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Modulatory effect of berberine on adipose tissue PPARγ, adipocytokines and oxidative stress in high fat diet/ streptozotocin-induced diabetic rats

Ayman M. Mahmoud[1*], Marwa M. Abdel-Rahman[2], Nermin A. Bastawy[2], Hassan M. Eissa[2]

[1]Physiology Division, Zoology Department, Faculty of Science, Beni-Suef University, Egypt.
[2]Physiology Department, Faculty of Medicine, Cairo University, Egypt.

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ABSTRACT

The current study was designed to investigate the anti-hyperglycemic and antioxidant effects of berberine (BBR) in high fat diet/streptozotocin (HFD/STZ)-induced type 2 diabetic rats, focusing on the role of adipose tissue peroxisome proliferator activated receptor gamma (PPARγ), resistin and inflammatory cytokines. Type 2 diabetes was induced by feeding rats with HFD for 4 weeks followed by a single intraperitoneal injection of 35 mg/kg body weight STZ. Diabetic rats were supplemented with 50 and 100 mg/kg BBR orally for 4 weeks. HFD/STZ-induced diabetic rats showed a significant increase in serum glucose and fructoseamine, and significant decrease in body weight and serum insulin. Serum pro-inflammatory cytokines were significantly increased in serum of the diabetic rats. BBR significantly ameliorated body weight, and serum glucose, insulin and pro-inflammatory cytokines. In addition, diabetic rats exhibited a significant increase in liver lipid peroxidation and nitric oxide levels, and declined antioxidant defenses, an effect that was reversed following treatment with BBR. Adipose tissue PPARγ mRNA was significantly down-regulated while resistin mRNA was markedly up-regulated in diabetic rats. BBR treatment significantly ameliorated both PPARγ and resistin mRNA expression. In conclusion, BBR attenuates hyperglycemia and its associated oxidative stress and inflammation, possibly through potentiation of the antioxidant defenses and up-regulation of PPARγ expression.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia resulting from either defect in insulin secretion or insulin action (American Diabetes Association, 2010; Mahmoud *et al*., 2012). Type2 DM is the most prevalent form of the disease and accounts for more than 90% of all patients (Tripathi and Srivastava, 2006). In 2015, the International Diabetes Federation (IDF) anticipated that the number of DM patients was 415 million which is expected to increase to 642 million by 2040 (IDF, 2015). If ineffectively controlled, chronic hyperglycemia in type 2 DM can cause numerous complications in different body organs (IDF, 2015). Type 2 diabetic patients are characterized by insulin resistance and impaired insulin secretion (Sharma *et al*., 2011). The main mechanisms provoke insulin resistance in T2DM are glucotoxicity, lipotoxicity, oxidative stress, inflammation, endoplasmic reticulum stress and amyloid deposition in the pancreas (Weir and Bonner-Weir, 2004).

Adipose tissue plays a central role in insulin sensitivity and energy expenditure (Attie and Scherer, 2009), and dysfunction in adipocytes is associated with insulin resistance and type 2 DM (Blüher, 2009). Adipocytes secrete diverse adipocytokines such as adiponectin, resistin and inflammatory cytokines. Increased levels of tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, IL-1β and resistin as well as reduced adiponectin can exacerbate insulin resistance (Maedler *et al*., 2002; Blüher, 2009).

* *Corresponding Author*
Ayman Mahmoud, Physiology Division, Zoology Department, Faculty of Science, Beni-Suef University, Egypt.
Email: ayman.mahmoud @ science.bsu.edu.eg

The current treatment approaches for type 2 DM include diet, exercise and several pharmacological agents. The latter are associated with adverse effects such as weight gain, hypoglycemia and edema (Geirch, 2003; Kahn, 2003). Berberine (BBR) is an isoquinoline alkaloid originally isolated from *Coptis chinensis* (Huanglian) (Leng *et al*., 2004). BBR has been reported to exhibit multiple pharmacological activitiessuch as anti-inflammatory, anticancer, antimicrobial, hepatoprotective and antioxidant properties (Cho *et al*., 2005; Yu *et al*., 2005; Choi *et al*., 2006; Germoush and Mahmoud, 2014; Mahmoud *et al*., 2014). Recent studies have demonstrated that BBR has remarkable beneficial effects as an anti-hyperglycemic and it reduces weight gain in diabetic patients (Yin *et al*., 2008; Zhao *et al*., 2008). However, the direct anti-diabetic mechanism of BBR is not completely understood. We hypothesized that modulation of adipose tissue peroxisome proliferator activated receptor gamma (PPARγ), a master regulator of glucose and lipid metabolism, and adipocytokines partially mediates BBR's anti-diabetic efficacy. We have recently reported that BBR activates PPARγ in the liver of drug-intoxicated rats (Mahmoud *et al*., 2014). Therefore, we have attempted to investigate the modulatory role of BBR on PPARγ and resistin expression levels, oxidative stress and inflammation in high fat diet (HFD)/streptozotocin (STZ)-induced type 2 diabetic rats.

MATERIALS & METHODS

Chemicals

Berberine chloride, streptozotocin (STZ), pyrogallol, thiobarbituric acid (TBA), glutathione (GSH) and 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) were purchased from Sigma Company (USA). All other chemicals used were commercially available and of analytical grade.

