Bulletin of Faculty of Pharmacy, Cairo University (2014) **52**, 1–7

Cairo University

Faculty of Pharmacy

Cairo University

**Bulletin of Faculty of Pharmacy, Cairo University**

www.elsevier.com/locate/bfopcu
www.sciencedirect.com


ORIGINAL ARTICLE

# Antihyperglycemic and antihyperlipidemic effects of the methanol extracts of *Cleome ramosissima* Parl., *Barleria bispinosa* (Forssk.) Vahl. and *Tribulus macropterus* Boiss.

**Shahira M. Ezzat [a,*], Essam Abdel-Sattar [a], Fathalla M. Harraz [b], Salah A. Ghareib [c]**

[a] *Department of Pharmacognosy, Faculty of Pharmacy, Cairo University, 11562 Cairo, Egypt*
[b] *Department of Pharmacognosy, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt*
[c] *Department of Pharmacology and Toxicology, Faculty of Pharmacy, King Abdulaziz University, Jeddah 21589, Saudi Arabia*

Received 23 August 2013; accepted 25 December 2013
Available online 11 February 2014

**KEYWORDS**

Antidiabetic;
Hypolipidemic;
Insulin restoring;
*Cleome ramosissima*;
*Barleria bispinosa*;
*Tribulus macropterus*

**Abstract** The antihyperglycemic and antihyperlipidemic effects of the methanolic extracts of the aerial parts of *Cleome ramosissima* Parl. (Cleomaceae), *Barleria bispinosa* (Forssk.) Vahl. (Acanthaceae) and *Tribulus macropterus* Boiss. (Zygophyllaceae) were evaluated in streptozotocin (STZ) induced diabetic rats at a dose of 500 mg/kg bw. The reduction in fasting blood glucose level (BGL) was observed in the following order *C. ramosissima*, *B. bispinosa* and *T. macropterus* at the 4th week of administration. *C. ramosissima* and *T. macropterus* also showed significant increase in plasma insulin by 100.6% and 189.9%, respectively. The studied plant extracts induced an increase in both utilization and tolerance of glucose in diabetic rats. The hypolipidemic effect of *C. ramosissima* and *T. macropterus* was demonstrated by a significant reduction in plasma total cholesterol (TC) (42.6% and 37.2%, respectively) and low density lipoprotein cholesterol (LDL-C) (48.0% and 42.1%, respectively) and the increase of high density lipoprotein cholesterol (HDL-C) by 81.0% and 91.9%, respectively. *B. bispinosa* decreased the blood levels of LDL-C

* Corresponding author. Address: Department of Pharmacognosy, Faculty of Pharmacy, Cairo University, Kasr El-Ainy St., 11562 Cairo, Egypt. Tel.: +20 1222336716; fax: +20 2 25320005.
E-mail address: shahyelkomy@hotmail.com (S.M. Ezzat).

Peer review under responsibility of Faculty of Pharmacy, Cairo University.

ELSEVIER Production and hosting by Elsevier

 http://dx.doi.org/10.1016/j.bfopcu.2013.12.002

and increased the levels of HDL-C, while it did not affect the TC blood levels. The present data suggest that *C. ramosissima* and *T. macropterus* have both antihyperglycemic and hypolipidemic effects with high insulin-secreting activity.



## 1. Introduction

The worldwide epidemic of type 2 diabetes has been stimulating the search for new concepts and targets for the treatment of this incurable disease. Globally, the occurrence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025.[1] It has become a serious metabolic disorder and is now one of the leading causes of death in the world.

Diabetes mellitus, specifically type 2, is often associated with dyslipidemia. Elevated levels of plasma free fatty acids play a pivotal role by contributing significantly to insulin resistance. A patient with elevated low-density lipoprotein (LDL) and decreased high density lipoprotein (HDL) will have a high risk of experiencing cardiovascular disorders,[2,3] that is why diabetic patients usually experience various vascular complications, such as atherosclerosis, diabetic nephropathy and neuropathy.[4] Treating dyslipidemia therefore will be important to reduce macrovascular disorders in diabetic patients.

