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Original article

Antidiabetic and antihyperlipidemic effect of *Duvalia corderoyi* in rats with streptozotocin-induced diabetes

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ABSTRACT

Diabetes mellitus (DM) is a metabolic syndrome distinguished with glucose increasing in blood, insulin resistance, and hyperlipidemia. It results in decease of millions of people yearly. *Duvalia corderoyi* is a traditional diabetes and hypertension medicine from the Arabian region. *D. corderoyi* extract was administered to diabetes rats for estimate its anti-diabetic and antihyperlipidemic activities in Wistar rats were induced using (60 mg/kg) of streptozotocin (STZ) intraperitoneally. The rats were randomly divided into five groups: control, diabetic, diabetic receiving glibenclamide, and two diabetic *D. corderoyi*-treatment groups. Rats were weighted weekly, and the biochemical analysis were carried out in serum, and liver homogenate samples. Body weight of diabetic rats was lessening significantly *D. corderoyi* improved body weight, glucose concentration, lipid profiles, hepatic enzymes, urea, creatinine, insulin, and HDL-C. These results are the first to indicate the potential antidiabetic and antihyperlipidemic activities of *D. corderoyi*.

1. Introduction

Diabetes mellitus term define the heterogeneous metabolic disorder marked by the occurrence of hyperglycemia resulted from insulin secretion impairment, insulin action defective or both. An estimated reported 3% of global peoples were suffering from this disease, and the WHO expected that in 2025 the rate of diabetics will be 6% (Attele et al., 2002; Andrade-Cetto and Heinrich, 2005; Punthakee et al., 2018). In 2011, the world has a population of seven billion people, 366 million adults between 20 and 79 years of age have diabetes (IDF, 2011). DM is the utmost notable chronic conditions of pancreatic hormones and involves hyperglycemia and disrupted lipid, carbohydrate, and protein metabolism. These effects are resulted from deficiency of insulin and insulin resistance, or together (Katzung, 2012), and participate in the increased generation of free radicals (Saravanan and Ponmurugan, 2011). There are many complications related to chronic diabetes, especially with regard to blood vessels that cause eyes and kidney disease, in addition to an increase cardiovascular disease risk (CVD) (Punthakee et al., 2018). Oxidative stress acts a critical part in diabetes long-term complications and is accompanying by the high peroxidation of lipid (Elangovan et al., 2000). Clinical and experimental studies of DM have indicated that augmented oxidative stress and modifications in antioxidant capacity induce the complications of diabetes mellitus (Baynes, 1991).

As the prevalence of DM increases, there is an urgent need for highly effective drugs and greatly reduce side effects. A wide variety of drugs are currently used to treat DM, while reducing blood glucose, these drugs have a tendency to cause obesity and hyperandrogenemia. There are many plants that are widely used for therapeutic purposes of certain diseases including DM, because plants are believed as the fewer in their toxicity, cost less, and cause fewer side reactions comparing with artificial medications (Stavric, 1994). Antioxidants within dietary plants are appropriate choice for the prevention of, or protection from, the damage of organs that occurring by the species of free radical (Stavric, 1994; Corcoran et al., 2007). Epidemiological researches indicate that administration of fresh vegetables, fruits and the foods that slightly processed guarantee better defense from oxidative stress

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diseases such as cancer, obesity, cardiovascular disease, type 2 diabetes, and cataracts (Halvorsen et al., 2002).

The therapeutic efficacy of most medicinal plants used to treat DM is not sufficiently validated (Babu et al., 2002). Therefore, is important to investigate drugs from traditional medicinal plants. Recent technical experiments have shown that many herbs are effective against diabetes (Kar et al., 1999). The Asclepiadaceae-Apocynaceae family consists of 2500–3000 species including 170–200 genera. These include *Duvalia, Orbea, Huernia, Caralluma, Hoodia, Stapelia, Echidnopsis, Edithcolea, Frerea, Huerniopsis, Larryleachia, Orbeanthus, Piaranthus, Pseudolithos, Quaqua, Rhytidocaulon, Stapelianthus, Tavaresia, Tridentea,* and *Tromotriche*, which are all originate in the Arabian Peninsula, from Saudi Arabia to South Yemen (Leach, 1988; Bruyns, 1998; Szymczak and Kwiatkowski, 2003; Bruyns, 2005; Thiv and Meve, 2007; Bruyns, 2010; Sireesha et al., 2017). Most members of this family have medicinal benefits. Plants such as *Marsdenia tenacissima, Hemidesmus indicus, Cryptolepis buchanani* and *Caralluma umbellata*, are used in traditional drug systems to treat some diseases such as asthma, cough, liver disorders and cancer, besides being used as antinociceptive and anti-inflammatory drugs (Alzahrani et al., 2015).

Duvalia species are succulent, perennial plants with stemshapes that vary from globose to finger-like. In cross section their stems have four or five angles. It is characterized by its green legs that turn red when exposed to sunlight. Its triangular leaves do not last long and have bile glands. Additionally, the outer parts of the coronal lobes are obtuse and can be rounded or not rounded (Meve, 1997).

D. corderoyi is one family plant Apocynaceae, it is one of the cactus succulent plants that endemic in Yemen, Saudi Arabia. It grows in dry regions, is used in some Arabic countries including Yemen, Saudi Arabia, and Oman, against the hunger, and as a vegetable by the country peoples for centuries. *D. corderoyi* is known for its use in appetite regulation and for stomach disease. In our study, we attempted to estimate the antidiabetic and antihyperlipidemic effects of *D. corderoyi* in rats with streptozotocin-induced diabetes.

2. Materials and methods

2.1. Chemicals

Glibenclamide was obtained from UFC Biotechnology (Buffalo, NY, USA). Streptozotocin was obtained from Thermo Fisher (Kandel) (GmbH, Karlsruhe, Germany). All drugs were stored at the recommended temperature (below 20 °C). Carboxymethyl cellulose was obtained from Loba Chemicals (Mumbai, India). Phosphate-buffered saline (PBS) was obtained from Hoefer Inc. (San Francisco, USA).

2.2. Plant collection and identification

D. corderoyi stems were collected from various sources in Yemen and Saudi Arabia. The plant was identified and authenticated by Dr. Hassan Ibrahim (Associate Prof. of Plant Taxonomy), Biology Department Herbarium, Faculty of Science, Sana'a University, Yemen. The specimen of the plant was retained in the herbarium with voucher specimen No. BHSS 1500. The plant samples were air dehydrated for one month, milled, packaged in polyethylene bags, and stored at 4 °C under dark conditions for later use. Plant samples were air dehydrated for one month, milled, and stored until use at 4 °C after packaged in special bags.

2.3. Preparation of D. corderoyi methanol extract (MDC)

Powdered *D. corderoyi* stem samples were macerated in methanol for 72 h to allow for sufficient extraction at room temperature (15–25 °C) with periodic agitation. The soluble substances were separated by filtration using filter paper Whatman No. 1. The fluid filtrate was concentrated and evaporated completely at 60 °C by rotary evaporation for maximum yield. The yield was calculated, and the samples were collected and stored in the dark at 4 °C for future use (Ramachandraiahgari et al., 2012).

Powdered *D. corderoyi* samples were washed with tap water and pulverized after drying on blotting paper. Then 100 g of milled plant ingredients were extracted by methanol in a Soxhlet extractor, and the MDC was dried in a rotary evaporator.