Experimental animals

Male albino rats (*Rattus norvegicus*) weighting about 140-160 g were used as experimental animals in the present investigation. They were obtained from the animal house of Faculty of Medicine, Cairo University, Giza, Egypt. The animals were kept under observation for about 10 days before the onset of the experiment for acclimatization. The chosen animals were housed in plastic good aerated cages at normal atmospheric temperature (24 ± 2°C) as well as normal 12 hours light/dark cycle. They were given access of water and supplied daily with standard diet of known composition. All animal procedures were undertaken with the approval of Institutional Animal Ethics Committee of the Faculty of Medicine, Cairo University.

Development of high fat diet (HFD)-fed low dose STZ-treated type 2 diabetic rats

The rats received HFD (58% fat, 25% protein and 17% carbohydrate, as a percentage of total kcal) *ad libitum*. The composition and preparation of HFD were described by Reed *et al*.(2000). After 4 weeks of dietary manipulation, rats were injected intraperitoneally (i.p.) with 35 mg/kg STZ dissolved in cold citrate buffer (pH 4.5) in a dose volume of 1 ml/kg (Mahmoud *et al*., 2012). Seven days after STZ injection, rats were screened for blood glucose levels. Rats having serum glucose ≥ 200 mg/dl, after 2 h of glucose (3 g/kg) intake were considered diabetic.

Experimental design:

Twenty-four rats were allocated into 4 groups, each consisting of six (N = 6) animals and were subjected to the following treatments:

Group 1 (Control): normal rats received normal diet and the vehicle 1% carboxymethylcellulose (CMC) by gastric intubation daily for 4 weeks and served as control rats.

Group 2 (Diabetic): diabetic rats received 1% CMC by gastric intubation daily for 4 weeks.

Group 3 (Diabetic + 50 mg BBR): diabetic rats received 50 mg/kg berberine (Germoush and Mahmoud, 2014) dissolved in 1% CMC by gastric intubation daily for 4 weeks.

Group 4 (Diabetic + 100 mg BBR): diabetic rats received 100 mg/kg berberine (Mojarad and Roghani, 2014) dissolved in 1% CMC by gastric intubation daily for 4 weeks.

The rats were allowed to continue to feed on their respective diets until the end of the study. By the end of the experiment, overnight fasted animals were sacrificed and blood samples were collected, left to coagulate and centrifuged at 3000 rpm for 15 min to separate serum. Liver samples were immediately excised and perfused with ice-cold saline. Frozen samples (10% w/v) were homogenized in chilled saline and the homogenates were centrifuged at 3000 rpm for 10 min. The clear homogenates were collected and used for subsequent assays. Visceral adipose tissue samples were collected and kept at -80°C for RNA isolation.

Biochemical study

Oral glucose tolerance test (OGTT)

OGTT was performed using blood samples obtained from lateral tail vein of rats deprived of food overnight. Following the administration of glucose solution (3 g/kg), successive blood samples were then taken at 30, 60, 90 and 120 min. Blood samples were left to coagulate, centrifuged, and clear sera were obtained for determination of glucose concentration according to the method of Trinder (1969) using reagent kit purchased from Spinreact (Spain).

Determination of serum insulin and pro-inflammatory cytokines

Serum levels of insulin, TNF-α, IL-6 and IL-1β were determined using specific ELISA kits (R&D systems, USA) following the manufacturer's instructions. The concentrations of assayed parameters were measured specrophotometrically at 450 nm. Standard curves were constructed by using standard proteins and concentrations of the unknown samples were determined from the standard plots.

Determination of Homeostasis Model of Insulin Resistance (HOMA-IR)

The insulin resistance was evaluated by homeostasis model assessment estimate of insulin resistance (HOMA-IR; Haffner, 2000) as follows:

$$\text{HOMA-IR} = \frac{\text{Fasting insulin (}\mu\text{U/ml) x Fasting blood glucose (mmol/L)}}{22.5}$$

Assay of lipid peroxidation and antioxidant defenses:

Lipid peroxidation levels in liver homogenates were assayed by measurement of malondialdehyde (MDA) formation according to the method of Preuss *et al*. (1998). Liver NO level was assayed as nitrite using a reagent kit purchased from Biodiagnostics (Egypt), according to the method of Montgomery and Dymock (1961). Reduced glutathione (GSH) content and activity of the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were measured according to the methods of Beutler *et al*. (1963), Marklund and Marklund (1974), Cohen *et al*. (1970) and Matkovics *et al*. (1998), respectively.

RNA isolation and reverse transcriptase polymerase chain reaction (RT-PCR)

Gene expression analysis was performed according to the method of Mahmoud (2013). Total RNA was isolated from adipose tissue samples using total RNA isolation kit (Fermentas, USA). RNA was purified and spectrophotometrically quantified. cDNA was synthesized from 2 µg RNA by using a reverse transcription kit (Fermentas, USA). The cDNA produced was amplified by Green master mix (Fermentas, USA) using the set of primers listed in Table 1. The reaction tubes were placed on a double heated led thermal cycler, and the reaction series included initial denaturation at 95°C for 2min followed by 35 cycles. PCR products were separated using agarose gel electrophoresis on a 1.5% gel. cDNA bands were observed using UV transilluminator. Gel images were analyzed using the freewareImageJ (NIH, USA), and values were normalized to the quantity of β-actin, and presented as % mRNA relative to control.

Table 1: Primer pairs used for PCR.

