

Antidiabetic and antioxidant effects of tannic acid and melatonin on streptozotocin induced diabetes in rats

Eman Mohamad Esmail^{1*}, Amira M Abo-youssef¹ and Mohamed AbdAllah Tohamy²

¹Department of Pharmacology, Faculty of Pharmacy, Beni-Suef University, Beni Suef, Egypt

²Department of Pharmacology, Faculty of Veterinary Medicine, Beni-Suef University, Beni Suef, Egypt

Abstract: The present investigation aimed to study the possible antidiabetic and related antioxidant potentials of tannic acid and melatonin in streptozotocin (STZ) induced diabetes in rats. Four groups of rats received intraperitoneal one dose of 50mg/kg body weight STZ for the induction of diabetes. The first group served as diabetic control group and received the vehicle. Four days after induction of diabetes, the remaining three groups received glibenclamide (6mg/kg/day), tannic acid (1 g/kg/day) and melatonin (10 mg/kg/day) for two weeks. A fifth group served as vehicle control group. At the end of the experimental period, blood samples and liver samples were collected for the determination of diabetes correlated biomarkers. Treatment of diabetic rats with tannic acid or melatonin attenuated most of the changes associated with STZ induced diabetes. The present results evidenced the beneficial effects of tannic acid and melatonin in diabetes management.

Keywords: Diabetes mellitus, tannic acid, melatonin, rat.

INTRODUCTION

Diabetes mellitus is a major health trouble extending throughout the world which is caused by decreased insulin secretion or action that results in hyperglycemia and disturbance in metabolic process (Murali *et al.*, 2007). The characteristic signs of diabetes include reduced body weight, polyuria, polydipsia and polyphagia (Cooke and Plotnick, 2008). People (usually with type 1 diabetes) may also suffer from incidence of diabetic ketoacidosis, a metabolic disorder characterized by nausea, vomiting, abdominal pain, acetone odor on the breath, deep breathing and in severe cases decreased level of consciousness (Kitabchi *et al.*, 2009). Inappropriate treatment of diabetes leads to undesirable complications such as vascular dysfunctions, nephropathy, neuropathy and retinopathy (Rahimi *et al.*, 2005).

The purpose of diabetes management is to obtain a natural lifespan similar to those of healthy individuals, for achieving this aim, it is necessary to inhibit the beginning and deterioration of vascular problems (Kaku, 2010). Pharmacological interventions in the treatment of type 2 diabetes mellitus (T2DM) include insulin therapy and/or oral hypoglycemic agents such as sulfonylureas, biguanides, alpha-glucosidase inhibitors and amylin analogues (Sharma, *et al.*, 2015a).

Glibenclamide, also known as Glyburide, is an anti-diabetic drug of sulfonylureas class. It was developed in 1966 (Lad, 2014). It catalyzes release of insulin from pancreatic cells, possibly by inhibiting ATP-sensitive K⁺

channel activity present in the plasma membrane (Schmid-Antomarchi *et al.*, 1987). Glibenclamide exerts undesirable side effects as hypoglycemia and weight gain (Rani *et al.*, 2014).

Tannic acid (TA) is water-soluble polyphenol present in different plants such as tea, coffee, red wine, nuts, fruits and many plant foods (Turgut *et al.*, 2013). It is a natural antioxidant compound which is effective as food preservative (Gülçin *et al.*, 2010b). TA was shown to have antidiabetic properties (Oliveira *et al.*, 2005; Babby, *et al.*, 2014), nephroprotective effect (Tikoo *et al.*, 2007; Ahmad and Sultana, 2012), lipid lowering action (Yugarani *et al.*, 1993; Park *et al.*, 2002) and antioxidant potential (El-Sayed *et al.*, 2006; Turgut *et al.*, 2013).

