Atherosclerosis, a chronic inflammatory disease, develops in response to damage to the vessel wall. It is characterized by the infiltration of mononuclear blood cells into the intima, foam cell formation, the proliferation of arterial smooth muscle cells and accumulation of connective tissue components in the inner lining of the arteries, resulting in thickening and hardening of arterial walls that may eventually block the arteries (Ross, 1999; Glass and Witztum, 2001).

Cardiovascular disease (CVD) is the leading cause of cardiovascular morbidity and mortality worldwide and two-thirds of all cardiovascular fatalities occur in developing countries (Okrainec et al., 2004). It is expected that CVD will be the largest cause of disease burden worldwide, by 2020 (Yusuf et al., 2001a; 2001b). Further, the World Health Organization has estimated that 60% of the world's cardiac patients will be Indians by 2010, and that by 2015, half of all deaths in India are likely to be caused by coronary heart disease (CHD). It has also been estimated that CVD will be the most important cause of mortality in India by the year 2015 (Gilski and Borkenhagen, 2005). Epidemiological reports documented coronary artery disease (CAD) to contribute 33% of cardiovascular deaths in India and have also projected that it will be 8 million in India, by 2020 (Gupta and Gupta, 1996; Gupta, 2000).

Hypercholesterolemia is one of the most important risk factors for atherosclerosis and subsequent CVD (Steinberg, 2002). Hypercholesterolemia causes malfunctioning of the liver, which apparently occurs through microvesicularstenosis due to the intracellular accumulation of lipids (Assy et al., 2000). Acyl-CoA:cholesterol acyl-transferase (ACAT) is the enzyme primarily responsible for the esterification of cholesterol in all mammalian cells. ACAT has been implicated in intestinal mucosal absorption of cholesterol and in the synthesis of the cholesterol esters which are
incorporated into very low-density lipoproteins (VLDL) or stored in fatty cells (Krause et al., 1993; 1995). Fatty streak, the earliest recognizable lesion of atherosclerosis, consists mainly of lipid-laden macrophages (foam cells) derived primarily from recruited monocytes. The recruitment and subsequent transendothelial migration of circulating monocytes, an initial event in the pathogenesis of atherosclerosis, is mediated predominantly by stress-induced endothelial dysfunction and cellular adhesion molecules (Springer, 1990). The nature and clinical significance of an atherosclerotic plaque is dependent not only on the formation and progression of atherosclerosis, but also on the vascular remodeling response to the atherosclerosis (Chatzizisis et al., 2007a). Expansive remodeling is associated with high-risk plaques, whereas constrictive remodeling is associated with stable fibrous plaques (Chatzizisis et al., 2007a; 2007b; 2008). C-reactive protein (CRP) is one of the substances present in the atherosclerotic lesion, more specifically in the vascular intima, where it co-localizes with monocyte, monocyte-derived macrophages and lipoproteins (Torzewski et al., 1998; Zwaka et al., 2001). Further, CRP stimulates reactive oxygen species (ROS) and is considered solely as a biomarker of inflammation (Szmitko et al., 2003); it is now viewed as a prominent participant in endothelial dysfunction and atherosclerosis (Verma and Yeh, 2003).

A cholesterol-rich diet induces free radical production, oxidative stress and hypercholesterolemia (Bulur et al., 1995). Oxidative stress, a state resulting from disruption of the delicate balance between oxidative and antioxidative processes, is believed to play an important role in the pathogenesis of hypercholesterolemic atherogenesis (Steinberg, 1989). Thus, feeding animals with cholesterol has often been used to elevate serum or tissue cholesterol levels to study the etiology of hypercholesterolemia-related metabolic disturbances (Bocan, 1998). Hypercholesterolemia also manifests with signs of inflammation, such as white cell migration into the endothelium and expression of adhesion molecules (Li et al., 1993). Various inflammatory cells, such as macrophages and lymphocytes, have a potency to generate ROS (Russwurm et al., 1994). The systemic response to inflammation results
in an increase in the level of oxidized lipids in serum and in the enhancement of the oxidative modification of low-density lipoprotein (LDL) cholesterol (Memon et al., 2000). The ‘oxidative modification hypothesis’ of atherosclerosis proposes that oxidation of LDL cholesterol is an early event in atherosclerosis and that oxidized LDL (Ox-LDL) contributes to atherogenesis; lipid peroxidation occurs in arterial macrophages as well as in lipoproteins (Aviram, 2000). Further, CRP has a pro-oxidative effect (Kobayashi et al., 2003), and both oxidative and inflammatory processes are believed to be involved in the pathogenesis of atherosclerosis (Hansson, 2005). It has been well established that inflammation plays a central role in the pathogenesis of atherosclerosis and, further, various inflammatory markers predict the incidents of CVD (Cesari et al., 2003; Tuomisto et al., 2006). Thus, there is evidence that oxidative stress contributes to the development of atherosclerosis in the vascular wall through the formation of ROS (Shi et al., 2000).

