# Medicinal Plants from Jordan in the Treatment of Diabetes: Traditional Uses vs. *In Vitro* and *In Vivo* Evaluations – Part 2

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**Key words**
- traditional medicine
- medicinal plants
- diabetes
- Jordan

## Abstract

Diabetes mellitus is the most common metabolic disorder affecting millions worldwide. It is recognized as a global major health problem. As alternatives to the available orthodox medicines, plants are considered a potential source for the treatment of diabetes within traditional ethnomedicine practices. In the Jordanian traditional medicine a significant selection of ethnobotanicals is promoted for their antidiabetic activity. Literature surveys demonstrate the benefit of several ethnobotanicals as antidiabetic agents evaluated in *in vitro* and *in vivo* systems in the form of their crude extracts and/or isolated pure compounds with varying degrees of hypoglycemic or antihyperglycemic bioactivities. This mini review discusses the preparatory forms in which these plants are consumed, their reported phytoconstituents, and the results of their reported antidiabetic bioactivity.

**Supporting information** available online at http://www.thieme-connect.de/ejournals/toc/plantamedica

## Introduction

Diabetes mellitus (DM), the world's most common metabolic disorder, results from a defect in insulin secretion, insulin action, or both [1]. It is projected that the global prevalence of diabetes is escalating. At least 250 million individuals worldwide suffer from diabetes, and this number will double by 2030. Increases in complications will undoubtedly follow increasing pervasiveness of diabetes [2].

The regional prevalence of diabetes in MENA (Middle Eastern and North Africa) countries is 7.7% [3]. Standing at 10.1%, Jordan has the ninth highest incidence of diabetes. Several national surveys indicated that the prevalence of type 2 diabetes and impaired fasting glycemia is in an unprecedented increase with an epidemiological transition in Jordan [4–6]. More than 80% of diabetes deaths occur in low- and middle-income countries. Endocrine, nutritional, and metabolic diseases represent 7.9% of deaths in Jordan [7–8]. Located in the Middle East, Jordan covers 92 300 km$^2$ with high geographical and ecological diversity. Its varied topography and climate result in the junction of four biogeographical regions **Fig. 1S**, and these crossroads engender the country with substantial biodiversity that is at large understudied or, even worse, left unexplored [9]. The Mediterranean region provides the vast majority of the recorded 2500 wild plant species, including medicinal, poisonous, edible, and ornamental ones. There are more than 140 wild edible plants listed such as *Rumex crispus, R. vesicarius, Gundelia tournefortii, Origanum syriacum, Foeniculum vulgare*, and *Chicorium pumilum*. Some of these edible and culinary plants are used by local communities for generations for their medicinal value [10–12].

In Jordan, where traditional medicine plays a partial role in imparting the primary health care, vegetables, culinary herbs, and medicinal plants are among the main choices in the management of diabetes [13,14]. However, it is officially neither integrated in the health care system nor recognized in national policies of the country. The objective of this mini review is to underline the ethnopharmacological practices related to 30 selected ethnobotanicals with claimed antidiabetic properties in light of their comprehensive scientific evaluation.

**received** March 17, 2011
**revised** May 22, 2011
**accepted** May 24, 2011

**Bibliography**
**DOI** http://dx.doi.org/10.1055/s-0031-1279983
Published online June 14, 2011
Planta Med 2011; 77: 1210–1220 © Georg Thieme Verlag KG Stuttgart · New York · ISSN 0032-0943

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## Discussion

Surveys based on interviews with herbalists and search engines indicated that in the Jordanian traditional medicine almost 70 plant species belonging to 38 families were consumed by diabetic patients. The majority of the used plants are native to Jordan while others like *Zingiber officinalis, Terminalia chebula*, or *Emblica officinalis* are recognized as plants of nonindigenous origin [13,15–17].

