Antioxidative and Hypoglycemic Effects of *Delonix elata* and *Vachellia farnesiana* Leaves Extracts on Streptozotocin-Induced Diabetic Male Rats

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**ABSTRACT**

Diabetes Mellitus (DM) is known to be a group of metabolic disorders characterized by an elevated glucose level. Plants are the most promising causes of new therapeutic agents. The usual usage of plant products for the managing of DM has grown up because of the nominal side-effects with the minimal economy as controlling of diabetes without the side-effects is a challenge. The drugs prepared from the plants may play a major role in the treatment. This study aims to inspect the hypoglycemic with antioxidant potentiality of leaves extract from *Delonix elata* (DELE) and *Vachellia farnesiana* (VFLE) in streptozotocin (STZ) male rats with DM. This study incorporates 80 Wistar male rats categorized into eight groups. Normal control rats were appeared in group 1. Untreated DM rats termed as DM controls as in group 2. Groups 3-5 involve the DELE, VFLE and DELE plus VFLE as DM rats. Groups 6-8 were treated as normal rats with DELE, VFLE and DELE plus VFLE respectively. The DM control group inhibited decrease in body weight and increased in the serum levels of glucose, HbA1c, protein and lipid profiles, creatinine, BUN, ALT, AST and MDA, whereas, serum insulin, GPx and CAT levels were reduced. In Gr3-5 of DM rats, extracts disclosed clear influence at body weight, glucose, HbA1c, protein and lipid profiles, liver and kidney functions parameter, and oxidative stress markers. The results revealed the extracts exhibited significant anti-oxidant and hypoglycemic activity which could be the appearance of pharmacologically active ingredients. However, these extracts can be applied alternatively in dealing DM and allied complications. In conclusion, the novel of these plant extracts further should be investigated to reconfirm for predicting their clinical potential as a phytomedicine for DM treatment.

**Keywords:** Diabetes, streptozotocin, *Delonix elata*, *Vachellia farnesiana*, antioxidant, blood, rat.

**Introduction**

Diabetes Mellitus (DM) is categorized as elevated serum glucose levels and known as the metabolic disorder (Baquer et al., 1998). Global prevalence of DM is rising profligately (Azizidooost et al., 2019). The World Health Organization (WHO) has reported that the Kingdom of Saudi Arabia (KSA) ranks second in the prevalence of DM in the Middle East region and seventh in the world (Robert et al., 2017). Oxidative stress is defined as imbalance between oxidants and anti-oxidants. Defense capacity of the body is recommended as optimal mechanism underlying complications with DM and other diseases (Atalay and Laaksonen, 2002). Numerous amendments in DM individuals are oxidative in nature and depend on enlarged oxidative stress (Baynes, 1991). The role of oxidative stress in the etiology of DM and its complications has been increasingly recognized (Brownlee, 2004; Wang et al., 2017; Jiang et al., 2018; Ito et al., 2019; Wang et al., 2019).

Streptozotocin (STZ, 2-deoxy-2-(3-(methyl-3-nitrosoureido) -Dglucopyranose) is a naturally occurring chemical, a broad-spectrum antibiotic that is particularly toxic to the insulin-producing β-cells of the pancreas. STZ is a synthetic antineoplastic agent and is used clinically for the treatment of metastatic islet cell carcinoma of the pancreas. STZ is commonly used to induce DM and it is a highly selective cytotoxic agent to insulin producing pancreatic islet β-cells and is shown to induce DM in various animal models including mice and rats. The chemical induction of DM with STZ has gained popularity because of the relative ease of rendering normal animals diabetic (Luippold et al., 2016; Abraham et al., 2107; Abdelhamid et al., 2108; Banerjee et al., 2019; Zhang et al., 2109).