2.4. Analysis of D. corderoyi using GC–MS

GC–MS analysis of the extract was performed using Agilent GC–MS. The sample was injected into silica capillary column (30 m × 0.25 mm I.D. × 0.25 μm film thickness). The initial oven temperature was programmed from 70 °C; hold for 2.0 min, to 305 °C at 20 °C/min and hold for 1 min. Helium gas (99.999%) was used as carrier gas at a constant flow rate of 1.2 mL/min. The injector temperature was set at 250 °C and the ion source temperature was set at 230 °C. Total GC running time was 50 min. The relative percentage amount of each compound was calculated by NIST08 library (Gallo and Sarachin, 2009; Juliet et al., 2018; Kyslychenko et al., 2010; Lalitha et al., 2015; Vidal et al., 2016; Vlaisavljevic et al., 2014).

2.5. Animals

Wistar albino male rats (Fifty) with a weight of 300 ± 20 g were gotten from Experimental Centre of Animal Care, faculty of Pharmacy, King Saud University, Riyadh, Saudi Arabia. Rats were kept individually in stainless steel cages at temperature (22 °C), 12 h light/dark cycle, under relative humidity of 50% ± 5. The protocol of experimental and conditions were accepted by the official Review Board at Princess Nourah University, Riyadh, KSA (IRB Number18-0051).

2.6. Diabetes induction

After acclimatization for a week, rats were fasted overnight. The next day the streptozotocin dose was calculated based on body weight. Streptozotocin was diluted by (0.1 M) citrate buffer solution (pH 4.5), and intraperitoneal injection of 60 mg/kg of body weight was administered to 40 rats. The same volume of buffer solution was given to normal control rats. Glucose concentrations of rats measured after 72 h, using test strips glucometer (ACCU-CHEK Active, Germany). One droplet of blood samples was loaded from a tail vein incision onto each strip. Rats of 250 mg/dL blood glucose or above were considered as diabetic.

2.7. Experimental treatments

The rats were randomly divided into five groups each group contains 10 rats, the rats groups then named and treated as follows: Control, normal control; DMC, diabetes mellitus control; GBC, diabetic rats administered glibenclamide (600 μg kg^{1}/day); MDC100, diabetic rats administered MDC (100 mg·kg^{1}/day); and MDC200, diabetic rats administered MDC (200 mg·kg^{1}/day) the period of treatment was 30 days for all groups.

After the experimental period, rats were weighed and anesthetized with diethyl ether. Heart punctures were used for blood samples collection into unpreserved tubes, then centrifuged at 3000 rpm for 10 min to obtain blood serum. Liver sections were taken and packaged in aluminium foil. All samples were at −80 °C until required for analysis.

2.8. Tissue preparation

Liver samples weighing 0.2 g were homogenized with a ten-fold amount of ice cold PBS (pH = 7.4) by a homogenizer (Ultra-Turrax IKA, Deutschland, Germany) at high speed for 5–10 s. The homogenates were then relocated in 1.5 mL tubes and kept at −80 °C for further use.

2.9. Monitoring rat body weight

The rats were weighted every week through the study period and liver weight was measured using a specialized balance (Adam HCB 3001, UK) at the end of the experiment.

2.10. Biochemical measurements

2.10.1. Glucose and insulin levels

Serum glucose and insulin levels were measured using Colorimetric Assay Kits (Cayman Chemical, Ann Arbor, Michigan).

2.10.2. Lipid profiles

Serum and liver total cholesterol, triglycerides, LDL-C, and HDL-C levels in were determined by enzymatic colorimetric methods using diagnostic kits (Crescent, Jeddah, KSA).

2.10.3. ALT and AST

The Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) activities were assessed using kits in serum as instructed by the manufacturer's (UDI, Dammam, KSA).

2.10.4. Creatinine and urea

Creatinine in serum was measured by colorimetric assay kit (Cayman Chemical, Ann Arbor, Michigan). Urea was measured using a Urea kit (MyBioSource, San Diego, California, USA) according to the producer's instructions.

2.11. Statistical analysis

The study results were analysed statistically by SPSS V. 21 software. Data were expressed as mean and stand deviation (Mean ± SD). One-way analysis of variance ANOVA and turkey's multiple post hoc test were utilized for determine the significant differences ($P < 0.05$) between groups.

3. Results

3.1. D. corderoyi compounds

The GC–MS spectrum of the methanolic extract of *Duvalia corderoyi* showed the presence of 41 compounds. Some of the identified compounds were biologically active (Table 1).

3.2. Body weight changes

As it appears in the Table2. Body weights of all rats' groups were similar at the starting of the experiment. In weeks two and three, weight decreased in all groups, except in the control, which increased. In week four the average body weights of GBC, MDC200, and MDC100 rats began to increase compared with those in the diabetic control group, which continued to lose weight. Statistically, there was no difference in weight during week one. In week two the weights of rats of the control, GBC, and DMC groups significantly exceeded those of rats in the MDC100 and MDC200. In week three, the weights of rats in the control, GBC, and MDC200 groups were highly significantly different than those in the DMC and MDC100 groups. In week four, all treatment groups displayed highly significant improvements in body weight compared by diabetic rats at $P < 0.05$ level.

3.3. Glucose and insulin levels

The effects of the *D. corderoyi* extract on serum glucose and insulin concentrations in rats STZ-induced diabetes were measured at the end of the experiment (Fig. 1). Glucose levels were higher in the diabetic control DMC rats than in the control, GBC, MDC100, and MDC200 rats. Highly significant differences were observed between DMC rats and rats from all other groups, with $P < 0.05$. Also, significant differences were appeared between the rats of the control, GBC, and MDC100, MDC200 groups, while there were no significant differences between rats of the MDC100 and MDC200 groups (Fig. 1A). Serum insulin levels were higher significantly in control group and significantly lower in the DMC diabetic control rats (Fig. 1B). Compared with those measured in the DMC group, insulin levels in the GBC, MDC100, and MDC200 groups were elevated, with highly significant and moderately significant differences for the GBC and MDC200 groups, respectively. While there are no significant differences between the MDC100 and DMC groups at the $P < 0.05$ level.

3.4. Triglycerides in serum

Triglyceride concentrations were elevated in all streptozotocin-induced rats (Fig. 2A). Treatment with glibenclamide and *D. corderoyi* extract decreased the level of serum triglycerides. This effect was strongest in the GBC group, followed by the MDC200 and MDC100 groups. Statistically no significant differences were found between control group and all treated rats' groups at the $P < 0.05$ level. But a significant difference was obtained between DMC rats' group and all other groups ($P < 0.05$).

3.5. Cholesterol levels in serum

The DMC group had the highest serum cholesterol concentration, followed by MDC100, GBC, control, and MDC200 groups (Fig. 2B). The changes between the DMC group and each of the control and treatment groups were high significantly at the $P < 0.05$ level. Treatment with 200 $mg{\cdot}kg^{1}{\cdot}day^{1}$ of *D. corderoyi* extract produced the greatest significant difference in cholesterol lowering from the DMC control at the $P < 0.05$ level.

3.6. LDL-C in serum

Compared to the negative control, serum LDL-C concentrations were augmented significantly at $p < 0.001$ in DMC, and at $p < 0.01$ in all treated groups (Fig. 2C). The LDL-C levels were lowest in the GBC group followed by the MDC200, MDC100 groups and then the MDC group. Highly significant differences ($P < 0.05$) were noticed between the DMC and the control, GBC, MDC200, and MDC100 groups. While no significant differences were found between all of the treatment groups.

3.7. HDL-C in serum

Serum HDL-C concentrations were decreased in all with streptozotocin-induced diabetes rats. HDL-C levels remained high (84.43 mg/dL) in the control group. After the treatment period, HDL-C rose again in the GBC, MDC200, and MDC100 groups to 78.41, 77.41, and 45.54 mg/dL, respectively. Statistical analysis revealed that HDL-C levels in the control, GBC, MDC200, and MDC100 groups rose with significant differences to those of the DMC group ($P < 0.05$). There were no significant differences

Table 1
GC–MS analysis of methanol extract of bioactive compounds from *Duvalia corderoyi*.

