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REVIEW ARTICLE

Plants used for the treatment of diabetes in Jordan: A review of scientific evidence

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Abstract

Context: Diabetes is a serious disease which has reached epidemic proportions in many parts of the world. Despite the tremendous developments in medicinal chemistry, traditional medicine is still a common practice for the treatment of diabetes.

Objectives: In Jordanian traditional medicine, 69 plant species are used by diabetic patients to reduce glucose levels in blood. The aim of the present study is to report these plants and link their traditional use with scientific evidence confirming their claimed activity. The plant part(s) used, method(s) of preparation, common Arabic names, and other ethnopharmacological uses are also listed.

Materials and methods: The literature and databases (SciFinder, PubMed, ScienceDirect and Scirus) have been thoroughly investigated and the plants used have been grouped according to the reported scientific evidence.

Results: Results showed that 40 plants have been reported to possess hypoglycemic activities in *in vivo*/*in vitro* experiments. Five plant species did not exhibit *in vivo* hypoglycemic activity, while 24 plants had not been studied for such an activity. Twenty plants had been screened for their α-amylase/α-glucosidase inhibitory activities.

Discussion: The reported *in vivo* and *in vitro* hypoglycemic as well as α-amylase/α-glucosidase inhibitory activities of these plants are discussed.

Conclusion: Additional *in vitro* and *in vivo* studies are needed to test the hypoglycemic activity of the plants with claimed antidiabetic activity which has not yet been evaluated. Identification of the active ingredients of potent plants might generate lead compounds in drug discovery and development.

Keywords: Medicinal plants, hypoglycemic, α-amylase, Jordan

Introduction

Jordan is a small country with high geographical and ecological diversity. About 2500 plant species were identified, from which 490 species belonging to 100 families are categorized as medicinal plants. In Jordan, the use of herbs for the treatment of a wide variety of diseases is quite common. It is estimated that more than 60% of the population still relies on using herbal medicine in their daily life. This percentage is higher in rural and desert areas as compared to urban ones. The uses vary from the treatment of common yet mild conditions (such as headache, diarrhea and, constipation) to more serious ones (such as hypertension, arthritis, ulcers, diabetes, and kidney stones) (Al-Khalil, 1995; Fawzi, 1998; Abu Irmaileh & Afifi, 2000; Oran & Al-Eisawi, 1998). Although modern medicine is available, herbal medicine has often maintained popularity for historical and cultural reasons. Despite the fact that the practice of traditional medicine is based on hundreds of years of belief and observation, scientific investigation of the efficacy of these plants is essential, especially when it comes to treatment of very serious diseases such as diabetes.

Diabetes mellitus (DM) is known to be the most common metabolic disorder worldwide. Based on WHO reports (2004), the occurrence of type II diabetes affects more than 170 million individuals worldwide. It

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is estimated that the total number of people suffering from diabetes will reach 239 million by the year 2010 (Ajlouni et al., 1999; Hamdan & Afifi, 2004; Hoffman, 1998; Kameswararao et al., 2003; Vats et al., 2002). If diabetes is neglected over long periods of time, the metabolic abnormalities are capable of contributing towards the development of complications such as nephropathy, retinopathy, neuropathy, and cardiovascular diseases (Bate & Jerums, 2003; Das et al., 2008; Watkins, 2003). In short, diabetes causes and will continue to cause morbidity, mortality, and long-term complications thus deserving every attention to solve, or at least minimize, disease-related problems. In Arabic, diabetes is called "Sukkary" meaning "related to sugar".

The plant kingdom generally, and medicinal plants in particular, have become targets in searching for drugs and in the management and treatment of chronic diseases. The ever increasing reports on traditional medicine from different parts of the world support this trend. In countries where traditional medicine plays a dominant role in imparting the primary health care, vegetables, culinary herbs, and medicinal plants are one of the main choices in the management of diabetes. Contrary to insulin dependent DM (IDDM), non-insulin dependent DM (NIDDM) could be partially managed by using herbal products – already widely practiced throughout the world. In this aspect, plants can be considered as an effective dietary adjunct in the management of DM and a potential source for the discovery of orally active antidiabetic agents. Despite the huge number of plants with claimed hypoglycemic properties used all over the world, only a small fraction of about 250,000 higher plants have been screened in depth for their hypoglycemic activity, and an even smaller number has been researched to identify the active ingredients.

In this article, plants recommended and used by diabetic patients for the treatment of DM in Jordan are reviewed. All related ethnopharmacological data concerning the method(s) of preparation and various uses are mentioned. The literature was investigated for scientific evidence in the use of these plants for the management of diabetes. The investigated plants are grouped according to the reported scientific evidence.

Materials and methods

The literature was thoroughly investigated for any scientific evidence indicating traditional use of 69 plant species in the management of diabetes. To this end, searches in various databases such as SciFinder, PubMed, ScienceDirect, and Scirus were performed. Accordingly, the used plant species are classified into four groups. These are:

1. Plants with *in vitro*/*in vivo* tested hypoglycemic activities
2. Plants with tested α-amylase/α-glucosidase inhibitory activities
3. Plants with no proven *in vivo* hypoglycemic and antidiabetic activities
4. Recommended plant species without reported *in vivo*/*in vitro* hypoglycemic activities

Classification of the plants based on the reported scientific evidence

Plants with in vitro/in vivo *tested hypoglycemic activities*

Achillea santolina L. (Asteraceae) (santolin yarrow) This biennial to perennial herb has an aromatic smell and is characterized as having typical yellow flowering heads. It is widely distributed in Jordan and found on waste ground and cultivated marginal land (Al-Eisawi, 1998). Oral administration of 0.1 g/kg/day of the aqueous extract of *A. santolina* to steptozocin (STZ)-induced diabetic rats showed significant reduction in blood glucose levels. It is assumed that the antidiabetic effect may be attributed to its anti-oxidative potential (Yazdanparast et al., 2007).

Ajuga iva L. (Labiatae) (herb ivy) This common Mediterranean perennial with purple corolla is used in Jordanian traditional medicine for its stimulant activity of the nervous and cardiovascular systems as well as for the treatment of female sterility. Its hypoglycemic potential has been previously discussed in several studies. Administration of a lyophilized *A. iva* aqueous extract for 4 h at a dose of 4.2 μg/min/100 g body weight (BW) to STZ-diabetic rats reduced plasma levels of glucose by 24%. Simultaneously, a decrease in cholesterol and triglyceride levels was also observed (El-Hilaly et al., 2007). Earlier, El-Hilaly and Lyoussi (2002) demonstrated potent hypoglycemic activity for lyophilized aqueous extract of this herb in normoglycemic and STZ-diabetic rats after acute and subchronic (3 weeks) treatment at a dose of 10 mg/kg BW orally. The hypolipidemic activity of the *A. iva* aqueous extract on STZ-diabetic rats was significant after a single dose and 3 weeks of repeated treatments (El-Hilaly et al., 2006).

Allium cepa L. (Liliaceae) The hypoglycemic activity of *A. cepa* (onion) has been well established since 1963, when Sharaf et al. (1963) found that *A. cepa* was among the plants that showed hypoglycemic effect when tested on alloxan-diabetic rats. This was confirmed later by Mathew and Augusti (1975), who also showed that juice expressed residue of onion, when fed to diabetic patients along with their food, controlled their hyperglycemia effectively. Recently, the hypoglycemic, as well as, hypolipidemic action of *A. cepa* were associated with antioxidant activity (Campos et al., 2003). Kumari and Augusti (2002) studied and compared the antidiabetic and antioxidant effects of *S*-methyl cysteine sulfoxide (SMCS) isolated from *A. cepa* and two standard drugs; glibenclamide and insulin, in alloxan-diabetic rats for 2 months. It was found that the probable mechanism of action of SMCS and glibenclamide may be partly dependent on the stimulation of insulin secretions in addition to their individual actions.

The latter are known to have stimulating effects on glucose utilization and the antioxidant enzymes, such as superoxide dismutase, and catalase. In the amelioration of diabetes, the standard drugs showed a better action. As an antioxidant, however, SMCS proved to be a better one. In a similar experiment, Sheela et al. (1995) showed that the sulfoxide amino acids; SMCS and *S*-allylcysteine sulfoxide – derived from *A. cepa* and *A. sativum* – have a preventive effect against synthesis of liver cholesterol compared to glibenclamide and insulin. Moreover, oral administration of allyl propyl disulfide isolated from onion (100 mg/kg/day for 15 days) improved the glucose tolerance of alloxan-diabetic rabbits and reduced their fasting blood sugar values (Augusti et al., 1974). A preliminary clinical trial on diabetic patients showed that the regular use of onions (50 g/day) reduced the insulin requirement of a patient from 40 to 20 units/day. The antidiabetic activity of onion may be of pharmaceutical significance since, when the two extracts were fed to diabetic rats, onion callus tissue culture extracts indicated much higher antidiabetic activity as compared to natural onion bulbs (Kelkar et al, 2001; Ahn et al., 2006). Consumption of onion skin extract (0.5%) for 7 weeks significantly reduced the levels of plasma glucose, insulin- and blood-glycated haemoglobin in db/db mice (Lee et al., 2008).