Although several therapies are currently used in the treatment of diabetes, draw backs such as cost, hypoglycemia, weight gain, gastrointestinal disturbances, and liver toxicity are major concerns to search for alternative approach or medicine to treat or control diabetes.[5] On the other hand, traditionally used medicinal plants can provide an alternative approach to treat diabetes. The available traditional medicines (used to control or manage diabetes) contain a number of these plants, this is because the plants are antioxidant rich therapies and are virtually free of adverse effects.[6] Fortunately, the World Health Organization (WHO) has listed as many as 21,000 plants, which are used for medicinal purposes around the world.

It is also noteworthy to mention that many plants are considered valuable antidiabetic drugs, for instance the oral administration of the methanol extract of the aerial parts of *Barleria lupulina* Lindl. (Acanthaceae) exerted a significant hypoglycemic effect in STZ-induced hyperglycemia in rats.[7] On the other hand, *Cleome droserifolia* (Forssk.) Del. (Cleomaceae) has also been reported to be a famous antihyperglycemic agent.[8–13] In addition, the genus *Tribulus* is rich in steroidal glycosides,[14] these compounds are reported to be active antidiabetic agents.[15,16]

Therefore, in our program of biological screening of plants growing in the western region of the Kingdom of Saudi Arabia for their Antidiabetic activity, and regarding the chemotaxonomical point of view it was found logic to choose plants of the same genera as those proving antidiabetic activity, such as *Barleria bispinosa, Cleome ramosissima*, and *Tribulus macropterus* for their antidiabetic activity, especially because the preliminary phytochemical screening showed similarities between the chemical composition of our plants and that of the aforementioned species.

## 2. Materials and methods

### 2.1. Chemicals

Streptozotocin (STZ) and α-D-glucose were purchased from Sigma–Aldrich (St Louis, MO, USA). Carboxymethylcellulose sodium (CMC-Na) was purchased from Acros Organics (NJ, USA), while heparin sodium was purchased from Merck, (Darmstadt, Germany). Insulin kit (Coat-A-Count Insulin) was purchased from Siemens, Medical Solutions Diagnostics (Los Angeles, USA). All other biodiagnostic kits were purchased from Diagnostic and Research Reagents (Giza, Egypt).

### 2.2. Plant material and extraction

The aerial parts of *C. ramosissima* Parl., *B. bispinosa* (Forssk.) Vahl. and *T. macropterus* Boiss. were collected from Al-Hadda road, Al-Baha and Jeddah, respectively, Saudi Arabia, in March 2008 and were dried in shade. A specimen of each plant was deposited in the herbarium of college of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia (CR1040, BB1002 and TM1162, respectively). The powdered plant material (500 g) in each case was extracted with methanol using Ultra-turrax T25 homogeniser (Janke & Kunkel, IKA Labortechnik, Stauten, Germany) (3 × 2000 ml). The vehicle was distilled off under reduced pressure and the dried methanol extract was kept at 4 °C.

### 2.3. Phytochemical screening

The methanol extracts of the aerial parts of *C. ramosissima, B. bispinosa* and *T. macropterus* were screened for carbohydrates and/or glycosides, flavonoids, tannins, saponins and/or triterpenes and alkaloids through applying various chemical tests.[17]

### 2.4. Animals

Male Wister rats, weighing 150–200 g, were used in this study in accordance with the guidelines of the Biochemical and Research Ethics Committee at the King Abdulaziz University, Jeddah, Saudi Arabia. Animals were purchased from the animal house of the King Fahed Medical Research Center, King Abdulaziz University. Animals were housed for two days under standard conditions (well ventilated, temperature 22 ± 2 °C, relative humidity 50–60% and 12 h day and night cycle). Food consisted of normal rat chow and water was provided *ad libitum*. Care was taken to avoid stressful conditions. All experimental procedures were performed between 8 and 10 a.m. All the experimental works with the animals were carried out after obtaining approval from the Institutional Animal Ethics Committee.