Melatonin is the main pineal hormone synthesized in epiphysis in the retina, extra orbital lacrimal glands, Harderian's glands, gastrointestinal tract and in bone marrow cells (Bojková *et al.*, 2006). It is shown to have different physiological effects. Melatonin was reported to have anti diabetic effect (Sharma *et al.*, 2015b; Peschke *et al.*, 2012), nephroprotective effect (Elbe *et al.*, 2012; Hrenak *et al.*, 2015), lipid lowering action (Hussain 2007; Cardinali *et al.*, 2011) and antioxidant effect (Guney *et al.*, 2011; Salido *et al.*, 2012).

The purpose of the existing research was to investigate the protective effect of TA and melatonin in streptozotocin induced diabetic rats and to evaluate their possible effects on insulin resistance, liver glycogen, lipid profiles and kidney functions tests, In addition to oxidative stress biomarkers.

*Corresponding author: e-mail: dr_emanema3el@hotmail.com

MATERIALS AND METHODS

Experimental animals

Experiments were performed using male Wistar Albino rats weighing 100-150g supplied from the National Research Center, Cairo, Egypt. Animals were housed in plastic cages (28cm x 43cm x 18cm) and were maintained under conventional laboratory conditions (Temperature 25°C under 12-h light/12-h dark cycle) throughout the study. They were fed standard pellet chow (El-Nasr Chemical Co., Cairo, Egypt) and were allowed water ad libitum. All rats were acclimatized for minimum period of one week prior to the beginning of study. All experimental protocols were approved by the ethics committee at the Faculty of Pharmacy, Cairo University.

Drugs, chemicals and kits

Glibenclamide was provided as a gift from the Arabic Drug Company (ADCo), Egypt. Tannic acid, melatonin and STZ were obtained from Sigma Aldrich (USA). Insulin radioimmunoassay kit was obtained from Coat-a-Count-DPC (USA). Glucose, cholesterol, and triglycerides kits were obtained from Spinreact (Spain). While creatinine and urea kits were obtained from Hannover (Germany). All other chemicals are of analytical grades and were obtained from Sigma Aldrich (USA), Prolabo (France), El Nasr Pharmaceutical and Chemical Industries (Egypt) and Merck (Germany).

Glibenclamide was suspended in 2% Tween 80 and administered in a dose of 6mg/kg/po (Erejuwa *et al.*, 2011). Tannic acid was dissolved in distilled water and administered in a dose of 1g/kg/po (Nakamura *et al.*, 2001). Melatonin was suspended in 2% Tween 80 and administered in a dose of 10mg/kg/po (Paulis *et al.*, 2010). Treatments were freshly prepared shortly before administration to animals.

Induction of diabetes mellitus

Experimental diabetes was induced in 18 h fasted rats by single intraperitoneal injection of STZ in a dose of 50 mg/kg (Hounsom *et al.*, 1998). STZ was freshly prepared in cold 0.1 M citrate buffer (pH 4.5) (Becker *et al.*, 1996). Diabetes was confirmed at the third day of STZ injection by the presence of glucosuria using gluckotest strips.

Experimental design

After the acclimatization period animals were randomly divided into five groups (n= 6) placed in individual cages and classified as follows:

Group I (Normal control group). This group was injected with citrate buffer 2 ml/kg and received 2% tween 80. Group II (diabetic control group) received single dose of STZ. Group III, IV and V received single dose of STZ (diabetic rats) and four days later treated with glibenclamide, tannic acid and melatonin respectively for 14 days.

Blood collection and serum preparation

At the end of the treatment period, blood samples were collected from the retro-orbital venous plexus using heparinized microhematocrit capillary tubes according to the technique described by Cocchetto and Bjornsson, (1983). Blood samples were collected in centrifuge tubes containing traces of sodium fluoride to prevent glycolysis as described by Chan *et al.*, (1989). Blood samples were allowed to clot at room temperature, and then centrifuged at 3000 r.p.m. for 20 minutes to separate the serum for the determination of serum glucose, insulin, and lipid peroxide levels. Sufficient amount of blood samples was collected in heparinized tubes containing 50µl heparin sodium (5000 IU/ml) for the determination of urea, creatinine, cholesterol, triglycerides, reduced glutathione (GSH) and superoxidedismutase (SOD) levels. After collection of blood samples, rats were sacrificed and their livers were rapidly isolated and placed in cooling mixture of ice and salt.

