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# Hypoglycaemic activity of 2-dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione in streptozotocin-induced diabetic mice through ameliorating metabolic function and regulating peroxisome proliferator-activated receptor $\gamma$

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## Abstract

**Introduction:** Diabetes mellitus is characterized by hyperglycaemia causing changes in plasma proteins, which leads to insulin resistance, secretion defects or both. The present study aimed to evaluate the ability of 2-dodecyl-6-methoxy-cyclohexa-2,5-diene-1,4-dione (DMDD) isolated from *Averrhoa carambola* L. roots to lower hyperglycaemia and to investigate its potential mechanism in diabetic mice.

**Material and methods:** DMDD was isolated using a column chromatographic technique. Experimental mice were fed with a high-fat diet for a month and were intravenously injected with streptozotocin (80 mg/kg, 54<sup>th</sup> dose). Diabetic mice were orally administered DMDD (12.5, 25, 50 mg/kg) and 50 mg/kg pioglitazone for 15 days. Fasting blood glucose (FBG), fasting blood insulin (FINS), pancreatic insulin content, interleukin-6 (IL-6), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), as well as serum total cholesterol (TC), triglyceride (TG) and free fatty acid (FFA) were determined. Adipose tissue was assessed by histological examination, immunohistochemistry, western blot and reverse transcription-polymerase chain reaction methods.

**Results:** DMDD significantly increased the insulin level (all  $p < 0.05$ ). In contrast, FBG, IL-6, TNF- $\alpha$ , TC, TG and FFA were significantly decreased (all  $p < 0.05$ ). However, DMDD induced the activation of adipocyte peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ), confirmed by increased protein and mRNA expression of PPAR- $\gamma$ .

**Conclusions:** DMDD possessed hypoglycaemic activity due to its potential mechanism involving PPAR $\gamma$ -mediated adipocyte endocrine regulation.

**Key words:** *Averrhoa carambola* L., diabetes, mechanism, adipocyte, endocrine, peroxisome proliferator-activated receptor  $\gamma$ .

## Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both [1]. Type 2 diabetes accounts for nine in ten total diabetes diag-

55 noses [2], whereas the incidence of type 1 diabetes is estimated to be increasing by 3% per year [3]. The research has estimated that the prevalence of diabetes has increased in recent decades, and the worldwide mortality from diabetes has increased to 1.3 million deaths in 2010 [4], whereas in China, the number of diabetic patients is forecast to increase from 52.0.8 million in 2000 to 42.3 million in 2030 [5].

*Averrhoa carambola* L. (family: Oxalidaceae), also known as the star fruit, is one of the most commonly used herbs in Chinese plant medicine for the treatment of diabetes [6]. Many studies have evaluated the hypoglycaemic activity of *Averrhoa carambola* L. [7–11]. It has been reported that the roots of *Averrhoa carambola* L. could lower hyperglycaemia in KKAY diabetic mice [12]. Several medicinal plants contain compounds that possess antidiabetic activity [13]. Natural compounds and synthetic derivatives possessing a 1,4-benzoquinone moiety are associated with a range of biological properties [14] including antidiabetic activity [15]. 2-Dodecyl-6-methoxy-cyclohexa-2,5-diene-1,4-dione (DMDD) isolated from *Averrhoa carambola* L. roots is a 1,4-benzoquinone derivative [16].

Hyperglycaemia and hypercholesterolaemia are common characteristics of the dyslipidaemia associated with insulin resistance and type 2 diabetes mellitus [17]. Excess lipids are stored in adipose and ectopic tissue. Decreasing the number of large adipocytes through induction of apoptosis is one strategy to reduce hypertriglyceridaemia, which increases insulin sensitivity [18]. In addition, many studies have reported that lipid homeostasis is also controlled by peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ) ligands which could regulate the endocrine function of adipocytes [19]. Increased-PPAR- $\gamma$  expression was associated with insulin sensitivity, which promotes  $\beta$ -cell preservation [20]. According to our previous studies, total extract of *Averrhoa carambola* L. root could lower the interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$  level in serum and liver tissue [21]. This may indicate that *Averrhoa carambola* L. root exerts a hypoglycaemic effect by regulating the level of adipocytokines.

Therefore, the present study aimed to evaluate hypoglycaemic activity of DMDD of *Averrhoa carambola* L. roots as well as to investigate its hypoglycaemic mechanism associated with adipocyte endocrine regulation.

## Material and methods

### Plants

The roots of *Averrhoa carambola* L. were collected from Lingshan County, Guangxi Province, China, and were identified by Prof. Maoxiang Lai. The plant collections were carried out on private

land, and the owner of the land has confirmed and given permission for us to conduct the study on the site. The voucher specimen (no. 20100605) was deposited in the herbarium of the Guangxi Institute of Chinese Medicine and Pharmaceutical Science, Guangxi, China.

