INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by inherited and acquired deficiency in insulin production by pancreas. Such a deficiency results in increased concentrations of glucose in blood, which in turn damage the blood vessels and nerves. Globally, diabetes prevalence is similar in men and women but it is slightly higher in men less than 60 years of age and in elderly women. In developed countries majority of people develop diabetes after the age of 64. The rate of development of diabetes in India would reach 79.4 million and China with 42.3 million by 2030 (Yang, 2013).

Diabetes is associated with a marked increase in the risk for atherosclerotic vascular disorders including coronary, cerebrovascular and peripheral artery disease. Cardiovascular disease (CVD) could account for disabilities and high mortality rates in patients with diabetes (Yu et al., 2010). Conventional risk factors including hyperlipidemia, hypertension, smoking, obesity, lack of exercise and a positive family history contributes to macrovascular complications in type 2 diabetic patients and non-diabetic subjects. The levels of these factors in diabetic patients are certainly increased, but not enough to explain the exaggerated risk for macrovascular complications in diabetic population. Macrovascular complications of diabetes have been shown to start before the onset of diabetes. Several clinical studies have confirmed the increased risk of CVD in patients with impaired glucose tolerance (IGT). Since insulin resistance-related postprandial metabolic derangements are thought to play a central role in the development and progression of CVD in patients with IGT, amelioration of postprandial metabolic disturbance is a therapeutic target for the prevention of CVD in these high-risk patients (Yamagishi et al., 2009).

Cardiovascular disease is the most prevalent and detrimental complication of diabetes mellitus. The incidence of cardiovascular mortality in diabetic subjects
without a clinical history of previous cardiac events is as high as the incidence in non-diabetic subjects with a history of myocardial infarction. This inordinate increase in the risk of coronary events in diabetic patients is attributed to multiple factors, including glycation and oxidation of proteins and increased prevalence of classic risk factors of coronary disease such as hypertension, obesity and dyslipidemia (Mooradian, 2003).

The term cardiovascular disease (CVD) includes heart disease, stroke and all other diseases of the heart and circulation, such as hardening and narrowing of the arteries supplying blood to the legs, which is known as peripheral vascular disease (PVD). However, heart disease and stroke are the two most common forms of CVD. People with diabetes have a fivefold increased risk of CVD compared with those without diabetes. The reasons are prolonged, poorly controlled blood glucose levels, which affect the lining of the body's arterial walls. This increases the likelihood of furring up of the vessels, forming narrowing of the coronary arteries (atherosclerosis). People with Type 2 diabetes often have low HDL cholesterol and raised triglyceride levels, both increasing the risk of atherosclerosis. High blood pressure, smoking, obesity and physical inactivity are also risk factors for CVD (Yamagishi et al., 2009).

Diabetic heart disease (DHD) may include coronary heart disease (CHD), heart failure and diabetic cardiomyopathy. In CHD, a waxy substance called plaque (plak) builds up inside the coronary arteries. These arteries supply the heart muscle with oxygen-rich blood. Plaque is made up of fat, cholesterol, calcium and other substances found in blood. When plaque builds up in the arteries the condition is called atherosclerosis. Plaque narrows the coronary arteries and reduces blood flow to heart muscle. The build-up of plaque also makes it more likely that blood clots will be formed in the arteries. Blood clots can partially or completely block blood flow. CHD can lead to chest pain or discomfort called angina, irregular heartbeats called arrhythmias, heart attack or even death. Diabetic cardiomyopathy is a disease that damages the structure and function of the heart. This disease can lead to heart failure and arrhythmias, even in people who have diabetes but who may not have CHD (Mardikar et al., 2010).
A strong link between diabetes and heart disease is now well established. Studies from Joslin Diabetes Centre showed a two to threefold increase in the incidence of heart disease in patients with diabetes compared with those without diabetes (Donald et al., 2004). Women with diabetes have an even greater risk of heart disease compared with those of similar age who do not have diabetes. In fact, cardiovascular disease leading to heart attack or stroke is by far the leading cause of death in both men and women with diabetes. Another major component of cardiovascular disease is poor circulation in the legs, which contributes to a greatly increased risk of foot ulcers and amputations (Ganda, 2013).

Several advances in the treatment of heart disease over the past two decades have improved the chances of surviving a heart attack or stroke. However, as the incidence of diabetes steadily increases the number of new cases of heart disease and cardiovascular complications also increases. Unfortunately, in patients with diabetes, improvement in survival has been less than half as much as in general population (Yamagishi, 2009). In particular, aggressive lowering of plasma low-density lipoprotein (LDL) levels, which can be achieved with statins or statins combined with other hypocholesterolemic drugs has been shown to be extremely beneficial (Goff et al., 2007).

