischemia reperfusion injury (Birnbaum et al., 2005), hyperhomocysteinemia (Senaratne, 2000) and cerebral ischemia (Seisjo, 1992) in albino rats. The cellular events at the target organs were assessed on the basis of hemodynamic parameters, various biochemical markers and histopathological studies / infarct size measurement.