### 2.5. Acute toxicity study

Twenty-four adult male Wister rats were used to test the methanol extract of each plant and the animals of each group were divided into four subgroups ($n = 6$) and received increasing doses of 100, 250, 500, and 1000 mg/kg body weight daily for a period of 3 weeks. The animals were observed during the first hour continuously and then every hour for 6 h, then after 12 and 24 h, and finally after every 24 h up to 3 weeks for any physical signs of toxicity such as writhing, gasping, palpitation and decreased respiratory rate or mortality.[18]

### 2.6. Evaluation of the effects of C. ramosissima, B. bispinosa and T. macropterus on hyperglycemic rats

#### 2.6.1. Induction of diabetes

Diabetes was induced by an intraperitoneal (ip) injection of a fresh solution of a single dose of STZ (in 0.1 M sodium citrate buffer, pH 4.5) in a dose of 55 mg/kg body weight, to overnight fasting rats.[19] Ten days after STZ administration, rats with fasting blood glucose levels (BGL) between 20 and 30 mmol/L (360–540 mg/dl) were selected and divided into 5 groups (groups II – VI) eight rats each.

#### 2.6.2. Experimental design

*Group I:* Animals of this group were served as normal control and received an equivalent volume of the 0.1 M sodium citrate buffer.

*Group II:* Animals of this group were STZ-induced diabetics, received a single daily dose of 1% CMC-Na starting at the 11th day, and this group served as the control diabetic group.

*Group III:* Animals of this group were diabetics and received a single daily dose of glibenclamide in a dose of 5 mg/kg starting at the 11th day and served as the glibenclamide-treated group.

*Group IV–VI:* Diabetic rats received the methanol extracts of *C. ramosissima*, *B. bispinosa* and *T. macropterus*, respectively, in a dose of 500 mg/kg body weight each as single daily dose starting at the 11th day. The doses of the extracts were determined as 500 mg/kg/day from preliminary short-term pilot study with a range of variable doses in our laboratory.

Vehicle, glibenclamide and plant extracts were given orally (po) by gavage as single daily treatments for 4 weeks. Blood samples were collected from tail vein and fasting BGL of the overnight fasted animals was measured before the treatment and at days 7, 14, 21 and 28 from the treatment.

#### 2.6.3. Estimation of plasma glucose and tissue glycogen

Fasting plasma glucose was estimated using the glucose oxidase peroxidase method.[20] The results are presented in Table 1.

#### 2.6.4. Oral glucose tolerance test (OGTT)

At the end of the 28th day, 3 h after the last dose of the vehicle, glibenclamide or the extract, blood samples were withdrawn from tail vein of overnight fasting rats and BGL was determined, indicating zero time of the test. Glucose solution (50%) in a dose of 2.5 g/kg was given orally.[21] Blood samples were withdrawn at 15, 30, 60, 90 and 120 min after glucose loading and BGL was determined at these time intervals using One Touch Ultra. Curves of BGL (mg/dl) versus the time

**Table 1** Effect of treatment with the tested plant extracts on blood glucose levels of diabetic rats.

| Groups | Blood glucose level (mg/dl) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before treatment | After treatment | | | | | | | |
| | | 1st week | | 2nd week | | 3rd week | | 4th week | |
| | | X ± SE | % Reduction | X ± SE | % Reduction | X ± SE | % Reduction | X ± SE | % Reduction |
| Normal rats | 103 ± 3.82 | 102 ± 2.97 | | 102 ± 3.66 | | 98 ± 5.68 | | 111 ± 7.51 | |
| Diabetic rats | 394 ± 27.06 | 406 ± 22.75 | | 433.4 ± 17.01 | | 470 ± 31.80 | | 494. ± 31.22 | |
| DR + glibenclamide | 466 ± 18.76 | 456 ± 19.66 | 2.1% | 443 ± 22.7 | 6.97% | 376[a] ± 21.75 | 19% | 335[a] ± 25.60 | 30% |
| DR + *Cleome ramosissima* | 465 ± 15.91 | 513 ± 20.71 | +10% | 358[a] ± 29.29 | 23% | 322[a] ± 42.86 | 31% | 294[a] ± 61.54 | 37% |
| DR + *Barleria bispinosa* | 514.6 ± 14.58 | 501.8 ± 66 | 2.5% | 486 ± 39.05 | 5.7% | 440.6[a] ± 26.0 | 14% | 416[a] ± 34.87 | 19% |
| DR + *Tribulus macropterus* | 560 ± 29.51 | 553 ± 35.55 | 1.3% | 578 ± 33.91 | +3.2% | 384[a] ± '22.16 | 31% | 394[a] ± 9.27 | 30% |

Extracts were given orally in a dose of 500 mg/kg/day for 4 weeks.
DR: diabetic rats.
Statistical analysis was performed using paired Student's *t*-test.
[a] Statistically significant from corresponding before treatment value at $P < 0.05$.

intervals (min) constructed and the area under the curve (AUC) was calculated by the trapezoidal method. The AUCs of the curves of each group were compared and tested for significance from the control-diabetic group, to represent the glucose tissue utilization. The results are recorded in Table 2.