Gene	Primer (5'-3')
PPARγ	F: CCTGAAGCTCCAAGAATACC R: GATGCTTTATCCCCACAGAC
RETN (Resistin)	F: GCTCAGTTCTCAATCAACCGTCC R: CTGAGCTCTCTGCCACGTACT
β-ACTIN	F: AAGTCCCTCACCCTCCCAAAAG R: AAGCAATGCTGTCACCTTCCC

Statistical analysis

Data were analyzed using GraphPad Prism 5 software and all statistical comparisons were made by means of the one-way ANOVA test followed by Tukey's test *post hoc* analysis. Results were articulated as mean ± standard error (SEM) and a *P* value <0.05 was considered significant.

RESULTS

BBR represses body weight loss and hyperglycemia in HFD/STZ diabetic rats

Data concerning body weight changes of control, diabetic and diabetic rats treated with 50 and 100 mg/kg BBR are represented in Figure 1A. At start of the experiment, all experimental groups showed a non-significant ($P>0.05$) difference in their body weight. After 4 weeks of high fat diet manipulation, all fed rats exhibited significant ($P<0.001$) increase in body weight when compared with the normal diet-fed rats. At the end of the experiment (8^{th}Week), diabetic rats showed a significantly ($P<0.001$) decreased body weight as compared to the control rats. On the other hand, BBR significantly prevented diabetes-induced body weight loss at both the 50 mg ($P<0.01$) and 100 mg/kg doses.

OGTT of HFD/STZ-induced diabetic rats showed significantly ($P<0.001$) elevated fasting glucose levels and at 30, 60, 90 and 120 min after oral glucose loading when compared with the normal control rats, as depicted in Figure 1B. Oral supplementation of either 50 or 100 mg/kg BBR to HFD/STZ-induced diabetic rats significantly ($P<0.001$) alle*via*ted the blood glucose levels at all points of the OGTT. The OGTT area under curve (AUC) analysis of the glucose response in control and diabetic rats are represented in Figure 1C. HFD/STZ-induced diabetic rats exhibited a significant ($P<0.001$) increase in AUCs when compared with the normal control rats. Interestingly, treatment of the diabetic rats with either dose of BBR potentially ($P<0.001$) decreased OGTT AUC when compared with the diabetic control rats. The higher BBR dose seemed to be more effective.

Comparing the HFD/STZ-induced diabetic rats with the control, there was a significant ($P<0.001$) elevation of serum fructosamine concentration. Treatment of the HFD/STZ-induced diabetic rats with 50 mg/kg BBR significantly ($P<0.001$) ameliorated serum fructosamine concentration when compared with the diabetic group of rats. Similarly, oral supplementation of 100 mg/kg BBR markedly ($P<0.001$) decreased serum fructosamine concentration (Fig. 1D).

BBR ameliorates circulating insulin levels and insulin sensitivity in HFD/STZ diabetic rats

HFD/STZ-induced diabetic rats showed a significant ($P<0.001$) decrease in serum insulin levels when compared with the control ratsas depicted in Figure 2A. On the other hand, treatment of the HFD/STZ-induced diabetic rats with 50 mg/kg BBR significantly ($P<0.001$) ameliorated serum insulin levels when compared with the diabetic control rats. Treatment with the 100 mg/kg BBR dose markedly increased serum insulin levels as compared to diabetic rats ($P<0.001$) and diabetic rats treated with the lower BBR dose ($P<0.01$). Similarly, diabetic rats exhibited a significant ($P<0.001$) increase in HOMA-IR when compared with the normal control rats. Oral administration of BBR to HFD/STZ-induced diabetic rats significantly decreased HOMA-IR index at either 50 mg ($P<0.05$) or 100 mg/kg ($P<0.01$) dose (Fig. 2B).