Determination of serum glucose and insulin levels

Serum glucose level was determined using glucose diagnostic kit according to manufacturer's instructions based on the principle described by Trinder (1969). Insulin in serum samples was estimated using radioimmunoassay diagnostic kit according to the method of Mullner *et al.*, (1991).

Determination of β -cell function

β -cell function was estimated using HOMA (Matthews *et al.*, 1985), which is a computer-solved model of insulin-glucose interaction from which one can estimate the β -cell function from blood glucose and insulin level.

Determination of liver glycogen content

Liver glycogen content was estimated according to the method described by Kemp and Van Heijningen (1954).

Determination of plasma creatinine and urea levels

Plasma creatinine and urea levels were determined using reagent kits and following the method described by Murray *et al.*, (1984) and Fawcett and Scott, (1960) respectively.

Determination of plasma cholesterol and triglycerides levels

Plasma cholesterol and triglycerides levels were estimated according to the method described by Meiattini *et al.*, (1978) and Buccolo and David (1973) respectively following the attached manuals of the diagnostic kits (spinreact. Spain).

Determination of oxidative stress biomarkers

Blood malondialdehyde (MDA), SOD and GSH levels were estimated according to the methods described previously (Uchiyama and Mihara, 1978, Marklund and Marklund, 1974, Beutler *et al.*, 1963).

STATISTICAL ANALYSIS

Data were expressed as means \pm S.E.M. Statistical analysis was performed using statistical package (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY). One-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test was used for comparison of means of different groups. The level of statistical significance was set at $p < 0.05$.

RESULTS

Effects of tannic acid and melatonin on serum glucose and insulin levels, β -cell function and liver glycogen content

Streptozotocin showed significant increase in serum glucose level and significant reduction in serum insulin, β -cell function and liver glycogen content as compared to normal control values. Glibenclamide significantly decreased serum glucose level and increased serum insulin, β -cell function and liver glycogen content of the diabetic control value. TA and melatonin significantly lowered serum glucose level, and significantly elevated serum insulin level and liver glycogen content of the diabetic control values. In addition TA and melatonin significantly improved β -cell function as compared to diabetic control and glibenclamide treated groups values (table 1).

Effects of tannic acid and melatonin on kidney functions tests and lipid profile

As shown in table (2) streptozotocin significantly elevated plasma creatinine, urea, cholesterol and triglycerides levels as compared to normal control values. Glibenclamide, significantly decreased plasma creatinine, urea, cholesterol and triglycerides levels as compared to diabetic control values. TA significantly reduced plasma creatinine, cholesterol and triglycerides levels as compared to diabetic control values, while treatment with melatonin only showed significant reduction in creatinine and cholesterol levels as compared to diabetic control values.

Effects of tannic acid and melatonin on oxidative stress biomarkers

Streptozotocin significantly increased serum MDA level and significantly decreased blood GSH and SOD levels as compared to normal control values. Glibenclamide, TA and melatonin significantly reduced serum MDA level and significantly reduced blood GSH and SOD levels as compared to the diabetic control group (table 3).

DISCUSSION

Results of the current investigation showed that STZ produced significant rise in serum glucose level with

significant reduction in serum insulin level and β -cell function in rats. STZ is a diabetogenic agent (Rakieta et al., 1963) that causes pancreatic β -cell toxicity through DNA alkylating activity via its methylnitrosourea moiety (LeDoux et al, 1986; Murata et al., 1999). The increase in glucose production may be due to activation of glucose 6-phosphatase enzyme and reduction in glucokinase activity (Mason et al., 2000). The decreased insulin secretion could be attributed to the resultant hyperglycemia which produces abnormalities in insulin action and secretion (Evans et al., 2003).

