Preface
Diabetes mellitus is a metabolic disorder characterized by hyperglycemia with disturbance of metabolism of carbohydrate, fat and protein (Alberti and Zimmet, 1998). It currently affects millions of people worldwide and the incidence is rising. Diabetes is usually associated by increased production of reactive oxygen species (ROS) and/or impaired antioxidant defense systems, which result oxidative damage leading to ROS mediated diabetic pathogenesis (Pitozzi et al., 2003). Disturbances of antioxidants defense system in diabetes involves: enhancement of lipid peroxidation, alteration in antioxidant enzymes and impaired glutathione metabolism (Bagri et al., 2009).

It has already been established that chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and eventually the failure of organs, especially the eyes, kidneys, nerves, heart and blood vessels (Huang et al., 2005). In addition to hyperglycaemia, several other factors such as dyslipidemia or hyperlipidemia are involved in the development of cardiovascular complications related to diabetes which are the major causes of morbidity and death (Markku Laakso, 1995; Nabel, 2003). Earlier studies have shown that treatment with antioxidant reduces diabetic complications (Wohaieb and Godin, 1987). Efforts to discover antioxidants as useful drug candidates to combat diabetic complications are going on relentlessly.

Streptozotocin and alloxan are the most frequently used chemicals for pharmacological induction of diabetes and these models has been useful for the study of multiple aspects of the disease. The cytotoxic action of these diabetogenic agents is mediated by ROS, but both drugs differ in their mechanism of action (Federiuk et al., 2004; Lei et al., 2005).

Reactive oxygen species (ROS) such as superoxide radical $O_2^-$, hydroxyl radical (·OH) and non-free radical species, such as $H_2O_2$, singlet oxygen ($O_2$), and reactive nitrogen species (RNS) are generated in the body by exposure to sunlight, ultraviolet, ionizing radiation, or by chemical reactions and metabolic processes. Oxidative stress, an excessive production of ROS that outstrips antioxidant defense mechanisms, has been implicated in wide variety of pathological effects, such as Diabetes, DNA damage, cellular and metabolic injury, carcinogenesis, cardiovascular diseases, neurodegenerative diseases, inflammation and cellular degeneration related to ageing (Halliwell and Gutteridge, 1999).
Oxidative stress is increased in diabetes because of multiple factors. Dominant among these factors is glucose autoxidation leading to the production of free radicals. Other factors include cellular oxidation/reduction imbalances and reduction in antioxidant defenses (including decreased cellular antioxidant levels and a reduction in the activity of enzymes that dispose of free radicals). Another important factor is the interaction of advanced glycation end products (AGEs) with specific cellular receptors called AGE receptors. Elevated levels of AGE are formed under hyperglycemic conditions. Their formation is initiated when glucose interacts with specific aminoacids on proteins forming a compound that then undergoes further chemical reactions. Glycation of protein alters protein and cellular function, and binding of AGEs to their receptors can lead to modification in cell signaling and further production of free radicals (Penckofer et al., 2002).

To neutralize the toxic effects of ROS, mammalian cells have to develop several defense mechanisms. Among the various defense mechanisms, antioxidant-based mechanisms are extremely important because of the variety of antioxidant compounds and their ability to directly remove pro-oxidants thus ensuring maximum protection for specific biological sites. This system apparently developed throughout the evolutionary process in response to the changing concentration of oxygen in the atmosphere. The first line of defense is based on direct interaction with the ROS and their detoxification by low molecular weight antioxidants or protein scavengers. Typical low molecular weight antioxidants are vitamin E (α-tocopherol), vitamin C (ascorbic acid), uric acid, glutathione, β-carotene and ubiquinone. In addition, molecules such as histidine-related compounds and melatonin are also effective antioxidants.

One of the major complications of diabetes is cardiovascular disease. The incidence of cardiovascular disease in people with diabetes mellitus is three to four times of that in non-diabetic individuals. One of the potential mechanisms that could mediate the premature atherosclerosis in diabetes is oxidative stress. Oxidative stress plays a crucial role in atherogenesis and cause to oxidation of low density lipoprotein. Ox-LDL is not recognized by the LDL receptor but by the scavenger receptor pathway on macrophages,
which results in unregulated cholesterol accumulation, leading to foam cell formation (Jialal et al., 2002).

*Glibenclamide* (glyburide), a member of the second generation sulphonylureas, provides effective treatment for patients with moderate diabetes. Other than its glucose lowering effects, it seems to have antioxidant properties. Glibenclamide have restored liver CAT and SOD in STZ-induced diabetic rats (Elmali et al., 2004). Glipizide, another member of the second generation of sulphunylurea has also investigated for antioxidant properties. It seems to play a prominent role in scavenging free radicals and restoring antioxidant activities in the tissues of diabetic animals (Tuzun et al., 1999).

Mitochondria have been implicated in several human diseases, including mitochondrial disorders (Gardner and Boles, 2005), diabetes (Brownlee, 2001) and cardiac dysfunction (Lesnefsky et al., 2001), and in the aging process. Mitochondria play a pivotal role in the generation of oxidative stress because the respiratory chain is the major site of the cellular ROS production (Boveris and Chance, 1973). Mitochondria, on the other hand, are also targets of oxidative stress, containing various enzymes that are sensitive to inhibition by ROS (Tretter and Adam-Vizi, 2004). Mitochondria generate ROS when the flow of electrons in the respiratory chain is impaired. Studies on isolated (Starkov et al., 2004) as well as on *in situ* mitochondria (Sipos et al., 2003) have demonstrated that inhibition of the respiratory complexes results in an enhanced ROS production.