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Currently, usage of common drugs for DM treatment is costly with strong side effects (Schuster et al., 2005). Globally, the prevalence rate is growing towards the herbal medicine in the human disorders (Azizidoost et al., 2019). Traditional herbal medicines are assumed to have less side effects for treating to DM (Yin et al., 2008). Quick rising need is required for improving new strategies for prevention of DM with limited side effects (Yuan et al., 2016; Khavandi et al., 2013). Present literature documents 800 plant species confirm hypoglycemic activity (Rajagopal and Sasikala, 2008). Delonix and Acacia are genera of flowering plants dispersed in throughout the Southern region of Saudi Arabia. Delonix elata is a species from Fabaceae family, Caesalpinioideae sub-family. D. elata is used for joint pains and in flatulence which has antiinflammatory, antirheumatic, antihyperlipidemic, antimicrobial, antinoceptive and antioxidant activity (Krishnappa et al., 2016). The leaf part was scientifically evidenced to have cytotoxic, hepatoprotective and free radical scavenging activity (Babu and Goud, 2018). Vachellia farnesiana (Acacia farnesiana synonym) plant species belongs to Leguminoseae family; known as medicinal plants used in folk medicinal practices. Additionally, the extracts attained from Acacia have formerly publicized antimicrobial, antihelminthic and antioxidant properties (Alonso-Diaz et al., 2010; Cuchillo et al., 2010; Sanchez et al., 2013; Delgadillo Puga et al., 2015; Afsar et al., 2019). The present study aims to explore probable antioxidative and antidiabetic activity of D. elata and V. farnesiana leaves extracts in male rats.

Materials and Methods

Plant material

The plant leaves (D. elata and V. farnesiana) were freshly collected from outskirts of Al-Baha region of Saudi Arabia. Collected freshly leaves were washed, dried to a constant weight and crushed to moderately soft powder. Two hundred and fifty grams of leaves powder were added to eight liters of hot water and mixed for 180 min. The solutions for opted plants were boiled for an hour and cooled at room temperature. The decoction was filtered and the filtrates were evaporated to dryness under vacuum at 50 °C in a rotary evaporator. The dried residues were stored in airtight containers at -20 °C pending further experimental use.

Experimental animals

Male albino Wistar rats with a body weight of 196-223 grams were used for this study. Animals were maintained at 20±1°C with 65% of relative humidity with 12 hours of each dark and light cycle. Eating and drinking stuffs were supplied. The experiment was carried out as per King Abdulaziz University ethical committee.

Induction of experimental DM

Rats were fasted for DM induction for 12 hours without unrestricting to water. Freshly prepared STZ solution (60 mg/kg body weight) in citrate buffer (0.1M; pH-4.5) was inserted to overnight abstained rats. Diabetic state evaluated in STZ-treated rats by determining abstaining serum at 72 hours of post to STZ injection. Rats with blood glucose levels greater than 17 mmol/L were confirmed as diabetic models.

Experimental treatments

Normal and diabetic rats (n=10) were assigned into 8 groups. Normal rats (controls) are assigned in group1. Diabetic rats (controls) in group 2. Diabetic rats are categorized supplemented orally by DELE (group 3) and VFLE (group 4) of 300 mg/kg body weight/day. However, group 5 is combined combination of DELE (150 mg/kg) and VFLE (150 mg/kg) body weights/day. Normal rats of groups 6 and 7 are orally supplemented with DELE and VFLE of each 300 mg/kg body weight/day. Group 8 as combined combination is supplemented with DELE (150mg/kg) and VFLE (150 mg/kg) body weights/day.

Body weight

After the efficacious indicational experiment of DM, body weights of rats (normal and diabetes) were measured using electronic weighing balance during day 1 and after completion of 6 weeks as final body weight.
Hematobiochemical assay

After completion of 6 weeks, complete rats were fasted for 8 hours prior to blood samples collection, anesthetized and blood were drawn from orbital venous plexus. Blood samples were transferred in (1) heparinized blood samples were used for Hb1Ac tests. (2) Serum samples were unglued from non-heparinized blood sample centrifuged at 3000 rpm for 10 min and used for serum glucose, total protein, albumin, lipid profile, AST, ALT, creatine, BUN measurements using Dimension Vista® 1500 system, USA. As per Judzewitsch et al. (1982) was used to evaluate serum levels of insulin. Additionally, the levels of serum malondialdehyde (MDA), catalase (CAT) and glutathione peroxidase (GPx) were evaluated according to the methods of Ohkawa et al. (1979), Aebi (1984), and Paglia and Valentine (1967) respectively.

Statistical analysis

Statistical data were analyzed as mean ± standard deviation of variables in different groups using ANOVA variance. Software (SPSS), version 22.0 was applied for performing statistics. The significance levels were tested at \( P \leq 0.05 \).

Results

The body weights of all the experimental groups are shown in Fig1. After six weeks, maximum increase of body weight obtained in nondiabetic rats of 8 group (+47.7%) followed by groups 6 (45.7%), 7 (+45.1%) and 1 (+42.1%). Treated diabetic rats with DELE, VFLE and DELE+VFLE showed mild increase in body weight gain which is reached +16.3% (group 3) +15.0% (group4) and +19.1% (group 5). The non-significant body weight gain was noted in diabetic rats of group 2 (-17.2%).