Allium sativum L. (Liliaceae) Over 20 *Allium* species are found in the wild flora of Jordan. *A. sativum* (garlic), however, is extensively cultivated in Jordan (Al-Eisawi, 1982). Garlic extracts and several of the isolated compounds have been tested in *in vitro* and *in vivo* experiments for different biological activities (Omar et al., 2007). The effect of the crude extract, garlic oil, and pure compounds in reducing blood sugar in laboratory animals and in human has been thoroughly discussed (Zacharias et al., 1980; Swanston-Flatt et al., 1990; Sheela et al., 1995; Al-Zuhair et al., 1996; Kasuga et al., 1999; Islam & Choi, 2008). Garlic is one of the most popular traditional remedies universally used for its antidiabetic activities (Grover et al., 2002; Jouad et al., 2001; Li et al., 2004; Mukherjee et al., 2006; Liu et al., 2007; Modak et al., 2007). Tahiliani and Kar (2003) reported that *A. sativum* bulb extract (500 mg/kg/day) decreases thyroxine-induced hyperglycemia in rats, based on the reduction in serum glucose and thyroid hormone concentrations in plant extract treated rats. This, subsequently, led to justifying its use in thyroxine-induced hyperglycemia. It has been also reported that *A. sativum* extract is as effective as propylthiouracil (10 mg/kg/day). Oral treatment of STZ-diabetic rats with *A. sativum* (500 mg/kg of BW) lowered the blood glucose level, inhibited the formation of lipid peroxides, reactivated the antioxidant enzymes, and restored levels of GSH and metals (copper, zinc, iron, magnesium and selenium). *A. sativum* inhibited the generation of superoxide anions (O_2^-) in both enzymatic and nonenzymatic *in vitro* systems. The *in vivo* and *in vitro* protective effects of garlic were also compared with those of glibenclamide. It was concluded that in addition to its hypoglycemic properties, garlic is also capable of decreasing the oxidative load in DM (Chandra et al., 2008). Several other studies investigated the effect of garlic on enzymes, biochemical parameters, and minerals in STZ/alloxan-diabetic mice/rats (Dong et al., 2000; El-Demerdash et al., 2005; Jelodar et al., 2005; Kiss et al., 2006; Hosseini et al., 2007). In a recent study, Al-Qattan et al. (2008) observed a reduction of 45% in serum glucose and a reduction of 50% in protein clearance levels in garlic treated (500 mg/kg BW for 7 weeks) STZ-diabetic rats compared to non-treated diabetic rats. In examining the kidneys of both groups of rats, the positive influence of garlic in the progression of diabetic structural nephropathy was clearly evident. In a randomized, single-blind, placebo controlled clinical study, garlic tablets (300 mg twice daily for 2 weeks) significantly reduced serum total cholesterol and LDL cholesterol in type II diabetic patients (Ashraf et al., 2005). Agte et al. (2008) reported that, in *in vitro* experiments, garlic exhibited moderate free radical scavenging and insulin secretion activities.

Aloe vera L. *(Liliaceae) (medicinal aloe)* Aloes have long been used all over the world for their various medicinal properties. In the past 15 years there have been controversial reports on the hypoglycemic activity of *Aloe* species; probably due to differences in the parts of the plant used or the chosen diabetes model. Okyar et al. (2001) studied the hypoglycemic effect of *A. vera* leaf pulp and gel extracts on three groups of rats namely; non-diabetic (ND), type I and type II diabetic rats. *A. vera* leaf pulp and gel extracts were ineffective in lowering blood sugar levels of ND rats. *A. vera* leaf pulp extract showed hypoglycemic activity in IDDM and NIDDM rats, the effectiveness being enhanced for type II diabetes in comparison to glibenclamide. On the contrary, *A. vera* leaf gel extract showed hyperglycemic activity in NIDDM rats. It may therefore be concluded that the pulps of *A. vera* leaves, devoid of the gel, could be useful in the treatment of NIDDM. These findings were not in concordance with later reports by Rajasekaran et al. (2004) who showed that the alcohol extract of *A. vera* gel has hypoglycemic activity and claimed that the *A. vera* extract maintains the glucose homeostasis by controlling the carbohydrate metabolizing enzymes. This matter, naturally, requires further investigation. Nevertheless, Can et al. (2004) reported that *Aloe* gel extract has a protective effect comparable to that of glibenclamide against hepatotoxicity produced by diabetes if used in the treatment of type II diabetes. The positive influence of *A. vera* on the healing of full-thickness wounds in diabetic rats was reported by Chithra et al. (1998) and Abdullah et al. (2003). In addition, Davis and Maro (1989) showed that both *A. vera* and gibberellin similarly inhibited inflammation in a dose-dependent manner, suggesting that gibberellin or a gibberellin-like substance is an active anti-inflammatory component in *A. vera.* Finally, the supplementation of the plant extracts showed preventive

effects of the impairments in the hippocampus and cortex in STZ-induced diabetic mice by attenuating the oxidative damage in both brain regions possibly via antioxidative mechanisms (Parihar et al., 2004).

Ambrosia maritima L. (Asteraceae) (sea ragwood) In alloxan-diabetic rats, a dose of 1.5 mL of *A. maritima* suspension/100 g BW showed hypoglycemic effect after 16 days of treatment (Eskander & Won, 1995).

Artemisia herba-alba Asso. *(Asteraceae) (white wormwood)* The plant is used for the treatment of diabetes in many countries in the region including Iraq and Morocco (Ziyyat et al., 1997). Al-Shamaony et al. (1994) fed diabetic rats and rabbits with 0.39 g/kg BW of the aqueous extract of the aerial parts for 2–4 weeks. This showed a significant reduction in blood glucose level, prevented elevation of glycosylated hemoglobin level, and possessed a hypoliposis effect. Moreover, the extract exhibited a protective role against BW loss of diabetic animals. Al-Khazraji et al. (1993) proved that the aqueous extract of the leaves produced a significant reduction in blood glucose level, while the aqueous extract of roots and the methanol extract of the aerial parts of the plant produced almost no reduction in blood glucose level. Al-Waili (1986) carried out a preliminary clinical study whereby 15 patients with DM were treated with *A. herba-alba* aqueous extract. The results showed considerable lowering of blood sugar level and 14 out of 15 patients had good remission from diabetic symptoms.

Artemisia vulgaris L. (Asteraceae) (mugwort) Aboutabl et al. (2006) detected antihyperglycemic activity in alloxan-diabetic rats with the ethyl acetate extract of *A. vulgaris*. Pinitol, a cyclohexane polyol, isolated from this fraction also exhibited similar activity. Contrary to these findings, *A. vulgaris* extract was shown to be ineffective in reducing blood glucose level in hyperglycemic mice (induced by 75% glucose solution). In this study, diabetic rats even expressed an increased hyperglycemia post-treatment (Villaseñor & Lamadrid, 2006).

Avena sativa L. (Graminae) The common oat plant is a species of cereal grain grown for its seeds. Oats are generally considered "healthy", or classified as health foods, being touted commercially as nutritious. Oats contain more soluble fiber than any other grain. One type of soluble fiber, β-glucan, has proven to help lower cholesterol (Lia et al., 1997). A daily intake of a minimum of 3 g of β-glucan is believed to decrease the occurrence of coronary heart diseases (FDA, 1997). Wang et al. (2004, 2005) demonstrated a significant hypoglycemic effect of β-glucan in alloxan-diabetic rats. In another study, the effect of oat β-glucan on pancreatic function in alloxan-diabetic rats was studied. β-Glucan (200 mg/kg BW) significantly increased the serum insulin and C-peptide levels after 14 days and pancreatic cell restoration was observed (Wang et al., 2006).

Capparis spinosa L. (Capparaceae) (caper) *C. spinosa* is a perennial shrubby plant common on road sides and waste grounds throughout Jordan. All parts of this plant are used by Jordanians for their medicinal value, namely joint pain, rheumatic pain, and female sterility (seed), paralysis and chest diseases (bark), diuretic and astringent (root), and renal disinfectant, diuretic, and stimulant (flower buds). Fruits are known to be used for the treatment of diabetes (Boulos, 1983; Oran & Al-Eisawi, 1998). The plant is also used for culinary purposes as condiment (flower buds). The hypoglycemic activity of *C. spinosa* has been evaluated and established using laboratory animals. Eddouks et al. (2004) investigated the hypoglycemic effect of the fruits in normal and STZ-diabetic rats. Oral administration of *C. spinosa* fruit extract (20 mg/kg) in STZ-diabetic rats in single dose and in 14 days repeated treatments produced significant decrease in blood glucose levels. Blood glucose levels were normalized after 2 weeks from treatment.

Ceratonia siliqua L. (Fabaceae) (carob) Enrichment of Israeli ethnic food with *C. siliqua* gum significantly lowered glucose plasma levels in NIDDM patients (Feldman et al., 1995). *C. siliqua* gum is composed mainly of galactomannan, which may contribute to the reduction of glucose levels in blood.