#### 2.6.5. Estimation of plasma insulin level

At the end of the 28th day, 3 h after the last dose of the vehicle, glibenclamide or the extracts, blood samples were withdrawn from the orbital sinus of rats under light ether anesthesia into heparinized tubes. Samples were centrifuged at 3500*g* for 15 min for separation of plasma. Plasma samples were separated and kept at −20 °C for analysis when required. Insulin concentrations were determined by radioimmunoassay procedure using insulin kits. The results are presented in Table 3.

#### 2.6.6. Estimation of plasma lipid profile

At the end of the 28th day, blood lipids were determined using spectrophotometric assay techniques. Plasma of normal (group I), diabetic control (group II) and diabetic-treated (groups III–VI) rats was used for the determination of plasma TC, TG, LDL-C and HDL-C. The results are tabulated in Table 4.

### 2.7. Statistical analysis

Data are expressed as mean ± standard error (SE) of mean. Unless otherwise indicated, statistical analyses were performed using the one-way analysis of variance (ANOVA). If the overall *F*-value was found statistically significant ($P < 0.05$), further comparisons among groups were made according to *post hoc* Tukey's test. All statistical analyses were performed using SPSS GraphPad InStat 3 (GraphPad Software, Inc. La Jolla, CA, USA) software.

## 3. Results

### 3.1. Phytochemical screening

The methanol extracts of the aerial parts of *C. ramosissima, B. bispinosa* and *T. macropterus* were proved to contain glycosides, flavonoids, tannins and triterpenes, in addition the methanol extract of *T. macropterus* gave positive test for saponins.

**Table 2** Total area under the curve induced after glucose loading in diabetic rats pretreated with the tested plant extracts (500 mg/kg/day) for 4 weeks.

| Groups | Total AUC (mg/dl.min) (X ± SE) | % Reduction |
|---|---|---|
| Normal rats | 14,479 ± 480.42 | – |
| Diabetic rats | 70,108 ± 2077.06 | 0.00 |
| DR + Glibenclamide | 59,692[a] ± 1785.26 | 15% |
| DR + *Cleome ramosissima* | 53,947[a] ± 5303.16 | 23% |
| DR + *Barleria bispinosa* | 57,375[a] ± 3971.31 | 18% |
| DR + *Tribulus macropterus* | 60,675[a] ± 2091.27 | 19% |

DR: diabetic rats.
[a] Significantly different from the control values of diabetic rats at $P < 0.05$.

**Table 3** Effects of oral administration of the tested plant extracts (500 mg/kg) on plasma insulin levels in diabetic rats.

| Treatment | Insulin (μIU/ml) | % Change |
|---|---|---|
| Normal control | 7.48 ± 1.32 | |
| Diabetic control | 3.22[a] ± 0.387 | −56.9 |
| DR + Glibenclamide | 12.47[b] ± 2.39 | +272.7 |
| DR + *Cleome ramosissima* | 6.47[b] ± 0.67 | +100.6 |
| DR + *Barleria bispinosa* | 1.91[b] ± 0.34 | −41.0 |
| DR + *Tribulus macropterus* | 9.35[b] ± 0.93 | +189.9 |

The values are expressed as the mean ± SE of the mean.
DR: diabetic rats.
[a] Significantly different from the values of the normal rats at $P < 0.05$.
[b] Significantly different from the control values of diabetic rats at $P < 0.05$.

### 3.2. Toxicity study

No deaths were reported in the rats treated with different doses of the methanol extract of *C. ramosissima, B. bispinosa* and *T. macropterus* and rats did not show any apparent physical signs of drug-induced toxicity during the whole experimental period.