### Chemicals

43 Ethanol (EtOH), cyclohexane, ethyl acetate (EtOAc), n-butanol (n-BuOH), methanol (MeOH), Tween 80 and STZ were purchased from Sigma (St. Louis, MO, USA). Pioglitazone was purchased from Zhongmei Huadong Pharmaceutical Co., Ltd. (Hangzhou, China).

### Animals

38 Male Kunming mice (18–23 g) were purchased from the Laboratory Animal Centre, Guangxi Medical University, China. They were housed in a temperature-controlled room (22–25°C) with a 12 h light-dark cycle. The animals were fed with free access to standard rodent chow served by the Laboratory Animal Centre and free access to water ad libitum. The animal protocol was approved by the institutional ethical committee of Guangxi Medical University (approval no. 20110501202), and the study was conducted in accordance with the US guidelines (NIH publication no. 85-23, revised in 1985) for laboratory animal use and care.

### Isolation of DMDD

58 DMDD was prepared as previously described by Wen *et al.* [16], with a minor change. A powder from air-dried roots of *Averrhoa carambola* L. (12 kg) was extracted with 60% aq. EtOH under reflux three times (3 × 96 l, 1 h for each). The ethanol solution was concentrated under vacuum conditions to yield a syrup-like extract, which was suspended in H<sub>2</sub>O and then extracted with cyclohexane (3 × 20 l), EtOAc (3 × 20 l) and n-BuOH (3 × 20 l).

The cyclohexane extract (10.3 g) was subjected to open silica gel CC (3 × 80 cm, 200–300 mesh) via successive elution with a gradient of cyclohexane/EtOAc (100 : 0–0 : 100, each 200 ml) to yield seven fractions (fractions 1–7). Fraction 4 (5.0 g) was further separated by open silica gel CC (3 × 80 cm, 200–300 mesh) via successive elution with a gradient of cyclohexane/EtOAc (100 : 0–15 : 1, each 100 ml), producing 4 sub-fractions (fractions 41–44). Fraction 44 was re-crystallized with MeOH to yield 2-dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione (2350 mg). This compound was identified by FTIR spectroscopy using a Spectrum One PerkinElmer spectrophotometer and by <sup>1</sup>H and <sup>13</sup>C NMR analysis on a Bruker AV 600 instrument. The chemical structure of DMDD is illustrated below (Figure 1).

### Experimental design

Type 2 diabetic mice were established by high-fat diet and STZ injection. Experimental mice were fed with a high-fat diet for a month and the mice of the normal group were given standard rodent chow. Subsequently, STZ was freshly dissolved in saline-1% Tween 80 at the dose of 80 mg/kg body weight and was immediately intravenously injected into overnight-fasted mice tail vein, whereas the normal group was only given vehicle (saline-1% Tween 80). After 72 h, mice recording fasting blood glucose levels more than 11.1 mM were confirmed as diabetic and used in this experiment. DMDD was dissolved in saline-1% Tween 80 solution to obtain fixed doses of 12.5, 25 and 50 mg/kg. Mice were randomly divided into six groups, each group consisting of 10 mice:

- group 1: normal mice treated with saline-1% Tween 80 by gavage.
- group 2: diabetic mice treated with saline-1% Tween 80 by gavage.
- group 3: diabetic mice treated with 50 mg/kg pioglitazone by gavage.
- group 4: diabetic mice treated with 12.5 mg/kg DMDD by gavage.
- group 5: diabetic mice treated with 25 mg/kg DMDD by gavage.
- group 6: diabetic mice treated with 50 mg/kg DMDD by gavage.

Administration of pioglitazone and DMDD was done daily at the same time up to 15 days.

### Determination of fasting blood glucose (FBG)

All mice were fasted overnight. Levels of whole blood glucose were measured from the tail vein using an automatic glucometer, Accu-check Performa (Roche, Germany), on the initial, 7<sup>th</sup> and 15<sup>th</sup> day.

### Determination of serum fasting insulin (FINS), IL-6, TNF- $\alpha$ and lipids

After 15 days, mice were fasted overnight. Blood samples were collected from the eyes and immediately centrifuged at 3500 rpm/min for 10 min at 4°C to obtain serum which was then refrigerated at -70°C for determination of total cholesterol (TC), triglyceride (TG) and free fatty acid (FFA) levels using commercially available kits (Jiancheng Bioengineering Institute, Nanjing, China). By using the same serum, determination of FINS, IL-6 and TNF- $\alpha$  levels was done by Cusabio mouse ELISA kits (Huamei Biotech Co., Ltd., Hubei, China).