Cichorium intybus L. (Asteraceae) *C. intybus* (common chicory) is a bushy perennial herb with blue lavender, or occasionally white, flowers. It grows as a wild plant on roadsides and is cultivated for its leaves and eaten raw as a salad. Chicory is another example of food plants with reputed medicinal values in the local traditional medicine. Several reports discuss the hypoglycemic value of chicory. One and three weeks' treatment of STZ-diabetic rats with the methanol extract of *C. intybus* resulted in significant decrease of blood glucose levels in treated animals. After 2 weeks of treatment, 80% ethanol/water extract of *C. intybus* (125 mg/kg) decreased serum glucose level of STZ-diabetic rats by 20%. This was not associated with an increase in serum insulin level. These findings indicate that *C. intybus* does not induce insulin secretion from pancreatic β-cells (Pushparaj et al., 2007). A chicory inulin diet (6%) lowered plasma glucose levels after 25 days of treatment in STZ-diabetic mice (Jeong et al., 2005). Inulin from the chicory roots slightly increased the activity of the proteases in blood serum of STZ-diabetic rats while decreasing hyperglycemia (Tsisel'skii & Levistkii, 2007). In a recent study, Jurgonski et al. (2008) were unable to detect the effect of the polyphenol-rich chicory diet on the hyperglycemia in STZ-diabetic rats. The group did, however, observe a significant improvement in the hypertrophy of the liver and kidney.

Citrullus colocynthis L. (Schrad) (Cucurbitaceae) (colocynth) Infusions of *C. colocynthis* fruits are traditionally used as antidiabetic medication in Mediterranean countries. It has been reported that this plant, along

with *Trigonella foenum-graecum* and *A. herba-alba*, are among the most commonly used antidiabetic plants in Morocco (Ziyyat et al., 1997). The hypoglycemic and anti-hyperglycemic effects of *C. colocynthis* aqueous extract of the fruit, in normal and alloxan-diabetic rabbits, was investigated by Abdel-Hassan et al. (2000). In normal rabbits, oral administration of the aqueous extract (300 mg/kg) produced significant reduction in plasma glucose levels. Phytochemical screening revealed that the rind of *C. colocynthis* and its aqueous extract contain tertiary and quaternary alkaloids, glycosides, and saponins. The hypoglycemic effects of these components given orally at a dose of 50 mg/kg, were studied in normoglycemic rabbits. Results showed that the alkaloidal extract did not significantly lower the blood glucose levels, while the glycosidic extract significantly lowered the fasting glucose levels after 2–6 h. The effect was more pronounced with the saponin extract. Graded doses (10, 15, and 20 mg/kg) of saponin extract, when given orally to alloxan-diabetic rabbits, produced a significant reduction of plasma glucose concentration. These results suggest that the aqueous extract of the rind of *C. colocynthis* possesses hypoglycemic effects which could be mainly attributed to the presence of saponins and glycosidic components. Al-Ghaithi et al. (2004) reported that the oral administration of the aqueous extract of *C. colocynthis* can ameliorate some of the toxic effects of STZ. In an attempt to study the possible mechanism involved in the antidiabetic properties of the plant, Nmila et al. (2000) evaluated the insulinotropic effects of the different extracts of *C. colocynthis* seed components. The insulin secretory effects were studied *in vitro* in the isolated rat pancreas and islets in the presence of 8.3 mM glucose. All tested extracts, when perfused for 20 min at 0.1 mg/mL, immediately and significantly stimulated insulin secretion. This showed that different *C. colocynthis* seed extracts have an insulinotropic effect which could at least partially account for the antidiabetic activities of this plant.

Citrus sinensis (L.) Osbeck (Rutaceae) (sweet orange) The peel extract of this worldwide served table fruit showed a dose-dependent hypoglycemic activity in male rats with induced diabetes. This is in addition to its anti-thyroidal and insulin stimulatory properties (Parmar & Kar, 2008).

Coriandrum sativum L. (Umbelliferae) *C. sativum* (coriander) has been reputed as a traditional remedy in the treatment of diabetes. The effect of *C. sativum* on glucose homeostasis has been evaluated in normal and STZ-diabetic rats. A reduction in the level of STZ-induced hyperglycemia was observed in the group of rats treated for 12 days with *C. sativum* (Swanston-Flatt et al., 1990). Incorporation of *C. sativum* into the diet (62.5 g/kg) and drinking water (2.5 g/L) reduced hyperglycemia in STZ-diabetic mice. Moreover, in acute 20 min tests, 0.25-10 mg/mL aqueous extract of *C. sativum* caused 1.3–5.7-fold stimulation of insulin secretion from a clonal β-cell line. This effect of the aqueous extract of coriander was found to be equivalent to 10^{-8} M insulin; strongly indicating insulin-releasing and insulin-like activities of *C. sativum* (Gray & Flatt, 1999). Treatment of STZ-diabetic rats with each of *C. sativum* leaf, seed, and root extracts resulted in increased plasma insulin level. The extracts, however, did not affect the plasma glucose level (Hwang et al., 2001). Jelodar et al. (2007) could not detect significant hypoglycemic effect for *C. sativum* leaf extract in alloxan-diabetic rats after treatment for 15 days with a dose of 60 g/kg/BW/day.

Coridothymus capitatus (L.) Reichenb. (conehead thyme) Shabana et al. (1990) observed hypoglycemic effects in alloxan-diabetic rats after oral administration of *C. capitatus* extract.

Crataegus aronia L. Bosc. Ex DC (Rosaceae) (spiny hawthorn) This perennial thorny shrub is widely distributed in forests and mountains of Jordan. The health benefits of decoctions from leaves and unripe fruits of *C. aronia* in treatment of cardiovascular diseases, cancer, DM, and sexual weakness are well known in traditional Arab medicine. It has been reported that oral administration of leaves and unripe fruit decoctions of the plant lowered blood glucose levels in STZ-induced diabetic rats (Ljubuncic et al., 2005).

Cuminum cyminum L. (Umbelliferae) Several researchers have studied the benefits of *C. cyminum* (cumin) supplementation in the treatment of DM. The possible antidiabetic effect of cumin seeds was investigated on STZ-diabetic rats. A reduction in hyperglycemia and glucosuria was observed after treatment of the diabetic rats for 8 weeks with cumin powder (Willatagamuwa et al., 1998). In alloxan-diabetic rats, oral administration of *C. cyminum* aqueous extract (0.25 g/kg) caused a significant reduction in blood glucose level, tissue and plasma cholesterol levels, and free fatty acids and triglycerides. Histological examination of the pancreas of the cumin extract treated and non-treated diabetic rats indicated significantly reduced fatty changes and inflammatory cell filtrates in the pancreas of the former group. In this study, cumin supplementation was found to be more effective than glibenclamide in the treatment of DM (Dhandapani et al., 2002). Non-diabetic and alloxan-diabetic albino rats were treated for 6 weeks by intra-gastric intubation with aqueous cumin extract (0.25 g/kg). The level of the different enzymes in pancreas, liver, kidney, intestine, and aorta were significantly influenced in the treated group of rats. This, subsequently, indicated that the supplementation with cumin can reduce the free radical mediated oxidative stress to the cells in experimental DM (Surya et al., 2005). Recently, Agte et al. (2008) reported moderate *in vitro* insulin secretion activity for *C. cyminum.*

Eryngium creticum Lam. *(Umbelliferae) (field eryngo) E. creticum* has been used in folk medicine in rural areas

of Jordan to overcome the toxic effects of scorpion stings and as a hypoglycemic agent. Jaghabir (1991) investigated the hypoglycemic activity of an *E. creticum* aqueous decoction in normal and STZ-diabetic rats. A reduction in blood glucose levels in both normal and diabetic rats was observed.

Eucalptus globules Labill. (Myrtaceae) (eucalyptus) Addition of *E. globulus* to the diet (62.5 g/kg) and drinking water (2.5 g/L) reduced hyperglycemia and BW loss in STZ-diabetic mice (Gray & Flatt, 1998). Oral treatment of mice for 12 days with *E. globulus* extract reduced the level of hyperglycemia during the development of STZ-induced diabetes (Swanston-Flatt et al., 1990). In *in vitro* experiments, the aqueous extract of *E. globulus* (50 g plant extract/L) significantly decreased glucose diffusion across the gastrointestinal tract (Gallagher et al., 2003).

Geranium spp. (Geraniaceae) (geranium) About ten *Geranium* species are found in the flora of Jordan and are used locally for their diuretic, astringent, and antidiabetic activities (Al-Eisawi, 1982; Oran & Al-Eisawi, 1998). *G. graveolens* L. and *G. robertianum* L. are mainly recommended for their antidiabetic activities. A hypoglycemic effect in alloxan-diabetic rats was associated with *G. robertianum* suspension at a dose of 1.5 mL/100 g BW (Eskander&Won, 1995).

Juglans regia L. (Juglandaceae) (walnut) *J. regia* leaves and hulls have been used in traditional medicine for their astringent, keratolytic, antidiarrheal, antifungal, sedative, and hypoglycemic effects. Herbal preparations derived from walnut are used as hair dyes and skin colorants (Girzu et al., 1998). In Jordan, different shades of dark color hair dye can be imparted by mixing walnut hull powder with that of henna (*Lawsonia inermis* L.). Recently, Asgary et al. (2008) have demonstrated the antidiabetic effect of the ethanol extract (200 mg/kg) in alloxan-diabetic rats and compared this activity to that of glibenclamide. The results indicated similar potencies in the antidiabetic activity for both. An increased insulin level and, histopathologically, an increase in the size of islets of Langerhans cells supported these findings. Earlier, Jelodar et al. (2007) also reported significant hypoglycemic activity for *J. regia* extracts in alloxan-diabetic rats. Again, in this study, morphological examination of the pancreas clearly indicated hypercellularity of islet tissue and increased hyperchromic nucleus in pancreatic islets denoting possible regeneration of the β-cells of the pancreas.