### 3.3. Effect of extracts on plasma glucose level

STZ-diabetic rats showed significant increase in the levels of plasma glucose when compared to normal rats. Glibenclamide treatment of diabetic rats showed significant reduction in the plasma glucose level at 21st day of treatment compared to before treatment. On the other hand, oral administration of *C. ramosissima* extract significantly decreased the blood glucose levels. These effects started at the 2nd week of treatment and continued till the end of the 4th week and recorded 23%, 31% and 37% decrease compared to before treatment (Table 1). Similarly, *B. bispinosa* and *T. macropterus* produced significant reductions in blood glucose levels, started after the 3rd week of treatment and continued till the 4th week, (14% and 19%) and (31% and 30%), respectively (Table 1).

### 3.4. Effect of extracts on OGTT

The blood levels of glucose in control, diabetic group, diabetic-treated with glibenclamide or plant extract groups demonstrated a significant change in BGL after oral loading with 50% glucose solution. The rats of the diabetic group had a significant elevation in BGL throughout the total measurement period (120 min) with respect to normal control, also it did not come back to the initial value (0 min level) even at the end of the period tested (120 min).

Pretreatment of diabetic rats with gibenclamide induced a significant reduction (15%) in the AUC relative to the diabetic control group. However, pretreatment of the diabetic rats with *C. ramosissima*, *B. bispinosa* and *T. macropterus* produced significant reductions of the AUCs (Table 2). These reductions were as follows, 23%, 18%, and 14%, respectively.

### 3.5. Effect of extracts on plasma insulin level

The induction of diabetes significantly reduced the plasma insulin level by 56.9% (Table 3). After 4 weeks of po administration

**Table 4** Effects of oral administration of the tested plant extracts (500 mg/kg) on total cholesterol, triglycerides, high density lipoprotein and low density lipoprotein in diabetic rats.

| Treatment | Total cholesterol (TC) (mg/dL) | % Change | Triglycerides (TG) (mg/dL) | % Change | High density lipoprotein cholesterol (HDL-C) (mg/dL) | % Change | Low density lipoprotein cholesterol (LDL-C) (mg/dL) | % Change |
|---|---|---|---|---|---|---|---|---|
| Normal control | 125.71 ± 4.04 | | 87 ± 2.52 | | 29.57 ± 5.47 | | 78.70 ± 4.58 | |
| Diabetic control* | 239.99[a] ± 21.53 | +90.9 | 113.33[a] ± 11.15 | +30.3 | 20.56 ± 3.09 | −32.4 | 168.68 ± 8.75 | +114.3 |
| DR + glibenclamide | 178.28[a] ± 15.05 | −25.7 | 121.6 ± 14.62 | +7.3 | 41.84[a] ± 7.15 | +103.2 | 112.10 ± 8.02 | −33.5 |
| DR + *Cleome ramosissima* | 139.04[a] ± 8.81 | −42.2 | 109.60 ± 11.70 | −3.3 | 37.23[a] ± 5.66 | +81.0 | 87.70[a] ± 14.05 | −48.0 |
| DR + *Barleria bispinosa* | 189.71 ± 15.05 | −21.7 | 89.33 ± 11.85 | −21.2 | 40.44[a] ± 6.77 | +96.7 | 119.96[a] ± 15.77 | −28.9 |
| DR + *Tribulus macropterus* | 150.85[a] ± 21.04 | −37.2 | 90.00 ± 6.22 | −20.6 | 39.46[a] ± 5.84 | +91.9 | 97.68[a] ± 26.79 | −42.1 |

The values are expressed as the mean ± SE of the mean.
DR: diabetic rats.
* Significantly different from the values of the normal rats at $P < 0.05$.
[a] Significantly different from the control values of Diabetic rats at $P < 0.05$.

of glibenclamide, significant increase in plasma insulin level by 272.7% of diabetic control was produced. However, Oral administration of *C. ramosissima* and *T. macropterus* extracts significantly increased the insulin blood levels compared to the diabetic rats by 100.6% and 189.9%, respectively. On the other hand, *B. bispinosa* extract significantly decreased the blood levels of insulin by 41% of diabetic rats.