### Collection of tissues

After the blood samples were gathered, mice were sacrificed by cervical dislocation. An abdominal incision was performed to harvest pan-

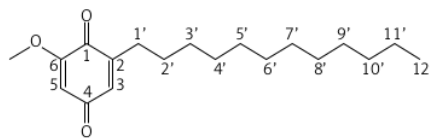


Figure 1. 2-dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione

creas and adipose tissue. The whole organs were cleaned with chilled normal saline on ice.

### Determination of pancreatic insulin content

The pancreas biologically was weighed before being placed into 6 ml of acidified ethanol (75% ethanol, 1.5% 12 mol/l HCl, and 23% H<sub>2</sub>O) and homogenized. The pancreas was incubated for 5 h at 4°C before being centrifuged (20,000xg, 4°C) and the insulin content of the supernatant was determined using a commercial mouse insulin ELISA kit (Cusabio, Wuhan, China). Pancreatic insulin content was expressed as micrograms of insulin per gram of pancreas tissue.

### Histology of pancreas and adipose tissue

The pancreas and adipose tissue (epididymal fat) specimens were fixed in 4% formalin solution and embedded in paraffin. Sections were cut at 4  $\mu$ m thickness with a microtome and deparaffinized with xylene. The sections were stained with haematoxylin-eosin (H&E) staining. Stained sections were observed under a light microscope (Olympus CX4, Japan).

### Immunohistochemistry of adipose tissue

4  $\mu$ m epididymal fat sections were obtained from paraffin-embedded tissues. Under deparaffinization, 0.3% (v/v) hydrogen peroxide was used to suppress endogenous peroxidase activity. The sections underwent a blocking step for 20 min with 5% normal goat serum diluted in PBS. Endogenous biotin and avidin binding sites were blocked by avidin and biotin, respectively. Sections were incubated with rabbit anti-mouse polyclonal PPAR- $\gamma$  (1 : 100) antibody (Santa Cruz Biotechnology, Inc. Texas, USA) in a moisture chamber and then treated with 3'-diaminobenzidine (DAB) 0.01% hydrogen peroxide (Sigma, St. Louis, MO USA). Sections were counterstained with haematoxylin. Photographs at a magnification of 200 $\times$  were analysed by applying a light microscope (Olympus, CX4 Japan).

### Measurement of protein expression of PPAR- $\gamma$ by Western blot

Epididymal fat samples were ground in liquid nitrogen. The total epididymal fat protein was

isolated using a western blotting kit (Dingguo Biotechnology, China) and separated by 10% SDS-polyacrylamide gel electrophoresis (PAGE). Then, the proteins were transferred onto a nitrocellulose membrane and blocked with 5% dried milk for 1 h. The primary antibody (1 : 1000 anti-PPAR- $\gamma$  (Abcam, USA) diluted in TBST containing 5% skim milk was added to the membrane and incubated at 4°C overnight. After three washes with TBST, the secondary antibody conjugated to horseradish peroxidase (1 : 5000) (Abcam, USA) was added to the membrane and incubated for 1 h. Immunoblots were developed on films using the enhanced chemiluminescence technique (Super Signal Westinghouse; Pierce Biotechnology, Rockford, IL). The densitometric analysis of the bands was determined with a UV light box (Gel Doc XR+, China). Following a stripping procedure the membranes were probed as above with a monoclonal anti- $\beta$ -actin antibody (1 : 1000). The data were normalized using  $\beta$ -actin as an internal control and standardized, with the vehicle control set to 1.0.

**Measurement of PPAR- $\gamma$  mRNA expression by real time polymerase chain reaction (RT-PCR)**

Total RNA was isolated from the epididymal fat pad of normal control, diabetic control and DMDD-treated diabetic mice using RNeasy Plus (Takara, Japan). An aliquot of 5  $\mu$ g of total RNA from each sample was reverse-transcribed to cDNA using the First-Strand cDNA Synthesis kit (Thermo Scientific, Massachusetts, USA). PCR amplification of 1  $\mu$ l of cDNA was carried out in a final volume of 50  $\mu$ l with the GeneAmp PCR System (Applied Biosystems, California, USA). PCR oligonucleotide sequences used are as follows:

Mouse PPAR- $\gamma$  primers creating a 153 bp amplicon (Invitrogen, California, USA): sense primer (forward): 5'-GGAGCCTAAGTTTGAGTTTGCTGTG-3',

anti-sense primer (reverse): 5'-TGCAGCAGGTTGCTTGGATG-3'.

Mouse  $\beta$ -actin primers creating a 200 bp amplicon (Invitrogen, California, USA): sense primer (forward): 5'-GAGCTATGAGCTGCCTGACG-3', anti-sense primer (reverse): 5'-AGTTTCATGGATGCACAGGA-3'.

Cycling conditions were as follows: 94°C for 30 s, 50–68°C for 30 s, and 72°C for 60 s, for 11 cycles after an initial step of 95°C for 15 min. A final elongation step of 72°C for 10 min completed the PCR. The PCR samples were electrophoresed on 2% agarose gels at 100 V and stained with SYBR green and photographed on a 280 nm UV light box (Gel Doc XR+, China).