Laurus nobilis L. (Lauraceae) Bay leaf is one of the most popular culinary herbs in the East and West. Among different health benefits, its antidiabetic potential is well accepted in Jordanian traditional medicine. Yanardag and Can (1994) investigated the effects of *L. nobilis* leaf extract on blood glucose levels of normal and alloxan-diabetic rabbits. Significant hypoglycemic effect was only observed using the alcohol extract in doses of 200 and 600 mg/kg BW in diabetic rabbits.

Lupinus albus L. (Papillionaceae) *L. albus* L. (lupine) is a cultivated food plant in Jordan while *L. luteus* is indigenous. Debittered lupine seeds have long been used as a traditional remedy in the treatment of diabetes in Jordan and Palestine. In the past 35 years, several studies demonstrated the hypoglycemic effects of *L. albus* (Amin et al., 1988; Otoom et al., 2006). Dietary fiber from *L. albus* did not affect glucose and insulin levels in NIDDM volunteers (Feldman et al., 1995). In the newer investigations, detailed data on the hypoglycemic effect of lupine seeds have been presented. Pereira et al. (2001) demonstrated the insulin releasing activity of the aqueous lupine extract on isolated rat pancreatic islets. A 4-week treatment with *L. albus* extract (120 mg/kg BW) reduced the blood glucose levels and decreased the activity of the different enzymes in the liver of diabetic rats (cytochrome P450, NADPH-Cytochrome reductase, glutathione *S*-transferase, etc.) in comparison to non-treated alloxan-diabetic rats (Sheweita et al., 2002). Also, in alloxan-diabetic rats, lupine extract decreased the levels of glucose, urea, creatinine, and bilirubin in the plasma after 4 weeks' treatment with 1.5 mL aqueous suspension/100 g BW. This treatment restored the activities of several deranged enzymes in the plasma, liver, and testis to their normal level (Mansour et al., 2002). In glucose resistant mice, whole *L. albus* seed extract – when administered orally but not intraperitoneally – increased glucose tolerance thus indicating the influence of the seed extract on intestinal glucose absorption (Knecht et al., 2006).

Morus nigra L. (Moraceae) (black mulberry) The hypoglycemic effects of *M. nigra* and *M. alba* leaves, fruit and bark extracts were studied in normal and alloxan-diabetic mice. A single dose (500 mg/kg) of dried leaf extracts of both species and *M. nigra* bark extract decreased blood glucose levels in alloxan-diabetic mice. The leaf extracts of both *M. nigra* and *M. alba* produced maximum reduction after treatment for 7 consecutive days (Hosseinzadeh & Sadeghi, 1999). In STZ-diabetic rats, *M. alba* leaf extract decreased weekly food consumption throughout the 5-week treatment period. The resulting hypoglycemic effect was probably achieved through interference with food intake or prevention of gastrointestinal glucose absorption (Musabayane et al., 2006).

Nigella sativa L. (Ranunculaceae) (black cumin) *N. sativa* is one of the important and widely used medicinal plants of Jordan and other Middle Eastern countries. The powdered seeds, as well as the seed oil, are commonly taken mixed with honey as a food supplement to maintain good health. As a form of traditional medicine, it is used for the treatment of several diseases, including DM. The seeds, rich in fixed and volatile oils, are ingredients of bread, pastries, and other traditional foods.

Al-Zuhair et al. (1996) investigated the effect of the volatile oil extracted from *N. sativa* on the glucose and serum insulin levels on alloxan-diabetic rats. Although the oil exerted a significant hypoglycemic effect, it increased the blood glucose level when used together with glipizide (Al-Zuhair et al., 1996). Several other studies demonstrated the hypoglycemic effects of oral administration of *N. sativa* extracts, oil, and isolates in rats with alloxan- or STZ-induced diabetes (Kaleem et al., 2006; Houcher et al., 2007; Kanter, 2008). A 12-week treatment of diabetic rats with *N. sativa* resulted in a significant increase of the insulin immuno-reactive β-cells of the pancreas (Kanter, 2008). The insulin secretory effect of the *N. sativa* extracts were evaluated in *in vitro* experiments on isolated rat pancreatic Langernhans islets. A significant increase of glucose induced release of insulin from the islets was observed (Rchid et al., 2004). It has been also found that *N. sativa* has a protective effect in DM since it reduces the oxidative stress; a phenomenon involved in the pathogenesis of diabetes. This was stated when the herbal treatment started prior to induction of diabetes and was persistent throughout the treatment period (Kanter et al. 2004). It has been proposed that the antidiabetic activity might be due to the inhibition of enzymes involved in the neoglucogenesis pathway in the liver or by extra pancreatic actions rather than stimulated insulin release (El-Dakhakhny et al., 2002; Houcher et al., 2007). Najmi et al. (2008) found that *N. sativa* oil is effective in obese diabetic patients and this plant can be considered to beneficially add to the therapy of patients with insulin resistance syndrome. Recently, another study demonstrated that *N. sativa* directly inhibits the electrogenic intestinal absorption of glucose *in vitro* and assumed that *N. sativa* is as potent as metformin (Meddah et al., 2009).

Olea europea L. (Oleaceae) (olive tree) The olive tree is an evergreen tree native to Palestine. Olive fruits from different varieties are used as condiment and for the expression of oil. In traditional medicine, the leaf extract is used for its astringent, hypotensive, antibacterial, and antidiabetic properties (Gilani et al., 2005; Tahraoui et al., 2007). Oleuropein, the major secoiridoid compound of the olive leaves, has been studied for both hypolipidemic and hypoglycemic activities. Trovato and Forestieri (1993) reported hypoglycemic effects of the glycero-alcohol macerates and oleuropein from shoots and leaves of O. *europea* in alloxan-diabetic rats. Bennani-Kabchi et al. (1999, 2000) have demonstrated hypoglycemic, antihyperglycemic, and hypoinsulinaemic activities for *O. europea* leaf decoction in hypercholesterolemic insulin resistant sand rats. The findings of 16 weeks' treatment of alloxan-diabetic rabbits with oleuropein (20 mg/kg BW) resulted in significant improvement of glucose blood levels and most of the enzymatic and non-enzymatic antioxidants. This could indicate the role of oleuropein in inhibiting hyperglycemia and oxidative stress induced by diabetes (Al-Azzawie & Alhamdani, 2006). Recently, oleonolic acid – a triterpenoid acid – has been found to also possess antidiabetic activities by lowering serum glucose and insulin levels and enhancing glucose tolerance in mice fed with a high fat diet (Sato et al., 2007). It can be thus concluded that both oleuropein and oleanolic acid are involved in the antidiabetic effect of *O. europea* leaf extract.

Opuntia ficus-indica L. (Mill.) (Cactaceae) (Indian fig) The edible fruits and stems of *O. ficus-indica* and the polysaccharides isolated from it have been reported to exhibit antidiabetic and hypoglycemic activities (Alarcon-Aguilar et al., 2003; Lee et al., 2005; Yoon & Son, 2009). Commercially available capsules of *O. ficus-indica* were tested on normal and diabetic patients without reaching acute hypoglycemic effects (Frati-Munari et al., 1989, 1992).

Plantago ovate Forsk. (Plantaginaceae) (psyllium) Traditionally, the seeds of *P. ovata* are used in the treatment of chronic constipation, chronic bacillary and amoebic dysentery as well as in the management of diabetes and internal hemorrhoids. Hot water extract of husks of *P. ovata* reduced hyperglycemia in type I and type II DM by inhibition of intestinal glucose absorption and enhancement of motility. While the administration of the aqueous extract (0.5 g/kg BW) significantly improved glucose tolerance in normal, type I, and type II diabetic rat models, insulin secretion in perfused rat pancreas, isolated rat islets or clonal β-cells was not altered (Hannan et al., 2006).

Portulaca oleraceae L. (Portulacaceae) (purslane) *P. oleraceae* aqueous suspension exerted hypoglycemic effects after 16 days of treatment in alloxan-diabetic rats at a dose of 1.5 mL/100 g BW (Eskander & Won, 1995).

Prosopis farcta (Banks et Sol.) *Macbride (Mimosaceae) (Syrian mesquite)* The effect of the aqueous extracts of *P. fracta* on blood glucose levels of normal rats and STZ-diabetic rats was studied (Afifi, 1993). The results showed that the extract has significant hypoglycemic effect that needs to be further investigated.

Rheum ribes Linn. (Polygonaceae) (rhubarb) The effect of aqueous root extract of *R. ribes* was investigated by Hanefi et al. (2004). A decoction of *R. ribes* roots was given orally and tested for hypoglycemic effect in healthy and alloxan-diabetic mice. The results were compared to those of glibenclamide and control groups. Results indicated that the extract possesses hypoglycemic effect in diabetic animals.