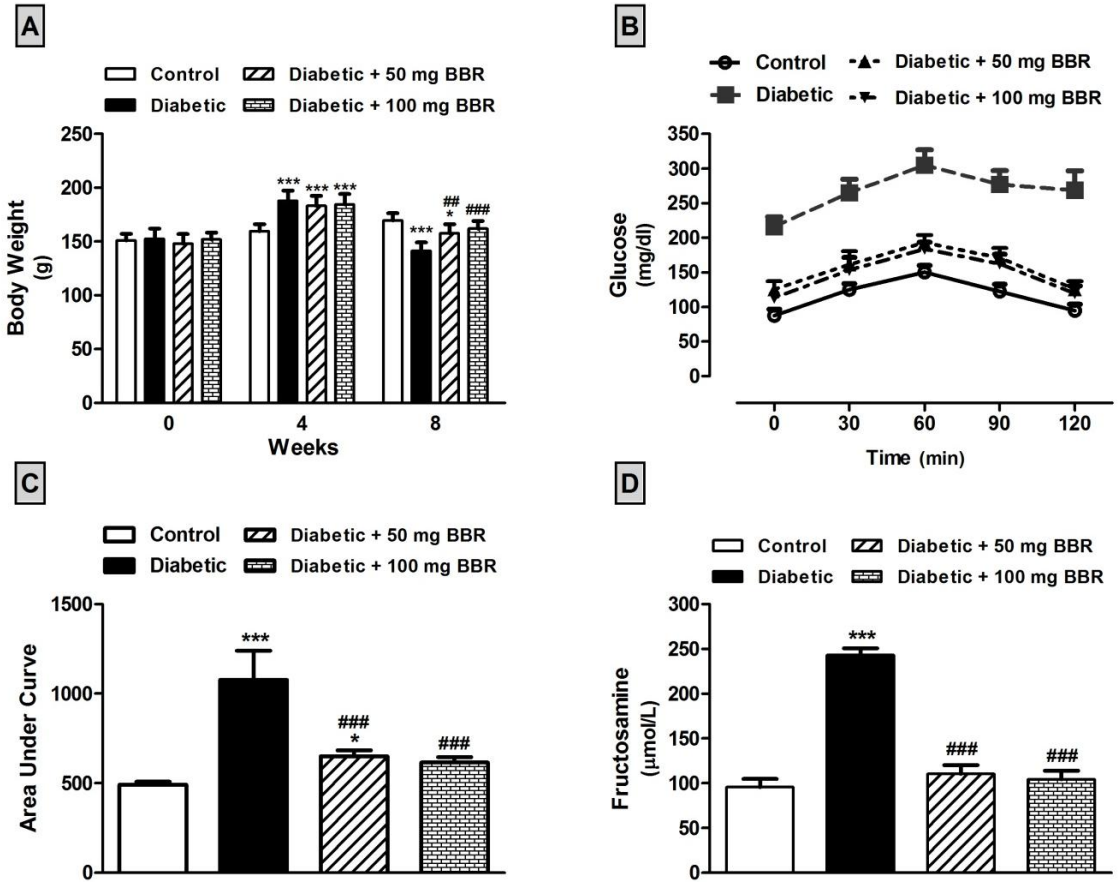

Fig1: Effect of BBR on (A) body weight, (B & C) glucose tolerance and (D) serum fructosamine levels in diabetic rats. Results are mean ± SEM (N = 6). **P*<0.05 and ****P*<0.001 vs Control, and ###*P*<0.001 vs Diabetic group.

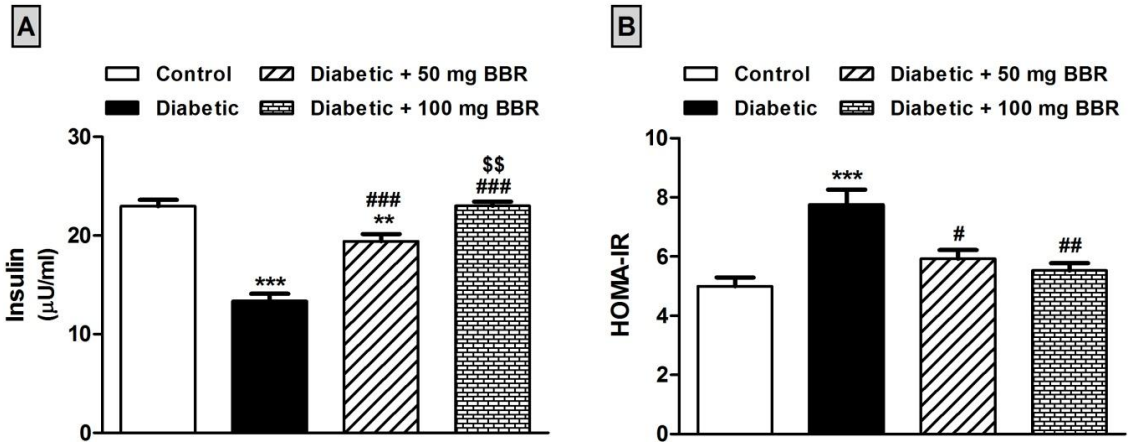

Fig. 2: Effect of BBR on (A) serum insulin and (B) HOMA-IR in diabetic rats. Results are mean ± SEM (N = 6). ***P*<0.01 and ****P*<0.001 vs Control, and #*P*<0.05, ##*P*<0.01 and ###*P*<0.001 vs Diabetic group.

BBR decreases pro-inflammatory cytokines production in HFD/STZ diabetic rats

Data describing the effect of BBR on circulating pro-inflammatory cytokines in diabetic rats are summarized in Table 2. HFD/STZ administration to rats produced a significant (*P*<0.001) increase in serum TNF-α levels when compared with the normal control rats. Oral supplementation of 50 mg/kg BBR markedly (*P*<0.001) decreased the elevated serum TNF-α when compared with the diabetic control rats. Similarly, treatment of HFD/STZ-induced diabetic rats with 100 mg/kg BBR significantly (*P*<0.001) ameliorated serum TNF-α level.

Serum IL-6 showed a significant (*P*<0.001) increase following HFD/STZ administration. Treatment of the HFD/STZ-administered rats with 50 mg/kg BBR significantly (*P*<0.001) improved serum IL-6 levels when compared with diabetic control rats. The higher BBR dose supplementation ameliorated serum IL-

6 levels (P<0.001) compared to HFD/STZ-administered rats. In addition, rats administered HFD/STZ showed a significant (P<0.001) increase in serum IL-1β levels and both tested doses of BBR produced a significant (P<0.001) effect compared to the diabetic group of rats.

Table 2: Effect of BBR on serum pro-inflammatory cytokines in diabetic rats.

	TNF-α (pg/ml)	IL-6 (pg/ml)	IL-1β (pg/ml)
Control	19.25 ± 1.38	33.85 ± 1.84	29.44 ± 2.96
Diabetic	76.79 ± 4.66***	81.13 ± 3.75***	100.35 ± 4.39***
Diabetic + 50 mg BBR	33.62 ± 3.13$^{*###}$	43.60 ± 2.79$^{###}$	48.12 ± 2.24$^{**###}$
Diabetic + 100 mg BBR	29.88 ± 1.69$^{###}$	36.47 ± 2.72$^{###}$	33.99 ± 2.78$^{###\$}$

Data are Mean ± SEM.
*P<0.05, **P<0.01 and ***P<0.001 versus Control.
###P<0.001 versus Diabetic.
$$P$<0.05 versus Diabetic + 50 mg BBR.