Reports on the concomitant use of plants accompanying the orthodox therapy are limited. Primarily, interviews with diabetes patients in specialized health centers of Jordan further signified a more diversified list of selected plants [14,18]. The reported plants were: *Camellia sinensis, Pimpinella anisum, Zingiber officinale, Matricaria chamomilla, Salvia triloba, Trigonella foenum-graecum, Nigella sativa, Lupinus albus, Teucrium polium, Allium sativum, Cinnamomum zeylanicum*, and *Olea europea.*

Locally, a preliminary screening of the critical pharmacological appraisal of the traditionally utilized botanicals was performed. It demonstrated that reports on diabetes interventional phytotherapies are scarce. Gharaibeh et al. [19] investigated the hypoglycemic effects of *Teucrium polium* in normal and STZ-diabetic rats. Hamdan and Afifi [20], Afifi et al. [21], and Kasabri et al. [22,23] undertook a comprehensive and complementary *in vitro* and *in vivo* testing for a vast array of indigenously recruited herbs, partially consumed as integral to the diet of the traditional communities; *Achillea santolina, Eryngium creticum, Geranium graveolens, Paronychia argentea, Pistacia atlantica, Rheum ribes, Sarcopoterium spinosum, T. pollium*, and *Varthemia iphionoides* have been identified as antidiabetic phytomedicines. This line of research findings could link and rationalize the ethnopharmacological use with new approaches in the prevention/modulation of postprandial hyperglycemia emerging from the therapeutic use of α-amylase and α-glucosidase inhibitors. Also, Al-Mustafa and Al-Thunibat [24] investigated the antioxidative potentialities of an extensive list of Jordanian antidiabetic phytomedicines. Moreover, pancreatic mechanistic studies were reported for the hypoglycemic bioactivities of cinchonain Ib from *Eriobotrya japonica* [25] and *Ferula asafoetida* [26]. Additionally, the hypoglycemic effects of *Ballota nigra* [27] and *Artemisia sieberi* [28] were evidenced in alloxan-diabetic rats.

Comparable to conventional diabetes pharmacotherapeutics, the significant efficacy of hypoglycemic herbs is achieved by increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from hepatocytes [29–31]. Certain herbs may ameliorate overt hyperglycemia substantially in clinical trials with well characterized action mechanisms [32,33]; their test results, however, are subject to several factors. Firstly, each herb contains multiple compounds, only a few of which may be therapeutically effective either alone or synergistically [34]. Secondly, different parts of an herb have different ingredient profiles. Thirdly, different extraction methods may yield different active ingredients [35]. Most recently, the antidiabetic activity of several flavonoids, polyphenols, terpenoids, coumarins and some alkaloids have been reviewed [36–39]. The reported secondary metabolites of the selected 30 plants are listed in **Table 1**. Especially important in the present review, flavonoids are the major class of secondary metabolites detected in most of the plants. Moreover, terpenoids have been reported in the discussed plant species with hypoglycemic activities [29,30].

Locally, one of the common practices is to assign certain species of a given genus a single common Arabic name with the expectation that all of them will perform ethnopharmacologically equally. This unjustifiable practice is based on species availability. In application, and despite scientific invalidity, the three *Artemisia,* both *Cichorium* spp., and the two *Crataegus* species have been the subject of such inappropriate convenience of designation.

Plants compiled in **Table 1**, demonstrating antidiabetic pharmacological activities, can be subgrouped as follows:

1. Spices: (*M. spicata, O. syriacum, L. nobilis, C. sativum, C. cyminum, C. spinosa*). Spices do not only improve the taste of the foods but do also contribute to the well-being of humans. Influence of the spices on the body metabolism and on the endocrine system has gained importance in the recent years. Numerous spices have been evaluated in animal experiments as well as clinical studies, and evidence has been obtained for their antidiabetic potential [40–43].
2. Vegetables and fruits: (*Cichorium intybus, C. pumilum, Opuntia ficus indica, Allium cepa Portulaca oleraceae, Crataegus aronia, C. azarolus, Citrus limon, C. paradisi*). Since appropriate diet, exercise, and weight reduction are essential in controlling the blood sugar, antidiabetic activities of many edible fruits and vegetables – in the form of aqueous and alcohol extracts – have been tested in diabetes animal models. Furthermore, clinical evidence for the antidiabetic activity is reported for two vegetables, namely for *C. intybus* and *A. cepa. A. cepa* exhibited hypoglycemic effects in type 1 and type 2 diabetic patients (**Table 1**). Exceptionally, *C. intybus*, possessing multiple action mechanisms in controlling the blood glucose level such as alpha amylase inhibitory activity, appetite regulation, and increasing insulin secretion (**Table 1**), has hypoglycemic activity in different animal models and clinically evidenced benefits in the reduction of diabetes risk (**Table 1**).
3. Medicinal herbs and nonedible parts of fruits: (*Artemisia herba-alba, A. judaica, A. vulgaris, Citrullus colocynthis, Aloe vera, Eucalyptus globules, Plantago major, P. ovata, Ruta chalepensis, Eryngium creticum and C. sinensis, Ceratonia siliqua, Juglans regia, Morus nigra*). For *A. herba-alba*, hypoglycemic, antihyperglycemic, and preventive effects have been illustrated in various animal models of diabetes. Nevertheless, *A. judaca* exhibited antidiabetic effects in STZ-diabetic rats, but *A. vulgaris* used locally for its antidiabetic activity has not been appraised pharmacologically. The remaining medicinal herbs, with the exception of *R. chalepensis*, have established antidiabetic activities. Richness in flavonoids, such as rutin, may raise plausible anticipation for *R. chalepensis* antidiabetic potentiality (**Table 1**). Several studies indicated the hypoglycemic benefits of flavonoids such as hesperidin, quercetin, luteolin, naringenin, and rutin in STZ-diabetic rats [44–48]. Leaf decoctions of common fruit trees – *C. siliqua, J. regia*, and *M. nigra* – and the peels of *C. sinensis* are praised throughout the country for their antidiabetic activities. These substantial efficacies have been clearly verified. Moreover, the antidiabetic efficiency of *C. siliqua* leaf extracts has been confirmed in type 2 diabetic patients (**Table 1**).

## Conclusion

Based on hundreds of years of belief and observation, a marked number of plant species are used by the inhabitants of Jordan for the treatment of diabetes. The traditional knowledge of plants