Salvia fruticosa Mill. (Lamiaceae) (Greek sage) *S. fruticosa* is a very common herb in Jordan. It is used as a tea alone or can be added to black tea and can also be used as a condiment for flavoring different meat dishes. In the Eastern Mediterranean area, as well as Jordan, it is known for its antidiabetic activities. Perfumi et al. (1991) studied the hypoglycemic activity of a 10% leaf infusion at an oral dose of 0.25 g/kg BW in normo- and alloxan-diabetic rabbits. After treatment for 7 consecutive days, the oral

dose caused significant reduction in blood glucose levels in alloxanized rabbits without exerting any effect on normal ones. Additionally, the hypoglycemic effect was observed by a single oral dose in both groups of rabbits which were orally loaded with glucose. Changes in the route of administration of glucose, from oral to intravenous, rendered *S. fructose* ineffective thus indicating that this plant is likely to cause hypoglycemia by reducing the intestinal absorption of glucose.

Sarcopoterium spinosum (L.) Spach (Rosaceae) (thorny burnet) This perennial spiny plant is found mainly in northern parts of Jordan. Several studies were carried out to demonstrate the hypoglycemic effects of *S. spinosum* extracts in normal and diabetic animals. Root and stem decoctions of *S. spinosum* were reported to be effective in the reduction of blood glucose levels in fasting rabbits while the fruit did not exhibit similar activity (Schluetz & Venulet, 1964). Mishkinsky et al. (1966) also found *S. spinosum* to be inactive by subcutaneous administration while confirming that the oral administration (2 g/kg) exhibited a significant hypoglycemic effect in fasting rabbits. Quisenberry and Gjerstad (1967) tested the hypoglycemic activity of the root bark clinically on a single diabetic patient and found the extract effective. The root bark decoction of *S. spinosum* produced a detectable hypoglycemia in alloxan-diabetic rats when the bark was obtained from plants during summer months (Shani et al., 1970). Slijepcevic and Kraus (1997) demonstrated hypoglycemic effect of isolated fractions of *S. spinosum* in alloxan-diabetic mice.

Teucrium polium L. (Lamiaceae) (felty germander) *T. polium* is widely distributed in Jordan and Palestine. Traditionally, in many Mediterranean countries, decoction of *T. polium* is used for its antispasmodic and antidiabetic activities. Gharaibeh et al. (1988) tested the hypoglycemic activity of the aqueous decoction of the aerial parts of *T. polium* in normoglycemic and STZ-diabetic rats. Results indicated that the extract caused a significant reduction in blood glucose level 4 h after intravenous administration and 24 h after intraperitoneal administration. This effect was attributed to the enhancement of peripheral metabolism of glucose rather than an increase in insulin release. Esmaeili and Yazdanparast (2004) observed a significant decrease in blood glucose concentration of STZ-diabetic rats after 6 weeks of consecutive oral treatment with ethanol/water extract of *T. polium*. Afifi et al. (2005) did not observe any significant difference between the alloxan-induced hyperglycemic and normoglycemic rabbits upon intranasal administration of 10% aqueous *T. polium* extract (0.1 mL/kg rabbit). Recently, Ardestani et al. (2008) evaluated the anti-oxidative potential of *T. polium* aqueous extract for protecting rat pancreatic tissue against STZ-induced oxidative stress. Results indicated that this plant may have protective effects on pancreatic tissue in STZ-induced oxidative stress based on its high oxidative potential.

Trigonella foenum-graecum L. (Leguminoseae) *T. foenum-graecum* L. is traditionally used as food or medicine for diabetes care. The extracts, powder, and gum of fenugreek's aerial parts and seeds have been reported to have antidiabetic and hypocholesterolemic properties in both animal models and human (Ribes et al., 1986; Amin et al., 1988; Ahmad et al., 1995; Ali et al., 1995; Abdel-Barry et al., 1997; Bordia et al., 1997; Al-Habbori & Raman, 1998; Gomez & Bhaskar, 1998; Khatir et al., 1999; Gupta et al., 2001; Vats et al., 2002). Ribes et al. (1986) investigated the effect of two fractions, rich in fibers or rich in saponins and proteins, on hyperglycemia in alloxan-diabetic dogs. Pancreatic hormone levels were additionally evaluated. The researchers found that the antidiabetic properties of the *T. foenum-graecum* seeds reside in the fibrous fraction. Activity has been attributed largely to the major alkaloid trigonelline, fenugreek's saponins, high fiber content, and to the amino acid 4-hydroxyisoleucine (Ali et al., 1995; Petit et al., 1995; Sauvaire et al., 1998). The latter compound was found to increase glucose-induced insulin-release through a direct effect on isolated islets of Langerhans in both rats and humans. This antihyperglycemic effect was linked to the delay in gastric emptying caused by the high fiber content, inhibition of carbohydrate digestive enzymes, reducing postprandial elevation in blood glucose level, and stimulation of insulin secretion (Ali et al., 1995; Faruque et al., 1998; Sauvaire et al., 1998). Tahiliani and Kar (2003) concluded that *T. foenum-graecum* seed extract decreases thyroxine-induced hyperglycemia in rats, based on the reduction in serum glucose and thyroid hormone concentrations in plant extract treated rats. Shah et al. (2006a, 2006b) demonstrated the significant hypoglycemic effect of trigonelline and 4-hydroxyisoleucine, isolated by column chromatography from fenugreek seeds, in alloxan-induced diabetic mice. The LD_{50} for this compound was also determined.

Urtica dioica L. *(Urticaceae) (stinging nettle)* In STZ-diabetic rats, Farzami et al. (2003) demonstrated that *U. dioica* extract enhances insulin secretion by islets of Langerhans and reduces blood sugar levels. In an *in vitro* method, aqueous extract of *U. dioica* (50 g/L) did not show a significant decrease in glucose movement in the gastrointestinal tract (Gallagher et al., 2003). Bnouham et al. (2003) could not demonstrate any hypoglycemic effect in alloxan-diabetic rats. However, they observed a significant antihyperglycemic effect (lasting for 3 h) following the oral glucose tolerance test (OGTT). This suggested that the aqueous *U. dioica* extract reduced intestinal glucose absorption. Golalipour and Khori (2007) examined the protective activity of *U. dioica* leaves on blood glucose concentration and β-cells in STZ-diabetic rats by administration of a hydroalcoholic extract (100 mg/kg/day) for 5 weeks intraperitoneally prior to induction of diabetes. The results obtained indicated that the protective administration of the plant extract

exhibited both hypoglycemic effect and protective activity on pancreatic β-cells in hyperglycemic rats. Prior to this study, Golalipour et al. (2006) could observe neither hypoglycemic nor regenerative effects on the β-cells of Langerhans in STZ hyperglycemic rats after treatment for 4 weeks with hydroalcoholic extract of *U. dioica* (100 mg/kg/day). In a recent study, Fazeli et al. (2008) showed that *U. dioica* hydroalcoholic extract (100 mg/kg/day) can help compensate the granule cell loss in the diabetic rat dentate gyrus which, subsequently, can ameliorate cognitive impairment in diabetes. The researchers could not detect any protective effect for the same extract using the same dose. Said et al. (2008) reported the safety and antidiabetic effect of a dry extract of leaves of *J. regia* L., *O. europea* L., *U. dioica* L., and *Atriplex halimus* L. based on *in vitro* and *in vivo* experiments.

Varthemia iphionoides Boiss and Blanche (Asteraceae) (goldy locks) The effect of the aqueous extracts of *V. iphionoides* on blood glucose levels of normal rats and STZ-diabetic rats was studied (Afifi et al., 1997). The results showed a significant hypoglycemic effect worthy of being further investigated.

Zea mays L. (Poaceae) (corn) Maize powder, corn silk polysaccharides, and *Z. mays* saponins were studied for their hypoglycemic activities in normal and alloxan/STZ-diabetic rats and mice. Their hypoglycemic activities were established (Zhang et al., 2005; Li et al., 2006, 2007; Miao et al., 2008). Suzuki et al. (2005) concluded that the water extract of the style of *Z. mays* suppresses the progression of diabetic glomerular sclerosis in STZ-diabetic rats, while the resistant starch of *Z. mays* did not influence blood glucose and insulin levels in these animals (Kim et al., 2003).

Zizyphus spina-christi (L.) Desf. (Rhamnaceae) (Christ thorn) *Z. spina-christi* is one of the plants commonly used in Egypt, Jordan, and many other Mediterranean countries for the treatment of different diseases. The effect of the butanol extract of *Z. spina-christi* leaves as well as its principle saponin glycoside, christinin-A, was investigated (Glombitz et al., 1994). In normal rats, treatment for 1 and 4 weeks produced insignificant changes in all studied parameters. However, in diabetic rats, the treatment significantly reduced serum glucose levels, liver phosphorylase, and glucose 6-phosphatase activities. Moreover, there was a significant increase in serum pyruvate level and liver glycogen content after 4 weeks of treatment. There was also marked improvement in glucose utilization in diabetic rats in both cases. Serum insulin and pancreatic cAMP levels showed significant increase in diabetic rats treated for a period of 4 weeks with the butanol extract of *Z. spina-christi*. In a similar study, Abdel-Zaher et al. (2005) studied the effects of *Z. spina-christi* butanol extract and christinin-A in normoglycemic and type I and type II diabetic rats. At a dose of 100 mg/kg BW, the plant extract and christinin-A showed identical potency. At this concentration, pretreatment with the extract improved oral glucose tolerance and potentiated glucose-induced insulin release while treatment with the extract decreased serum glucose levels and increased serum insulin levels. These effects of the *Z. spina-christi* extract were observed in type II diabetic rats while type I diabetic rats were not affected. The comparison of oral LD_{50} (3160 mg/kg) to that of glibenclamide (3820 mg/kg) renders *Z. spina-christi* a safe alternative in lowering blood glucose levels.