BBR attenuates hyperglycemia-induced oxidative stress in HFD/STZ diabetic rats

Lipid peroxidation, estimated as malondialdehyde (MDA), showed a significant (P<0.001) increase in the liver of HFD/STZ-induced diabetic rats when compared with their respective control group (Fig. 3A). Oral supplementation of the diabetic rats with either 50 or 100 mg/kg BBR markedly (P<0.001) decreased liver MDA content.

There was a non-significant difference (P>0.05) between the effects of both BBR doses on liver MDA. Similarly, the results revealed a significant elevation in NO levels (P<0.001) in the liver of HFD/STZ-induced diabetic group when compared with the normal control rats as depicted in Figure 3B. Oral administration of both doses of BBR significantly (P<0.001) decreased NO levels in the liver of HFD/STZ-induced diabetic rats.

Liver GSH content in the HFD/STZ-induced diabetic rats showed a significant (P<0.001) decrease when compared to the non-induced rats. Oral administration of 50 mg (P<0.01) as well as the 100 mg/kg (P<0.001) BBR doses markedly alle*via*ted liver GSH levels when compared with diabetic control rats; the high dose of BBR produced more potent effect as illustrated in Figure 4A.

Similar to GSH, SOD activity in liver of the HFD/STZ-induced diabetic rats was significantly (P<0.001) reduced when compared with untreated control group (Fig. 4B). Oral administration of either dose of BBR produced a significant elevation of SOD activity. Liver CAT (Fig. 4C) and GPx (Fig. 4D) followed the same pattern where their activity was significantly (P<0.001) declined in HFD/STZ-induced diabetic rats when compared with the normal control group. Oral supplementation of the low and high doses of BBR potentially Alleviated the activity of CAT and GPx in the liver of HFD/STZ-induced diabetic rats.

BBR modulates adipose tissue PPARγ and resistin gene expression in HFD/STZ diabetic rats

Gene expression analysis revealed a significant (P<0.001) down-regulation of PPARγ mRNA expression in adipose tissue of the HFD/STZ-induced diabetic rats when compared with the control group (Figure 5A). On the other hand, supplementation of the diabetic rats with either dose of BBR produced a significant (P<0.001) up-regulation of adipose tissue PPARγ mRNA.

Resistin expression showed a significant (P<0.001) up-regulation in adipose tissue of the HFD/STZ-induced diabetic rats when compared with their respective control group as represented in Figure 5B. Supplementation of either 50 or 100 mg/kg BBR dose significantly (P<0.001) up-regulated the expression of adipose tissue resistin mRNA.

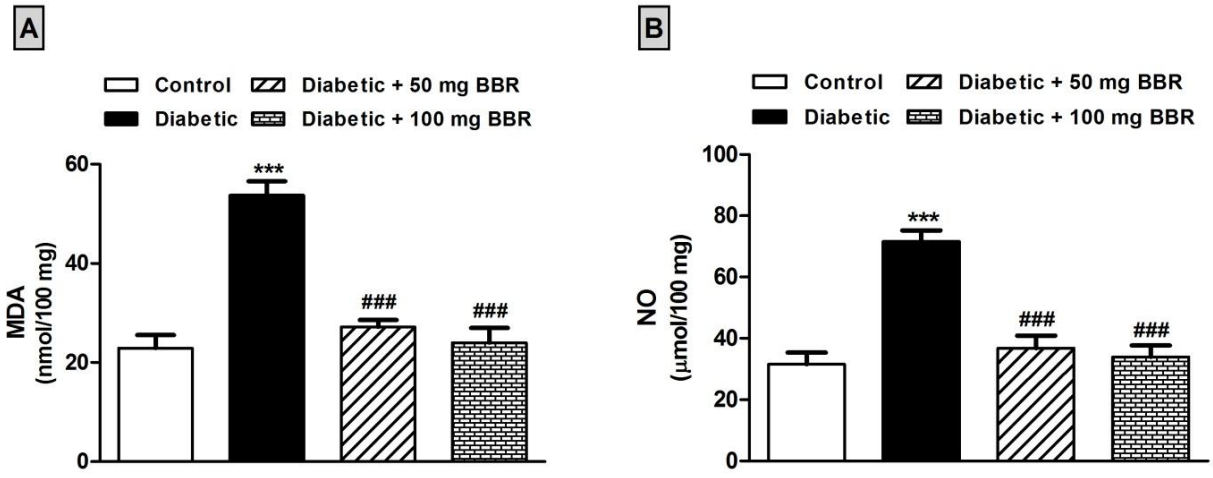

Fig. 3: Effect of BBR on liver (A) lipid peroxidation and (B) NO levels in diabetic rats. Results are mean ± SEM (N = 6).
***P<0.001 vs Control, and ###P<0.001 vs Diabetic group.