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

| No. | – Species<br>– Preparation Method<br>– References of ethnopharmacological indications | Reported phytoconstituents | Reported antidiabetic efficacy and/or action mechanism |
|---|---|---|---|
| 1 | **Asteraceae**<br>*Artemisia herba-alba* Asso. (syn.: *A. inculta*)<br>(decoction of flowers, shoots, leaves [15, 49, 50]) | Flavonoids [51]. Main essential oil components: *β*-thujone and *α*-thujone, 1,8-cineole, camphor, chrysanthenone, *trans*-sabinyl acetate, *trans*-pinocarveol, and borneol [52] | Significant and time-dependent hypoglycemic effect in normoglycemic and alloxan diabetic rabbits [53]. Preventive and antihyperglycemic effect in high-fat diet diabetes mice [54, 55] |
| 2 | **Asteraceae**<br>*A. judaica* L. (infusion of flowering tops [56, 57]) | Judaicin: a bitter principle [58]. Piperitone, *trans*-ethyl cinnamate, ethyl-3-phenyl propionate, spathulenol, *cis*-ethyl cinnamate, 2,6-dimethyl phenol, methyl cinnamate [59]. Flavonoids [60] | Antidiabetic effect sin STZ-diabetic rats via acting as an insulin-mimetic reversing the changes in the enzyme activities of cytochrome P-450 (2E1, 2B, and 2C) on *androst-4-ene-3,17-dione* metabolism [61] |
| 3 | **Asteraceae**<br>*A. vulgaris* L. (infusion of flowering head [15]) | Estrogenic flavonoids [62]. Jaceosidine, eupafolin, luteolin, quercetin, apigenine, aesculetin, esculetin-6-methylether, and scopoletin [63]. Yomogin [64]. Dicaffeoylquinic acids [65]. Sesquiterpene lactones and a novel aromatic compound [66]. *Trans*-thujone, *cis*- thujone, chrysanthenyl acetate, 1,8-cineole, sabinene, *β*-pinene, artemisia ketone, caryophyllene, oxygenated monoterpenes, sesquiterpenes [67]. Flavonoid aglycon: quercetin 3,7,3′-trimethyl ether [68] | None |
| 4 | **Asteraceae**<br>*Cichorium intybus* L.<br>(decoction of flowers, roots [69]) | Dietary fructans [70]. Anthocyanins [71]. Sesquiterpene lactones of guaiane and germacrane type. Lactucopicrin, 8-desoxylactucin, and three sesquiterpene lactone glycosides: crepidiaside B, sonchuside A, and ixerisoside D [72]. Lactucin and lactucopicrin: sesquiterpene lactones [73]. Quercetin, kaempferol, luteolin, apigenin, crysoeriol and caffeoyl derivatives, polyphenols [74]. Flavonoids [75]. A guaianolide sesquiterpene glycoside, cichotyboside [76]. Tannins, chlorogenic acid along with caffeic acid derivatives [77] | Antihyperglycemic effect in alloxan-induced diabetes mice [78] and clinically proven reduction on diabetes risk [79], which can be explained by a reduction in intestinal absorption of glucose [80]. Significant increases in catalytic concentration of *glutathione S-transferases* in the liver of diabetic NOD mice [81]. Its dietary inulin-type fructans promote secretion of endogenous gastrointestinal peptides involved in appetite regulation [82] and via reduction in the hepatic Glc-6-pase activity thus decreasing hepatic glucose production, with no possibility of inducing insulin secretion from pancreatic beta-cells [83], also through adipogenesis inhibition and PPARgamma upregulation, inhibition of protein tyrosine phosphatase 1B and regulation of insulin signalling markers [77, 84]. *α*-Glucosidase inhibition [85]. Insulin-sensitizing and insulin-secreting principles [86]. Neuroprotection by stimulating AChE activity in brains of alloxan diabetic rats [87] |
| 5 | **Asteraceae**<br>*Cichorium pumilum* L.<br>(decoction of aerial parts [50, 69]) | Flavonoids [88]; guaianolides [89]; eudesmanolides, eight lactucin-like guaianolides and phenolics, eudesmane-type sesquiterpene lactones [90] | None |
| 6 | **Cactaceae**<br>*Opuntia ficus-indica* (L.) Mill.<br>(edible fruits [15]) | Polyphenols and flavonoids: ferulic acid; the chief derivative of hydroxycinnamic acid, rutin, and isorhamnetin derivatives [91]. Betacyanins and betaxanthins [92]. Kaempferol and isorhamnetin glycosides (glucoside and rhamnoside) [93] | Hypoglycemic effects [94] |
| 7 | **Capparaceae**<br>*Capparis spinosa* L.<br>(decoction of flowers, fruits [69]) | Saccharides and glycosides, flavonoids, alkaloids, terpenoids and volatile oils, fatty acids and steroids [95]. Antioxidative capparoside (4-hydroxy-5-methylfuran-3-carboxylic acid, 1) [96]. Phenolics: rutin, tocopherols, carotenoids, and vitamin C [97]. Flavonoids, indoles, and phenolic acids [98] | Potent antihyperglycemic activity in STZ rats without affecting basal plasma insulin concentrations [99]. Hypoglycemic activity [95] |
| 8 | **Cucurbitaceae**<br>*Citrullus colocynthis* L. (Schrad)<br>(infusion of dry fruits, seeds [15, 56, 64, 100]) | Tertiary and quaternary alkaloids, glycoside and saponin components [101]. Phenolics and flavonoids [102] | Hypoglycemic and antihyperglycemic effects in normal and alloxan diabetic rabbits [101] and STZ diabetic rats [103] by partly preserving or restoring pancreatic beta-cell mass [104] and insulinotropic effect [105]. Clinical beneficial effect on improving the glycemic profile without severe adverse effects in type 2 diabetic patients [106] |