Plants with tested α-amylase/α-glucosidase inhibitory activities

A. cepa L. Alpha amylase has been looked at as a potential target to control diabetes for more than 30 years. All five flavonoids isolated from *A. cepa* were tested for their α-amylase inhibitory activity and their values were compared to that of acarbose, the latter being regarded to demonstrate 100% inhibitory activity. The flavonoid alliuocide G showed the most potent inhibitory activity (96.5%) compared to acarbose. The remaining flavonoids exerted inhibitory activities of different degrees (Mohamed, 2008). Methanol extract of onion skin inhibited yeast α-glucosidase with an IC_{50} of 0.159 mg/mL (Lee et al., 2008). Recently, Nickavar and Yousefian (2009) demonstrated the α-amylase inhibitory effect of the ethanol extract with an IC_{50} value of 16.36 mg/mL.

A. sativum L. Nickavar and Yousefian (2009) reported the α-amylase inhibitory activity for the ethanol extract of *A. sativum* to have an IC_{50} value of 17.95 mg/mL.

A. vera L. Based on the starch-iodine method, *A. vera* exhibited significant α-amylase inhibitory activity (99%) with an estimated IC_{50} of 0.08 mg/mL (Abu Soud et al., 2004).

L. albus L. Very mild α-amylase inhibitory activity (3%) was observed using the 50% methanol extract of *L. albus* (Abu Soud et al., 2004).

Paronychia argentea Lam. (Caryophyllaceae) (silver nailroot) This perennial is commonly found in fallow fields and waste places throughout Jordan. A 50% methanol/water extract of *P. argentea* exhibited significant α-amylase inhibitory activity (85%). The estimated IC_{50} (0.2 mg/mL) was compared to that of acarbose. The latter was found to be about 50 times more active than the *P. argentea* extract (Abu Soud et al., 2004). Hamdan and Afifi (2004) also reported significant α-amylase inhibitory activity for the aqueous extract of *P. argentea*.

Pistachia atlantica Desf. (Anacardiaceae) (Mount Atlas pistache) Aqueous extract of *P. atlantica* has been found to possess significant α-amylase inhibitory activity (Hamdan & Afifi, 2004).

S. spinosum L. Spach A 50% methanol extract of *S. spinosum* exhibited significant (85.2%) α-amylase inhibitory activity. The estimated IC_{50} was found to be 0.14 and appeared to be about 35 times less active than acarbose (Hamdan & Afifi, 2008).

T. polium L. Weak α-amylase inhibitory activity (5%) was observed with the 50% methanol extract of *T. polium* (Abu Soud et al., 2004).

T. foenum-graecum L. Water soluble *T. foenum-graecum* seed extract inhibited α-amylase more than α-glucosidase (McCue et al., 2005). A 50% methanol extract of the seeds reported to exhibit only 10% inhibitory activity (Abu Soud et al., 2004).

U. dioica L. Oenal et al. (2005) demonstrated α-glucosidase inhibitory activity for *U. dioica* aqueous extract while Hamdan and Afifi (2008) could not observe any such activity.

V. iphionoides Boiss and Blanche Ethanol and water extracts of the aerial parts of *V. iphionoides* exhibited potent α-amylase inhibitory activity. The ethanol fraction yielded several flavonoids (Al-Dabbas et al., 2006). Nevertheless, a 50% methanol extract did not exhibit any inhibitory activity (Abu Soud et al., 2004; Hamdan & Afifi, 2008).

Plants with no proven in vivo *hypoglycemic and diabetic activities*

Alchemilla vulgaris L. (Rosaceae) (lady's mantle) The oral treatment of mice for 11 days with *A. vulgaris* aqueous extract did not prevent the development of hyperglycemia and hypoinsulinemia once they were subsequently injected with STZ intraperitoneally. Food and fluid intake, BW gain, plasma glucose, and insulin concentrations were not altered in normal mice during the same period of treatment with the *A. vulgaris* extract (Swanston-Flatt et al., 1990).

Ferula persica Wild. (Umbelliferae) (sagapenum) The aqueous extract of *F. persica* did not exhibit hypoglycemic activity in normal and STZ-diabetic rats (Hamdan & Afifi, 2004).

P. argentea Lam. Treatment of STZ-diabetic rats with an aqueous *P. argentea* extract did not show hypoglycemic activity compared to untreated rats (Hamdan & Afifi, 2004).

Peganum harmala Linn. (Zygophyllaceae) *P. harmala* is a common herb of marginal and desert lands. In Jordan, the seeds and the oil extracted from the seeds of *P. harmala* are widely used for rheumatic conditions and arthritis. Hussain et al. (2004) could not detect any insulin secretagogue activity using the ethanol extract of *P. harmala*.

P. atlantica Desf. Hamdan and Afifi (2004) could not detect any hypoglycemic activity in STZ-diabetic rats using *P. atlantica* extract.

Recommended plant species without reported *in vivo/in vitro* hypoglycemic activities

Our literature survey showed that twenty-four plants, recommended by the Jordanian herbalists for the treatment of DM, had not been studied with regard to their hypoglycemic activities. These plants are: *Achillea fragrantissima* (Forsk.) Sch. Bip (Asteraceae), *Alhagi maurorum* Medicus (Leguminosae), *Anthemis pseudocotula* Boiss. (Asteraceae), *Artemisia judaica* L. (Asteraceae), *Cephalaria syriaca* Roemer et Schultes (Dipsacaceae), *Cichorium pumilum* L. (Asteraceae), *Citrus limon* (Linn.) Burm. (Rutaceae), *C. paradisi* Macfad, *Cleome droserifolia* (Forskal) Delil (Capparaceae), *Crataegus azarolus* L. (Rosaceae), *Cucurbita maxima* Duchesne (Cucurbitaceae), *Gundelia tournefortii* L. (Asteraceae), *Juniperus phoenicea* L. (Cupressaceae), *Matricaria aurea* (Loefl.) (Asteraceae), *Mentha spicata* L. (Labiatae), *Ononis natrix* L. (Leguminosae), *Origanum syriacum* L. (Labiatae), *Pistacia palaestina* Boiss. (Anacardiaceae), *Plantago major* L. (Plantaginaceae), *Quercus coccifera* L. (Fagaceae), *Ruta chalepensis* L. (Rutaceae), *Taraxacum cyprium* H. Lindb. (Asteraceae), *Triticum dicoccoides* (Koern. Ex Asherson & Graebner) Aaronsohn (Graminae), *Zygophyllum simplex* L. (Zygophyllaceae).

Results

The use of crude plant extracts is seen as a common practice in the traditional medicine which plays an important role in the health care in Jordan as well as in many parts of the world. It is estimated that more than 60% of the population in Jordan still rely on herbal medicine for the treatment of different diseases including DM, among others (Al-Khalil, 1995; Fawzi, 1998; Hamdan & Afifi, 2004; Oran & Al-Eisawi, 1998). In this review, the plants reccommended by the herbalists and used by the people for the treatment of DM are listed. The list is comprised of 69 plants (Table 1), all native flora of Jordan. Forty plants in the list were evaluated for their *in vivo*/*in vitro* hypoglycemic activities. Twenty plant species with claimed hypoglycemic activity and indigenous to Jordan, have been screened *in vitro* for their α-amylase inhibitory activity. *A. cepa*, *A. sativum*, *A. vera*, *S. spinosum*, *P. atlantica*, and *P. argentea* have been reported to possess potent inhibitory effect although *P. argentea* did not show *in vivo* hypoglycemic activity. Twenty-four plants of the list were not studied with regard to their hypoglycemic activities.

Discussion

Surveys carried out by Jordanian and regional researchers revealed that the list of medicinal plants used by the people living in urban areas and those reccommended

Table 1. Antidiabetic plants indigenous to Jordan used for the treatment of diabetes in folk medicine in Jordan.