Fig. 1: Changes of body weight after six weeks in control (group 1), STZ (group 2), STZ plus DELE (group 3), STZ plus VFLE (group 4), STZ plus DELE and VFLE (group 5), DELE (group 6), VFLE (group 7), and DELE and VFLE (group 8) treated rats.

Fasting glucose, insulin and HbA1c values were showed in Fig 2 A-C. Statistical significance was observed in fasting glucose in diabetic rats of group 2 \( (P \leq 0.000) \), group 3 \( (P \leq 0.000) \), group 4 \( (P \leq 0.000) \), and group 5 \( (P \leq 0.000) \); whereas, insulin values were decreased in diabetic rats of group 2 \( (P \leq 0.000) \), group 3 \( (P \leq 0.000) \), group 4 \( (P \leq 0.000) \) and group 5 \( (P \leq 0.001) \). HbA1c values were statistically enhanced in diabetic rats of group 2 \( (P \leq 0.000) \), group 3 \( (P \leq 0.001) \), group 4 \( (P \leq 0.000) \) and group 5 \( (P \leq 0.001) \) compared with normal control rats of group 1.
A

Groups

Glucose (mmol/L)

Control  STZ  STZ + DELE  STZ + VFEL  STZ + DELE + VFLE  DELE  VFLE  DELE + VFLE

B

Groups

Insulin (µIU/L)

Control  STZ  STZ + DELE  STZ + VFEL  STZ + DELE + VFLE  DELE  VFLE  DELE + VFLE

*  **
The results of Table 1 show the levels of serum total protein, albumin, triglycerides and cholesterol. In comparison with normal control rats of group 1, the value of serum total protein was increased in diabetic rats of group 2 \((P \leq 0.001)\), while these parameters were not changed in other treated groups. Insufficient alteration was detected in serum albumin levels in all the treated groups equated with normal control rats of group 1. Remarkable elevation in triglycerides was observed in diabetic rats in groups 2 \((P \leq 0.001)\), 4 \((P \leq 0.02)\) and 5 \((P \leq 0.03)\). A significant increase in cholesterol levels were recorded in diabetic rats of groups 2 \((P \leq 0.004)\), 4 \((P \leq 0.03)\) and 5 \((P \leq 0.002)\).

Table 2 demonstrates the ALT, AST, creatinine and BUN levels. A significant increase was observed in ALT levels in groups 2 \((P \leq 0.000)\), 4 \((P \leq 0.003)\) and 5 \((P \leq 0.000)\) when compared with normal control rats. Diabetic rats of groups 2 \((P \leq 0.000)\), 3 \((P \leq 0.03)\), 4 \((P \leq 0.000)\) and 5 \((P \leq 0.001)\) showed statistically increase of serum AST. Serum creatinine levels were found to be increase
in diabetic rats of groups 2 (P ≤ 0.002), 4 (P ≤ 0.05) and 5 (P ≤ 0.02). BUN levels were significantly evoked in diabetic rats of groups 2 (P ≤ 0.000), 4 (P ≤ 0.000) and 5 (P ≤ 0.001) when compared with normal control rats of group 1.

Table 2: The values of serum ALT, AST, creatinine and BUN of control (group 1), STZ (group 2), STZ plus DELE (group 3), STZ plus VFLE (group 4), STZ plus DELE and VFLE (group 5), DELE (group 6), VFLE (group 7) and DELE plus VFLE (group 8) treated rats after six weeks.

| Treatments          | Parameters | ALT (U/L) | AST (U/L) | Creatinine (µmol/L) | BUN (mmol/L) |
|---------------------|------------|-----------|-----------|---------------------|--------------|
| Control             |            | 45.17±3.06| 109.23±5.50| 35.63±2.46          | 6.68±0.37    |
| STZ                 |            | 131.22±13.52\(^b\) | 215.50±9.35\(^b\) | 57.17±7.91\(^b\) | 18.57±3.46\(^b\) |
| STZ + DELE          |            | 48.33±4.14 | 124.17±10.16\(^a\) | 38.18±6.70       | 7.22±1.50    |
| STZ + VFLE          |            | 67.77±9.27\(^a\) | 165.00±13.22\(^a\) | 43.52±6.42\(^a\) | 11.53±1.48\(^a\) |
| STZ + DELE and VFLE|            | 66.83±3.76\(^a\) | 155.67±18.53\(^b\) | 45.62±5.73\(^a\) | 11.40±1.83\(^a\) |
| DELE                |            | 46.33±2.89 | 110.33±2.42 | 34.83±2.87         | 6.73±0.64    |
| VFLE                |            | 46.00±3.06 | 113.00±4.23 | 35.77±2.05         | 6.66±0.74    |
| DELE + VFLE         |            | 45.83±3.490| 112.33±6.09 | 36.17±2.52         | 6.25±0.87    |

Data represent the means ± SD of 6 animals per group. \(^a\) Indicates a significant difference between control and treated groups. \(^b\) Indicates a significant difference between group 2 and groups 3, 4, 5, 6, 7 and 8.