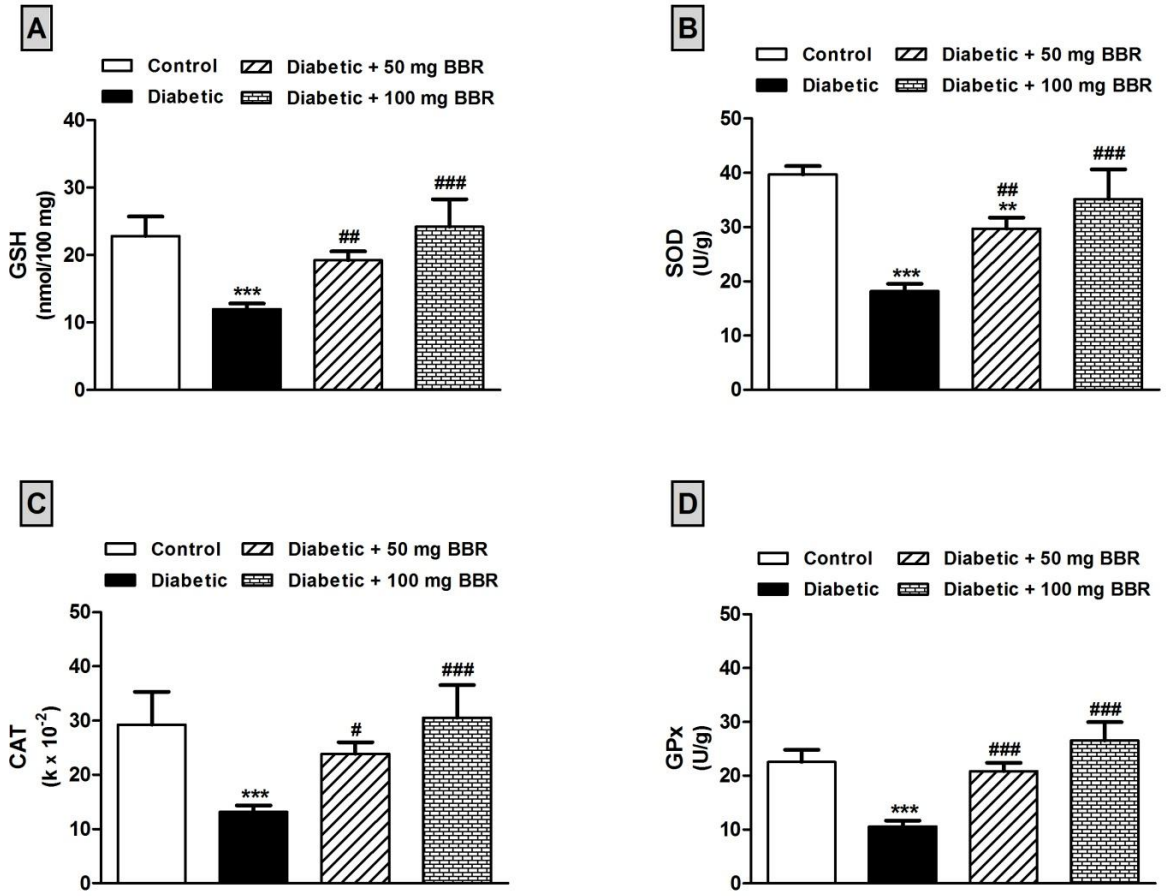

Fig. 4: Effect of BBR on liver (A) GSH, (B) SOD, (C) CAT and (D) GPx in diabetic rats. Results are mean ± SEM (N = 6). ***P*<0.01 and ****P*<0.001 vs Control, and #*P*<0.05, ##*P*<0.01 and ###*P*<0.001 vs Diabetic group.

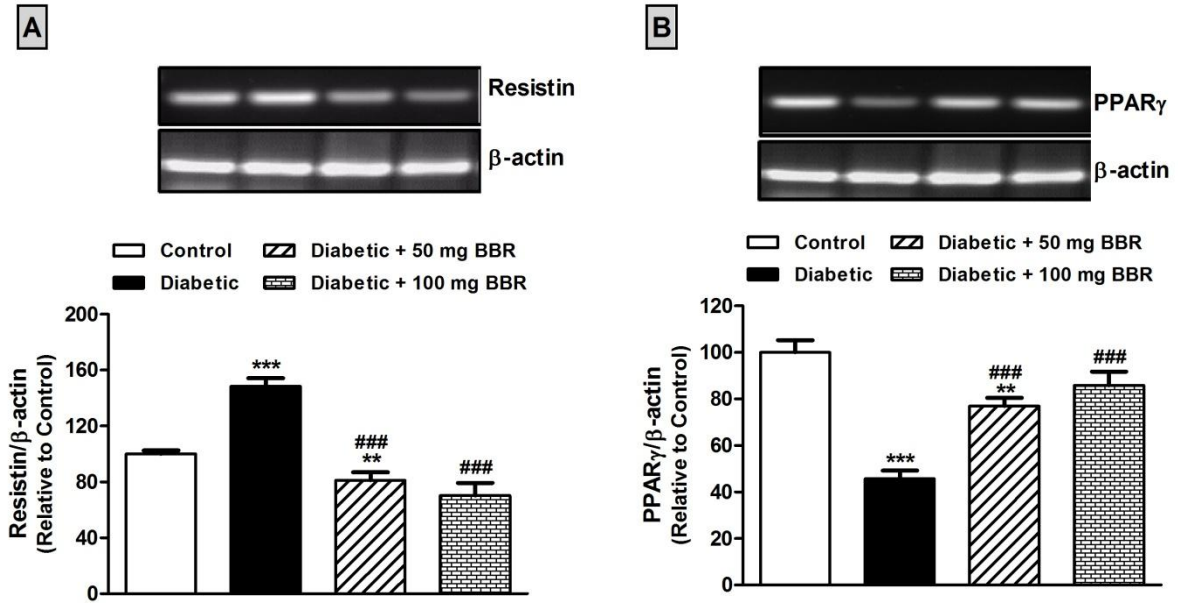

Fig. 5: Effect of BBR on adipose tissue (A) Resistin and (B) PPARγ mRNA expressionin diabetic rats. Results are mean ± SEM (N = 6). ***P*<0.01 and ****P*<0.001 vs Control, and ###*P*<0.001 vs Diabetic group.