No.	Species	Family name	Common name	Plant parts	Method of Preparation	Other Uses	References for anti-diabetic activity
1	*Achillea fragrantissima* (Forsk.) Sch. Bip[d]	Asteraceae	Qaisoom	Leaves and shoots	Infusion	Cold, cough, abdominal pain, arthritis inflammation, kidney stones	Abu-Irmaileh & Afifi, 2000
2	*Achillea santolina* L.[a]	Asteraceae	Kaisoom, jeaidat el-sabian	Leaves, flowering branches	Infusion	Cold, anticolic, kidney stones	Oran & Al-Eisawi, 1998
3	*Ajuga iva* L. (Schreber)[a]	Labiatae	Missaykah	Herb	Decoction	Catarrh, headache, feminine sterility	Oran & Al-Eisawi, 1998
4	*Alchemilla vulgaris* L.[c]	Rosaceae	Rjel elasad	Leaves, roots	Decoction	Inflammation	Aburjai et al., 2007
5	*Alhagi marourum* Medicus [d]	Leguminosae	Aqol	Roots	Decoction	Urinary tract infection	Oran & Al-Eisawi, 1998
6	*Allium cepa* L.[a, b]	Liliaceae	Basal	Leaves	Row bulbs, oil	Cholesterol reduction	Lev & Amar, 2002; Said et al., 2002; Otoom et al., 2006
7	*Allium sativum* L.[a, b]	Liliaceae	Thome	Bulb/cloves	Fresh and dried raw cloves, bulbs	Asthma, cholesterol reduction, hypotensive	Otoom et al., 2006
8	*Aloe vera* L.[a, b]	Liliaceae	Sabra morrah	Leaves' juice	Infusion	Kidney sand and stone, burns and skin diseases, wounds	Abu-Irmaileh & Afifi, 2000
9	*Ambrosia maritima* L.[a]	Asteraceae	Ghubayrah, damsis	Herb	Infusion	Rheumatism, asthma	Oran & Al-Eisawi, 1998
10	*Anthemis pseudocotula* Boiss[d]	Asteraceae	Kahwan	Flowering head, leaves	Infusion	Bactericide, antifungal, anti-tumor	Oran & Al-Eisawi, 1998
11	*Artemisia herba-alba* Asso.[a] (syn.: A. inculta)	Asteraceae	Sheech	Flowers, shoots, leaves	Decoction	Cold, hypercholesterolemia, kidney stones	Al-Khalil, 1995; Abu-Irmaileh & Afifi, 2000; Aburjai et al., 2007
12	*A. judaica* L.[d]	Asteraceae	Baethran	Flowering tops	Infusion	Antispasmodic	Hudaib et al., 2008
13	*A. vulgaris* L.[a]	Asteraceae	Baethran	Flowering head	Infusion	Abdominal pain, dysentery	Abu-Irmaileh & Afifi, 2000
14	*Avena sativa* L.[a]	Graminae	Shufan	Seeds	Infusion	Stomach and intestinal catarrh	Oran & Al-Eisawi, 1998
15	*Capparis spinosa* L.[a]	Capparaceae	Kabbar	Flowers, fruits	Decoction	Rheumatism, male and female sterility	Oran & Al-Eisawi, 1998
16	*Cephalaria syriaca* (L.) Roemer et Schultes d	Dipsacaceae	Zewan	Aerial parts	Infusion	Inflammation	Al-Khalil, 1995
17	*Ceratonia siliqua* L.[a]	Fabaceae	Harrub	Leaves	Decoction	Laxative, diuretic	Said et al., 2002
18	*Cichorium intybus* L.[a]	Asteraceae	Hendiba	Flowers, roots	Decoction	Antiseptic anemia, antipyretic	Oran & Al-Eisawi, 1998
19	*C. pumilum* L.[d]	Asteraceae	Hendiba	Aerial parts	Decoction	Fever, stomach and liver troubles	Al-Khalil, 1995; Oran & Al-Eisawi, 1998
20	*Citrullus colocynthis* L. (Schrad) [a]	Cucurbitaceae	Handal	Dry fruits, seeds	Infusion	Rheumatism	Dafni, 1984; Abu-Irmaileh & Afifi, 2000; Hudaib et al., 2008

Table 1 continued on next page

Table 1. Continued.

No.	Species	Family name	Common name	Plant parts	Method of Preparation	Other Uses	References for anti-diabetic activity
21	*Citrus limon* (Linn.) Burm.[d]	Rutaceae	Leimoon	Fruits	Fresh	Refreshing, stomachic, general health	Lev & Amar, 2002
22	*C. paradisi* Macfad[d]	Rutaceae	Grapefuit	Fruits	Raw	Heart diseases, weight loss	Oran & Al-Eisawi, 1998
23	*C. sinensis* (L.) Osbeck[a]	Rutaceae	Bourtaqal	Peels	Decoction	Carminative, stomachic	Oran & Al-Eisawi, 1998
24	*Cleome droserifolia* (Forskal) Delil[d]	Capparaceae	Magnuna	Leaves	Decoction	Liver diseases	Oran & Al-Eisawi, 1998
25	*Coriandrum sativum* L.[a]	Umbelliferae	Kuzbara	Seeds	Decoction	Carminative, stomachic, digestive	Otoom et al., 2006
26	*Coridothymus capitatus* (L.) Reichenb. fil.[a] (syn. *Thymus capitatus* (L.) Hoffmanns.& Link)	Lamiaceae	Za'ter farisi	Leaves	Infusion	Heart diseases, respiratory system inflammations	Said et al., 2002
27	*Crataegus aronia* L. Bosc. ex DC [a]	Rosaceae	Za'rur	Flowers, fruits	Decoction	Digestive system, urinary system, rheumatism	Ali-Shtayeh et al., 2000
28	*Crataegus azarolus* L.[d]	Rosaceae	Za'rur	Flowers, fruits	Decoction	Heart diseases, cancer, sexual weakness	Said et al., 2002
29	*Cucurbita maxima* Duchesne[d]	Cucurbitaceae	Al-qra'al asfar	Seeds	Dry seeds	Ulcer	Abu-Irmaileh & Afifi, 2000
30	*Cuminum cyminum* L.[a]	Umbelliferae	Kammun	Fruits	Dry fruits	Flatulence, stomach disorders	Otoom et al., 2006
31	*Eryngium creticum* Lam.[a]	Umbelliferae	Qursaneh	Aerial parts	Decoction	Snake bites, infertility	Dafni, 1984
32	*Eucalyptus globulus* Labill. [a]	Myrtaceae	Kalebtuz	Leaves, oil	Decoction	Respiratory system diseases, fever	Otoom et al., 2006
33	*Ferula persica* Wild.[c]	Umbelliferae	Haltit	Roots, resin	Decoction	Abortion	Abu-Irmaileh & Afifi, 2000, Lev & Amar, 2002
34	*Geranium graveolens* L.[a]	Geraniaceae	Utryye	Leaves	Decoction	Diuretic, stomachic	Al-Khalil, 1995; Oran & Al-Eisawi, 1998
35	*Gundelia tournefortii* L.[d]	Asteraceae	Kaoob	Roots	Decoction	Laxative, emollient	Al-Khalil, 1995
36	*Juglans regia* L.[a]	Juglandaceae	Djauz	Leaves	Decoction	Skin diseases, diarrhea	Oran & Al-Eisawi, 1998, Said et al., 2002
37	*Juniperus phoenicea* L.[d]	Cupressaceae	Ar-Ar	Fruits, leaves	Decoction	Rheumatism	Al-Khalil, 1995
38	*Laurus nobilis* L.[a]	Lauraceae	Ghar	Fruit, leaves	Decoction	Rheumatic and neuralgic pain, wound treatment	Lev & Amar, 2002
39	*Lupinus albus* L.[a]	Papilionaceae	Thurmus	Seeds	Boiled seeds	Emollient, vermifuge	Otoom et al., 2006
40	*Matricaria aurea* (Loefl.)[d]	Asteraceae	Babonej	Flower heads	Decoction	Cold, abdominal pain	Dafni, 1984; Abu-Irmaileh & Afifi, 2000
41	*Mentha spicata* L.[d]	Labiatae	Na'na berriye	Seeds and oil	Infusion	Arthritis	Lev & Amar, 2002
42	*Morus nigra* L.[a]	Moraceae	Tut	Leaves	Decoction	Teeth and gum inflammations	Said et al., 2002

Table 1 continued on next page

Table 1. Continued.