No	Retention time (min)	Name	Peak area (%)	Compound nature	Biological activity
1	11.739	Benzofuran, 2,3-dihydro-	0.35	Phenyl derivative	n
2	14.777	Propane, 1,2,3-trimethoxy-	1.01		n
3	18.148	Phenol, 2,4-bis(1,1-dimethylethyl)-	0.44	Phenol	n
4	19.532	Benzenemethanol, alpha-1-propenyl-	0.77	Phenyl alcohol	n
5	19.704	11-Tricosene	0.57	Aliphatic alkene	1Sex pheromone in some beetle males (genus Chauliognathu)
6	20.431	Megastigmatrienone	1.76	Ketone	2,3Aroma nature and cytotoxic activity
7	21.644	Phenol, 2,5-bis(1-methylpropyl)-	0.66	Phenol	n
8	22.765	Tetradecanoic acid	0.58	Organic acid	n
9	22.908	alpha-D-Glucopyranoside, alpha-D-glucopyranosyl	0.36	Disaccharide	n
10	23.366	4,5-Pyrimidinediamine, 6-methyl-	0.76	Nitrogenous base	n
11	26.17	n-Hexadecanoic acid	8.88	Organic acid	4Anti-inflammatory, antioxidant, pesticide
12	28.911	*cis*-Vaccenic acid	2.55	Organic acid	n
13	29.248	Octadecanoic acid	0.58		n
14	42.386	Silicic acid, diethyl bis(trimethylsilyl) ester	5.70	Acid	5Antioxidant, antimicrobial
15	42.741	Silicic acid, diethyl bis(trimethylsilyl) ester	3.82	Ester	5Antimicrobial, antitumor
16	43.421	β-Sitosterol	13.60	Steroid	6Antimicrobial, anti-inflammatory, anticancer, antiarthritic, antiasthma, Diuretic
17	44.474	Lupeol	21.35	Triterpene	7Antiprotozoal, antimicrobial, anti-inflammatory, anti-tumor and chemopreventive properties. A Dipeptidyl peptidase-4 inhibitor and prolyl oligopeptidase inhibitor

n, no activity reported.

Table 2
The effect of the *Duvalia corderoyi* extract on body weight of rats streptozotocin-induced diabetic (mean, SD, n = 10).

Groups	1st W		2nd W		3rd W		4th W	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Control	301.30	8.82	319.50^{a}	6.84	338.10^{a}	7.65	359.60^{a}	7.20
DMC	298.40	11.87	253.80^{a,b}	13.46	192.90^{c}	27.30	161.40^{c}	22.98
GBC	295.90	13.96	264.50^{a,b}	17.09	253.60^{b}	21.67	276.40^{a,b}	15.26
MDC100	296.10	11.28	229.10^{b}	8.03	173.10^{c}	24.70	170.80^{b}	11.63
MDC200	298.80	13.56	248.10^{b}	18.17	225.70^{b}	12.69	259.90^{b}	10.82

The letters in columns indicate differences of significant at $p < 0.05$. W, week.

between the control and treatment groups, and the treatment groups did not significantly differ from each other (Fig. 2D).

3.8. Liver lipid profiles

We assessed the effect of the *D. corderoyi* extract on liver triglycerides, total cholesterol, LDL-C and HDL-C levels in rats with streptozotocin-induced diabetes (Fig. 3). Liver total cholesterol in DMC was upper than that of other groups. Liver cholesterol in the GBC, MDC100, and MDC200 groups decreased to below that of the control. Liver triglycerides (TG) concentration was high in the DMC group in comparison with the control, with high significant differences ($P < 0.05$). Liver TG of the groups treated with GBC and *D. corderoyi* was significantly reduced compared with that of DMC. Correspondingly, liver LDL-C was elevated significantly in STZ-induced diabetes rats in comparison with that of the control. Levels of liver LDL-C in GBC, MDC100, and MDC200 groups were significantly reduced compared with those in the MDC group ($P < 0.05$). In contrast to liver LDL-C, streptozotocin lowered the liver HDL-C, but the administration of *D. corderoyi* clearly improved the levels of liver HDL-C, especially in MDC200, where there was significant improvement, with results close to those of the GBC and control groups. For the MDC100 group, liver HDL-C levels also improved but didn't significantly differ from those of the DMC group.

3.9. ALT and AST

We examined the effect of *D. corderoyi* extract on the serum ALT and AST activities in rats with streptozotocin-induced diabetes (Fig. 4). The ALT and AST activities were elevated significantly in DMC group compared with those of the control

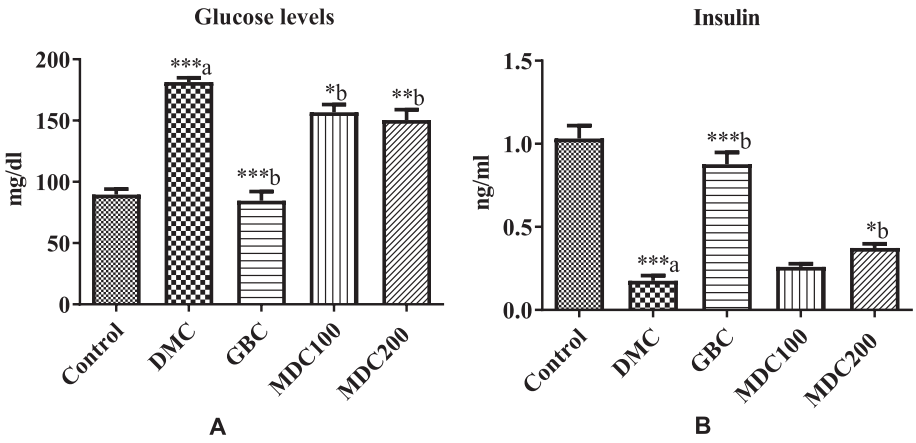

Fig. 1. The effect of *Duvalia corderoyi* on serum glucose and insulin concentration in diabetic rats. Data are the mean ± SD. *** = p < 0.001, ** = p < 0.01, * = p < 0.05 are the significant difference in comparing with normal control. The letters indicate significant difference from diabetic rats. Control, normal control; DMC, diabetes mellitus control; GBC, diabetic rats administered glibenclamide (600 μg·kg^{1}·day^{1}) for 30 days; MDC100, diabetic rats administered MDC (100 mg·kg^{1}·day^{1}) for 30 days; and MDC200, diabetic rats administered MDC (200 mg·kg^{1}·day^{1}) for 30 days.