Notable enhancement in the value of serum MDA was observed in diabetic rats of groups 2 (P ≤ 0.000), 3 (P ≤ 0.001), 4 (P ≤ 0.000) and 5 (P ≤ 0.002) (Fig. 3A). Significant declines in the value of serum CAT were observed in diabetic rats of groups 2 (P ≤ 0.000), 3 (P ≤ 0.001), 4 (P ≤ 0.001) and 5 (P ≤ 0.01) (Fig. 3B). Figure 3C showed that the values of serum GPx were statistically inhibited in diabetic rats of groups 2 (P ≤ 0.000), 3 (P ≤ 0.003), 4 (P ≤ 0.001) and 5 (P ≤ 0.004). As shown in Figures 2 and 3, and Tables 1 and 2, the values of all measured biochemical parameters were remarkably unchanged in normal rats supplemented with DELE (group 6), VFLE (group 7) and DELE plus VFLE (group 8) compared with normal control rats.

A

![Graph showing comparison of MDA values across different groups](image-url)
Fig. 3A-C: The levels of serum MDA (A), CAT (B) and GPx (C) in control (group 1), STZ (group 2), STZ plus DELE (group 3), STZ plus VFLE (group 4), STZ plus DELE and VFLE (group 5), DELE (group 6), VFLE (group 7) and DELE plus VFLE (group 8) treated rats after six weeks.*Indicates a significant difference between control and treated groups. **Indicates a significant difference between group 2 and groups 3, 4, 5, 6, 7 and 8.

Discussion

DM is known to be as non-modifiable disease ripens throughout the world. DM can lead to T1DM, T2DM with micro and macrovascular complications (Tian et al., 2017). In the current era, medicinal plants are gaining immense important because of their various photoconstituents with
distinctive properties. The present study confirms induction in STZ leads to decrease in body weight gain and insulin value associated with increases glucose, HbA1c and total protein, triglycerides and cholesterol values in normal control diabetic rats. The function of STZ has an ability to hoard in pancreatic β-cells through glucose transporter 2 (GLUT-2). Furthermore, STZ causes a generation of reactive oxygen species (ROS) in β-cells. Pancreatic β-cells consists of weak antioxidant may damage nucleic acid, apoptosis and destruction of β-cells (Lenzen et al., 2008; Garcia-Lafuente et al., 2009). This theory confirms increase in the glucose and HbA1c values and decrease in insulin. HbA1c is the gold standard test to confirm the minimum of 90 days of average value of glucose levels and high levels confirm the poor control of glucose levels (Mahajan and Mishra, 2011).

STZ-induced DM is associated with characteristic loss in body weight inversely relate to raise in muscle wasting which occurs due to loss in tissue proteins (Swanston-Flatt et al., 1990). Preservation of catabolism occurs due to decrease in body weight, which could be due to the proteolytic breakdown of tissue proteins in amino-acids further oxidized as cells were not able to fascinate blood glucose for the source of metabolic energy. However, these amino acids may be utilized as gluconeogenic precursors in liver. Additionally, glycojenolysis and lipolysis might contribute towards decrease in body fat in DM cases (Franz et al., 2003; Postie et al., 2004; Sekar et al., 2005). The reduction in body weight of DM rats is could be the muscle loss and adipose tissues that dependent to insulin for using of glucose as fuel (Ashrafi et al., 2017).

In the pathogenesis of DM, lipids play a vibrant role; associated with major abnormalities in fatty acid metabolism (Tomkin, 2008). Hypertriglycerideremia and hypercholesterolemia are known to be the common cause of lipid abnormalities in DM (Leiter et al., 2006). A significant raise in triglycerides and cholesterol can be accredited to endogenous changes in lipid homeostasis cause with DM. Mahe et al. (1995) documented hypercholesterolemia in STZ-induced DM rats results from increase in intestinal absorption and synthesis in cholesterol. Abnormal serum lipids levels in DM rats might be due to disturbance in the regulation of the activity of the hormone-sensitive enzyme, lipase, by insulin due to its deficiency or absence. In diabetic condition, the concentration of serum free acids is elevated as a result of free fatty acid outflow from fat deposited, where the balance of the free fatty acid esterification- triglyceride lipolysis cycle is displaced in favour of lipolysis (Maghrain et al., 2004; Sirwalker et al., 2004). Elevation in both triglycerides and cholesterol levels could be the increase in cholestrogenesis, uptake in fatty acids and triglycerides deposits in liver (Babu et al., 1997; Rajasekaran et al., 2006).