Involvement of mitochondria in hyperglycemia-induced apoptotic pathways has been observed in diabetic neuropathy (Schmeichel et al., 2003), impaired kidney function (Verzola et al., 2002), and myocardial abnormalities (Cai et al., 2002). Nevertheless, the role of hyperglycemia on the function of renal mitochondrial respiratory complex has not been thoroughly investigated. A few studies have indicated that diabetes induces alterations in the activities of mitochondrial respiratory complexes and mitochondrial respiration in the kidney (Katyare et al., 2005).

Experimental and epidemiological studies have shown that the plasma hypercholesterolemic state could contribute to the development of atherosclerosis and related cardiovascular system diseases (CVD) which are the most common cause of death in both western and eastern societies (Epstein, 1992). Indeed, clinical trials have
demonstrated that the increase in plasma low density lipoprotein cholesterol (LDL-C) levels is implicated in the early development and progression of atherosclerosis. However, high density lipoprotein cholesterol (HDL-C) is an anti-atherogenic fraction (Martin et al., 1986). Triglycerides (TGs) may also be a risk factor, especially in individuals with diabetes (West et al., 1983).

In hyperlipidemic conditions, enzymatic as well as non-enzymatic antioxidative defence systems such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), ascorbic acid, and reduced glutathione (GSH) are altered leading to ROS mediated damage (Araujo et al., 1995). Oxidative stress is an early event in the evolution of hyperlipidemia, and it has been suggested that appropriate support for enhancing antioxidant supply in subjects with abnormally elevated lipid levels can attenuate the course of the disease (Yang et al. 2008).

3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA) is a key rate limiting enzyme involved in the cholesterol biosynthetic pathway (Goldstein and Brown, 1990). Therefore, inhibition of HMG-CoA reductase decreases intracellular cholesterol biosynthesis (Steinberg et al., 1989). HMG CoA reductase inhibitors are the most commonly prescribed class of lipid lowering drug.

A logical strategy, to prevent or to treat atherosclerosis and reduce the incidence of cardiovascular disease events, is to target hyperlipidemia by drugs and/or dietary intervention. Lipid lowering drugs like fibrates, statins and bile acid sequestrants are used to treat hyperlipidemia and are known to possess some side effects (Chattopadhyaya et al., 1996). With this aim, efforts to develop effective and better hypolipidemic drugs have led to discovery of natural products and have stimulated the search for new lipid-lowering agents from this source.

Natural products and their derivatives have historically been invaluable as a source of therapeutic agents. Mushrooms have long been valued as tasty, nutritious food by different societies worldwide. To the ancient Romans they were “the foods of the Gods” resulting from bolts of lightning thrown to the earth by Jupiter during thunder storms; the Egyptians considered them as “a gift from the God Osiris”; while the Chinese viewed them as “the elixir of life”. A large number of animal studies, using both normal and diabetic
animals, have demonstrated a hypoglycemic effect of mushrooms and mushroom components. This effect appears to be mediated via mushroom polysaccharides (possibly both alpha- and beta-glucans) via a direct interaction with insulin receptors on target tissues, although this mechanism remains to be confirmed. According to current dietary recommendations for preventing and treating for cardiovascular diseases, edible mushroom presents an appropriate nutritional value and its consumption can affect some known cardiovascular risk biomarkers. Mushroom intake clearly has a cholesterol-lowering effect or hypocholesterolemic effect by different mechanisms such as decreasing very-low-density lipoproteins, improving lipid metabolism, inhibiting of activity of HMG-CoA reductase, and consequently preventing the development of atherosclerosis. The antioxidant and anti-inflammatory compounds occurring in mushrooms also may contribute to reduce the atherosclerosis risk.

*Phellinus rimosus* is a parasitic host specific poly pore mushroom often found growing on jack fruit tree trunks in Kerala. It is a less extensively studied species of the genus *Phellinus*. Earlier investigations showed that ethyl acetate and methanol extract of *P. rimosus* possessed antioxidant, antitumor and hepato protective activities (Ajith and janardhanan 2001, 2002 and 2003). Further cancer chemopreventive as well as antimutagenic activities of *P. rimosus* has also reported. (Ajith and janardhanan 2006, 2011). Anti-inflammatory, anti-arthritic as well as radio protective activities of a polysaccharide protein complex (PPC-Pr) isolated from *P. rimosus* is also been reported (Meera et al., 2009 a, b). Recent investigation demonstrated the radio protective activity of polysaccharide protein complex isolated from *P. rimosus* (Jini et al., 2011) in mice.

However, no reports are available on the antidiabetic and hypolipidemic effect of *P. rimosus*. Hence, we examined the effect of *P. rimosus* on lipid peroxidation, blood glucose, serum insulin, and nonenzymic and enzymic antioxidants activities in blood, liver, kidneys and pancreas of diabetic rats and hypolipidemic and antioxidant effects by determining the lipid profile and a panel of oxidative stress markers after the intervention in hyperlipidemic rats. The effect of *P. rimosus* on mitochondrial antioxidant status, Krebs cycle dehydrogenases such as Isocitrate dehydrogenase (ICDH), α-ketoglutarate dehydrogenase activity (α-KGDH), Succinate dehydrogenase (SDH) and Malate dehydrogenase (MDH) and electron transport chain complexes (I, III and IV) in streptozotocin induced diabetic rats were also investigated.