

REPORT

Screening of the Anti-hyperglycemic activity of some medicinal plants of Jordan

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Abstract: Diabetes represents a group of common diseases that are characterized by dysregulation of blood glucose levels. Plants are traditionally used for management of diseases including diabetes. In this study, we screened the anti-diabetic effect of extracts of 21 plants grown in Jordan. Extracts of plants were screened for their antihyperglycemic activity. Diabetes was induced in Sprague Dawley rats using Alloxan. Plant extracts were dosed at 1gm/kg. Blood glucose was measured at baseline and at every hour for 3 hours. Results showed that five plants out of the 21 screened showed antihyperglycemic activity. These plants are *Phoenix dactylifera* L., *Tecoma stans* (L.) Kunth, *Cichorium pumilum* Jacq., *Phaseolus vulgaris* L., and *Teucrium polium* L. On the other hand, *Sarcopoterium spinosum* (L.) Spach. and *Brassica oleracea* L. var. *capitata* significantly increased blood glucose levels in diabetic rats. The following plant extracts showed neutral effect on blood glucose levels: *Plantago major* L., *Taraxacum cyprium* H. Lindb, *Artemisia inculta* Delile, *Marrubium vulgare* L., *Inula viscosa* (L.) Ai, *Rubus sanguineus* Friv, *Coriandrum sativum* L., *Cucurbita pepo* var. *ovefera*, *Cucumis sativus* L., *Hordeum vulgare* L., *Apium graveolens* L., *Avena sativa* L., *Helianthus annuus* L., and *Anethum graveolens* L. In conclusion, Jordanian medicinal plants might be useful for managements of blood glucose levels in patients with diabetes.

Keywords: Diabetes, plant extract, antihyperglycemic.

INTRODUCTION

Diabetes is a term used to describe a group of diseases in which the individuals suffer from inability to regulate blood sugar either because insulin synthesis is miss-regulated, or because the body's cells show resistance to insulin, or both (Schofield and Sutherland, 2012). Globally, more than 300 million people have diabetes and thus it is considered as one of the most common non-communicable diseases (Rosiak *et al.*, 2014). In addition, the prevalence of diabetes increases with years (Rosiak *et al.*, 2014). In the USA, the burden of diabetes was estimated to be \$218 billion in 2007 (Dall *et al.*, 2010). Diabetes patients suffer from several symptoms that include general body weakness, frequent urination, persisted thirst, weight changes, numbness in hands and feet, slow healing of wounds and male erectile dysfunction (McAulay *et al.*, 2001). Diabetes patients may also experience long-term complications, which develop slowly after having the disease and include ketoacidosis, nephropathy, neuropathy, hypertension, stroke and gastroparesis (Bucala, 2014).

Control of blood glucose is critical for treatment of diabetes and prevention of its associated complications. Current medications that are utilized in the treatment of diabetes are associated with side effects, drug non-response and limited capacity in restoring normal blood glucose homeostasis (Franciosi *et al.*, 2013). Therefore, finding new potent agents for treatment of diabetes with lesser side effects is of great significance for treatment of diabetes. Plants were traditionally used for management of diseases. Recently, a number of studies have shown the usefulness of some plants in lowering blood glucose in diabetic patients. For example, the seeds of *Securigera securidaca*, which is a herb that belongs to Fabaceae family, have been shown to be effective in decreasing blood glucose in experimental animals (Ghorbani *et al.*, 2014). Similar findings were reported for *Acacia farnesiana* (Kingsley *et al.*, 2014), *Momordica charantia* L. (Nkambo *et al.*, 2013) and *Rhizophora mucronata* (Pandey *et al.*, 2014). Additionally, Literature surveys demonstrated the benefit of several ethno botanicals as antidiabetic agents evaluated *in vitro* and *in vivo* systems in the form of their hypoglycemic or antihyperglycemic bioactivities (Afifi and Kasabri, 2013, Afifi-Yazar *et al.*, 2011). In the current study, we screened 21 medicinal plants for their antidiabetic effect using Alloxan-induced