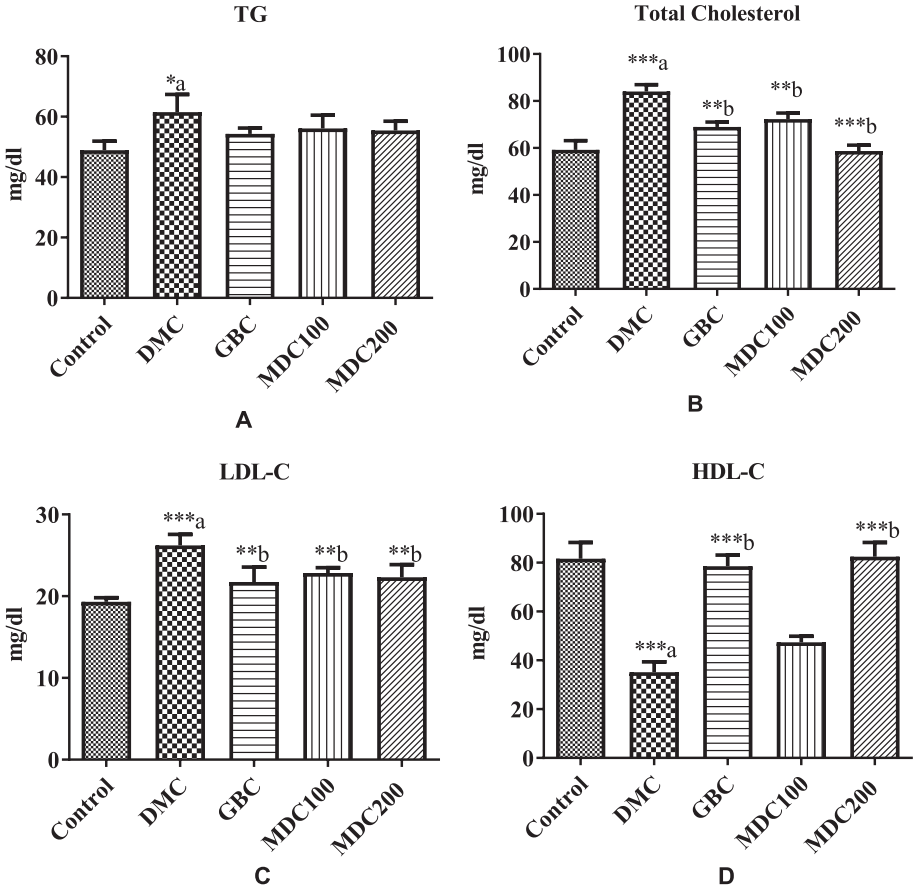

Fig. 2. The effect of *Duvalia corderoyi* extract on serum cholesterol, triglycerides, LDL-C and HDL-C levels in STZ-induced diabetic rats. Data are the mean ± SD. *** = p < 0.001, ** = p < 0.01, * = p < 0.05 are the significant difference in comparing with normal control. The letters indicate significant difference from diabetic rats. Control, normal control; DMC, diabetes mellitus control; GBC, diabetic rats administered glibenclamide (600 μg·kg^{1}·day^{1}) for 30 days; MDC100, diabetic rats administered MDC (100 mg·kg^{1}·day^{1}) for 30 days; and MDC200, diabetic rats administered MDC (200 mg·kg^{1}·day^{1}) for 30 days.

rats. Rats treated with glibenclamide and *D. corderoyi* extracts had decreased serum ALT and compared with the control. ALT activity in the GBC and MDC200 groups dropped significantly compared with that of DMC, but no significant differences were accrued between MDC100 and DMC at the P < 0.05 level. AST activity decreased in all treatment groups, showing a highly significant difference from that measured in the DMC group at the P < 0.05 level.

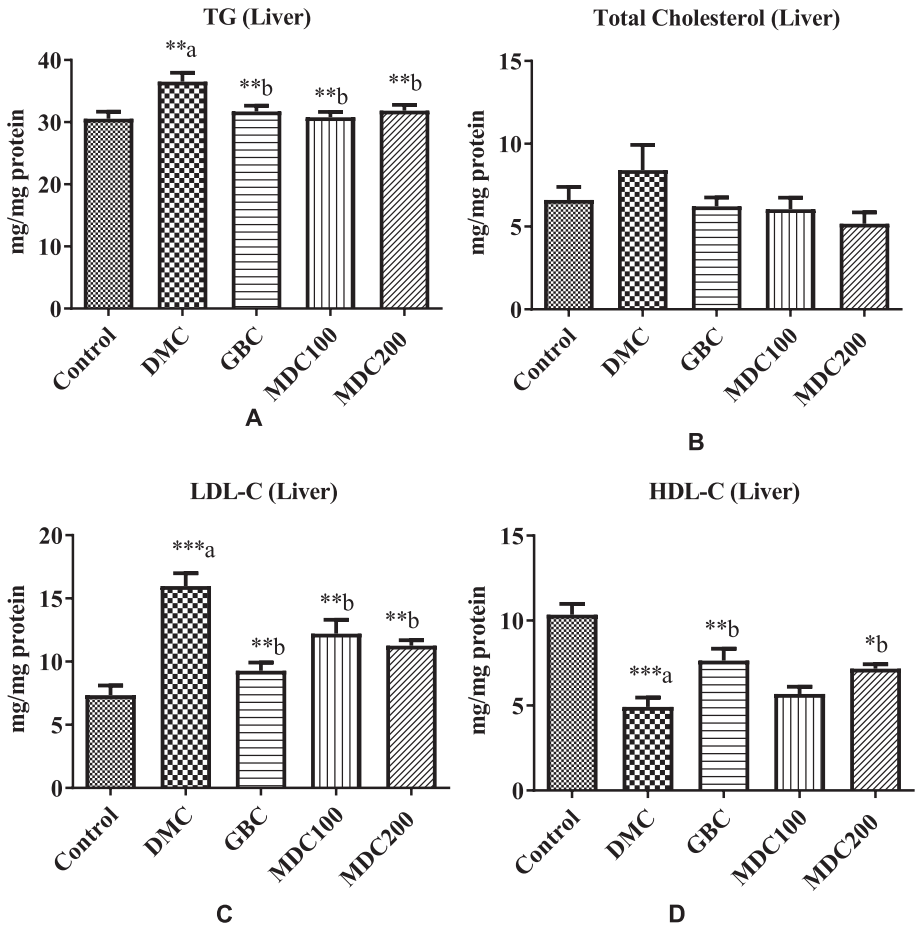

Fig. 3. The effect of *Duvalia corderoyi* extract on liver total cholesterol, triglycerides, and LDL-C, HDL-C levels in STZ- induced diabetic rats. Data are expressed as mean ± SD. *** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$ are the significant difference in comparing with normal control. The letters indicate significant difference from diabetic rats. Control, normal control; DMC, diabetes mellitus control; GBC, diabetic rats administered glibenclamide (600 μg·kg^{1}·day^{1}) for 30 days; MDC100, diabetic rats administered MDC (100 mg·kg^{1}·day^{1}) for 30 days; and MDC200, diabetic rats administered MDC (200 mg·kg^{1}·day^{1}) for 30 days.

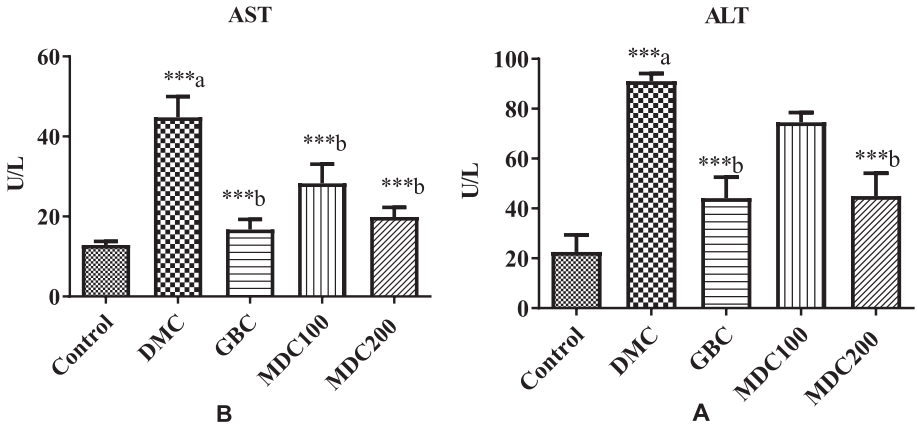

Fig. 4. The effect of *Duvalia corderoyi* extract on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities in serum of the STZ-induced diabetes rats. Data are themean ± SD. *** = $p < 0.001$, ** = $p < 0.01$, *= $p < 0.05$ are the significant difference in comparing with normal control. The letters indicate significant difference from diabetic rats. Control, normal control; DMC, diabetes mellitus control; GBC, diabetic rats administered glibenclamide (600 μg·kg^{1}·day^{1}) for 30 days; MDC100, diabetic rats administered MDC (100 mg·kg^{1}·day^{1}) for 30 days; and MDC200, diabetic rats administered MDC (200 mg·kg^{1}·day^{1}) for 30 days.