**Statistical analysis**

Statistical analysis was performed using SPSS software package (version 16.0). Results are expressed as the means  $\pm$  SEM (N = 10). Within-group comparisons were performed using the one-way ANOVA method. A value of  $p < 0.05$  was considered statistically significant.

**Results**

**Effect of DMDD on FBG and FINS**

In the present study, DMDD was isolated from roots of *Averrhoa carambola* L. We evaluated the effect of administration of DMDD on activity of hypoglycaemia in diabetic mice induced by STZ. Table I shows that the levels of FBG significantly decreased after administration of DMDD, compared with untreated diabetic mice. Prolonged DMDD administration was in line with its hypoglycaemic activity. In addition, FINS serum levels were also increased significantly in DMDD-treated diabetic mice, when compared to untreated diabetic mice. Diabetic mice treated with pioglitazone also showed improvement of FBG and FINS levels.

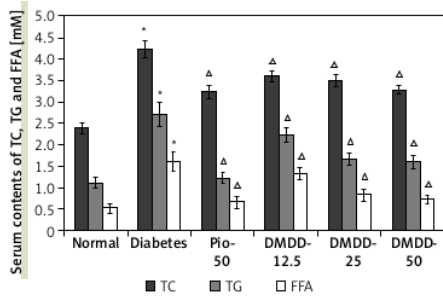
**Table I.** Effect of DMDD on FBG and FINS levels of normal and STZ-induced diabetic mice groups after 15 days of treatment

Groups	Blood glucose level [mM]			FINS [mIU/l]
	Initial	7 days	15 days	
Normal	6.8 $\pm$ 0.2	6.3 $\pm$ 0.5	6.3 $\pm$ 0.3	28.43 $\pm$ 0.41
Diabetic control	24.4 $\pm$ 0.8 <sup>a</sup>	26.7 $\pm$ 1.2 <sup>a</sup>	28.9 $\pm$ 0.4 <sup>a</sup>	14.44 $\pm$ 0.91 <sup>a</sup>
Diabetic + 50 mg/kg Pio	24.1 $\pm$ 1.2	21.1 $\pm$ 0.8 <sup>b</sup>	17.1 $\pm$ 1.3 <sup>b</sup>	23.30 $\pm$ 0.57 <sup>b</sup>
Diabetic + 12.5 mg/kg DMDD	24.5 $\pm$ 0.9	22.1 $\pm$ 0.8 <sup>b</sup>	20.3 $\pm$ 1.1 <sup>b</sup>	35.56 $\pm$ 1.31 <sup>b</sup>
Diabetic + 25 mg/kg DMDD	24.2 $\pm$ 0.7	23.1 $\pm$ 1.0 <sup>b</sup>	19.4 $\pm$ 0.7 <sup>b</sup>	35.86 $\pm$ 1.21 <sup>b</sup>
Diabetic + 50 mg/kg DMDD	24.6 $\pm$ 0.7	22.0 $\pm$ 0.7 <sup>b</sup>	19.9 $\pm$ 1.3 <sup>b</sup>	38.25 $\pm$ 3.03 <sup>b</sup>

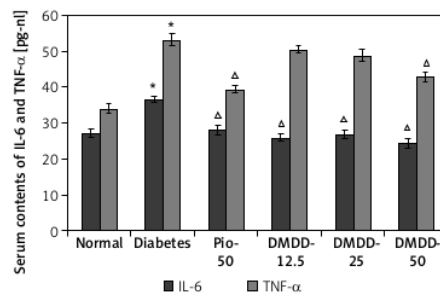
All values are given as mean  $\pm$  SEM (10 mice in each group). <sup>a</sup> $P < 0.01$  compared with normal control group, <sup>b</sup> $p < 0.01$  compared with diabetic control group.



Hypoglycaemic activity of 2-dodecyl-6-methoxycyclohexa-2,5-diene-1,4-dione in streptozotocin-induced diabetic mice through ameliorating metabolic function and regulating peroxisome proliferator-activated receptor  $\gamma$



**Figure 2.** Effect of DMDD on lipid profiles. All values are given as mean  $\pm$  SEM (10 mice in each group)  
\* $p < 0.05$  compared with normal group;  $\Delta p < 0.05$  compared with diabetes group.



**Figure 3.** Effect of DMDD on serum contents of IL-6 and TNF- $\alpha$ . All values are given as mean  $\pm$  SEM (10 mice in each group)  
\* $p < 0.05$  compared with normal group;  $\Delta p < 0.05$  compared with diabetic group.