No.	Species	Family name	Common name	Plant parts	Method of Preparation	Other Uses	References for anti-diabetic activity
43	*Nigella sativa* L.[a]	Ranunculaceae	Qzha, Hab al-soda	Seed	Seed oil	General tonic, arthritis	Otoom et al., 2006
44	*Olea europaea* L.[a]	Oleaceae	Zaitoon	Oil, leaves	Decoction	Cold, hypercholesterolemia	Oran & Al-Eisawi, 1998, Otoom et al., 2006; Hudaib et al., 2008
45	*Ononis natrix* L.[d]	Leguminosae	Wasba	Whole plant	Decoction	Intestinal spasm, fever	Hudaib et al., 2008
46	*Opuntia ficus indica* (L.) Mill.[a]	Cactaceae	Saber	Fruits	Edible fruits	Diuretic	Abu-Irmaileh & Afifi, 2000
47	*Origanum syriacum* L.[d]	Labiatae	Za'ter	Leaves	Decoction	Cold, abdominal pain, loss of memory	Abu-Irmaileh & Afifi, 2000
48	*Paronychia argentea* Lam.[b, c]	Caryophyllaceae	Rejel Elhamam	Herb	Decoction	Urinary tract infection, kidney stones	Dafni, 1984; Oran & Al-Eisawi, 1998
49	*Peganum harmala* Linn.[c]	Zygophyllaceae	Harmal	Seeds	Decoction	Cold, rheumatic pain	Lev & Amar, 2002
50	*Pistacia atlantica* Desf. [b, c]	Anacardiaceae	Butum	Leaves	Decoction	Antiseptic	Oran & Al-Eisawi, 1998
51	*P. palaestina* Boiss [d]	Anacardiaceae	Butum	Shoot, leaves roots	Decoction	Antihypertensive, antispasmodic	Aburjai et al., 2007
52	*Plantago major* L.[d]	Plantaginaceae	Lisan al hamal	Seeds	Decoction	Indigestion, sterility, eye diseases	Oran & Al-Eisawi, 1998
53	*P. ovata* Forskal[a]	Plantaginaceae	Qreta, kibash	Seeds	Decoction	Chronic constipation, dysentery	Oran & Al-Eisawi, 1998
54	*Portulaca oleraceae* L.[a]	Portulacaceae	Baqleh	Herb	Decoction	Pulmonary diseases, laxative, wound healing	Oran & Al-Eisawi, 1998, Said et al., 2002
55	*Prosopis farcta* (Banks et Sol.) Macbride[a]	Mimosaceae	Yanboot	Roots	Decoction	Kidney stones, antihypertensive, diuretic	Dafni, 1984; Al-Khalil, 1995; Said et al., 2002
56	*Quercus coccifera* L.[d]	Fagaceae	Balloot	Galls	Decoction	Astringent, chronic diarrhea, dysentery, ulcer treatment	Al-Khalil, 1995
57	*Rheum ribes* Linn.[a]	Polygonaceae	Rabbas	Roots	Decoction	Hypertension, kidney sand and stones, obesity	Abu-Irmaileh & Afifi, 2000
58	*Ruta chalepensis* L.[d]	Rutaceae	Feijen Southab	Leaves, buds, roots	Decoction	Antispasmopdic, arthritis, skin diseases	Aburjai et al., 2007
59	*Salvia fruticosa* Mill. (syn. *S. triloba* L.)[a]	Lamiaceae	Meramiyye	Leaves	Infusion	Stomach ache, intestinal disorders	Said et al., 2002, Otoom et al., 2006
60	*Sarcopoterium spinosum* (L.) Spach.[a, b]	Rosaceae	Bellan	Roots	Infusion, decoction	Digestion, stomach ache	Dafni, 1984; Al-Khalil, 1995; Oran & Eisawi,1998; Said et al., 2002; Aburjai et al., 2007, Hudaib et al., 2008
61	*Taraxacum cyprium* H. Lindb.[d]	Asteraceae	Hendiba berriye	Herb	Infusion	Chronic constipation, eczema	Oran & Al-Eisawi, 1998

Table 1 continued on next page

Table 1. Continued

No.	Species	Family name	Common name	Plant parts	Method of Preparation	Other Uses	References for anti-diabetic activity
62	*Teucrium polium* L.[a]	Lamiaceae	Ja'deh	Shoots, leaves, aerial parts	Decoction	Abdominal pain, urinary tract infection	Dafni, 1984; Al-Khalil, 1995; Oran & Al-Eisawi, 1998; Abu-Irmaileh & Afifi, 2000; Said et al., 2002; Aburjai et al., 2007
63	*Trigonella foenum-graecum* L.[a, b]	Leguminoseae	Hulbah	Seeds	Infusion	Kidney sand and stones, general weakness	Al-Khalil, 1995; Oran & Al-Eisawi, 1998, Lev & Amar, 2002, Abu-Irmaileh & Afifi, 2000, Said et al., 2002, Otoom et al., 2006
64	*Triticum dicoccoides* (Koern. Ex Asherson & Graebner) Aaronsohn[d]	Graminae	Kamh	Grains	Dry, infusion	Calmative	Oran & Al-Eisawi, 1998
65	*Urtica dioica* L.[a, b]	Urticaceae	Qurreis	Herb	Decoction	Liver diseases, cancer, stomach pain, skin and hair	Otoom et al., 2006
66	*Varthemia iphionoides* Boiss and Blanche [a, b]	Asteraceae	Qtteileh	Shoots, leaves	Decoction	Abdominal pain	Abu-Irmaileh & Afifi, 2000; Hudaib et al., 2008
67	*Zea mays* L.[a]	Poaceae	Dur'a	Kernel	Decoction	Urinary tract, weight loss	Otoom et al., 2006
68	*Zygophyllum simplex* L.[d]	Zygophyllaceae	Hamad	All plant	Decoction	-	Oran & Al-Eisawi, 1998
69	*Zizyphus spina-christi* (L.) Desf.[a]	Rhamnaceae	Sader, nabaq	Fruits, leaves, bark	Infusion	Abdominal pain, laxative, astringent	Said et al., 2002

a. Plants with *in vitro*/*in vivo* tested hypoglycemic activity.
b. Plants with tested α-amylase/α-glucosidase inhibitory activities.
c. Plants with no proven hypoglycemic and antidiabetic activities.
d. Recommended plant species without reported *in vivo*/*in vitro* hypoglycemic activities.

by the herbalists in the big cities for the treatment of DM is quite long (Dafni et al., 1984; Al-Khalil, 1995; Oran & Al-Eisawi, 1998; Abu Irmaileh & Afifi, 2000; Hamdan & Afifi, 2004). The list includes 69 species of indigenous plants. As shown in Table 1, in addition to their claimed antidiabetic property, most of the plants recommended are used for the treatment of several other diseases. In a survey carried out by Abu Irmaileh and Afifi (2000), more than 100 herbalists throughout the country were interviewed. Consistently similar recommendations for each plant species were obtained. The survey revealed also that most of the herbalists were not educated or trained formally in the field of herbal medicine except for their expertise gained from their predecessors. The lack of regulations and knowledge among the herbalists highlighted an important question about the efficacy of using the plants for the treatment of chronic diseases. The literature was hence investigated in the search for documentation of hypoglycemic effects of plants being recommended by herbalists to confirm their claimed effect.

Assay methods used to screen the plants for their hypoglycemic activities were diverse and not directly comparable. *In vivo* techniques relied on the use of various laboratory animals such as mice, rats or rabbits with normoglycemia and/or induced hyperglycemia (alloxan or STZ). Clinical trials on diabetic human subjects were also performed. The duration of administration of the plant substance (crude plant extracts, fractions, or isolated substances) also presented great variations. The concentration of the plant material, its route of administration, and dosage are other

parameters hindering results comparison and forcing the acceptance of published results accordingly.

One of the possible mechanisms for hypoglycemic effect could be through decreasing the absorption of ingested sugars. This could be achieved if the enzymes responsible for degradation of complex carbohydrates were inhibited. The *in vitro* technique used for the determination of the antidiabetic activity of the different plant extracts included α-amylase/α-glucosidase inhibitory activity. α-Amylase is reputed as a potential target to control diabetes for more than 30 years. This test is believed to give insight into the mechanism of the hypoglycemic activity of the antidiabetic plants. Therefore, some of the local plants used in the treatment of diabetes in Jordan were screened for their α-amylase inhibitory activity by Abu Soud et al. (2004) and Hamdan and Afifi (2004). *A. vera*, *P. atlantica,* and *P. argentea* showed significant (more than 80%) α-amylase inhibitory activity. While in the case of *A. vera* the activity was attributed to cinnamic acid derivatives, the activity for *P. argentea* was most likely due to flavonoid compounds. Some plant extracts, such as *A. vera* and *A. cepa*, showed they can provide an integrated care treatment for diabetes, in which a single extract exhibited both a hypoglycemic activity and an anti-oxidative one, the latter of these activities protects the liver and kidney from complications caused by diabetes. In a recent study, Hamdan and Afifi (2008) further screened an additional thrity-five plant species from the Jordanian flora for their α-amylase inhibitory activity. Four of the screened plants exhibited significant (more than 80%) α-amylase inhibitory activity. Only one of these active extracts, namely *S. spinosum*, is used in traditional medicine for its antidiabetic activity. The other three extracts [*Osyris alba* L. (Santalaceae), *Hypericum triquetrifolium* Turra (Hypericaceae) and *Arbutus andrachne* L. (Ericaceae)], on the other hand, are not listed among the plant species with antidiabetic/hypoglycemic activities.

Due to the high ecological diversity in Jordan, plants recommended by the local herbalists differ depending on the location and the environment. For example, the use of *S. spinosum* is well-known for the treatment of DM in the northwestern parts of the country with the Mediterranean climatic influxes, while in the northeast with the Saharo-Arabian climate, *A. maurorum* and *R. ribes* are the preferred species. In central Jordan and near the Dead Sea area, *A. herba-alba, T. polium,* and *C. colocynthis* are widely used for the treatment of all types of DM (Aburjai et al., 2007; Hudaib et al., 2008).

Although proper diagnosis of DM depends on clinical examination and laboratory tests, symptomatic diagnosis of the disease (such as increased urination, weight loss, fatigue, and thirst) is common among the rural and desert area healers.

Conclusions

It has been found that 65.2% of the 69 plants used for the treatment of DM in Jordan have been studied for their *in vivo* hypoglycemic activity, of which 54.1% have been proved to be active. Around 34.8% of the plants with claimed activity have not been evaluated. Hence, despite the use of herbal medicine for generations, scientific evidence and confirmation is still needed. Furthermore, *in vitro* and *in vivo* studies should be carried out to confirm the claimed activity for the recommended but not tested plant species. Studies should also focus on the identification of the active ingredient(s) of potent plant species which might be used as lead compounds for drug discovery and development.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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