Data of the present investigation showed that treatment of diabetic rats with TA showed significant decrease of serum glucose, increase in insulin secretion and improvement in β -cell function of diabetic rats. Babby et al., (2014) reported that TA significantly reduced blood glucose level as well as increased insulin secretion in treated diabetic rats. Polyphenols including phenolic acids inhibit carbohydrate breakdown and glucose absorption in the intestine, induce insulin release from pancreatic β -cells, reduce hepatic glucose liberation and stimulate insulin receptors (Hanhineva et al., 2010).

According to the results of the current investigation, treatment of diabetic rats with melatonin showed significant improvement in glucose concentration, elevation of insulin level and amelioration of β -cell function. Amin et al., (2015) reported that melatonin ameliorated hyperglycemia and hypoinsulinemia caused by diabetes. Melatonin controls blood glucose level by binding to hepatocytes (Poon et al., 2001; Lardone et al., 2014) and by regulating glucose uptake in adipocytes through modulation of glucose transporters (GLUT) expression (Lima et al., 1998; Lardone et al., 2014). Furthermore previous researches revealed that melatonin treatment induces pancreatic β -cells regeneration which leads to reduction in serum glucose level in diabetic rats (Kanter et al., 2006; Cardinali et al., 2011).

Data of the present study reported that STZ significantly reduced liver glycogen content in rats. This reduction may be due to the decrease in enzymatic activity of glucokinase, hexokinase and phosphofructokinase in diabetic rats (Murphy and Anderson, 1974). TA showed significant elevation of liver glycogen content. Similar result was shown by Babby et al., (2014) who reported that TA significantly increased liver glycogen content in STZ treated rats. A possible explanation for this improvement is that TA increases insulin secretion (Babby et al., 2014) and insulin increases intracellular glycogen deposition through activation of glycogen synthase and inhibition of glycogen phosphorylase (Sharma and Garg 2012).

Similarly, melatonin showed significant elevation of liver glycogen content. Melatonin administration in diabetic

Table 1: Effects of tannic acid and melatonin on serum glucose and insulin levels, β -cell function and liver glycogen content.

Treatment groups	Serum glucose (mg/dl)	Serum insulin (μ IU/ml)	B-cell function %	Liver glycogen (mg/g wet liver)
Normal control	109.16 \pm 7.56	16.30 \pm 1.58	7.34 \pm 0.54	23.98 \pm 0.64
Diabetic control	385.64 \pm 29.49*	3.00 \pm 0.15*	0.38 \pm 0.03*	10.9 \pm 0.99*
STZ + Glibenclamide	255.35 \pm 21.29 ^{*a}	18.63 \pm 0.58 ^a	3.23 \pm 0.24 ^{*a}	21.03 \pm 2.09 ^a
STZ + Tannic acid	254.27 \pm 17.69 ^{*a}	21.70 \pm 1.53 ^a	5.74 \pm 0.56 ^{*ab}	18.54 \pm 0.54 ^{*a}
STZ + Melatonin	241.85 \pm 8.73 ^{*a}	21.37 \pm 1.07 ^a	5.01 \pm 0.48 ^{*ab}	18.07 \pm 1.81 ^{*a}

Table 2: Effects of tannic acid and melatonin on kidney functions tests and lipid profile

Treatment groups	Plasma creatinine (mg/dl)	Plasma Urea (mg/dl)	Plasma cholesterol (mg/dl)	Plasma triglycerides (mg/dl)
Normal control	0.46 \pm 0.02	23.38 \pm 1.45	57.52 \pm 3.3	87.50 \pm 6.83
Diabetic control	0.73 \pm 0.06*	30.64 \pm 2.25*	91.01 \pm 7.48*	158.22 \pm 14.12*
STZ + Glibenclamide	0.40 \pm 0.03 ^a	16.54 \pm 1.41 ^{*a}	67.42 \pm 4.68 ^a	86.02 \pm 3.03 ^a
STZ + Tannic acid	0.41 \pm 0.02 ^a	24.53 \pm 1.81 ^b	60.16 \pm 2.09 ^a	88.37 \pm 5.95 ^a
STZ + Melatonin	0.47 \pm 0.02 ^a	24.57 \pm 0.62 ^b	55.75 \pm 2.07 ^a	132.39 \pm 11.13 ^{ab}