### 3.6. Effect of extracts on plasma lipid profile

Diabetic rats showed significant increase in the blood levels of TC, TG and LDL-C (Table 4). The recorded increases were 90.9%, 30.3% and 114.3%, respectively of the values of the normal rats. On the other hand, HDL-C was significantly reduced by 32.4% of the value of the normal rats. Oral administration of glibenclamide significantly decreased the blood levels of TC and LDL-C by 25.7% and 33.5% of the diabetic rats, respectively. However, the level of HDL-C significantly increased by 103.2%. Glibenclamide did not significantly change the blood level of TG. Administration of *C. ramosissima* to diabetic rats significantly reduced the blood levels of both TC and LDL-C by 42.2% and 48.0%, respectively, while the HDL-C level increased by 81.0%. *B. bispinosa* significantly decreased the blood levels of LDL-C by 28.9%, while it did not affect the TC and TG blood levels. On the other hand, it significantly increased the levels of HDL-C by 96.7%. Administration of *T. macropterus* to diabetic rats significantly decreased the blood levels of TC and LDL-C by 37.2% and 42.1%, relative to the diabetic control rats, respectively. It significantly increased the blood level of HDL-C by 91.9% of the control diabetic rats.

## 4. Discussion

Non-insulin dependent diabetes mellitus or type 2 diabetes is the much more prevalent form of diabetes accounting for more than 90% of all diabetes cases and causes serious socioeconomic problems especially in developing countries.[22]

This investigation aimed at studying the antihyperglycemic and hypolipidemic effects of the methanol extracts of *C. ramosissima*, *T. macropterus*, and *B. bispinosa* on STZ-induced diabetes in rats, especially that the toxicity study proved the safety of these extracts. STZ is commonly used laboratory chemical to induce experimental type 2 diabetes in animals. STZ mediated alkylation of pancreatic deoxyribonucleic acid causes the generation of superoxide, hydrogen peroxide, nitric oxide and hydroxyl radicals which are responsible for β-cells damage and necrosis resulting in diabetes.[23] Therefore, in our study STZ-diabetic rats showed significant increase in the levels of plasma glucose when compared to normal rats. Findings of the present work concerning the anti-hyperglycemic effect of *C. ramosissima* are in agreement with those reported by Nicola et al. (1996)[10], who reported that the extract of *C. droserifolia* significantly suppressed the rise in peripheral blood glucose concentrations, both in the basal (fasting) state and after glucose intake.

Similarly, *B. bispinosa* and *T. macropterus* produced significant reductions in blood glucose levels, which started after the 3rd week of treatment and continued till the 4th week, these also were in accordance with the reported data, where the level of serum glucose significantly reduced after administration of saponin fraction isolated from *Tribulus terrestris*, by 26.25% and 40.67% in normal and diabetic mice, respectively.[16] In another study, the decoction (saponin rich fraction) of *T. terrestris* significantly inhibited the gluconeogenesis and influenced glycometabolism on normal mice.[24]

The plant extracts subjected to this study can be arranged in a descending order according to their possible capability to reduce the blood glucose level and hence their possible antidiabetic activities as follows: *C. ramosissima*, *T. macropterus* and *B. bispinosa*. As regards to the antihyperglycemic activity of glibenclamide at the selected dose levels, the extracts of *C. ramosissima* showed higher activity; while *T. macropterus* exhibited similar activity, however, *B. bispinosa* demonstrated, a lower antihyperglycemic activities than glibenclamide.

The effect of the tested extracts on glucose tolerance and glucose tissue utilization was studied in diabetic rats. Glucose loading was done 3 h after the administration of vehicle, glibenclamide and the extracts. Induction of diabetes produced a significant increase of the AUC to 70,108 vs 14,479 mg/dl/min of normal rats (Table 2). This indicated the reduction of glucose tissue utilization, increased hepatic glucose production and hyperglycemia. Pretreatment of diabetic rats with *C. ramosissima*, *B. bispinosa* and *T. macropterus* produced significant reductions of the AUCs. These results revealed that the studied plant extracts induced an increase in glucose utilization and glucose tolerance. In

addition, these extracts may also reduce gluconeogenesis. This was approved after the determination of plasma level of insulin at the end of the experiment.