The present significant increase in the levels of serum ALT and AST as markers of liver function, and creatinine and BUN as markers of kidney function in the diabetic control rats suggested that DM could induce hepatic and renal injuries. Liver and kidney are the major organs connected with biochemical pathways to regulate homeostasis. The enhanced levels of ALT and AST might be leakage in the enzymes and functional loss integrity of cell membrane in liver (Swamy et al., 2018). Diabetic hyperglycemia induces growth in creatinine, BUN and uric acid, is considered to be significant markers of renal dysfunction (El-Demerdash et al., 2005; Saeed et al., 2008). Abnormal levels creatinine and urea in DM rats were compared with controls is an indication of renal dysfunction and metabolic disturbance induced by STZ-DM (Helal et al., 2014).

In this study, MDA levels were increased in STZ-induced DM rats and CAT and GPx levels were lowered when compared with normal control group. The increase in MDA levels confirms oxidative stress sustained sufficiently could cause free radical in cellmembrane; thus, MDA is confirmed as good indicator for assessing oxidative stress in degenerative diseases as DM (Padalkar et al., 2012). The serum antioxidant enzyme activities (CAT and GPx) were lowered in DM rats which attributed to induction of hyperglycemia; main cause for regulation in free radical levels in ROS which can lead to lipid peroxidation and altered antioxidant defense and further impair in glucose metabolism (Balasubhashini et al., 2004). Hyperglycemia in DM causes oxidative stress through persuading free radical formation via glucose autoxidation, poloyl pathway and non-enzymatic glycation of proteins (Obrosova et al., 2002). Abnormal normal levels of free radical can harm the cellular organelles and enzymes (Maritim et al., 2003). Further, formation of free radicals was grown and antioxidant potential was lowered in DM rats. Imbalance of both oxidant and antioxidant defense system was seen in modification of antioxidant factors such as MDA, CAT and GPx which were used as markers in the oxidative stress studies (Al-Rawi et al., 2011; Kulkarni et al., 2014; Omodanisi et al., 2017; Oguntibeju, 2019).

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The current results indicate the treatment with extracts significantly reduced the alterations of body weight and biochemical parameters induced by STZ. The present results indicate that these extracts decrease glucose and HbA1c levels and increase insulin level in diabetic rats. Moreover, protein and lipid profiles, liver and kidney markers and oxidative stress markers were improved in diabetic rats supplemented with leaves extracts. Hypoglycemic effect of certain plants has been ascribed to insulin effect by growth in pancreatic secretion of insulin through β-cells (Pari and Amarnath Satheesh, 2004). Some plant extracts are known to inhibit hepatic production of glucose (Eddouks et al., 2003). DM treatment with plant medicines has proven safer than the synthetic drugs (Yeh et al., 2003). Oxidative stress in DM has been documented to co-exist with decrease in endogenous anti-oxidant status and is caused by dysfunction in pancreatic β-cells (Kajimoto and Kaneto, 2004); plays a major role in DM pathogenesis and its complications such as atherosclerosis, nephrotic, neurological and renal diseases (Sepici-Dincel et al., 2007). Oxidative stress is suggested as mechanism underlying DM and diabetic complications, which results from an imbalance between radical generating and radical scavenging systems (Neethu et al., 2014). The current study confirmed that oral administration of DELE, VFLE and DELE+VFLE prevented oxidative stress in STZ-induced diabetic rats. The protective action of these extracts possibly via their antioxidant effect in reversing biochemical alteration induced by DM. Therefore, the hypoglycemic properties of these extract can be credited to rich antioxidant contents. Additionally, the probable possible mechanism of hypoglycemic effects on these extracts might be affecting the pancreatic insulin to lowers the glucose levels. Moreover, the present study results also in agreement with benefiting the leaves extracts for management of DM. Further research is required to support the use of natural products in managing DM. Finally, the extracts should be further investigated to isolate the active constituents for hypoglycemic activity and development of new drugs for DM treatment.

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