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diabetes rat model. The selection of these plants was based on their known traditional use for the management of diabetes or related-metabolic diseases within Jordan or the Middle East and North Africa (MENA) region, as these regions have similar natural flora and socio-cultural aspects. Some of these uses were actually documented for diabetes, for examples, *Phaseolus vulgaris* (Al-tabaa, 1984, Rouaiha, 1978, Kotb, 1985, Quraan and Karim, 1986), *Brassica oleracea* L. (Al-odat, 1987, Rouaiha, 1978, Quraan and Karim, 1986), *Sarcopoterium spinosum* (L.) Spach. (Al-Aboudi and Afifi, 2011, Al-khalil, 1995, Kasabri *et al.*, 2011b, Quraan and Karim, 1986), *Tecoma stans* L. (Kotb, 1985), *Teucrium polium* L. (Al-Aboudi and Afifi, 2011, Al-khalil, 1995, Afifi *et al.*, 2005, Kasabri *et al.*, 2011b, Wazaify *et al.*, 2011, Kotb, 1985), *Artemisia inculata* Delile (Al-Aboudi and Afifi, 2011, Al-khalil, 1995, Rouaiha, 1978), *Cucumis sativus* L. (Al-tabaa, 1984, Rouaiha, 1978), *Avena sativa* L. (Al-Aboudi and Afifi, 2011, Rouaiha, 1978), *Plantago major* L. (Al-Aboudi and Afifi, 2011, Al-tabaa, 1984), *Cichorium pumilum* Jacq. (Al-khalil, 1995, Al-tabaa, 1984) *Cucurbita* *ssp.* (Al-Aboudi and Afifi, 2011), *Coriandrum sativum* L. (Al-Aboudi and Afifi, 2011), and *Taraxacum cyprium* H. Lindb (Al-Aboudi and Afifi, 2011).

MATERIALS AND METHODS

Plant materials used in the current study were collected during the months of May through August of the summer season from various locations of the North of Jordan. Taxonomic identification of the plants was confirmed by Professor Jammel Lahaam, Department of Biological Sciences, Faculty of Science, Yarmouk University, Irbid-Jordan. A voucher specimen from each plant was deposited at the Medicinal Plants Museum, Faculty of Pharmacy, Jordan University of Science and Technology, Irbid-Jordan. The plant materials were shade dried and ground in a Wiley grinder (Model 5657 HAAN, Germany) with a 2 mm diameter mesh. Powdered plant materials (20g/each) were percolated in EtOH (80%). The combined ethanol extracts were concentrated in vacuum to give a dried extract.

Animals

Adult male Sprague Dawley rats weighing 180 to 210g were housed on a 12:12 hr light/dark schedule (lights on at 7AM) in metal cages (6 rats per cage) at 25°C with *ad libitum* access to standard rodent chow and water. All procedures involving animals were approved by Animal Care Use Committee (ACUC) of Jordan University of Science and Technology. After arrival at the research facility, all rats were allowed one week to acclimate before manipulations began.

Induction of diabetes

Alloxan-induced diabetes was instituted by a single intraperitoneal injection of alloxan monohydrate (150mg/kg body weight; Sigma-Aldrich, St Louis, MI, USA)

following a 12 hours fasting from food, but not water. Induction of diabetes was confirmed by measuring blood glucose 72 hours after the injection of alloxan using a glucose analyzer (Accu-Check Performa, Roche Diagnostic GmbH, Mannheim, Germany). Animals with blood glucose of >300 mg/dl were considered diabetic, and were included in the study.

Animals groups and administration of plant extracts

In addition to having a control group that was non-diabetic and was administered only the vehicle, animals with diabetes were randomly assigned into various groups. The diabetes-non-treated group, which was not administered any plant extract. The diabetes + glibenclamide group, which served as a positive control, and was administered glibenclamide (0.3mg/kg). The plant extract groups (n=22 groups), which were distributed as one animal group per each plant extract from table 1. After measuring baseline blood glucose, each of the plant extracts dosed at 1g/kg or glibenclamide were administered via oral gavage. Thereafter, blood glucose was measured every hour for 3 hours. Each animal group contained 6 animals. Blood glucose measurements were done in triplicates.

STATISTICAL ANALYSIS

All statistics were carried out using the GraphPad Prism (4.0) computer program. Comparisons were made using repeated-way ANOVA test followed by Tukey posttest. P values <0.05 were considered significant. All values were represented as mean ± SEM.