Table 3: Effects of tannic acid and melatonin on oxidative stress biomarkers

Treatment groups	Serum MDA (nmol/ml)	Blood SOD (μ g/ml)	Blood GSH (mg%)
Normal control	1.41 \pm 0.09	45.74 \pm 4.21	40.93 \pm 1.87
Diabetic control	2.80 \pm 0.22*	18.3 \pm 1.38*	25.07 \pm 0.83*
STZ + Glibenclamide	1.37 \pm 0.12 ^a	40.51 \pm 4.00 ^a	33.67 \pm 2.61 ^a
STZ + Tannic acid	1.63 \pm 0.12 ^a	41.96 \pm 2.25 ^a	35.6 \pm 2.09 ^a
STZ + Melatonin	1.61 \pm 0.15 ^a	41.27 \pm 3.18 ^a	33.2 \pm 1.34 ^a

*^a^b are significantly different from normal control, diabetic control and glibenclamide respectively at $p < 0.05$ using one way ANOVA followed by Tukey-kramer multiple comparisons test. Results were expressed as mean \pm S.E.M. for six rats per group.

animals elevates liver glycogen content in order to counteract the resulted hyperglycemia. This amelioration may be due to increased phosphorylation of subcellular signals at the level of protein kinase C (PKC), protein kinase B (PKB), and glycogen synthase kinase 3 β (Shieh *et al.*, 2009).

The present study revealed that, STZ significantly increased plasma creatinine and urea levels. STZ induced hyperglycemia may be nephrotoxic either by formation of glycosylated end products as a result of reaction of glucose with proteins or by increasing oxidative stress and stimulation of protein kinase C (PKC) that results in increased cytokines formation (Park and Han 2002; Friedman 1999; Ha and Kim 1999). In the present study TA and melatonin showed significant reduction in plasma creatinine in STZ-induced diabetic rats. TA effect may be due to inhibition of ROS formation, lipid peroxidation, and oxidative stress in kidney tissues (Akomolafe *et al.*, 2014). While Protective properties of melatonin could be attributed to regulation of mitochondrial homeostasis (Martin *et al.*, 2002) and reduction in the lipid peroxidation, which is considered as an initial incident in the kidney damage (Longoni *et al.*, 2002).

In the present investigation, STZ caused significant elevation of plasma cholesterol and triglycerides levels. Mirmohammadlu *et al.*, (2015) revealed that serum lipid irregularities may be due to disturbance of fatty acid metabolism. Moreover, low insulin level may increase lipolysis that elevates cholesterol and triglyceride levels (Kumar *et al.*, 2012). TA significantly reduced plasma cholesterol and triglycerides while melatonin reduced cholesterol without any effect on plasma triglycerides. Mustafa and Abd Elrahman (2015) reported that tannins reduce lipid absorption from the intestine, reduce cholesterol production and decrease cellular uptake of oxidized LDL. Melatonin inhibits cholesterol absorption (Hussain 2007), inhibits cholesterol biosynthesis and interacts with LDL-cholesterol receptors (Cardinali *et al.*, 2011).

Results of the current investigation showed that STZ significantly increased serum MDA level and significantly decreased blood GSH and SOD level. This effect may be attributed to the hyperglycemia as glucose may undergo auto-oxidation to produce a highly reactive radical. This increases advanced glycation end-product (AGE) production and catalyzes the transformation of

molecular oxygen to O₂⁻ that increases reactive oxygen species ROS (Stephens *et al.*, 2009). TA and melatonin decreased serum MDA and increased blood GSH and SOD levels. This antioxidant effect may be due to induction of antioxidant enzymes production by the influence of TA (Gülçin *et al.*, 2010a; Baskar *et al.*, 2012) and melatonin (Guney *et al.*, 2011).

CONCLUSIONS

According to the findings of the present research, it was revealed that tannic acid as well as melatonin could improve hyperglycemia, kidney functions, lipid profile and oxidative stressed associated STZ-induced DM in rats. Further researches are warranted to validate these conclusions.

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