### Effect of DMDD on lipid profiles

Hyperglycaemia is almost always accompanied by hyperlipidaemia. Thus, we also evaluated the effect of DMDD administration on hypolipidaemic activity in STZ-induced diabetic mice.  $\Delta$  treatment with DMDD for 15 days, levels of TC, TG and FFA in serum of diabetic mice were significantly decreased, compared with untreated diabetic mice (Figure 2).

### Effect of DMDD on IL-6 and TNF- $\alpha$

IL-6 and TNF- $\alpha$  adipocytokines secreted by adipose tissue have been confirmed to be adipocyte-derived factors that are correlated with an inflammatory response that leads to the development of diabetes. In our study, serum levels of IL-6 and TNF- $\alpha$  were significantly increased in untreated diabetic mice, compared with normal mice. DMDD administration for 15 days signifi-

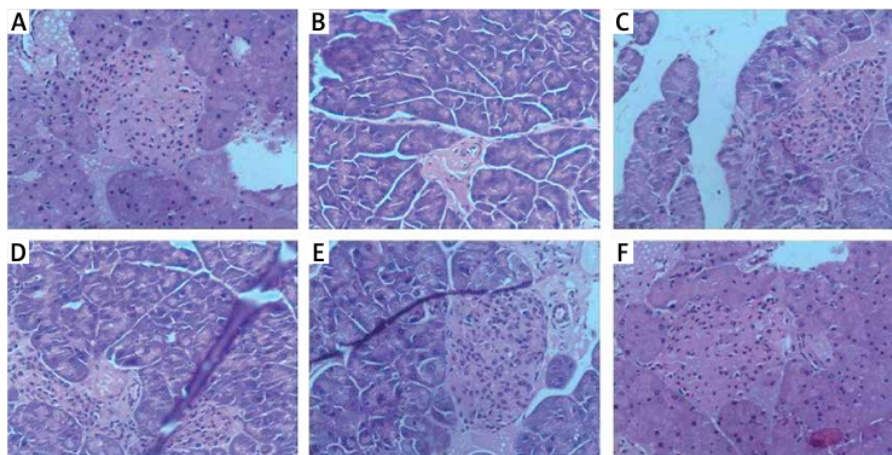
cantly lowered the IL-6 level, and 50 mg/kg DMDD significantly lowered the TNF- $\alpha$  level (Figure 3).

### Effect of DMDD on pancreatic histology

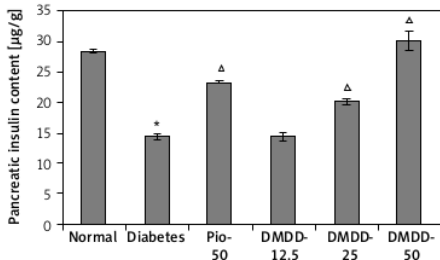
Islet cells of normal mice were compactly arranged, with negligible intercellular space, and no inflammatory cells were observed. Pancreatic islets in untreated diabetic mice (D) had obvious architectural disarray that also extended into the surrounding exocrine tissue. Islets isolated from mice treated with DMDD and pioglitazone also showed architectural disarray but to a lesser extent than untreated diabetic mice (Figure 4).

### Effect of DMDD on pancreatic insulin content

The effect of DMDD on pancreatic insulin content in normal and streptozotocin (STZ)-induced diabetic mice is shown in Figure 5. The pancreatic insulin content was significantly ( $p < 0.01$ )



**Figure 4.** Histological observations of pancreas tissue. A – Normal mice, B – untreated diabetic mice, C – diabetic mice treated with 50 mg/kg pioglitazone, D – 12.5 mg/kg of DMDD, E – 25 mg/kg of DMDD, F – 50 mg/kg of DMDD



**Figure 5.** Effect of DMDD on insulin level in pancreas tissue. All values are given as mean ± SEM (10 mice in each group)

\**p* < 0.05 compared with normal group; <sup>Δ</sup>*p* < 0.05 compared with diabetic group.

reduced in untreated diabetic mice as compared with normal mice. After treatment with pioglitazone and DMDD for 15 days, the pancreatic insulin content of diabetic mice was increased significantly (*p* < 0.01) when compared with untreated diabetic mice, especially at doses of 25 and 50 mg/kg DMDD.