RESULTS

In this study, we investigated the antihyperglycemic activity of 22 ethanol extracts of Jordanian medicinal plants (table 1) against alloxan-induced diabetes in animals. Results shown in table 2 indicate that some plant extracts possess antihyperglycemic activity. For example, the extract of *Phoenix dactylifera* L. significantly reduced (P<0.01) hyperglycemia in diabetic animals starting from the first hour of administration. Additionally, the extracts of *Tecoma stans* (L.) Kunth (P<0.05), *Cichorium pumilum* Jacq. (P<0.01), *Phaseolus vulgaris* L. (P<0.05), and *Teucrium polium* L. (P<0.01) significantly reduced blood glucose after 3hrs of administration. On the other hand, the extracts of *Sarcopoterium spinosum* (L.) Spach. and *Brassica oleracea* L. var. capitata significantly increased (P<0.05) blood glucose, which is in controversy to their traditional reported use. The following plant extracts showed neutral effect on blood glucose levels: *Plantago major* L., *Taraxacum cyprium* H. Lindb, *Artemisia inculata* Delile, *Marrubium vulgare* L., *Inula viscosa* (L.) Aï, *Rubus sanguineus* Friv, *Coriandrum sativum* L., *Cucurbita pepo* var. *ovefera*, *Cucumis sativus* L., *Hordeum vulgare* L., *Apium graveolens* L., *Avena sativa* L., *Helianthus annuus* L. and *Anethum graveolens* L.

Table 1: Plant extracts used in the study

Scientific name	Family	Plant parts used
<i>Plantago major</i> L.	Plantaginaceae	Leaves
<i>Taraxacum cyprium</i> H. Lindb	Asteraceae/ Compositae	Aerial parts
<i>Artemisia inculta</i> Delile	Asteraceae/ Compositae	Aerial parts
<i>Marrubium vulgare</i> L.	Lamiaceae/ Labiatae	Leaves
<i>Sarcopoterium spinosum</i> (L.) Spach.	Rosaceae	Roots
<i>Inula viscosa</i> (L.) Ait.	Asteraceae/ Compositae	Leaves
<i>Tecoma stans</i> (L.) Kunth ex. HBK.	Bignoniaceae	Leaves
<i>Rubus sanguineus</i> Friv	Rosaceae	Leaves
<i>Cichorium pumilum</i> Jacq.	Asteraceae/ Compositae	Leaves
<i>Coriandrum sativum</i> L.	Apiaceae/ Umbelliferae	Aerial parts
<i>Phaseolus vulgaris</i> L.	Fabaceae/ Leguminosae	Fresh pods
<i>Cucurbita pepo</i> var <i>ovefera</i>	Cucurbitaceae	Fresh fruits
<i>Cucumis sativus</i> L.	Cucurbitaceae	Fresh fruits
<i>Brassica oleracea</i> L. var. <i>capitata</i>	Cruciferae	Fresh leaves
<i>Brassica oleracea</i> L. var. <i>capitata</i>	Cruciferae	Dried seeds
<i>Hordeum vulgare</i> L.	Graminae	Dried fruits
<i>Apium graveolens</i> L.	Apiaceae/Umbelliferae	Dried seeds
<i>Teucrium polium</i> L.	Lamiaceae/Labiatae	Aerial Parts
<i>Phoenix dactylifera</i> L.	Palmae	Unripe fruit
<i>Avena sativa</i> L.	Graminae	Dried grains
<i>Helianthus annuus</i> L.	Asteraceae/Compositae	Dried seeds
<i>Anethum graveolens</i> L.	Apiaceae/Umbelliferae	Fruits

DISCUSSION

The findings of this study show the antihyperglycemic activity of extracts of some medicinal plants in Alloxan-induced diabetes rat model. Five plants out of the 21 screened ones showed antihyperglycemic activity. These plants are *Phoenix dactylifera* L., *Tecoma stans* (L.) Kunth, *Cichorium pumilum* Jacq., *Phaseolus vulgaris* L., and *Teucrium polium* L.

The antihyperglycemic activity of *Phoenix dactylifera* L. started directly after treatment and persisted for at least 3 hours after treatment. This antihyperglycemic effect might be attributed to the high fruit contents of flavonoid compounds such as - diosmetin 7-O- β -L-arabinofuranosyl (1 \rightarrow 2) β -D-apiofuranoside (1) and diosmetin 7-O- β -D-apiofuranoside (2) compounds that have been shown to possess such activity (Salib *et al.*, 2013). Other members that belongs to *Areaceae* such as *Cocos nucifera* Linn., *Serenoa repens* and *Roystonea regia* were previously shown for their antihyperglycemic activity (Naskar *et al.*, 2011, Sosnowska and Balslev, 2009). *Phoenix dactylifera* L. has been shown also to possess protection against chemicals-induced hepatotoxicity (Abdelaziz and Ali, 2014) and peripheral neuropathy (Zangiabadi *et al.*, 2011).