The best way to prevent or delay the development of cardiovascular disease is to prevent diabetes itself. National Institute of Health-sponsored study, the Diabetes Prevention Program and other studies have proven that modest weight reduction and a 30-minute exercise routine five days a week can reduce the development of type 2 diabetes. Weight control and smoking cessation are two important lifestyle measures that have an impact on preventing heart disease. Even in overweight people, regular physical activity has major cardiovascular benefits (Tsunosue et al., 2010).

One reason for the poor prognosis in patients with both diabetes and ischemic heart disease seems to be an enhanced myocardial dysfunction leading to accelerated heart failure (diabetic cardiomyopathy). Thus, patients with diabetes are unusually prone to congestive heart failure. Several factors probably underlie
diabetic cardiomyopathy: severe coronary atherosclerosis, prolonged hypertension, chronic hyperglycemia, micro vascular disease, glycosylation of myocardial proteins and autonomic neuropathy. Improved glycemic control, better control of hypertension and prevention of atherosclerosis with cholesterol-lowering therapy may prevent or mitigate diabetic cardiomyopathy. An early clinical trial suggested that sulfonyl ureas used for the control of hyperglycemia are cardiotoxic and may exacerbate diabetic cardiomyopathy (Grundy et al., 2011). Obesity is a common problem in diabetes and is estimated to account for approximately 60% of type 2 diabetes (Dixon et al., 2011).

Though cardiomyopathy is often not curable, there are many treatment alternatives that could effectively control the symptoms for an improved quality of life for those with the disease. The treatment choice is largely based on the cause and type of cardiomyopathy as well as the extent of damage caused to the heart muscle. Medications commonly used to treat heart failure associated with diabetic cardiomyopathy, ischemic cardiomyopathy and restrictive cardiomyopathy includes sulfonylureas, prandin, starlix, (Increases insulin secretion), avandia, actos (Helps the cells to respond more effectively to insulin), metformin (Decreases the liver’s glucose production), precose, glyset (Slows intestinal absorption of some carbohydrates), beta-adrenergic (beta) blockers (prevent further heart enlargement and scarring and decrease the risk of sudden death), diuretics (decreases symptoms of shortness of breath, swelling, and bloating), positive inotropic medications (strengthen the contractions of the heart), vasodilators (reduce symptoms of heart failure), aldosterone blockers (help to balance electrolytes in the body and also to prevent heart and blood vessel scarring, stiffening, and enlargement) and antiarrhythmic (alter the way in which electrical currents are transmitted through the heart muscle). As well as being a risk factor for stroke, diabetes and other high blood glucose conditions have adverse effects on both short and long-term prognosis for stroke victims (Grundy et al., 2011).

Plant-based eating patterns combined with exercise have been found to improve diabetes control and reduce the need for medication in intervention trials as
far back as 1976. Low-fat, plant-based eating patterns have shown efficacy in reducing LDL cholesterol concentrations and result in significant reductions in CVD risk and cardiovascular events (Berkow and Barnard, 2006). Plant-based eating pattern that includes nuts, soy and soluble fiber can reduce LDL cholesterol by 25–30% an amount comparable to that which could be achieved with statin drugs (Ferdowsian and Barnard, 2009).

Many plants have been used for the treatment of diabetes mellitus in Indian system of medicine and in other ancient system of the world. Out of these only a few have been evaluated as per modern system of medicine. From many such plants only extracts have been prepared and their usefulness evaluated in experimental diabetes in animals. In some plants like Allium cepa, Allium +sativum, Ficus bengalensis, Gymnema sylvestre and Pterocarpus marsupium active hypoglycaemic principles have been isolated and their mechanism of action studied. Most of them seem to act directly on pancreas (pancreatic effect) and stimulate insulin level in blood. Some have extra pancreatic effect also by acting directly on tissues like liver, muscle and alter favourably on the activities of the regulatory enzymes of glycolysis, gluconeogenesis and other pathways. Since the plant products have less side effects, they have the potential as good hypoglycemic drugs. They may also provide clues for the development of new and better oral drugs for diabetes (Shukia et al., 2000).