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**Table 1** Selected plants indigenous to Jordan used for the treatment of diabetes in folk medicine. *(continued)*

| No. | – Species<br>– Preparation Method<br>– References of ethnopharmacological indications | Reported phytoconstituents | Reported antidiabetic efficacy and/or action mechanism |
|---|---|---|---|
| 9 | **Fabaceae**<br>*Ceratonia siliqua* L.<br>(decoction of leaves [107]) | Flavonoids: mainly myricetin [108]. Phenolics: mainly gallotannins and proanthocyanidins, tannins, flavonol-glycosides, and traces of isoflavonoids [109–112]. Tannins [113] | Significantly decreased the glucose response to and glycemic index of fibers-enriched food in type 2 diabetic subjects. It also tended to decrease their insulinemic response and insulinemic index [114]. Increases total and acylated plasma ghrelin accompanied by enhanced lipid metabolism, thus suggesting higher lipid utilization and suppressed lipolysis, without affecting fasting concentrations of glucose, TAG, total ghrelin, NEFA, insulin, and leptin [115] |
| 10 | **Graminae**<br>*Avena sativa* L.<br>(infusion of seeds [69]) | Beta-glucan, minerals, B complex vitamins, protein, fat, minerals [116]. Avenanthramide [117] | Improving glycemic, insulinemic, and lipidemic responses [118]. Oatmeal test seemed to be a good, noninvasive screening test in diabetic gastropathy in type 1 diabetes, but has no diagnostic value in type 2 diabetes [119]. Depression of the glycemic index by high levels of beta-glucan fiber making it a useful functional food component for reducing postprandial glycemia [120, 121]. Significantly improved whole-body insulin sensitivity [122, 123] induced changes of postprandial peptide YY and ghrelin responses [124] and increased postprandial cholecystokinin levels [125]. Dihydroavenanthramide D protects pancreatic beta-cells from cytokine and STZ toxicity [117] |
| 11 | **Juglandaceae**<br>*Juglans regia* L.<br>(decoction of leaves [69, 107]) | Ellagic acid [126]. Hydrolysable tannins [127]. Diaryl-heptanoids [128]. Unsaturated fatty acids, tocopherols, phospholipids, sphingolipids, sterols, hydrocarbons, and volatile compounds, phenolic compounds [129] | Dramatic hypoglycemic effect in experimental diabetes rats; where density of islets in pancreatic tissue, percent of beta cells, and islets size increased significantly thereby signifying regeneration of islets or beta cells [130–132], thus, recommended in prevention of DM and its late complications [133] |
| 12 | **Labiatae**<br>*Mentha spicata* L.<br>(infusion of seeds, oil [56]) | Protocatechuic aldehyde, protocatechuic acid, chrysoeriol, 5,6-dihydroxy-7,8,3′,4′-tetramethoxyflavone, nodifloretin [134]. Two lignans named spicatolignan A and spicatolignan B [135]. Carvone; monoterpene ketone [136] and menthone [137]; flavonoids [138]; piperitenone oxide 1,8-cineole [139] | None |
| 13 | **Labiatae**<br>*Origanum syriacum* L.<br>(decoction of leaves [15]) | Monoterpene glucosides [140], oxygenated monoterpenes and sesquiterpenes [141]. Polar phenolic analytes; hydroxyl-benzoates, hydroxyl-cinnamates, and flavonoids [142]. Carvacrol, thymol, and thymoquinone [143]. Rosmarinic, oleanolic, and ursolic acids [144]. γ-terpinene and p-cymene [145] | None |
| 14 | **Lauraceae**<br>*Laurus nobilis* L.<br>(decoction of fruit, leaves [56]) | Cinnamtannin B-1 [146]. Flavonoid *O*-glycosides, flavonoid *C*-glycoside. Catechin and cinnamtannin B1 [147] | Hypoglycemic effects in normal and alloxan-diabetic rabbits [148]. Improvement of glucose and lipid profile of type 2 diabetes patients [149] |
| 15 | **Liliaceae**<br>*Allium cepa* L.<br>(raw bulbs, oil, leaves [18, 56, 107]) | Flavonoid glycosides [150]; *S*-alk(en)yl cysteine sulfoxide metabolites [151, 152]; *S*-allylcysteine sulfoxide, *S*-methylcysteine sulfoxide, and diallyl trisulfide [153]; quercetin [154]; onionin A [155] | Antidiabetic [41] via stimulating effects on glucose utilization and partly dependent on the stimulation of insulin secretions [156]. Hypoglycemic effect in STZ-diabetic rats coupled to decrease in the total serum lipid, triglyceride, and atherogenic index and increase in HDL-cholesterol/total cholesterol ratio, and reducing renal oxidative stress [157]. Clinical hypoglycemic effects in type 1 and type 2 diabetic patients [158] |
| 16 | **Liliaceae**<br>*Aloe vera* L. (infusion of leaves, juice [15]) | Cinnamoyl, *p*-coumaroyl, feruloyl, caffeoyl aloesin [159]. Phenols, flavonoids, ascorbic acid, β-carotene and α-tocopherol [160]. Mannose polymers with some glucose and other sugars; mainly acemannan, glycoproteins, enzymes, amino acids, vitamins, and minerals [161]. Anthraquinones: aloesin, aloe-emodin, and barbaloin, *N*-terminal octapeptide derived from verectin [162] and triglucosylated naphthalene glycoside [163] | Hypoglycemic or antidiabetic effects [164] thereby indicated for the treatment of diabetes and dyslipidemia [165] |