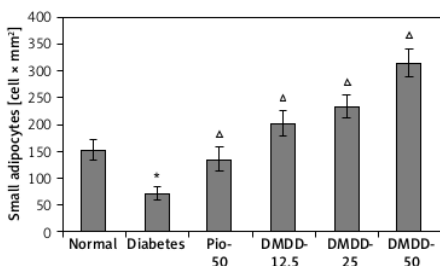
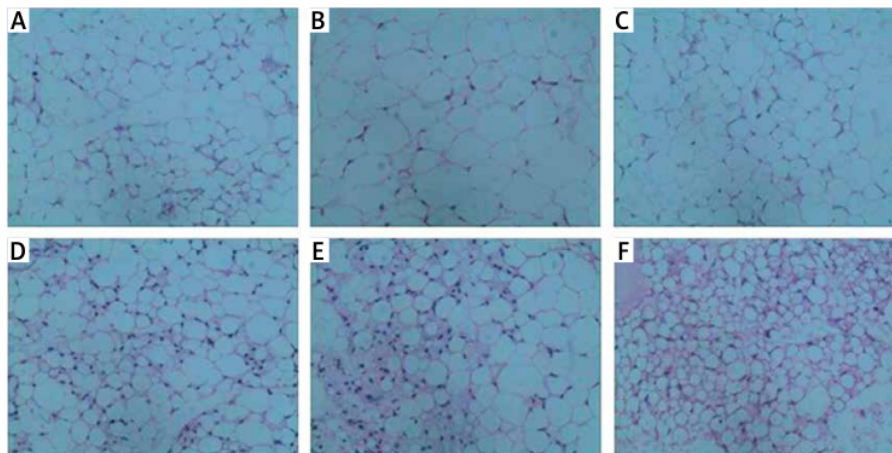
#### Effect of DMDD on histology and immunohistochemistry of adipose tissue

Increased levels of circulating serum lipids and excess lipid accumulation in non-adipose tissues

are improved by PPAR-γ ligands. In our investigation, we performed a study of the histology and immunohistochemistry of adipose tissue using epididymal fat. After treatment with pioglitazone or DMDD, histological examination of adipose tissue showed an increase in the number of small adipocytes compared with untreated diabetic mice. Further observation revealed macrophage infiltration in adipocytes (Figure 6). Immunohistochemical staining of adipose tissue revealed that the number and intensity of PPAR-γ-positive adipocytes were evidently increased in diabetic mice treated with DMDD and pioglitazone (Figure 7).

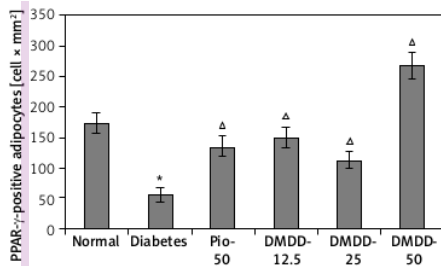
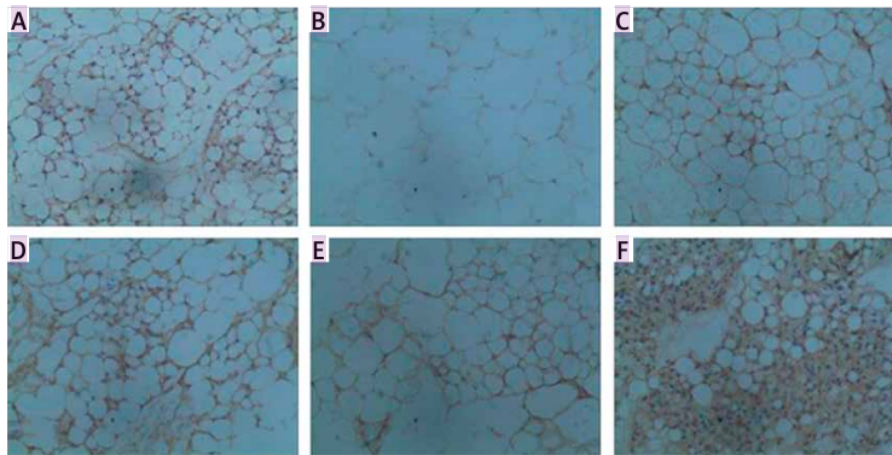
#### Effect of DMDD on protein and mRNA expression of PPAR-γ

The PPAR-γ protein level in epididymal fat was examined using western blot analysis, as shown in Figure 8. The protein levels of PPAR-γ were significantly (*p* < 0.05) lowered by 19.47% in untreated diabetic mice compared with normal mice. Pioglitazone administration significantly (*p* < 0.01) increased PPAR-γ protein expression by 28.41% compared with untreated diabetic mice. DMDD administration at doses of 12.5, 25 and 50 mg/kg significantly (*p* < 0.01) increased PPAR-γ protein expression by 25.73%, 32.86% and 59.75%, respectively.



**Figure 6.** Histological observations of epididymal fat. **A** – Normal mice, **B** – untreated diabetic mice, **C** – diabetic mice treated with 50 mg/kg pioglitazone, **D** – 12.5 mg/kg of DMDD, **E** – 25 mg/kg of DMDD, **F** – 50 mg/kg of DMDD

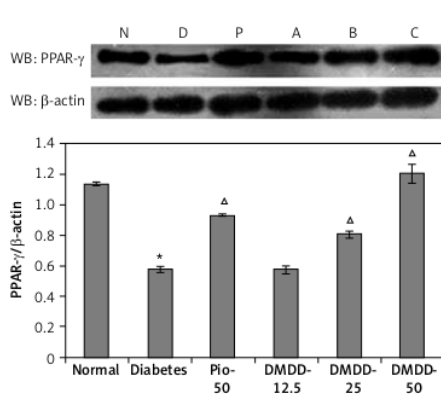
Values are given as mean ± SEM (10 mice in each group). \**p* < 0.05 compared with normal group, <sup>Δ</sup>*p* < 0.05 compared with diabetic group.



