1.1 Introduction

In the recent years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects (Rajasekaran et al., 2001) such as hypoglycemia, weight gain, gastrointestinal symptoms and peripheral edema as compared to synthetic drugs (Black et al., 2007; Del et al., 2007). The World Health Organization (WHO) has listed 21,000 plants, which are used in healthcare around the world. Among these 2500 species are in India, out of which 150 species are used commercially (WHO, 2008). India is one of the largest producer and consumer of medicinal herbs and is called as botanical garden of the world. WHO estimates that herbal medicines provide primary healthcare for approximately 3.5 to 4 billion people worldwide, and about 85% of traditional medicine involves the use of plant extracts which may be called “modern herbal medicine” (Farnsworth, 1988). Medicinal plants are important for pharmacological research and drug development, not only when the plant constituents are used directly as therapeutic agents, but also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds (Murti et al., 2011; Adeyi et al., 2012). The plant contains a large number of constituents such as flavonoids, alkaloids, steroids, triterpenoids, lipids, lignins, carbohydrates, proteins and glycoproteins which are responsible for their pharmacological and therapeutic activity (Talele et al., 2012). Phytochemical screening has been carried out to identify these phytoconstituents from the various extracts and then these are subjected to pharmacological evaluation to screen their therapeutically potential. It is estimated that about 25% of the drugs prescribed worldwide are derived from plants and 121 such active compounds are in use. Of the total 252 drugs in WHO essential medicine list, 11% is exclusively of plant origin.
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(Rates, 2001). Nearly 80% of African and Asian population depends on traditional medicines for their primary healthcare (WHO, 2008).

In India, about 80% of the rural population uses medicinal herbs or indigenous systems of medicine (Mukherjee and Wahile, 2006). Generally, in traditional system of medicine, many herbal drugs are combined in the form of a multi-herbal formula to enhance their functions. The herbal constituents are selected to emphasize the therapeutic actions or to reduce the toxicity or side effects of compounds from other herbal species in the mixture (Bansky and Barolet, 1990). Oral hypoglycemic agents like sulphonylureas and biguanides are still the major players in management of the diabetes but there is growing interest in herbal remedies due to side effects associated with the oral hypoglycemic agents (Patel and Srinivasan, 1997). Therefore, there is a need to search more effective and safe herbal drugs for diabetes and its complications (Pari and Maheshwari, 1999).

Diabetes is a metabolic disorder of impaired carbohydrates, fat and protein metabolism, characterized by hyperglycemia, polyuria, polydipsia and weight loss in spite of polyphagia due to insulin deficiency or insulin resistance which results in decrease utilization of carbohydrate and excessive glycogenolysis and gluconeogenesis from amino acid by fatty acids (Pontiroli et al., 1994; Gruden et al., 2005). The prevalence of diabetes is 6.4%, affecting 285 million adults, in 2010 and will increase to 7.7% and affecting the 439 million adults by 2030 (Shaw et al., 2010). Type I diabetes (insulin dependent) is caused due to insulin insufficiency because of lack of functional beta cells. Patients suffering from this are therefore totally dependent on exogenous source of insulin while patients suffering from Type II diabetes (insulin independent) are unable to respond to insulin and can be treated with dietary changes, exercise and medication (Fowler, 2008). Type II diabetes is the more
common form of diabetes constituting 90% of the diabetic population. Symptoms for both diabetic conditions may include: (i) high levels of sugar in the blood; (ii) unusual thirst; (iii) frequent urination; (iv) extreme hunger and loss of weight; (v) blurred vision; (vi) nausea and vomiting; (vii) extreme weakness and tiredness; (viii) irritability, mood changes etc. (Andrew, 2000).

Persistent hyperglycemia lead to various microvascular complications that includes nephropathy, retinopathy, neuropathy and macrovascular complications that includes coronary artery disease, leading to myocardial infarction or angina, stroke (mainly ischemic type), peripheral vascular disease, which contributes to intermittent claudication (exertion-related foot pain) as well as diabetic foot and these complications leads to significant morbidity and mortality in patients with diabetes (Altan, 2003; Halder et al., 2003; Thomas and Viberti, 2005).

