Introduction

Diabetes Mellitus (DM) is the World’s largest endocrine metabolic disorder characterized by hyperglycaemia with disturbance of carbohydrate, fat and protein metabolism resulting from defects in either insulin secretion or insulin action or both (American Diabetes Association, 2014). According to International Diabetes Federation (IDF), the global prevalence of diabetes is predicted to grow from 366 million in 2011 to 552 million by 2030 (International Diabetes Federation, 2011). In type 1 diabetes mellitus (T1DM) or insulin dependent diabetes mellitus (IDDM), the body does not produce insulin due to autoimmune destruction of pancreatic islets and thus insulin injections are required. Type 2 diabetes mellitus (T2DM) or non insulin dependent diabetes mellitus (NIDDM) is a chronic and progressive illness that occurs in 80% of the total diabetic cases due to the failure of pancreatic β-cells to produce sufficient amount of insulin or impairment of insulin action (World Health Organization, 2014). India has emerged as the World’s second most popular country pronounced with T2DM which is over 50 million people, than any other nation (Harsha et al., 2012). The prevalence of T2DM in India increases due to poor glycemic control and can predispose diabetic patient to other complication compared to western countries. Chronic hyperglycemia causes negative impact on large number of organs and tissues (Poitout and Robertson, 2008). The signs and symptoms of diabetes commonly include polydipsia, polyphagia, blurred vision, slow healing wounds and severe loss of body weight. Early detection and treatment of DM can decrease the risk of developing the complications of diabetes (Punithavathi et al., 2008).

Several pathological events are involved in the development of diabetes, ranging from the destruction of the β-cells of the pancreas with a subsequent insulin
deficiency to insulin resistance (Saltiel and Kahn, 2001). Deficient insulin action is a hallmark characteristic of the diabetic condition. Glucose homeostasis is controlled by a highly coordinated interaction of insulin secretion, glucose uptake by tissues and hepatic glucose production (Kahn, 2003). In normal, insulin signal transduction is initiated when insulin binds to the insulin receptor, which further leads to the stimulation of several intracellular protein substrates including insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2). IRS proteins play a major role in glucose homeostasis and are highly expressed in liver (Valverde et al., 2003). Since IRS proteins are a critical link in hepatic insulin signaling, it has been hypothesized that the decreased expression of IRS proteins in liver may be a key molecular lesion of hepatic insulin resistance (Sun et al., 2002). One of the important metabolic effect of insulin on glucose uptake is the translocation of glucose transport proteins (GLUTs) from intracellular storage vesicle to the plasma membrane; GLUT-2 is the most abundant isoform in liver, whereas GLUT-4 in muscles and adipose tissues. GLUTs expressions are downregulated due to relative insulin insufficiency (Bryant et al., 2002).

Chronic hyperglycemia has been hypothesized to contribute oxidative stress either by excess generation of reactive oxygen species (ROS) or by altering the cellular redox balance. This occurs via increased polyol pathway flux, increased intracellular formation of advanced glycation end products (AGEs), activation of protein kinase C (PKC) and overproduction of superoxide anions by the mitochondrial electron transport chain (Ahmad et al., 2005; Brownlee, 2001). Over glycation of proteins such as hemoglobin and albumin results in the formation of “AGEs” which triggers rapid generation of free radicals and upregulates the inflammatory pathways in liver, skeletal
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muscle and adipose tissues (Ramasamy et al., 2005). Excess generation of ROS and reactive nitrogen species (RNS) are a key component in the development of complications invoked by hyperglycemia (Bandeira et al., 2013). Free radicals are formed in normal physiology however, become deleterious if not quenched by a cascade of antioxidants systems (Gulcin et al., 2002). ROS generation is neutralized by a battery of antioxidants, which can be classified into two categories as enzymatic and non-enzymatic antioxidant systems (Wiernsperger, 2003). Overproduction of ROS and reduced activation of antioxidant enzymes shifts the antioxidants balance in favour of stress. Indeed, it is known that free radicals induced oxidative stress is a key event in diabetic complications (Maritim et al., 2003).

Nuclear factor-κB (NF-κB) mediated expression of inducible nitric oxide synthase (iNOS) and subsequent NO production plays a major role in T2DM and its associated complications (Kim et al., 2007). Hyperglycemia mediated oxidative stress activates stress sensitive signaling pathways, including NF-κB, which enhances the activation of inflammatory cells with increase in production of proinflammatory mediators such as tumour necrosis factor-α (TNF-α) and interleukins (ILs) (Baker et al., 2011; Evans et al., 2002; Nunokawa et al., 1996).

Pharmacotherapy for T2DM was developed based on hypoglycemic effects. The oral hypoglycemic agents that are in clinical practice include sulfonylureas, biguanides and glitazones (Rajalakshmi et al., 2009; Anuradha et al., 2004). All of these pharmacological modalities have restricted efficacy and certain adverse effects such as hypoglycemia, liver toxicity, lactic acidosis, diarrhoea etc. (Donath and Ehses, 2006). The management of diabetes without any side effect is still a challenge. Hence, recent research is focused on natural products for the development of newer drug leads
from phytoconstituents with more efficacy without any long-term side effects than the existing hypoglycemic agents (Guerreiro et al., 2007).

Apart from the conventional antidiabetic treatment, antioxidant therapy might be beneficial in ameliorating the complications of diabetes (Garg and Bansal, 2000). Flavonoids are the most important constituents found in many natural resources. These are diverse group of polyphenolic compounds which are produced as secondary metabolites by various plants in appreciable quantities (Havsteen, 2002). Flavonoids are natural antioxidants that exhibit a wide range of biological effects, including antibacterial, anti-inflammatory, antiallergic, antithrombotic and vasodilatory action (Cook and Samman, 1996). Due to their abundance in dietary products and potential pharmacological and nutritional effects, the flavonoids are of considerable interest for the drug development (Khan et al., 2012).

Chrysin (5, 7- Dihydroxyflavone) is one of the biologically active flavonoid present in many plants, honey and propolis. Like other flavonoids it possess wide pharmacological action such as antidiabetogenic, anti-inflammatory, antioxidant, antihypertensive and anticancer effects (Samarghandian et al., 2011; Hadjmohammadi and Nazari, 2010; Pichichero et al., 2010). In this view, the present study has been developed to understand the antidiabetic mechanism of chrysin in T2DM. Even though chrysin have proved for antidiabetic effect, sufficient in-depth knowledge on the molecular actions has not yet been clearly defined. In the present study streptozotocin-nicotinamide (STZ-NA) induction of T2DM in experimental rats has been chosen to assess the antihyperglycemic, antioxidative and antinflammatory effects of chrysin.
Aim and Objectives

Aim

The overall aim of the present study is to reveal the ameliorative potential of chrysin (5, 7-Dihydroxyflavone) against streptozocin-nicotinamide (STZ-NA) induced T2DM in rats.

Objectives

The antidiabetic potential of chrysin has been evaluated with the following objectives:

- To assess the hypoglycemic effect of chrysin on STZ-NA induced experimental T2DM rats.
- To understand the effect of chrysin on hyperglycemia mediated oxidative stress in STZ-NA induced experimental T2DM rats.
- To investigate the role of chrysin on glucose homeostasis and insulin signaling in STZ-NA induced experimental T2DM rats.
- To evaluate the protective role of chrysin on inflammatory biomarkers in STZ-NA induced experimental T2DM rats.