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Potential impact of *Paracentrotus lividus* extract on diabetic rat models induced by high fat diet/streptozotocin

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Abstract Antioxidant therapy has been thought to be effectual for the prevention and treatment of various diseases including diabetes. Therefore, the present study was designed to investigate the potency of *Paracentrotus lividus* extract (PLE) for alleviating the complications that resulted after induction of the diabetic rat models (T1DM and T2DM) using high fat diet (HFD)/streptozotocin (STZ). Thirty six male Wistar albino rats were assigned into normal control, T1DM and T2DM untreated, and PLE treated diabetic rat groups. Induction of T1DM was performed by streptozotocin injection (60 mg/kg of dissolved in sodium citrate buffer, 0.1 mol/L, i.p). T2DM induction through 4 weeks of high fat diet (HFD) intervention was followed by a single low dosage of STZ (30 mg/kg dissolved in 0.1 mol/L citrate buffer at pH 4.5, i.p). Both diabetic rat models showed a significant increase in serum; levels of fasting glucose, total protein, bilirubin, activities of arginase, transaminases (AST and ALT), alkaline phosphatase (ALP), γ glutamyl transferase (GGT), lipid profile parameters, and liver malondialdehyde (MDA). However, T1DM and T2DM rats have decreased levels of serum insulin, and liver glucose 6 phosphate dehydrogenase (G6PD), glutathione reduced (GSH), nitric oxide (NO), and antioxidant enzymes. Furthermore, the present study showed the hypoglycemic, hypolipidemic, and antioxidant potency of the PLE as confirmed by its ability for ameliorating most of the alterations caused in the studied parameters of diabetic rats. In conclusion, PLE may be useful as therapy against oxidative stress and liver damage in both types of diabetes mellitus and is therefore recommended for further studies.

Introduction

Diabetes is really a devastating epidemic of the 21st century and is becoming the third killer of the health of human beings after cancer, cerebrovascular and cardiovascular diseases. Not only it takes a heavy toll of lives around the world but imposes a serious financial burden on the sufferers and their family members (Bhattacharjee et al., 2014). Diabetes mellitus (DM) is a common metabolic disease with many side effects (Ziaee et al., 2013; Pang et al., 2015). Diabetes is characterized by hyperglycemia resulting in insulin resistance and/or insulin secondary deficiency caused by the failure of beta- (β-) pancreatic cells (Damasceno et al., 2014). Diabetes caused impaired

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metabolism of proteins and lipids (Hosseini et al., 2014). Several experimental models of type 1 and type 2 diabetes are available in rats (Fuentes-Antrás et al., 2015). Type 1 diabetes mellitus (T1DM) is one of the most prevalent autoimmune diseases in the western world (van den Brandt et al., 2010). Type 1 diabetic patients often present acute symptoms of diabetes and markedly increased glucose levels and in some cases ketoacidosis appears (Damasceno et al., 2014). On the other hand, type 2 diabetes mellitus (T2DM) is characterized by reduced pancreatic beta-cell function and systemic insulin resistance, leading to metabolic dysfunction throughout the body (Onur et al., 2014). The beta cells normally compensate insulin resistance by secreting larger amounts of insulin to maintain the glucose homeostasis (Riguera, 1997). In the course of time, however, this beta cell function gets impaired leading to deterioration in glucose homeostasis and subsequent development of impaired glucose tolerance and frank diabetes (Lebovitz and Banerji, 2004). Type 2 diabetes is frequently not diagnosed until complications appear (Damasceno et al., 2014).

Streptozotocin (STZ) is an antibiotic produced by *Streptomyces achromogenes* and is also used as an FDA-approved drug in the metastatic cancer of pancreatic islets cells (Kahraman et al., 2015). It inhibits glucose oxidation and glucose-induced insulin secretion in beta cells via nitric oxide production, alkylation, and DNA fragmentation (Lenzen, 2008). STZ leads to kidney and liver toxicity as well as beta cell damage (Dufrane et al., 2006). STZ is widely used in studies of experimental type-1 diabetes because it selectively destroys pancreatic β cells through the generation of ROS and alkylation of deoxyribonucleic acid (DNA) (Lenzen, 2008). The use of fat-fed/STZ-treated rat models imitates natural disease incidence and metabolic characteristics typical of persons at increased risk of type 2 diabetes because of both insulin resistance and obesity (Srinivasan et al., 2005).