Diabetic nephropathy is microvascular complication affecting 25–40% of Type I or Type II diabetic patients and it increases by 6% per year (Maclsaac and Jerums, 2003), characterized by thickening of basement membranes and mesangial expansion with progression into glomerulosclerosis, tubular necrosis and interstitial fibrosis, which ultimately result in renal failure (Paeksakon et al., 2002). Hyperglycemia may lead to end stage renal damage through both metabolic and non metabolic pathways. The non-enzymatic glycation of proteins with irreversible formation and deposition of reactive advanced glycation end products (AGE) have been noted to play a major role in the pathogenesis of diabetic nephropathy (Brownlee, 1992). Further, diabetic nephropathy is associated with hyperactivity of sorbitol-aldose reductase pathway (Cooper, 1998), hyperactivity of hexosamine biosynthetic pathway, activation of protein kinase C (Gruden et al., 2005) and MAPK (Komers et al., 2007) and overexpression of growth factors and cytokines i.e.
transforming growth factor-β, vascular endothelial growth factor, platelet-derived growth factor and insulin-like growth factor (Gojo et al., 2007).

Moreover, elevated glucose concentration in diabetes has been noted to induce oxidative and nitrosative stress (Allen et al., 2005) which activate intracellular RAAS and release endothelin-1 and prostaglandins (Okumura et al., 1999) to deteriorate the function of kidney. In addition, up-regulation of transforming growth factor-β (TGF-β) and consequent overproduction of extracellular matrix molecules have been implicated in the progression of diabetic nephropathy.

The experimental evidences suggest that hyperlipidaemia is a major risk factor involved in diabetic nephropathy by increasing the expression of sterol regulatory element–binding protein (SREBP), which synthesizes triglycerides and low density lipoprotein (LDL) in diabetic kidney to induce glomerulosclerosis (Molitch et al., 2004 and Wang et al., 2005). Activation of peroxisome proliferator activated proteins (PPAR-α) has been reported to produce hypolipidemic action (Balakumar et al., 2007). Treatment with fenofibrate, a PPAR-α agonist significantly improved the function of endothelium by increasing nitric oxide (NO) bioavailability and reducing the level of LDL and down regulation of expression of tumor necrosis factor-α (TNF-α) (Yang et al., 2004). Further, fenofibrate has been shown to reduce glomerular hypertrophy, mesangial matrix expansion and suppression of expression of plasminogen activator inhibitor-1 (PAI-1) and TGF-β1 (Chen et al., 2006; Park et al., 2007). Therefore, fenofibrate has been employed as standard drug (Staels et al., 1998).

A close correlation between arterial blood pressure and the rate of decline in GFR has also been shown in overt diabetic nephropathy. Statistical analyses did not reveal a lowest threshold for the adverse effect of high systemic blood pressure on the fall in GFR (Rossing et al., 2002). A meta-analysis of trials with ACE-I in diabetic
nephropathy showed that these agents lead to a reduction in the risk of progression from microalbuminuria to overt nephropathy and they seem to be superior, in terms of renal protection, to other anti-hypertensive agents. Treatment with ACE inhibitor also seemed to have long-term effects with preservation of diabetic nephropathy function, i.e. GFR, over at least eight years (Mathiesen et al., 1999). Early intervention with ACE-I and blood pressure reduction already in normotensive patients with microalbuminuria has been shown to be beneficial both in Type I and Type II diabetes (Ravid et al., 1993). Several clinical trials using angiotensin receptor blockers (ARB) in patients with diabetes have shown similar renoprotective effects as ACE-I, both in Type I and in particular, Type II diabetes (Lewis et al., 1993). The use of ACE inhibitor and ARB can lead to renal protection in diabetic nephropathy but still nephropathy may continue to progress but at a slower rate. A more effective blockade of the effects of Angetensin II by reducing both synthesis and its binding to the type I receptor, i.e. a combination therapy with ACE-I and ARB has shown an additive effect on blood pressure and markers of renal function such as albuminuria (Mongenson et al., 2000). Clinical trials have also indicated that ACE-I and ARB may be more effective than traditional antihypertensive treatment in reducing the progression towards ESRD (Deferrari et al., 2002). It is nevertheless clear that treatment of hypertension is an important task in preventing and postponing the development of diabetic nephropathy. In the UKPDS trial more than 2/3 of the patients with Type II diabetes and hypertension needed at least two antihypertensive agents to achieve a mean blood pressure of 144/82. A combination of blood pressure-lowering agents will thus be required in most hypertensive patients with Type II diabetes. In the Swedish national guidelines for diabetes care, ACE-I has been recommended as a first choice in patients with Type I diabetes and signs of incipient
or overt diabetic nephropathy. The renoprotective effect of lisinopril has been well reported in basic and clinical studies (Amann, 2003; Benigni et al., 2003). Therefore, lisinopril has been employed as a standard drug in the present study (Arora et al., 2010).