3.10. Creatinine and urea

Urea and creatinine were measured in serum of all experimental rats (Fig. 5). The concentration of creatinine and urea increased significantly in all diabetic rats compared with the corresponding control rats. The management of diabetic rats with *D. corderoyi* extracts and glibenclamide were significantly reduced. The alterations in creatinine to near-control levels. However, the decrease in urea levels in rats treated with *D. corderoyi* was not significant.

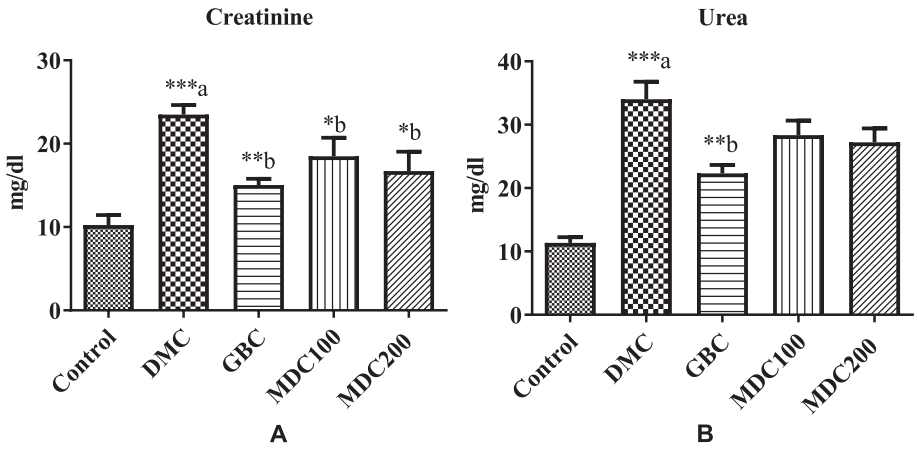

Fig. 5. The effect of *Duvalia corderoyi* extract on creatinine and urea in rats with STZ-induced diabetes rats. Data are expressed as mean ± SD. *** = $p < 0.001$, ** = $p < 0.01$, *= $p < 0.05$ are the significant difference in comparing with normal control. The letters indicate significant difference from diabetic rats. Control, normal control; DMC, diabetes mellitus control; GBC, diabetic rats administered glibenclamide (600 μg·kg^{1}·day^{1}) for 30 days; MDC100, diabetic rats administered MDC (100 mg·kg^{1}·day^{1}) for 30 days; and MDC200, diabetic rats administered MDC (200 mg·kg^{1}·day^{1}) for 30 days.

4. Discussion

4.1. Body weight changes

We observed that streptozotocin-induced diabetes results in decreased body weight, which is according to the Al-Shamaony et al. (1994). This weight loss might be due to Loss of body muscles of rats with diabetes (Swanston-Flatt et al. 1990). Consistent with our results, treatment of diabetic rats with root extracts of *Anthocleista djalonensis* or glibenclamide also improve body weight when compared with untreated diabetic rats (Okokon et al., 2012). Here, we also showed that body weight of the diabetic (untreated) rats was reduced significantly in comparing with to the control group. The rats that treated with *Euryale ferox* Salisb. had much higher body weights ($p < 0.05$) than did normal rats (Danish et al., 2015).

4.2. Glucose and insulin levels

Several findings support the use of traditional plants for diseases related to oxidative stress treatment including diabetes, cardiovascular, cancer and other diseases (Duke and Vásquez, 1994; Duke et al., 2009). Numerous traditional Indian plants such as *Aloe vera, Adhatoda zeylanica*, and *Brassica juncea* have antihyperglycemic activity (Khera and Bhatia, 2014). A recent *in vitro* study reported that *Caralluma fimbriata* (Apocynaceae) extract exhibited potent inhibitory activity against enzymes involved in glucose metabolism (Shenai and Roy, 2017). Previous studies have reported that various *Caralluma* genus species can significantly decrease blood glucose levels and ultimately control diabetes (Habibuddin et al., 2008). Consistent with our results, a methanolic extract and fractions of *Caralluma tuberculata* showed significant antihyperglycemic effects (Abdel-Sattar et al., 2013). *Huernia boleana* (Apocynaceae), growing in high-altitude south western areas of the Kingdom of Saudi Arabia, has significant hypoglycemic activity in STZ-induced diabetes rats (Alzahrani et al., 2015).

Telosma procumbens (Blanco) Merr. (Apocynaceae) treatment of mice led to a decrease in overall diabetes (Cajuday and Amparado, 2014). The appendix volatiles and floral volatiles *D. corderoyi* contains phenolic compounds (Castro and Demarco, 2008). The concentration of phenol compounds in *D. corderoyi* was 48.3%, and the plant also contained fatty acid derivatives, *cis*-geranyl acetone, benzenoids, monoterpenoids, sesquiterpenoids, and other compounds (Jürgens et al., 2006). *D. corderoyi* was also contains phenols, benzyl alcohol, hexanoic acid, and nonanoic acid (Formisano et al., 2009). A significant antioxidant and antidiabetic effects were reported for the flavonoids that isolated from *Cynanchum acutum* L. (Asclepiadaceae) (Fawzy et al., 2008).

The hypoglycemic effects of *D. corderoyi* described in this study can be referred to its phenolic compounds. Phenols are correlates positively with antioxidant latent, They have strong activity as antioxidants and thus perfect protection from various diseases (Williams et al., 2004), supporting the potential use of phenols in production of new drugs with to treatment the diseases that related to oxidative stress- (Tauchen et al., 2016). In this study, *D. corderoyi* treatment had a corrective effect on insulin secretion and glucose concentrations in the serum of diabetic rats. Supporting our results, blood glucose and insulin levels were restored in diabetic rats by *Gymnema sylvestre* treatment (Aralelimath and Bhise, 2012). Likewise, *Caralluma tuberculata* caused rising in insulin levels significantly (Abdel-Sattar et al., 2013).

Type 2 diabetes results from a mixture of insulin resistance and reduced insulin secretion. *D. corderoyi* extract may be of interest in conduct of type 2 diabetes because it might affect insulin secretion. Our results show that *D. corderoyi* improves serum glucose and secretion of insulin.

4.3. Triglycerides in serum

Alterations in lipid concentration, found in 40% of diabetics (Ravi et al., 2005), that similarly were observed in this study in rats with streptozotocin-induced diabetes. Here, the increasing in triglycerides concentrations in diabetic rats it may be due to insulin resistance, an increase in insulin, and glucose intolerance (Zavaroni et al., 1989). Aralelimath and Bhise (Aralelimath and Bhise, 2012) found that treatment with *G. sylvestre* extract reduced the levels of cholesterol and triglycerides compared with those in their diabetic control groups. The findings of the present work showed that treatment by that *D. corderoyi* caused decreasing in lipid levels like triglycerides in STZ-induced diabetic rats in parallel with glucose improving, insulin, cholesterol, LDL-C and HDL-C levels.