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**Table 1** Selected plants indigenous to Jordan used for the treatment of diabetes in folk medicine. *(continued)*

| No. | – Species<br>– Preparation Method<br>– References of ethnopharmacological indications | Reported phytoconstituents | Reported antidiabetic efficacy and/or action mechanism |
|---|---|---|---|
| 17 | **Moraceae**<br>*Morus nigra* L.<br>(decoction of leaves [107]) | Anthocyanins [166]. Olcancolic acid, apingenin, cyclocommunol, morusin, cyclomorusin, kuwanon C, daucosterol [167]. Essential minerals, nutritive components, total phenols, and alkaloid contents [168]. A new 2-arylbenzofuran derivative, mornigrol D, G, and H along with norartocarpetin, dihydrokaempferol, albanin A, albanin E, moracin M, and albafuran C [169] | Antihyperglycemic propensity via significant increases in catalytic concentration of *glutathione S-transferases* in the liver of diabetic NOD mice [170, 171] |
| 18 | **Myrtaceae**<br>*Eucalyptus globulus* Labill.<br>(decoction of leaves, oil [18]) | Heteroxylan composed of galactosyl, 4-*O*-methyl-glucuronosyl and xylosyl residues [172]. Ellagic acid derivatives; 3-*O*-methylellagic acid 4′-*O*-α-L-2′′-*O*-acetyl-rhamnopyranoside, 3-*O*-methylellagic acid 4′-*O*-α-L-rhamnopyranoside, ellagic acid, and 3-O-methylellagic acid [173]. β-sitosterol, betulinic acid, stigmasterol, euscaphic acid, 2a-hydroxybetulinic acid, macrocarpal B, macrocarpal A, oleanolic acid, 3,4,3′-O-trimethylellagic acid, 3-*O*-methylellagic acid 4′-*O*-(2′′-O-acetyl) -α-L-rhamnopyranoside, camaldulenside (cypellocarpin C, 3-*O*-methylellagic acid 4′-O-α-L-rhamnopyranoside, 3-*O*-methylellagic acid, ellagic acid, and gallic acid [174]) and cypellocarpa C [175] | *In vitro* stepwise enhancement of insulin secretion from the clonal pancreatic beta-cell line (BRIN-BD11) and enhancement of 2-deoxyglucose transport, glucose oxidation, and incorporation of glucose into glycogen in mouse abdominal muscle [176, 177]. Antihyperglycemic action not exerted via the stimulation of insulin secretion but via enhancement of peripheral glucose uptake, exerting an antioxidative activity demonstrated by the increase of catalase, superoxide-dismutase, and gluthatione-peroxidase activities in the liver and kidney, and a lowering of lipids peroxidation level in these organs [178]. Significantly improved the hyperglycemia, polydipsia, polyphagia, and also compensated weight loss of diabetic rats, in addition to treatment of candidiasis in normal and diabetic rats [179]. Noticeably, dose-dependent amelioration of diabetic states by partial restoration of pancreatic beta cells and repair of STZ-induced damage in rats [180] |