Induction of diabetes significantly reduced the blood insulin levels, this effect may be due to the ability of STZ in the given dose to induce partial damage of the pancreatic β-cells,[25] as STZ was reported to induce a dose-dependent damaging effect on pancreatic β-cells.[26] Oral administration of *C. ramosissima* and *T. macropterus* extracts for 4 weeks significantly increased the insulin blood levels, compared to the diabetic rats and this may be through stimulation of the activity of the remnant pancreatic β-cells.

Hyperlipidemia is one of the major cardiovascular risk factors. It has been demonstrated that insulin deficiency in diabetes mellitus leads to a variety of derangements in metabolic and regulatory processes, which in turn leads to accumulation of lipids such as TG and TC in diabetic patients,[27] for this reason, the induction of diabetes in rats in the present study significantly increased the blood levels of total cholesterol (TC), triglycerides (TG) and low density lipoprotein cholesterol (LDL-C), while the high density lipoprotein cholesterol (HDL-C) significantly reduced (Table 4). These findings are in accordance with that reported by Felix et al. (2001).[28] In normal condition, insulin increases the receptor-mediated removal of LDL-C and therefore a decrease in insulin activity during diabetes causes hypercholesterolemia. Administration of the methanol extracts of *C. ramosissima*, *B. bispinosa* and *T. macropterus* for 4 weeks to diabetic rats improved the lipid profile almost to the normal levels (Table 4). One of the most common side effects of some antihyperlipedemic drugs, that decrease TC, is the reduction of the cardioprotective HDL-C.[29] Interestingly, *C. ramosissima*, *B. bispinosa* and *T. macropterus* not only lowered TC and LDL levels, but also increased HDL-C level.

In conclusion, *C. ramosissima*, *B. bispinosa* and *T. macropterus* exhibited antihyperglycemic activity. The possible mechanism by which these plants bring about their antidiabetic activity may be through stimulation of the activity of the remnant pancreatic ß-cells (synthesis, release, cell regeneration/revitalization), the insulin-like activity of the plant extracts or the increase of glucose uptake in lipocytes. Their hypolipidemic effect may be due to the low activity of cholesterol biosynthesis enzymes and/or low level of lipolysis, which are under the control of insulin. Hypolipidemic effects could prevent or be helpful in reducing the complications of lipid profile seen in some cases of diabetes in which hyperglycemia and hypercholesterolemia coexist.

All of these actions may be responsible for the reduction and/or abolition of diabetic complications. The plants could be also regarded as potential antihyperlipidemic agents that may need further studies to be established.

## 5. Conflict of interest

None.

## Acknowledgment

The authors are grateful to the Deanship of Scientific Research, King Abdulaziz University, KSA (Project No. 046/428) for funding this study, and to Mr. Islam Farouk and Mr. Alaa El-Din Essam for technical assistant.