4.4. Cholesterol levels in serum

The hypercholesterolemia is associated with Insulin deficiency (Tchobroutsky, 1978; Rodrigues et al., 1986). The reduction in cholesterol and other lipids in this study was dependent on the concentration of *D. corderoyi*. Similarly, animals treated using *Cynanchum acutum* (Apocynaceae) at different doses showed that

the decreasing in glucose, TC and TG and insulin increasing were dose-dependent (Estakhr et al., 2012). *Alhagi maurorum* caused significant decreases in TC, TG, LDL-C, and VLDL-C levels compared to the diabetic group, and increased HDL-C concentrations (Sheweita et al., 2016).

4.5. LDL-C in serum

Consistent with our results, treatment with *G. sylvestre* reduced LDL-C in streptozotocin-dosed diabetic rats (Aralelimath and Bhise, 2012). A previous study also found that treatment with poly herbal combinations of six medicinal plants caused a significant decrease in, TC, LDL-C, and TG levels (Patil et al., 2012).

Administration of *Euryale ferox* Salisb. Significantly improved altered TC, TG, LDL, and HDL levels with dose-dependent way (Danish et al., 2015). On the other hand, the levels of both VLDL-C and LDL-C were decreased in diabetic rats in comparison with control (Danish et al., 2015). LDL-C levels were decreased by 25.78% and 53.04% on treatment with 5% and 10% *Aloe vera* juice-fortified bread, respectively (Al-Muammar et al., 2016). Our results, revealed that LDL-C concentration of diabetic rats was lowered correspondingly with the increasing of *D. corderoyi*, also LDL-C lowering was positively correlated with the decreasing of glucose, TC and TG and with insulin and HDL-C increasing from other sites.

4.6. HDL-C in serum

As in our study, HDL increased 46.32 mg/dL from baseline by administration of 200 mg/kg of *G. sylvestre* (Aralelimath and Bhise, 2012). Likewise, Patil et al. (2012) suggested that along with the improved lipid profile by treatment with herbal combinations, the enhancement action on HDL can also limit coronary hazards. HDL-C levels were significantly increased by *Aloe vera* juice-fortified bread. Treatment with 5% and 10% *Aloe vera* juice-fortified bread enhancement HCL-C 18.96% and 27.99%, respectively (Al-Muammar et al., 2016).

According to our results, it can be suggested that anti-diabetic effect of *D. corderoyi* extract can explained by serum glucose enhancing through insulin secretion improving, which could also be attributed to the mechanism for the alteration of TG, TC, LDL-C and HDL-C levels in diabetic rats.

4.7. Liver lipid profiles

Triglyceride was higher significantly in the liver and plasma of diet-induced obesity untreated mice with compared to that of regular diet-fed mice (Kim et al., 2009). After 8 weeks of treatment with processed *Aloe vera* gel, liver and plasma triglyceride decreased significantly in a dose-dependent manner (Kim et al., 2009).

The increase of cholesterol in liver of STZ-induced diabetic rats that occurred in our study may be due to increasing in cholesterol synthesis. The current study revealed significant in glucose reducing as well as cholesterol, triglycerides and LDL-C and increase in HDL-C levels in the liver of diabetic rats that treated by the *D. corderoyi* extract for 30 days. This alteration may be explained by clearance increasing and production decreasing in endogenous cholesterol and triglycerides transporters.

4.8. ALT and AST

Previously, the augmented ALT activities has been recognized as a marker of risk of diabetes type 2 suggesting that the liver plays a role in the disease pathogenesis (Vozarova et al., 2002). A significant reduction of 10.90% and 19.34% in AST, and of 11.69% and 17.74% in ALT after administration of 5% and 10% *Aloe vera* juice-fortified bread, respectively, was reported (Al-Muammar et al., 2016). Water and ethanolic *Alhagi maurorum* extracts led to significantly improved hepatic function in diabetic rats (Sheweita et al., 2016). Similar to our results, administration of *Lavandula stoechas* reduced ALT and AST activity in diabetic rats (Sebai et al., 2013). This study exhibited significant inhibition effect of *D. corderoyi* on ALT and AST activities in diabetic induced rats, it suggests that those properties confirmed the potentials of *D. corderoyi* as an effective anti-diabetic medicinal plant.

4.9. Creatinine and urea

Welters et al. (1996) mentioned that elevation of plasma urea can be considered an important marker of renal dysfunction. *Aloe barbadensis* attenuated the elevation in creatinine in serumand urea nitrogen in blood notaffected on ions and uric acid (Chatterjee et al., 2012). In contrast to our results, *Moringa stenopetala* extract did not significantly change urea or creatinine levels (Ghebreselassie et al., 2011). Creatinine and urea levels were increased by Alloxan, and treatment by essential oils of *Lavandula stoechas* L. showed significant protection against hepatic and renal dysfunction (Sebai et al., 2013).

In the present study, one-month treatment with *D. corderoyi* caused decreasing in creatinine and urea concentration, but with creatinine it was more effective than in urea concentration. The effects of *D. corderoyi* was depend on it concentration, where the high concentration (200 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$) of *D. corderoyi* was more effective.

5. Conclusions

Our results evidently demonstrate the anti-diabetic, antihyperlipidemic, and protective effects of the *D. corderoyi* extract against diabetes induced by streptozotocin injection in rats. To our knowledge, this study provides the beginning of a scientific verification of traditional use of *D. corderoyi* as an antidiabetic, antihyperlipidemic, and protective medicinal plant. The findings of this study may have broad implications in functional food industry, therapeutic nutrition and it can be used to develop medical drugs that have the ability to treat diseases including diabetes. Also, diabetic patients may use *D. corderoyi* to treatment diabetes and prevent oxidative stress-induced complications. Although, further researches are necessary to estimate and identify the chemical composition of *D. corderoyi* and to evaluate the antioxidant activity in-vitro and anti-oxidative stress defense effects of *D. corderoyi* in-vivo.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Abdel-Sattar, E.A., Abdallah, H.M., Khed,r A., Abdel-Naim, A.B., Shehatam I.A., 2013. Antihyperglycemic activity of Caralluma tuberculata in streptozotocin-induced diabetic rats. Food Chem. Toxicol. 59, 111–117. https://doi.org/10.1016/j.fct.2013.05.060.

Al-Muammar, M., Elsadek, M.F., El-Shafie, M., 2016. Potential effect of fortified pan bread with aloe vera juice on alloxan-induced diabetic rats. Afr. J. Tradit. Complement. Altern. Med. 13 (1), 17–24 https://doi.org/10.21010/ajtcam.v13i1.3.

Al-Shamaony, L., al-Khazraji, S.M., Twaij, H.A., -Shamaony et al. (1994). Hypoglycaemic effect of Artemisia herba alba. II. Effect of a valuable extract on some blood parameters in diabetic animals. J. Ethnopharmacol. 43 (3), 167–171. https://doi.org/10.1016/0378-8741(94)90038-8.

Alzahrani, S.O., Alwagdani, A.M., Alotaibi, A.M., Hamaidi, M.G., Nasr, A., Al-Remawi, M., Gouda, Y.G., Mohamad, K.M., 2015. Study of the antidiabetic activity of Huernia Sp. Nov. aff. Boleana growing in high altitude areas of Southwest Saudi Arabia. Ann. Biol. Sci. 3 (4), 15–20.

Andrade-Cetto, A., Heinrich, M., 2005. Mexican plants with hypoglycemic effect used in the treatment of diabetes. J. Ethnopharmacol. 99 (3), 325–348. https://doi.org/10.1016/j.jep.2005.04.019.