**Figure 7.** Effect of DMDD on immunohistochemistry of epididymal fat. **A** – Normal mice, **B** – untreated diabetic mice, **C** – diabetic mice treated with 50 mg/kg pioglitazone, **D** – 12.5 mg/kg of DMDD, **E** – 25 mg/kg of DMDD, **F** – 50 mg/kg of DMDD

All values are given as mean  $\pm$  SEM (10 mice in each group), \* $p < 0.05$  compared with normal group,  $^{\Delta}p < 0.05$  compared with diabetic group.

Figure 9 shows the effect of DMDD on PPAR- $\gamma$  mRNA expression in epididymal fat of diabetic mice. The level of PPAR- $\gamma$  mRNA was significantly lower in diabetic mice than in normal mice. DMDD treatment increased mRNA expression of PPAR- $\gamma$  significantly ( $p < 0.01$ ) compared with untreated diabetic mice.

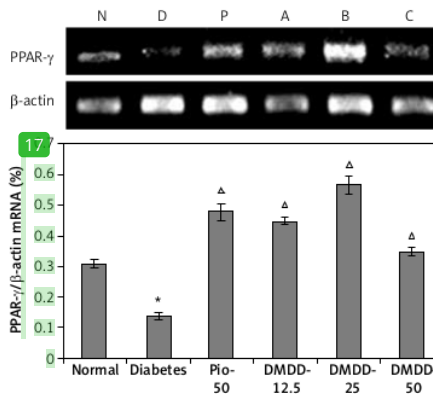


**Figure 8.** Effect of DMDD on expression of PPAR- $\gamma$  protein

Values are given as mean  $\pm$  SEM (3 mice in each group), \* $p < 0.05$  compared with normal group,  $^{\Delta}p < 0.05$  compared with diabetic group.

## Discussion

Diabetes mellitus is characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both [1]. The current treatment of diabetes targets the two main pathogenic defects of the disease, namely  $\beta$ -cell dysfunction and



**Figure 9.** Effect of DMDD on expression of PPAR- $\gamma$  mRNA

Values are given as mean  $\pm$  SEM (3 mice in each group), \* $p < 0.05$  compared with normal group,  $^{\Delta}p < 0.05$  compared with diabetic group.



insulin resistance. DMDD isolated from *Averrhoa carambola* L. roots is a 1,4-benzoquinone derivative [16]. Natural compounds and synthetic derivatives possessing a 1,4-benzoquinone moiety are associated with a range of biological properties [14], such as anti-diabetes [15, 22–24], anti-inflammatory [22], and anti-hyperlipidaemic activities [24].

Furthermore, several factors such as hyperglycaemia, hyperlipidaemia, inflammation and insulin resistance affect regeneration of pancreatic  $\beta$ -cells. Diminishing these factors leads to increased insulin secretion [25]. In fact, the progressive decline of  $\beta$ -cell function over time does not seem to be an irreversible process; some data suggest that treatment can temporarily improve  $\beta$ -cell function [26]. Gupta *et al.* reported that embelin, a 1,4-benzoquinone, protects pancreatic  $\beta$ -cells, leading to increasing insulin secretion [15]. These findings are in line with our present study showing that DMDD possessed hypoglycaemic activity. On the other hand, levels of the serum adipocytokines IL-6 and TNF- $\alpha$  were significantly decreased after administration of DMDD. The FINS serum levels in DMDD-treated diabetic mice were also significantly increased, as well as the insulin secretion indexes of DMDD-treated mice. Thus, DMDD might induce secretion of insulin and improvement of  $\beta$ -cell damage through its ability to alleviate blood glucose and the inflammatory response. Meanwhile, DMDD showed a higher increase of pancreatic insulin content (30.1  $\mu$ g/g) than that observed for pioglitazone (23.3  $\mu$ g/g). The secretion of insulin could be associated with the increased pancreatic insulin content. The insulin levels in DMDD groups were even above normal levels. We thought that DMDD could enhance the insulin sensitivity of diabetic mice, but insulin resistance still exists. Histologically, both acinar and islet components of pancreas in DMDD-treated diabetic mice are structurally similar to each other, suggesting that the islet is returning to its normal structure. This phenomenon was most obvious at 50 mg/kg DMDD. Additionally, this finding [67] strengthened by previous studies that describe [14] an increase in the mitotic index of  $\beta$ -cells in injured pancreata, and show that  $\beta$ -cell regeneration can result from the proliferation of pre-existing  $\beta$ -cells [27].