Phytochemicals are chemicals found in plants that protect plants against bacteria, viruses, and fungi. Eating large amounts of brightly colored fruits and vegetables (yellow, orange, red, green, white, blue, purple), whole grains/cereals and beans containing phytochemicals may decrease the risk of developing certain cancers as well as diabetes, hypertension and heart disease. The action of phytochemicals varies by color and type of a food. They may act as antioxidants or nutrient protectors or prevent forming carcinogens (cancer causing agents) (Andrews, 2012). Anthocyanins are found in red and blue fruits (such as raspberries and blueberries) and vegetables. They help to slow the aging process, protect against heart disease and tumors, prevent blood clots and fight inflammation and
allergies. Lutein is found in leafy green vegetables. It may prevent macular degeneration and cataracts as well as reduce the risk of heart disease and breast cancer. Lycopene is found primarily in tomato products. When cooked, it appears to reduce the risk for cancer and heart attacks. Phenolics are found in citrus fruits, fruit juices, cereals, legumes and oilseeds. It is thought to be extremely powerful and is studied for a variety of health benefits including slowing aging process, protecting against heart disease and tumors and fighting inflammation, allergies and blood clots (Goepp, 2009).

Antioxidants are natural substances that exist as vitamins, minerals and other compounds in foods. They are believed to help to prevent disease by fighting free radicals, substances that harm the body when left unchecked. Free radicals are formed by normal bodily processes such as breathing and by environmental contaminants like cigarette smoke. Without adequate amounts of antioxidants, these free radicals travel throughout the body damaging cells. Part of this cellular damage leads to one of the major known factors in the development of heart disease and oxidation of cholesterol (Weintraub et al., 2008).

*Albizia saman* (*A.saman*) (*rain tree*) is a traditional remedy for colds, diarrhoea, headache, intestinal ailments and stomach ache. Root decoction is used in hot baths for stomach cancer. The alcoholic extract of the leaves are used to treat tuberculosis (Arumugam et al., 2011). Saponin-like alkaloid pithecolobin has been isolated from the bark and the seed. The plants are used to cure acute bacillary dysentery, enteritis, diarrhoea, colds, sore throat and headache. A decoction of the inner bark or fresh cambium and leaves are used to treat anaphylactic dermatitis, eczema and skin pruritus (Raghavendra et al., 2008).

*Nelumbo nucifera* (*N.nucifera*) *Gaertn* (*Family-Nymphaeaceae*) is a well-known plant in ancient medical sciences. The leaf of Nelumbo nucifera Gaertn (family Nymphaeaceae) has been used for summer heat syndrome as home remedy in Japan and China and it has recently been used to treat obesity (Ono et al., 2006).
N. nucifera has been used for various medicinal purposes by Chinese herbalists. Flavonoids in the leaves of Nelumbo nucifera Gaertn (lotus leaves) have many pharmacological activities. Some of these flavonoids include hyperin, isoquercetin and astragalin. Nelumbo nucifera is an excellent remedy for treating abdominal cramps, diarrhoea and other upsets. It contains some disease fighting elements, it has antiseptic properties and guards against bacteria and parasites. Irritants like sunburn or fungal rashes may be treated by applying herbal derivatives directly to the skin. Its preventive benefits against chronic conditions and disorders are noteworthy as well. Sacred lotus is a fantastic tool for boosting body's protection against cancer and kidney problems (Jung et al., 2008).

There is no scientific or medicinal validation on the cardio tonic activity of the medicinal plant Albizia saman and white Nelumbo nucifera. Therefore the present study was carried out to find out the cardio protective effect of Albizia saman leaves and white Nelumbo nucifera flowers against Isoproterenol. So, the present research entitled “Biochemical changes in patients with diabetic cardiomyopathy during drug therapy and the cardio protective effect of selected medicinal plants on Isoproterenol induced Swiss albino rats” was carried with the following objectives:

- To assess the medical status of patients with diabetic cardiomyopathy before and during the treatment.
- To analyse the phytochemical components of selected medicinal plant Albizia saman (leaves) and white Nelumbo nucifera (whole flower).
- To evaluate the free radical scavenging activity of various extracts of the selected medicinal plant samples.
- To evaluate the total antioxidant activity of various extracts of the selected medicinal plant samples.
- To find out the active components in the selected plant samples using HPTLC, HPLC, FT-IR and GC-MS analysis.
To assess the effect of methanolic extract of *A. saman* leaves and white *N. nucifera* flowers on experimentally induced diabetic rats.

Assessment of the enzymic and non enzymic antioxidant activity in heart homogenate of experimental animals.

Histopathological findings of the heart section on experimental animals.