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Anti-inflammatory effects of tyrosol in streptozotocin-induced diabetic Wistar rats

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ABSTRACT

The anti-inflammatory effect of tyrosol (4-(2-hydroxyethyl)), a phenolic compound in olive oil (20 mg/kg body weight), in streptozotocin (STZ)-induced diabetic rat was evaluated. Diabetic rats showed significant ($P < 0.05$) increase in plasma glucose and lipid peroxidation products and significant ($P < 0.05$) decrease in plasma insulin and enzymatic and non-enzymatic antioxidants in the liver and pancreas. The levels of inflammatory marker, C-reactive protein in plasma and protein expressions of nuclear factor-kappa B p65, tumour necrosis factor-alpha and interleukin-6 in the liver and pancreas were significantly ($P < 0.05$) increased in STZ-induced diabetic rats. Conversely, daily oral treatment with tyrosol for 45 days significantly ($P < 0.05$) restored all the above mentioned parameters to near normal levels. The immunohistochemical studies confirm the anti-inflammatory effects of tyrosol. Tyrosol exerts anti-inflammatory effects on the liver and pancreas of STZ-induced diabetic rats via its antioxidant activity, hence it may play an important role in the management of diabetes mellitus.

1. Introduction

Diabetes mellitus (DM) is a major and growing public health problem throughout the world, with an estimated worldwide prevalence of 415 million people in 2015 which is expected to increase to 642 million people by 2040 (International Diabetes Federation, 2015). DM is a heterogeneous metabolic disorder characterised by the presence of persistent hyperglycaemia as a result of disrupted insulin-signalling. There are mainly two types of DM, type 1 and type 2 in which over 90–95% of patients are suffering from type 2 DM (T2DM). T2DM is characterised by the progression of diminishing insulin sensitivity and pancreatic β-cell dysfunction. Inflammatory processes play a vital role in the development of DM and its late complications, suggesting that DM is an inflammatory disease (Yang et al., 2014). Oxidative stress and inflammation are the major factors involved in the cardiovascular complications of patients with T2DM (Hermans, 2007).

Persistent hyperglycaemia in DM leads to an increase in the oxidative stress because of the overproduction of free radicals, especially reactive oxygen species (ROS), which in turn cause lipid peroxidation (LPO) and membrane damage via autoxidation of glucose (Rosen et al., 2001). These free radicals further damage the carbohydrates, proteins and DNA, thereby inhibiting normal functioning of these biomolecules. In addition, hyperglycaemia causes overproduction of free radicals that deplete antioxidant system (Matough, Budin, Hamid, Alwahaibi, & Mohamed, 2012). The development of primary complications of DM is promoted by increased oxidative stress, decreased antioxidant defence system and by LPO (Rudge et al., 2007).

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Chemical compounds: Tyrosol (PubChem CID: 10393); Streptozotocin (PubChem CID: 2733335); Glibenclamide (PubChem CID: 3488).
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It has been reported that increased oxidative stress promotes the activation of transcription factor nuclear factor-kappa B (NF-κB) p65, which leads to the synthesis of various proinflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Mariappan et al., 2010; Panicker & Kartha, 2010), thereby modulating the insulin response in liver and muscles (Chang & Chuang, 2010; Dewanjee, Das, & Sahu, 2009). In view of these, therapeutic agents that can bring about tight glycaemic control as well as reducing the degree of oxidative stress and the production of proinflammatory cytokines are very much essential to lessen the complications of DM (Unger, 2008).