In addition, abnormalities in lipid metabolism are associated with insulin resistance [25]. We observed that TC, TG and FFA of untreated diabetic mice were significantly increased. DMDD administration improved hyperlipidaemia in serum. In comparison to DMDD, pioglitazone was more effective at lowering TG than TC. This result is strengthened by a clinical study [37] showing that after treatment with pioglitazone, patients had significant reductions in triglycerides (–15.2%)

and total cholesterol (–9.0%) [28]. Decreases in very-low-density lipoprotein levels were in line with reduced TG levels [29–31].

Many studies have reported that lipid homeostasis is controlled by PPAR- $\gamma$  ligands [19]. Adipocytokines IL-6, TNF- $\alpha$  and PPAR- $\gamma$  are closely related to type 2 diabetes and its complications. By reducing IL-6 and TNF- $\alpha$  levels, the inflammatory response will also be lowered. In addition, increased PPAR- $\gamma$  expression was associated with insulin sensitivity, leading to  $\beta$ -cell preservation [20]. PPAR- $\gamma$  expression is dramatically higher in fat than in liver, and in particular muscle [6]. In addition, pioglitazone, a thiazolidinedione, is a PPAR- $\gamma$  agonist, and the anti-diabetic mechanism is associated with enhancing the insulin sensitivity of adipose tissue. Hence, epididymal fats were used in our study to further investigate the role of PPAR- $\gamma$  in hypoglycaemia. The immunohistochemical study revealed that PPAR- $\gamma$  was highly expressed in epididymal fat of diabetic mice treated with DMDD and pioglitazone. Interestingly, the number of PPAR- $\gamma$ -positive adipocytes in the 50 mg/kg DMDD group was much higher than that in the pioglitazone group. DMDD showed a better activation effect than pioglitazone and PPAR- $\gamma$  agonists. Furthermore, the number and intensity of PPAR- $\gamma$ -positive adipocytes were greater than in untreated diabetic mice. Moreover, rodent and human studies have shown that adipose enlargement was associated with decreased insulin responsiveness [32].

Histological examination of epididymal fat revealed that DMDD and pioglitazone increased the number of small adipocytes. This may be due to their stimulatory effect on PPAR- $\gamma$ -mediated adipocyte differentiation. Previous studies have supported that activation of PPAR- $\gamma$  in 3T3-L1 preadipocytes was associated with differentiation of preadipocytes into mature adipocytes [33]. The stimulation of adipocyte differentiation results in an increased population of small adipocytes, which are more insulin sensitive. The increase in the number of small adipocytes may also account for the reduction in hypertriglyceride, since smaller fat cells are known to be more sensitive to the antilipolytic action of insulin [34]. Thus, DMDD might play a key role in white adipocyte differentiation.

The possible mechanism by which DMDD increases the number of small size adipocytes might be by stimulating expression of differentiation markers such as C/EBP $\alpha$  and A2COL6, and concomitantly stimulating expression of genes involved in maturation of adipocytes, such as PEPCK and FAS, to increase the capacity of fat storage. This notion is supported by Martin *et al.*, [32] reported that activated PPAR- $\gamma$  can stimulate the expression of adipocyte-specific genes involved in

adipocyte differentiation, such as C/EBP $\alpha$  [35]. In fact, genes involved in lipid uptake and storage, such as PEPCK, lead to increase uptake of FFA to be stored in adipocytes and reduce release of FFA into the circulation. This is in line with our finding showing that administration of DMDD reduced serum levels of FFA in diabetic mice. The results demonstrated that DMDD may exert a hypoglycaemic effect through regulating the expression of PPAR- $\gamma$ , which mediates the endocrine function of adipocytes and reduces lipid profiles.

In conclusion, however, in our present study we found adipose tissue infiltrated by macrophage cells. This finding might be explained by the appearance of newly differentiated adipocytes within a few weeks after the death of PPAR- $\gamma$ -ablated adipocytes. Stienstra *et al.* reported that activation of PPAR- $\gamma$  promotes macrophage infiltration into adipose tissue, supporting this hypothesis [36]. However, PPAR- $\gamma$  simultaneously reduces inflammatory gene expression, as evidenced by reductions in serum IL-6 and TNF- $\alpha$  levels in DMDD-treated diabetic mice, which were observed in the present study. In summary, DMDD possessed hypoglycaemic activity through a mechanism involving PPAR- $\gamma$ -mediated adipocyte endocrine regulation and insulin secretion.

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Kintoko Kintoko and Xiaohui Xu contribute equally to this work.

#### Conflict of interest

The authors declare no conflict of interest.

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