Liver as the major target organ of insulin plays important roles in the development of insulin resistance and type 2 diabetes mellitus, and the underlying mechanisms are still not fully understood (Leng et al., 2014). Previous clinical studies documented liver disease as a major cause of mortality in patients with DM (Clouston and Powell, 2004; Jin et al., 2005). The scope of liver disease in DM includes the non-alcoholic fatty liver disease (NAFLD), characterized by fat accumulation in hepatocytes. Conditions like hypertriglyceridemia and hypercholesterolemia are described as a cause of NAFLD (Al-Jameil et al., 2014). Several organizations, recommend that lifestyle modifications, such as nutrition therapy, has been shown to help some patients to achieve better lipid levels (Jaiswal et al., 2014). In addition, hyperglycemia in diabetic patients is associated with alteration in glucose and lipid metabolism and modification in liver enzyme levels (Jenson et al., 1998).

Hyperglycemia has been identified as a major cause for reactive oxygen species (ROS) generation (Forbes et al., 2008). Oxidative stress is currently suggested as the mechanism underlying diabetes and diabetic complications (Cade, 2008; Lupachyk et al., 2013). Oxidative stress results from an imbalance between radical generating and radical scavenging mechanisms i.e. increased free radical production or abridged activity of antioxidant defenses or both (Ahmed et al., 2014). Szkudelski (2001) reported that oxidative stress is increased in experimental models of streptozotocin (STZ)-induced diabetes mellitus in rats. DM impaired glutathione metabolism, and caused alterations in the antioxidant enzymes and generation of lipid peroxides (McLennan et al., 1991; Strain, 1991).

Increased oxidative stress has been implicated in the etiology (especially type 1) and pathology (both type 1 and type 2) of diabetic complications (Robertson and Harmon, 2006; Rolo and Palmeira, 2006). Pancreatic beta cells exposed to hyperglycemia and reactive oxygen species displayed reduced insulin secretion and increased insulin resistance (Sakai et al., 2003). It is therefore suggested that suppression of oxidative stress in beta cells may prevent or delay the onset of type 1 and progression of type 2 diabetes and related complications. Several studies have also shown that treatment with antioxidants protects against the onset of diabetes (Kaneto et al., 1999; Yu et al., 2006).

The handling of this disorder requires increased physical activity, healthy eating or diet and administration of anti-diabetic drugs and/or insulin. However, the currently available anti-diabetic drugs are far from being satisfactory. This may partly be attributed to the fact that diabetes is a disorder with multifactorial and heterogeneous etiologies (Erejuwa, 2014). Besides, these agents are costly and, in some cases, not readily available. Although several synthetic hypoglycemics are developed the safe and effective treatment paradigm is yet to be developed (Bhattacharjee et al., 2014). Therefore, a large percentage of the populations are resorting to complementary and alternative medicine (CAM) (Nahas and Moher, 2009). Insulin replacement therapy is the mainstay of treatment in patients with type 1 diabetes while type 2 diabetes should be regarded as a potentially preventable disease (Bastaki, 2005). Consequently, antioxidant therapy has been thought to be effectual for the prevention and treatment of various diseases including diabetes, because oxidative stress plays a key role in the pathogenesis of human diseases (Medina and Moreno-Otero, 2005).

In recent years, great attention has been paid to study the bioactivity of natural products due to their potential pharmacological utilization. However, majority of marine organisms are yet to be screened for discovering useful antibiotics (Bragadeeswaran et al., 2013). Marine organisms represent an excellent source for bioactive compounds (Bickmeyer et al., 2005) and modern technologies have opened vast areas of research for the extraction of biomedical compounds from ocean and seas to treat the deadly diseases (Bragadeeswaran et al., 2013).

Sea urchins are spiny-skinned marine invertebrates with a global distribution (Chung, 2013). It has shown that the use of sea urchin shells confers certain beneficial advantages, including antioxidant and pharmaceutical effects (Kim et al., 2002; Shankarlal et al., 2011). In sea urchin gonads polyhydoxylated naphthoquinone, echinochrome A, of which potent antioxidant activity has been reported (Lebedev et al., 2001). It was reported that 3-sulfonoquinovosyl-1-monoacylglycerol extracted from sea urchin intestine was effective in suppressing the growth of solid tumors (Sahara et al., 1997). There are much valuable information for new antibiotic discoveries and give new insights into bioactive compounds in sea urchin (Bragadeeswaran et al., 2013). Sea urchins have therefore received increased attention as a possible source of antibiotic replacements (Chung, 2013).

It was proposed here that the hyperglycemia-induced activation of stress pathways plays a key role in the development of not only the late complications in type 1 and type 2 diabetes,