Aralelimath, V., Bhise, S., 2012. Anti-diabetic effects of gymnema sylvester extract on streptozotocin induced diabetic rats and possible β-cell protective and regenerative evaluations. Dig. J. Nanomater. Biostruct. 7 (1), 135–142.

Attele, A.S., Zhou, Y., Xie, J., Wu, J.A., Zhang, L., Dey, L., Pugh, W., Rue, P.A., Polonsky, K.S., Yuan, C., 2002. Antidiabetic effects of Panax ginseng Berry extract and the identification of an effective component. Diabetes 51 (6), 1851–1858. https://doi.org/10.2337/diabetes.51.6.1851.

Babu, V., Gangadevi, T., Subranabuab, A., 2002. Antihyperglycemic effect of Cassia keinii leaf extract in glucose feed normal rats and alloxan-induced diabetic rats. Indian J. Pharmacol. 34, 409–415.

Baynes, J.W., 1991. Role of oxidative stress in development of complications in diabetes. Diabetes 40 (4), 405–412. https://doi.org/10.2337/diab.40.4.405.

Bruyns, P.V., 2005. Stapeliads of Southern Africa. Umdaus Press, Hatfield, Pretoria.

Bruyns, P.V., 1998. A revision of the genus Echidnopsis Hook.f. (*Asclepiadaceae*). Bradleya 6, 1–48.

Bruyns, P.V., 2010. A new species of Caralluma (*Apocynaceae–Asclepiadoideae–Ceropegieae*) from the Yemen. S. Afr. J. Bot. 76 (2), 249–251. https://doi.org/10.1016/j.sajb.2009.11.001.

Cajuday, L.A., Amparado, E.A., 2014. Hypoglycemic property of Telosma procumbens (Blanco) Merr. (Apocynaceae) in normal and alloxan-induced diabetic juvenile mice (Mus musculus). J. Phytopharmacol. 3 (2), 113–117.

Castro, M.M., Demarco, D., 2008. Phenolic compounds produced by secretory structures in plants: a brief review. Nat. Prod. Commun. 3 (8), 1273–1284.

Chatterjee, P., Mukherjee, A., Nandy, S., 2012. Protective effects of the aqueous leaf extract of Aloe barbadensis on gentamicin and cisplatin-induced nephrotoxic rats. Asian. Pac. J. Trop. Biomed. 2 (3), S1754–S1763. https://doi.org/10.1016/S2221-1691(12)60490-0.

Corcoran, M.P., Lamon-Fava, S., Fielding, R.A., 2007. Skeletal muscle lipid deposition and insulin resistance: effect of dietary fatty acids and exercise. Am. J. Clin. Nutr. 85 (3), 662–677. https://doi.org/10.1093/ajcn/85.3.662.

Danish, A., Vikas, K., Amita, V., Girija, S., Manju, S., 2015. Antidiabetic, antioxidant, antihyperlipidemic effect of extract of Euryale ferox Salisb with enhanced histopathology of pancreas, liver and kidney in streptozotocin induced diabetic rats. Springerplus. 4, 315–332.

Duke, J.A., Bogenschutz-Godwin, M.J., Ottesen, A.R., 2009. Duke's Handbook of Medicinal Plants of Latin America. CRC Press, Boca Raton, USA.

Duke, J.A., Vásquez, R., 1994. Amazonian Ethnobotanical Dictionary. CRC Press, Boca Raton, USA.

Elangovan, V., Shohami, E., Gati, I., Kohen, R., 2000. Increased hepatic lipid soluble antioxidant capacity as compared to other organs of streptozotocin-induced diabetic rats: a cyclic voltammetry study. Free Radic. Res. 32 (2), 125–134. https://doi.org/10.1080/10715760000300131.

Estakhr, J., Javadian, F., Ganjali, Z., Dehghani, M., Heidari, A., 2012. Anti-diabetic activity of cynanchum acutum extract in alloxan-induced diabetic rats. Int. J. Anim. Vet. Adv. 4 (4), 303–305.

Fawzy, G.A., Abdallah, H.M., Marzouk, M.S.A., Soliman, F.M., Sleem, A.A., 2008. Antidiabetic and Antioxidant Activities of Major Flavonoids of Cynanchum acutum L. (Asclepiadaceae) Growing in Egypt. Z. Naturforsch C. J. Biosci., vol. 63, 9-10, pp. 658–662.

Formisano, C., Senatore, F., Della Porta, G., Scognamiglio, M., Bruno, M., Maggio, A., Rosselli, S., Zito, P., Sajeva, M., 2009. Headspace Volatile Composition of the Flowers of Caralluma europaea N.E.Br. (*Apocynaceae*). Molecules. 14 (11), 4597–4613. https://doi.org/10.3390/molecules14114597.

Gallo, M.B., Sarachine, M.J. 2009. Biological Activities of Lupeol. Int. J. Anal. Pharm. Biomed. Sci., vol. 3 (special issue), pp. 46–66.

Ghebreselassie, D., Mekonnen, Y., Gebru, G., Ergete, W., Huruy, K., 2011. The effects of Moringa stenopetala on blood parameters and histopathology of liver and kidney in mice. Ethiop. J. Health. Dev. 25 (1), 51–57.

Habibuddin, M., Daghriri, H.A., Humaira, T., Al-Qahtani, M.S., Fafzi, A.A., 2008. Antidiabetic effect of alcoholic extract of Caralluma sinaica L. on streptozotocin-induced diabetic rabbits. J. Ethnopharmacol. 117 (2), 215–220. https://doi.org/10.1016/j.jep.2008.01.021.

Halvorsen, B.L., Holte, K., Myhrstad, M.C.W., Barikmo, I., Hvattum, E., Renbers, S.F., Wold, A.B., Haffner, K., Baugerod, H., Anderses, L.F., Moskaug, O., Jacobs J.r., D.R., Blomhoff, R., 2002. A systematic screening of total antioxidants in dietary plants. J. Nutr. 132 (3), 461–471. https://doi.org/10.1093/jn/132.3.461.

IDF. 2011. Diabetes Atlas, fifth ed.; International Diabetes Federation: Brussels, Belgium.

Juliet, S.Y., Kalimuthu, K., Vajjiram, C., Ranjitha, V., 2018. Evaluation and comparison of phytochemical, GCMS and FTIR analysis of wild and micropropagated cadaba fruticosa (L.). World. J. Pharm. Res. 7 (14), 746–760.

Jürgens, A., Dötterl, S., Meve, U., 2006. The chemical nature of fetid floral odours in stapeliads (*Apocynaceae-Asclepiadoideae-Ceropegieae*). New Phytol. 172 (3), 452–468. https://doi.org/10.1111/j.1469-8137.2006.01845.x.

Kar, A.1., Choudhary, B.K., Bandyopadhyay, N.G., 1999. Preliminary studies on the inorganic constituents of some indigenous hypoglycemic herbs on oral glucose tolerance test. J. Ethnopharmacol., vol. 64, 2, pp. 179–184. https://doi.org/10.1016/S0378-8741(98)00118-4.

Katzung, B.G., 2012. Basic and Clinical Pharmacology. McGraw-Hill Medical, USA.

Khera, N., Bhatia, A., 2014. Medicinal plants as natural anti diabetic agents. I.J.P.S.R., vol. 5, 3, pp. 713–29. http://dx.doi.org/10.13040/IJPSR.0975-8232.

Kim, K., Kim, H., Kwon, J., Lee, S., Kong, H., Im, S.A., Lee, Y.H., Lee, Y.R., Oh, S.T., J.o., T. H., Park, Y.I., Lee, C.K., Kim, K., 2009. Hypoglycemic and hypolipidemic effects of processed Aloe vera gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine, vol. 16, 9, pp. 856–863. https://doi.org/10.1016/j.phymed.2009.02.014.