DISCUSSION

The present data indicated a marked increase in serum glucose levels in HFD/STZ-induced diabetic rats. These results run parallel with the studies of Mahmoud *et al*. (2012, 2015) who demonstrated significant hyperglycemia in HFD/STZ diabetic rats. Administration of STZ induced rapid destruction of pancreatic β-cells in rats, which led to impaired glucose stimulated insulin release and insulin resistance, both of which are marked features of type 2DM (Farswan *et al*., 2009). Elevation of blood glucose may be attributed to the reduced entry of glucose to muscle, adipocytes and peripheral tissues (Beck-Nielsen, 2002), increased glycogen breakdown (Gold, 1970) and increased gluconeogenesis and hepatic glucose production (Raju *et al*., 2001). Hyperglycemia in the HFD/STZ-induced diabetic rats was confirmed by the significant increase in serum fructosamine levels. Fructosamine detects deterioration or improvement of blood glucose over a period of several days and is thus a putative measure of glycosylated proteins and screening test for diabetes mellitus (Donnelly, 1996; Ahmed *et al*., 2010). In addition, HFD/STZ-induced diabetic rats in the current study exhibited a significant decrease in circulating fasting insulin levels and increased HOMA-IR value, indicating insulin resistance state as we previously reported (Mahmoud *et al*., 2012, 2015).

Treatment of the HFD/STZ diabetic rats with either dose of BBR caused potential amelioration of glucose tolerance, fructosamine, body weight, serum insulin and insulin sensitivity. The glucose lowering effect of BBR in the present investigation is in agreement with previous studies showed that BBR decreases blood glucose in both dietary and genetic rodent models of type 2 diabetes (Leng *et al*., 2004; Lee *et al*., 2006; Yin *et al*., 2008). The anti-hyperglycemic properties of BBR could be explained through its ability to stimulate glycolysis *via* increasing glucokinase activity, suppressing hepatic gluconeogenesis and increasing insulin secretion (Hu *et al*., 2010; Chang *et al*., 2013). BBR induced activation of 5'-adenosine monophosphate kinase (AMPK) appears to be at the center of these anti-hyperglycemic effects. In this context, Chang *et al*. (2013) reported that BBR activates AMPK leading to increased glucose transporter-4 (GLUT4) translocation and improved insulin sensitivity in insulin resistant H9c2 cardiomyocytes. In addition, Zhang *et al*. (2012) demonstrated that BBR improved glucose metabolism in diabetic rats by inhibition of gluconeogenesis. In insulin resistant states, BBR inhibited fork head transcription factor O1 (FOXO-1), hepatic nuclear factor 4, and PPARγ coactivator-1α, resulted in suppressed expression of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, two rate-limiting enzymes in gluconeogenesis (Kim *et al*., 2009). The declined serum fructoseamine in BBR-treated diabetic rats could be a direct result of improved glycemic control. Also, Elgawish *et al*. (1996) and Mahmoud *et al*. (2012) reported that agents with antioxidant or free radical scavenging power may inhibit oxidative reactions associated with protein glycation. Therefore, BBR with its free radical scavenging capability effectively reduced the formation of glycated proteins. In the state of insulin resistance, BBR has been demonstrated to increase the expression of protein kinase B (Akt) signaling pathway, up-regulate insulin receptor substrate-2 (IRS-2) mRNA expression and improve insulin sensitivity in alloxan-induced diabetic C57BL/6 mice and nonalcoholic fatty liver disease in rats (Xie *et al*., 2011; Xing *et al*., 2011). It can be hypothesized that the possible mechanism of BBR's anti-hyperglycemic action may be through potentiating the pancreatic secretion of insulin from islet β-cells as well as alleviating insulin sensitivity. Previous data reported that BBR decreased hyperglycemia *via* islet protection in a model of type 1 diabetic mice (Chueh and Lin, 2011, 2012). Therefore, it could be noticed that BBR is able to increase insulin secretion in type 1 diabetes or type 2 diabetes characterized by poor β-cell function. Zhou *et al*. (2009) related this finding to BBR's antioxidant and anti-lipid peroxidation properties.

Diabetic rats exhibited marked increase in liver lipid peroxidation (LPO) and NO. Studies have demonstrated that reactive oxygen species (ROS) generation, associated with insulin resistance, resulted in damage of islet β-cells in models of type 2DM (Evans *et al*., 2003; Mahmoud *et al*., 2012). Oxidative stress contributed to the development of chronic diabetes complications including retinopathy, nephropathy and neuropathy (Rosen *et al*., 2001). ROS could react with polyunsaturated fatty acids which lead to LPO (Karthikesan *et al*., 2010), decreased membrane fluidity and changes in the activity of membrane-bound enzymes and receptors (Arulselvan and Subramanian, 2007). Moreover, hyperglycemia impairs the prooxidant/antioxidant balance and reduces antioxidant levels (Aragno *et al*., 2004). In our study, the activities of hepatic SOD, CAT and GPx decreased in diabetes group as reported earlier (Mahmoud *et al*., 2012) which could be due to inactivation caused by STZ-generated ROS.