Accumulating evidence has emphasised that biologically active components in functional foods may be used as complementary treatment for T2DM (Mirmiran, Bahadoran, & Azizi, 2014). Phenols from numerous foods and drinks have been actively studied as potential treatment for various metabolic and cardiovascular diseases. The antioxidant potential of phenols is mainly related to the ability of these compounds to scavenge free radicals produced by oxidative stress (Cadenas & Davies, 2000). In this context, tyrosol has received much attention because of its potent free radical scavenging and antioxidant actions. Tyrosol, 4-(2-hydroxyethyl) phenol, is a biologically active molecule, which comes under the category of natural phenolic antioxidant, has gained increasing attention as a dietary antioxidant. The principal source of tyrosol in the human diet is olive oil, but many other food sources such as argan oil, wine, sake and natural extracts contain tyrosol as a major constituent. Hydroxytyrosol, another phenolic compound present in olive oils, exhibits multi pharmacological activities such as antidiabetic (Jemai, Feki, & Sayadi, 2009), antioxidant, anticancer, anti-inflammatory and neuroprotective effects (Hu, He, Jiang, & Xu, 2014). Tyrosol exhibits potent bioactivities in living systems due to its high bioavailability (Canuelo et al., 2012; Tuck, Freeman, Hayball, Stretch, & Stupans, 2001). It exhibits antioxidant effect and scavenges peroxynitrite (De la Puerta, Martinez Dominguez, Ruiz-Gutierrez, Flavill, & Hoult, 2001) and superoxide anion (Bertelli et al., 2002). In the previous phase of our experiment, tyrosol significantly improved the activity of glutathione-s-transferase and the concentration of vitamin C and vitamin E in STZ-induced diabetic rat's tissues, by virtue of its antioxidant effect (Chandramohan, Pari, Rathinam, & Sheikh, 2015). In addition, it has anti-cancer, neuroprotective and cardioprotective effects (Ahn et al., 2008; Bu et al., 2007; Chernyshov, Plotnikov, Smoliakova, & Krasnov, 2007).

We have previously reported the anti-hyperglycaemic effect of tyrosol in STZ induced diabetic rats (Chandramohan et al., 2015). In continuation of our research on tyrosol, an attempt was made to evaluate the biochemical and molecular mechanisms of anti-inflammatory effects of tyrosol in STZ-induced diabetic rats. In addition to this, the efficiency of tyrosol was compared with glibenclamide, a standard oral hypoglycaemic drug.

2. Materials and methods

2.1. Chemicals

Streptozotocin (STZ) and tyrosol were purchased from Sigma–Aldrich (St. Louis, MO, USA). All other chemicals and solvents used in this study were of analytical grade and purchased from Hi Media (Mumbai, India) and SD-Fine Chemicals (Mumbai, India).

2.2. Experimental animals

Male albino Wistar rats, weighing about 180–220 g, were procured from Central Animal House, Department of Experimental Medicine, Rajah Muthiah Medical College and Hospital, Annamalai University. They were housed in clean, sterile, polypropylene cages under standard vivarium conditions (12 h light/dark cycles) with free access to feed (Hindustan Lever Ltd., Bangalore, India) and water. The experimental protocol was approved by the Institutional Animal Ethical Committee, Annamalai University (Reg. No. 1002, 2013).

2.3. Induction of experimental DM

DM was induced in overnight fasted rats by a single intraperitoneal injection of STZ (40 mg/kg body weight) dissolved in freshly prepared citrate buffer (0.1 M, pH 4.5). STZ injected rats were allowed to drink 20% glucose solution overnight to overcome the initial drug-induced hypoglycaemic mortality. The induction of DM in rats was confirmed by estimating the elevated plasma glucose levels, 72 h after STZ injection. Rats with fasting plasma glucose levels of more than 250 mg/dl were considered diabetic and chosen for the study.

2.4. Experimental design

A total of 30 rats (18 diabetic rats and 12 normal rats) were used and they were divided into five groups of six rats in each group as follows:

Group I: Normal control rats.
Group II: Normal rats given intra gastrically 1 ml of tyrosol (20 mg/kg body weight) dissolved in distilled water daily for 45 days.
Group III: STZ-induced diabetic control rats.
Group IV: STZ-induced diabetic rats treated with 1 ml of tyrosol (20 mg/kg body weight) intra gastrically dissolved in distilled water daily for 45 days.
Group V: STZ-induced diabetic rats treated with 1 ml of glibenclamide (600 μg/kg body weight) intra gastrically dissolved in distilled water daily for 45 days.

The dosage (20 mg/kg body weight) and duration of treatment (45 days) of tyrosol were based on a previous study (Chandramohan et al., 2015). At the end of the experimental period, all the rats were fasted overnight, anaesthetised intramuscularly using ketamine (24 mg/kg body weight) and sacrificed by cervical decapitation. Blood samples were collected in tubes containing potassium oxalate and sodium fluoride (3:1/w/w) mixture for the separation of plasma. Liver and pancreas tissues were excised and washed with ice-chilled saline thoroughly. Parts of the tissues were sliced and stored at –80 °C, another part was used for immunohistological examination and the remaining portions were homogenised in appropriate buffers for the estimation of various biochemical parameters.