The antihyperglycemic action of *Tecoma stans* (L.) Kunth that is observed in the current study in rats is in agreement

with previous studies that examined such effect in insulin-sensitive and insulin-resistant mice, cultured human adipocytes and streptozotocin-induced diabetic male Sprague-Dawley rats (Alonso-Castro *et al.*, 2010, Aguilar-Santamaria *et al.*, 2009). The antihyperglycemic effect of *Tecoma stans* could be due to alkaloids such as Tecomine (Costantino *et al.*, 2003). *Tecoma stans* (L.) Kunth has also been shown to lower blood cholesterol and to prevent weight-loss in diabetic rat model (Aguilar-Santamaria *et al.*, 2009, Costantino *et al.*, 2003).

Cichorium pumilum Jacq is a plant in the Asteraceae family with bluish-violet flowers and carrot-like root and edible leaves. This is the first study to show antihyperglycemic properties of this plant. Previous studies have shown antidiabetic activity of other members of Asteraceae family such as *Tridax procumbens* and *Sonchus oleraceus* (Petchi *et al.*, 2013, Teugwa *et al.*, 2013). *Cichorium pumilum* has also been shown to possess antitumor activity (Al-Akhras *et al.*, 2012). The mechanism by which the extract lowers body glucose requires further investigation.

The results showed antihyperglycemic effect for *Phaseolus vulgaris* L. fresh pods extracts. This is in agreement with previous literature that showed beneficial effect for *Phaseolus vulgaris* for glycemic control in diabetes patients (Olmedilla-Alonso *et al.*, 2013, Helmstadter, 2010). In addition, *Phaseolus vulgaris* has

Table 2: Blood glucose levels at 0, 1, 2, and 3 hrs post plant extract administration

Group	Time post administration				-P value
	0hr	1hr	2hr	3hr	
Control	76.8±8.8	69.5±9.25	66.5±10.24	55.5±7.99	0.21
Diabetes non-treated	441.3±51.4	380.0±40.2	386.9±24.5	411.3±27.6	0.13
Diabetes + Glibenclamide	495.3±12.3	491.4±17.2	461.9±16.7	425.3±14.9* [#]	0.00
<i>Plantago major</i> L.	486.6±11.7	480.4±14.9	529.6±42.2	525.0±35.1	0.14
<i>Taraxacum cyprium</i> H. Lindb	461.4±29.5	487.1±30.8	427.5±22.2	422.8±19.9 [#]	0.03
<i>Artemisia inculta</i> Delile	445.0±54.9	540.8±25.9	528.4±24.9	452.1±4.3	0.09
<i>Marrubium vulgare</i> L.	426.1±27.9	455.9±20.7	431.4±8.7	406.0±8.7	0.08
<i>Sarcopoterium spinosum</i> (L.) Spach.	382.8±56.7	423.0±40.5	434.2±33.5*	446.7±36.0*	0.01
<i>Inula viscosa</i> (L.) Ait.	420.5±23.0	424.5±19.8	436.5±15.6	420.5±19.1	0.52
<i>Tecoma stans</i> (L.) Kunth ex. HBK.	447.5±12.6	435.0±21.3	451.7±18.4	415.0±8.9* ^s	0.02
<i>Rubus sanguineus</i> Friv	393.0±36.9	398.0±39.1	396.5±35.0	381.5±40.1	0.73
<i>Cichorium pumilum</i> Jacq.	397.5±49.6	396.0±39.7	368.7±43.3	318.8±41.9* ^{#s}	0.00
<i>Coriandrum sativum</i> L.	447.5±7.4	447.5±11.5	429.2±13.3	421.7±15.1	0.06
<i>Phaseolus vulgaris</i> L.	427.5±27.2	427.5±36.9	429.2±39.1	392.8±28.3* ^{#s}	0.02
<i>Cucurbita pepo</i> var <i>ovefera</i>	386.9±51.5	409.8±15.9	396.0±13.2	392.8±23.1	0.94
<i>Cucumis sativus</i> L.	390.6±23.2	401.7±8.8	407.2±5.7	404.0±20.8	0.92
<i>Brassica oleracea</i> L. var. <i>capitata</i> (fresh leaves)	374.6±10.4	405.0±4.8*	399.2±6.3*	388.8±6.1	0.00
<i>Brassica oleracea</i> L. var <i>capitata</i> (Dried seeds)	438.9±21.6	429.3±22.2	423.2±15.8	421.4±6.5	0.55
<i>Hordeum vulgare</i> L.	456.8±9.9	469.6±10.6	481.0±22.8	461.5±32.8	0.59
<i>Apium graveolens</i> L.	439.0±4.3	427.9±4.9	428.3±5.2	392.6±2.99	0.05
<i>Teucrium polium</i> L.	437.7±3.8	446.9±4.2	438.9±3.5	419.9±3.6* ^{#s}	0.00
<i>Phoenix dactylifera</i> L.	448.2±2.6	428.6±5.1*	412.4±5.4*	414.5±4.5*	0.00
<i>Avena sativa</i> L.	507.9±40.8	543.3±31.2	530.1±34.3	521.8±30.4	0.55
<i>Helianthus annuus</i> L.	484.1±42.3	509.7±31.7	512.4±29.4	489.8±32.1	0.11
<i>Anethum graveolens</i> L.	389.5±47.9	436.6±25.7	478.4±11.9	479.0±8.7	0.05