The concentrations of MDA and NO in liver were decreased after treating diabetic rats with BBR, indicating the inactivation of LPO reactions and the decreased free radical generation. In addition, BBR improved GSH and reversed activity of the enzymatic antioxidants, which might be due to decreased oxidative stress as evidenced by decreased LPO.The molecular mechanisms for BBR-induced reduction in oxidative stress may be regulated by several pathways. In the diabetic state, BBR treatment up-regulated mRNA expression of SOD and increased the contents of SOD, GSH, and GPx in rat liver (Zhou and Zhou, 2011). BBR decreased the expression level of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a major source of ROS production (Cheng *et al*., 2013). BBR treatment attenuated non-alcoholic fatty liver disease in rats through up-regulation of uncoupling protein 2 (UCP2) expression, a mitochondrial inner membrane protein that is negatively associated with ROS production and oxidative stress (Yang *et al*., 2011). BBR has also been reported to induce nuclear translocation of the nuclear factor erythroid-2-related factor-2 (Nrf2), which activates the expression of antioxidant enzymes with a resultant reduction in oxidative stress (Hsu *et al*., 2012). Furthermore, BBR supplementation in rats increased the expression of sirtuin 1 (SIRT1), a deacetylase

with antioxidant activity (Gomes *et al*., 2012). In conjunction with oxidative stress, pro-inflammatory cytokines are elevated in the blood of both diabetic animals and human patients (Jain *et al*., 2003; Mahmoud *et al*., 2012). Increased pro-inflammatory cytokines including IL-6 lead to reduction in IRS-1 tyrosine phosphorylation and association with phosphatidylinositol (PI)-3 kinase, inhibition of Akt activation (Bastard *et al*., 2000; Senn *et al*., 2002) and suppressed lipoprotein lipase (LPL) activity (Greenberg *et al*., 1992). Studies have demonstrated that TNF-α was able to impair the ability of insulin to suppress hepatic glucose production (Lang *et al*., 1992) increase the circulating level of free fatty acids (Ryden *et al*., 2002) and inhibit insulin secretion (Kim *et al*., 2008). Treatment with BBR significantly decreased the circulating levels of the pro-inflammatory cytokines which explains its insulin sensitizing action. BBR was shown to reduce expression of these pro-inflammatory cytokines by suppressing phosphorylation of IκB kinase-β (IKK-β) serine residue, resulting in inhibited NF-κB (Jiang *et al*., 2011). In addition, BBR inhibited NF-κB through suppression of the Rho GTPase signaling pathway (Xie *et al*., 2013). Moreover, the anti-inflammatory effect of BBR may be mediated through AMPK (Mo *et al*., 2014).

Adipose tissue resistinmRNA expression showed significant up-regulation in diabetic rats, which ran parallel to serum glucose, insulin and HOMA-IR index. In accordance with our findings, resistin overexpression in transgenic mice fed a HFD produced significant hyperglycemia (Kushiyama *et al*., 2005) and HFD/STZ-diabetic rats showed elevated serum resistin levels (Ahmed *et al*., 2012). Different impacts of resistinon insulin sensitivity have been previously reported. These include: (1) resistin-induced reduction in IRS-1 and IRS-2 resulting in up-regulated expression of gluconeogenic enzymes in the liver (Moon *et al*., 2003); (2) resistin reduces liver, skeletal muscle and adipose tissue AMPK activity, thereby decreasing insulin sensitivity (Rajala *et al*., 2003); (3) resistin decreased activity of glycogen synthase in the presence and absence of insulin (Ferrer *et al*., 2003); and (4) resistin up-regulates CD36 in human macrophages and induces lipid accumulation (Xu *et al*., 2006). BBR supplementation to diabetic rats significantly down-regulated adipose tissue resistin expression. Therefore, the potent anti-diabetic effect of BBR in the present study could perhaps be attributed to its resistin modulating effect.

Another proposed mechanism of how BBR exerts its anti-diabetic effect is *via* PPARγ up-regulation. Our data showed that HFD/STZ-induced diabetic rats exhibited decreased adipose tissue PPARγ expression, an effect that was reversed following BBR supplementation.As a regulator of glucose and lipid metabolism, PPARγ controls energy homeostasis (Semple *et al*., 2006), stimulates the storage of fatty acids in adipocytes, promotes preadipocytedifferentiation and enhances insulin sensitivity (Lefebvre *et al*., 2006). PPARγ activation was reported to lower hepatic triglyceride content (Yamauci *et al*., 2001), activate hepatic glucokinase expression (Kim *et al*., 2004), enhance fatty acid oxidation through activating the AMPK pathway (Lefebvre *et al*., 2006), and increase glucose uptake in adipose tissue and skeletal muscle (Hevener *et al*., 2003). The effects of PPARγ activation on insulin sensitivity was also associated with the regulation of cytokines and adipocyte hormones involved in insulin resistance. In this context, activation of PPARγ was associated with down-regulation of the genes encoding TNFα and resistin (Lefebvre *et al*., 2006). Moreover, activated PPARγ decreased the synthesis of inducible nitric oxide synthase (Pascual *et al*., 2005) and its subsequent NO production. Furthermore, PPARγ up-regulated expression of the antioxidant enzymes SOD (Gong *et al*., 2012) and CAT (Okuno *et al*., 2008) in rodents; therefore attenuates oxidative stress. In conclusion, this study reveals that the anti-diabetic efficacy of BBR may be mediated *via* up-regulation of adipose tissue PPARγ in conjunction with down-regulation of resistin, oxidative stress and inflammatory cytokines. Through these capabilities, BBR exhibited anti-hyperglycemic, anti-oxidant and anti-inflammatory effects.

Conflict of Interest: Authors declares there are not conflict of interest.

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