In order to protect the tissues from damage caused by ROS, organisms possess enzymatic and non-enzymatic antioxidant systems (Parthasarathy et al., 2000). Protection against ROS and the breakdown products of peroxidized lipids and oxidized proteins is provided by enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (Gpx) and glutathione-S-transferase (GST). Non-enzymatic antioxidants, such as reduced glutathione (GSH), and vitamins C and E, play a vital role in protecting cells from oxidative stress by participating in various biochemical pathways. Increasingly, ROS have been found to contribute to the pathogenesis of many diseases in situations where antioxidant defence systems are impaired. Therefore, it would seem logical to neutralise the deleterious effects of ROS by boosting such antioxidant defence systems.

Recently, there has been renewed interest in finding naturally-occurring antioxidants for use in foods, cosmetics or medicinal materials to replace synthetic antioxidants, which are being restricted due to their carcinogenicity (Sasaki et al., 2002). The antioxidative phytochemicals, especially phenolic compounds found in
vegetables, fruits and medicinal plants, have received increasing attention for their potential role in prevention of human diseases (Cai et al., 2004). A number of animal studies have demonstrated that the consumption of polyphenols limits the development of atherosclerotic lesions. Supplementation of drinking water with dealcoholized wine, pomegranate juice and quercetin reduced the size of these lesions in apolipoprotein E-deficient mice (Hayek et al., 1997; Kaplan et al., 2001) and these effects are associated with reduced uptake of LDL cholesterol by macrophages, and decreased susceptibility of LDL to aggregation. Grape seed polyphenols, proanthocyanidins, have a hypocholesterolemic effect on rats fed a high-cholesterol diet (Tebib et al., 1994). Chrysin a natural flavonoid found in mushroom has recently been reported to have anticancerous effects (Fu et al., 2007). Piperine, the major active principle of black pepper, has been reported to show a wide range of pharmacological properties such as antioxidant (Mittal and Gupta, 2000), hepatoprotective (Koul and Kapil, 1993), anti-inflammatory (Mujumdar et al., 1990), immunomodulatory (Sunila and Kuttan, 2004) anti-tumourigenic (Nalini et al., 2006) and anti-hyperlipidemic (Vijayakumar and Nalini, 2006a) activities. Somova et al. (2003) reported that the naturally-occurring triterpenes, oleanolic acid and ursolic acid, possess hypoglycemic, anti-hyperlipidemic (anti-atherosclerotic) and antioxidant activities. Lupeol, also a triterpene, has been shown to exhibit anti-inflammatory (Geetha and Varalakshmi, 1998) and anti-hyperlipidemic (Sudhahar et al., 2006a) effects in experimental rat models. Ellagic acid, the phenolic compound present in fruits and nuts, including blueberries, blackberries, raspberries, strawberries and walnuts (Anderson et al., 2001; Sellappan et al., 2002; Talcott and Lee, 2002), has been found to have antimutagenic (Barch et al., 1996), hypolipidemic (Yu et al., 2005), antioxidative (Priyadarsini et al., 2002) and anticataractogenic (Sakthivel et al., 2008) properties. This may explain the current focus on experiments dealing with natural antioxidants to alleviate atherosclerosis induced by lipidemic-oxidative stress.

Interestingly, the use of tea extracts as dietary supplements arises from the fact that some tea compounds have beneficial protective effects against chronic diseases
(Chen et al., 2008). The presence of polyphenols in tea may contribute to its antioxidant effect by inhibiting ROS-generating enzymes (Stangl et al., 2007). The dietary intake of phenolic compounds in green tea (Vinson, 2004), red wine (Frankel, 1995), and olive oil (Aviram and Kassem, 1993) could inhibit oxidation of LDL and thereby reduce risk factors for CVD. Green tea contains many biologically active polyphenolic flavonoids, commonly known as catechins, which include epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG). EGCG, the principal constituent of green tea (Giakoustidis et al., 2006), has been characterized as an antioxidant (Xu et al., 2004) with antitumorigenic (Mukhtar and Ahmad, 2000), and antiangiogenic properties (Cao and Cao, 1999). Administration of EGCG has been reported to ameliorate various pathological states, including cerebral ischemia (Simonyi et al., 2005), cancer (Lin et al., 1999; Beltz et al., 2006), Parkinson’s disease (Nie et al., 2002; Guo et al., 2005; 2007) and Alzheimer’s disease (Bastianetto et al., 2006; Reznichenko et al., 2006; Avramovich-Tirosh et al., 2007). EGCG has also been found beneficial in treating obesity (Klaus et al., 2005; Kao et al., 2006c; Moon et al., 2007) and diabetes (Waltner-Law et al., 2002; Kao et al., 2006c; Wolfram et al., 2006).

In this study, an attempt has been made to determine whether EGCG, as a predominant catechin, could prevent or retard atherosclerosis in a rat (Rattus norvegicus) model. The investigation includes evaluation of lipid profile, antioxidant parameters, extent of lipid peroxidation and levels of hepatic marker enzymes; the results were correlated with histopathological observations. The inflammatory marker, CRP, that plays a significant role in the chronic inflammatory disease, atherosclerosis, has also been investigated. The study also includes an analysis of the expression of specific genes that are involved in pathogenesis of atherosclerosis. Thus, a multi-pronged approach has been executed to evaluate the efficacy of EGCG in preventing or retarding the onset of atherosclerosis.