Blood glucose was measured by mg/dl. Each animal group contained 6 animals. Each blood glucose measurement was done in triplicate.

* indicates significant difference from 0 hrs

indicates significant difference from 1 hr

^s indicates significant difference from 2 hrs

been shown to protect diabetes patients from cataract (Longo-Mbenza and Muaka, 2013). The antihyperglycemic activity of *Phaseolus vulgaris* L. might involve inhibition of the activity of α -amylase and enhancement of the activity of insulin-producing β -cells (Hernandez-Saavedra *et al.*, 2013, Gupta *et al.*, 2014).

Teucrium polium L. is a plant native to Mediterranean area. The result showed beneficial effect for this herb in lowering blood glucose in diabetic rats. Recent studies have shown a protection effect for *Teucrium polium* L. extract against the progression of hyperglycemia and decreases serum lipids and aspartate amino transferase activity in diabetic rats (Stefkov *et al.*, 2011, Shafiee-Nick *et al.*, 2012). In addition, treatment of with *Teucrium polium* L. protected diabetic rats from learning and memory impairment induced by the disease (Hasanein and Shahidi, 2012). The mechanism by which *Teucrium polium* L. lowers blood glucose might be due to high flavonoids content and enhancement of insulin secretion from β -cells (Mohseni, 2011, Stefkov *et al.*, 2011).

Two of the examined plants, *Sarcopoterium spinosum* (L.) Spach. and *Brassica oleracea* L. var. *capitata*, significantly increased blood glucose levels in diabetic rats. However, some previous reports showed antihyperglycemic effect for *Sarcopoterium spinosum* (L.) Spach (Kasabri *et al.*, 2011a, Kasabri *et al.*, 2011b, Rozenberg *et al.*, 2014). Given this discrepancy, we believe that the effect of these plants on blood glucose be confirmed using multi-dose or dose-response studies. In addition, no effect was observed for *Plantago major* L., *Taraxacum cyprium* H. Lindb, *Artemisia inculta* Delile, *Marrubium vulgare* L., *Inula viscosa* (L.) Ai, *Rubus sanguineus* Friv, *Coriandrum sativum* L., *Cucurbita pepo* var *ovefera*, *Cucumis sativus* L., *Hordeum vulgare* L., *Apium graveolens* L., *Avena sativa* L., *Helianthus annuus* L. and *Anethum graveolens* L. This is in contrast with some previous reports (Shukla *et al.*, 1991, Minaiyan *et al.*, 2011, Sreelatha and Inbavalli, 2012, Boudjelal *et al.*, 2012). The discrepancy in the findings could be due to utilized animal model, doses or used plant parts.

Among the limitation of the current study is that dose-response curves of the plants that gave positive result were not performed. In addition, active ingredients identification, phytochemical analysis and toxicity studies are yet to be carried out.

In conclusion, five plant extracts were shown to have antihyperglycemic activity; namely: *Phoenix dactylifera* L., *Tecoma stans* (L.) Kunth, *Cichorium pumilum* Jacq., *Phaseolus vulgaris* L., and *Teucrium polium* L. These results may have clinical significance in managements of diabetes.

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