## References

1. Ramachandran SA, Naveen KR, Rajinikanth B, Kbar M, Rajasekaran A. Antidiabetic, antihyperlipidemic and in vivo antioxidant potential of aqueous extract of *Angeissus latifolia* bark in type 2 diabetic rats. *Asian Pac J Trop Dis* 2012;S596–602.
2. Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease 11, genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest* 1973;**52**:1544–68.
3. Kaur J, Singh P, Sowers JR. Diabetes and cardiovascular diseases. *Am J Ther* 2002;**9**:510–5.
4. Sheetz MJ. Molecular understanding of hyperglycemias adverse effects for diabetic complications. *J Am Med Assoc* 2002;**288**:2579–88.
5. Prasad SK, Kulshreshtha A, Qureshi TN. Antidiabetic activity of some herbal plants in streptozotocin induced diabetic albino rats. *Pak J Nutr* 2005;**8**:551–7.
6. Patel SS, Shah RS, Goyal RK. Antihyperglycemic, antihyperlipidemic and antioxidant effects of Dihar, a poly herbal ayurvedic formulation in streptozotocin induced diabetic rats. *Indian J Exp Biol* 2009;**47**:564–70.
7. Suba V, Murugesan T, Bhaskana R, Rao L, Ghosh MP, Mandal SC, et al. Antidiabetic potential of *Barleria lupulina*. *Fitoterapia* 2004;**75**:1–4.
8. Yang SS, Mabry TJ, El-Fishawy AM, El-Kashoury EA, Abdel-Kawy MA, Soliman FM. Flavonoids of *Cleome droserifolia* (Forssk.) Del.. *Egypt J Pharm Sci* 1990;**31**:443–51.
9. Yaniv Z, Dafni A, Friedman J, Palevitch D. Plants used for the treatment of diabetes in Israel. *J Ethnopharmacol* 1987;**1987**(19):145–51.
10. Nicola WG, Ibrahim KM, Mikhail TH, Girgis RB, Khadr ME. Role of the hypoglycemic plant extract *Cleome droserifolia* in improving glucose and lipid metabolism and its relation to insulin resistance in fatty liver. *Boll Chim Farm* 1996;**135**:507–17.
11. Abdel-Hady NM. *Pharmacognostical investigation and biological verification of some recipes and preparations of natural origin for the treatment of diabetes* [MS thesis]. Faculty of Pharmacy (Girls), Al-Azhar University, Cairo, Egypt; 1998.
12. Abdel-Kawy MA, El-Deib S, El-Khyat Z, Mikhail YA. Chemical and biological studies of *Cleome droserifolia* (Forssk.) Del. Part-I. *Egypt J Biomed Sci* 2000;**6**:204–18.
13. Motaal AA, Ezzat SM, Haddad PS. Determination of bioactive markers in *Cleome droserifolia* using cell-based bioassays for antidiabetic activity and isolation of two novel active compounds. *Phytomedicine* 2011;**19**:38–41.
14. Wu G, Jiang S, Jiang F, Zhu D, Wut H, Jiang S. Steroidal glycosides from *Tribulus terrestris*. *Phytochemistry* 1996;**42**:1677–81.
15. Marles RJ, Farnsworth NR. Antidiabetic plants and their active constituents. *Phytomedicine* 1995;**2**:137–89.
16. Li M, Qu W, Wang Y, Wan H, Tian C. Hypoglycemic effect of saponin from *Tribulus terrestris*. *Zhong Yao Cai* 2002;**25**:420–2.
17. Wagner H, Baldt S, Zgainski EM. *Drogen analyse*. Berlin, New York: Springer-Verlag; 1983.
18. Buck WB, Osweiter GD, Van Glder A. *Clinical diagnostic veterinary toxicology*. 2nd ed. Iowa: Kendall/hunt Publishing Company; 1976 [52011].
19. Brosky G, Logothelopoulos J. Streptozotocin diabetes in the mouse and guinea pig. *Diabetes* 1969;**18**:606–9.
20. Trinder P. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. *Ann Clin Biochem* 1969;**6**:24–7.

21. Kirana H, Srinivasan B. *Trichosanthes cucumerina* Linn. improves glucose tolerance and tissue glycogen in non-insulin dependent diabetes mellitus induced rats. *Indian J Pharmacol* 2008;**2008**(40): 103–6.
22. Cheng D. Prevalence, predisposition and prevention of type 2 diabetes. *Nutr Metab* 2005;**2**:2–29.
23. Szkudelski T. The mechanism of alloxan and streptozotocin action in β-cells of the rat pancreas. *Physiol Res* 2001;**50**:536–46.
24. Li M, Qu W, Chu S, Wang H, Tian C, Tu M. Effect of the decoction of *Tribulus terrestris* on mice gluconeogenesis. *Zhong Yao Cai* 2001;**24**:586–8.
25. Cameron-Smith D, Habito R, Barnett M, Collier GR. Dietary guar gum improves insulin sensitivity in streptozotocin-induced diabetic rats. *J Nutr* 1997;**127**:359–64.
26. Anderson RA, Striffler J. Development of a streptozotocin-induced diabetic rat model for studies on the effects of cinnamon on glucose tolerance and insulin secretion. *FASEB* 2008;**22**: 1113–6.
27. Goldberg RB. Lipid disorders in diabetes. *Diabetes Care* 1981;**4**:561–72.
28. Omoruyi FO, Grindley PB, Asemota HN, Morrison EYSA. Increased plasma and liver lipid in STZ-induced diabetic rats: effect of Yam (*Dioscorea cayenensis*) or Dasheen (*Colocasia esculenta*) extract supplements. *Diabetol Croat* 2001;**30**: 87–92.
29. Wilson PWF. High density lipoprotein, low density lipoprotein and coronary heart disease. *Am J Cardiol* 1990;**66**:7A–10A.