Streptozotocin (STZ) is a glucosamine-nitrosoare compound, chemical name of 2-deoxy-2-(3-methyl-3-nitrosoareido)-D-glucopyranose (C$_{18}$H$_{15}$N$_{3}$O$_{7}$) (Szkudelski, 2001) that show selective cytotoxicity to pancreatic β cells. Administration of STZ at a dose of 40 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg and 65 mg/kg i.p. induces hyperglycemia in rats (Casey et al., 2005, Singh et al., 2005, Shah and Singh, 2006; Haidara et al., 2009). STZ induces hyperglycemia which activates PKC, aldose reductase, NADPH oxidase, formation of AGEs and increases Angetensin II levels (Brownlee, 2001; Chung et al., 2003; Onozato and Tojo, 2005). Hyperglycemia leads to development of diabetic nephropathy in 4-8 weeks, assessed in terms of serum creatinine, BUN, proteinuria, creatinine clearance, extracellular matrix deposition, dyslipidemia and consequent development of glomerulosclerosis and tubulointerstitial fibrosis (Budhiraja et al., 2006; Gojo et al., 2007; Alqattan et al., 2008).

*Jasminum grandiflorum* is scrambling subs erect twining evergreen shrub (Anonymous, 1987 and Anonymous, 2004), native to India, France, Italy, China, Japan, Morocco and Egypt (Chopra et al., 1958; Kirtikar and Basu, 1987; Chopra et al., 2002; Sharma et al., 2005). The leaves are opposite, entire ovate to somewhat elliptic in shape with acuminate mucronate apex, whereas flowers are terminal and axillary cymes, calyx lobes are long, linear (Cooke, 1967; Nadkarni, 1967). Roots are useful in cephalalgia, mental debility, chronic constipation, flatulence, strangury, sterility, dysmenorrhoea, amenorrhoea, ringworm, leprosy, skin diseases and giddiness. Leaves are useful in odontalgia, fixing loose teeth, ulcerative stomatitis,
leprosy, skin diseases, ototorhoea, otalgia, strangury, dysmenorrhoea, ulcers, wound, corns and flowers are useful in stomatopathy, cephalopathy, odontopathy, ophthalmopathy, leprosy, skin diseases, pruritis, strangury, dysmenorrhoea, ulcers, as refrigerant, ophthalmic and vitiated conditions of pitta (Warrier et al., 2004).

*Saraca asoca* (Roxb.) De Wilde, sacred tree belonging to family caesalpinaceae, found almost throughout India, except North-Western India, upto 750m also found in the Andaman Islands. The leaves are parpinnate with 6 to 12 leaflets, oblong and rigidly sum-coriaceous. The fruit is a pod flat, leathery with 4 to 8 ellipsoid- oblong and compressed seeds (Kumar et al., 2012).

The whole plant is claimed to possess medicinal properties and used for various ailments like diabetes, emollient, stomachic, blood disease, ulcers, menorrhagia, dyspepsia, inflammation, dysentery, haemorrhoids etc. (Bhadauria et al., 2012). Leaves extracts has been reported for antidepressant, analgesic, antipyretic, anti-inflammatory, antibacterial, antihelminthic, antimicrobial and antidiabetic activity due to the presence of phytochemicals like Carbohydrates, Proteins, Amino Acids, Flavonoids, Tannin, Saponin, Steroids (Kumar et al., 2012).

Polyphenolic compounds, flavonoids, terpenoids, saponins, polysaccharides and alkaloids are the major chemical moieties present in the plant species in various families and these major secondary metabolites tend to reverse or delay the diabetic complications by decreasing the persistent hyperglycemia, decreasing the formation of ROS, by increasing the secretion of insulin from β-cells and by inhibiting the formation of AGEs (Patel et al., 2012).