Kyslychenko, V., Karpiuk, U., Diakonova, I.A., Mohammad, S.D., 2010. Phenolic compounds and terpenes in the green parts of Glycine hispida. Adv. Environ. Biol. 4 (3), 490–494.

Lalitha, S., Parthipan, B., Mohan, V.R., 2015. Determination of Bioactive Components of Psychotria nilgiriensis Deb & Gang (Rubiaceae) by GC-MS Analysis. I.J.P.P.R., vol. 7, 4, pp. 802–809.

Leach, L.C., 1988. A revision of Huernia R. Br. (Asclepiadaceae). Excelsa Taxon. Ser. 4, 1–197.

Meve, U., 1997. The Genus Duvalia (*Stapelieae*). Springer-Verlag, Vienna, Austria, pp. 45–125.

Okokon, J.E., Antia, B.S., Udobang, J.A., 2012. Antidiabetic activities of ethanolic extract and fraction of Anthocleista djalonensis. Asian. Pac. J. Trop. Biomed. 2 (6), 461–464. https://doi.org/10.1016/S2221-1691(12)60076-8.

Patil, A., Nirmal, S., Pattan, S., Tambe, V., Tare, M., 2012. Antidiabetic effect of polyherbal combinations in STZ induced diabetes involve inhibition of α-amylase and α-glucosidase with amelioration of lipid profile. J. Phytopharmacol. 2 (1), 46–57.

Punthakee, Z., Goldenberg, R., Katz, P., 2018. Definition, classification and diagnosis of diabetes, prediabetes and metabolic syndrome. Can. J. Diab. 42, S10–S15. https://doi.org/10.1016/j.jcjd.2017.10.003.

Ramachandraiahgari, R., Somesula, S., Adi, P., Mannur, I., Enamala, M., Matcha, B., 2012. Protective role of ethanolic extract of aloe vera antioxidant properties on liver and kidney of Streptozotocin-induced diabetic rats. Dig. J. Nanomater. Bios. 7 (1), 175–184.

Ravi, K., Rajasekaran, S., Subramanian, S., 2005. Antihyperlipidemic effect of Eugenia jambolana seed kernel on streptozotocin-induced diabetes in rats. Food. Chem. Toxicol. 43 (9), 1433. https://doi.org/10.1016/j.fct.2005.04.004.

Rodrigues, B., Goyal, R.K., McNeil, J.H., 1986. Effects of hydralazine on STZ-induced diabetic rats-prevention of hyperlipidaemia and improvement in cardiac function. J. Pharmacol. Exp. Ther. 237, 299.

Saravanan, G., Ponmurugan, P., 2011. Ameliorative potential of S-allyl cysteine on oxidative stress in STZ induced diabetic rats. Chem Biol Interact. 189, 100–106. https://doi.org/10.1016/j.cbi.2010.10.001.

Sebai, H., Selmi, S., Rtibi, K., Souli, A., Gharbi, N., Sakly, M., 2013. Lavender (Lavandula stoechas L.) essential oils attenuate hyperglycemia and protect against oxidative stress in alloxan-induced diabetic rats. Lipids. Health. Dis. 12 (189), 1–9. https://doi.org/10.1186/1476-511X-12-189.

Shenai, A., Anitha, R., 2017. Antihyperglycemic activity of Caralluma fimbriata: an in vitro approach. Pharmacogn. Mag. 13, S499–S504. https://doi.org/10.4103/pm.pm_59_17.

Sheweita, S.A., Mashaly, S., Newairy, A.A., Abdou, H.M., Eweda, S.M., 2016. Changes in oxidative stress and antioxidant enzyme activities in streptozotocin-induced diabetes mellitus in rats: role of Alhagi maurorum Extracts. Oxid. Med. Cel.l Longev. 3, 1–8. https://doi.org/10.1155/2016/5264064.

Sireesha, M., Suresh, B.K., Venkata, N.R., Pullaiah, T., 2017. Caralluma Iasiantha: a review on its vital role in Indian traditional medicine. Res. J. Pharm. Biol. Chem. Sci. 8, 873–879.

Stavric, B., 1994. Role of chemopreventers in human diet. Clin. Biochem. 27, 319–322. https://doi.org/10.1016/0009-9120(94)00039-5.

Swanston-Flatt, S.K., Day, C., Bailey, C.J., Flatt, P.R., 1990. Traditional plant treatments for diabetes. Studies in normal and streptozotocin diabetic mice. Diabetologia 33, 462–464. https://doi.org/10.1007/bf00405106.

Szymczak, G., Kwiatkowski, M., 2003. Stapeliads (Asclepiadaceae) in collection of succulents in the Botanical Garden of the Maria Curie-Sklodowska University in Lublin. Biuletyn Ogrodow Botanicznych. 12, 137–140.

Tauchen, J., Bortl, L., Huml, L., Miksatkova, P.; Doskocil, I., Marsik, Petr., Panduro Villegas, P.P., Bendezu Flores, Y., Van Damme, Patrick., Lojka, B., Havlik, J., Lapcik, O., Kokoska, L. 2016. Phenolic composition, antioxidant and anti-proliferative activities of edible and medicinal plants from the Peruvian Amazon. Rev. bras. farmacogn., vol. 26, pp. 728–737. https://doi.org/10.1016/j.bjp.2016.03.016.

Tchobroutsky, G., 1978. Relation of diabetic control to development of microvascular complications. Diabetologia 15 (3), 143. https://doi.org/10.1007/BF00421230.

Thiv, M., Meve, U., 2007. A phylogenetic study of Echidnopsis Hook. f. (Apocynaceae- Asclepiadoideae) - taxonomic implications and the colonization of the Socotran archipelago. Plant. Syst. Evol. 265, 71–86 https://www.jstor.org/stable/23655753.

Vidal, Diogo M., Fávaro, Carla F., Guimarães, Matheus M., Zarbin, Paulo H.G., 2016. Identification and Synthesis of the Male-Produced Sex Pheromone of the Soldier Beetle Chauliognathus fallax (Coleoptera: Cantharidae). J. Braz. Chem. Soc. 27 (8), 1506–1511.

Vlaisavljevic, S., Kaurinovic, B., Popovic, M., Djurendic-Brenesel, M., Vasiljevic, B., Cvetkovic, D., Vasiljevic, S., 2014. Trifolium pratense L. as a potential natural antioxidant. Molecules 19 (1), 713–725.

Vozarova, B., Stefan, N., Lindsay, R.S., Saremi, A., Pratley, R.E., Bogardus, C., Tataranni, P.A., 2002. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 51, 1889–1895. https://doi.org/10.2337/diabetes.51.6.1889.

Welters, C.F., Deutz, N.E., Dejong, C.H., Soeters, P.B., 1996. Enhanced renal vein ammonia efflux after a protein meal in the pig. J. Hepatol. 31, 489–496. https://doi.org/10.1016/S0168-8278(99)80042-7.

Williams, R.J., Spencer, J.P., Rice-Evans, C., 2004. Flavonoids: antioxidants or signalling molecules. Free Radic. Biol. Med. 36 (7), 838–849. https://doi.org/10.1016/j.freeradbiomed.2004.01.001.

Zavaroni, I., Bonara, E., Pagilora, M., 1989. Risk factors for coronary artery disease in healthy persons with Hyperinsulinemia and normal glucose tolerance. N. Engl. J. Med. 320–702. https://doi.org/10.1056/NEJM198903163201105.