| 19 | **Plantaginaceae**<br>*Plantago major* L. (decoction of seeds [69]) | Ursolic acid [181]. Polysaccharides, lipids, caffeic acid derivatives, iridoid glycosides, terpenoids, alkaloids [182]. Phenolic glycoside [183]. Antioxidative flavonoids [184] | Significant antihyperglycemic effect in experimental diabetic rats [185, 186] |
| 20 | **Plantaginaceae**<br>*P. ovata* Forsk. (decoction of seeds [69]) | Neutral arabinoxylan [187]. Phytosterols; β-sitosterol and stigmasterol [188]. Saponin [189] | Fasting blood glucose and HbA1c showed a significant reduction, whereas HDL-Cholesterol increased significantly. LDL/HDL ratio was significantly decreased in diabetic outpatients [190] |
| 21 | **Portulacaceae**<br>*Portulaca oleraceae* L.<br>(decoction of herb [69, 107]) | β-sitosterol, β-sitosterol-glucoside, N,N′-dicyclohexylurea, and allantoin [191]. Portulene; a diterpene [192]. Phenolic alkaloids; oleracein A, oleracein B, and oleracein E [193]. Betacyanins [194] | Moderate antidiabetic activity via potent antioxidant potential in STZ-diabetic rats [195] |
| 22 | **Rosaceae**<br>*Crataegus aronia* L. Bosc. ex DC<br>(decoction of flowers, fruits [196]) | Phenolics and flavonoids [197] | Hypoglycemic and antiperoxidative bioactivities in experimental diabetic rats [198] |
| 23 | **Rosaceae**<br>*C. azarolus* L. (decoction of flowers, fruits [107]) | Polyphenols [199] | None |
| 24 | **Rutaceae**<br>*Citrus limon* (Linn.) Burm.<br>(fresh fruits [56]) | Hydroxycinnamates and polymethoxylated flavones in citrus peel molasses [200, 201]. Flavonoids: eriocitrin and hesperidin [202]. Phenolics and flavonoids [203]. Naringenin [204]. Limonoids: nomilin and limonin [205]. Ascorbic acid [206]. Flavonoid dimethylnobiletin [207] | Antioxidative in diabetic rats [202, 203]. Increases glucose uptake by skeletal muscle cells in an AMPK-dependent manner [204]. Cardiovascular friendly [208]. Anti-atherogenic bioactivities; inhibiting monocyte-to-macrophage differentiation and foam cell formation as well as hypolipidemic activity via enhancing LDL receptor gene expression and activity and decreasing acyl CoA: diacylglycerol acyltransferase 2 expression in HepG2 liver cells [207] |
| 25 | **Rutaceae**<br>*C. paradisi* Macfa<br>(raw fruits [69]) | Alkaloids, flavonoids, cardiac glycosides, tannins, and saponin [200]. Furanocoumarins [210]. Naringenin [204] and nootkatone [211]. 4′-geranyloxyferulic acid [212]. Limonoids: nomilin and limonin [205] | Hypoglycemic and hypolipidemic effects in normal and alloxan diabetic rats [209, 213]. Improving glycemic control in nondiabetic rats [214]. Increasing glucose uptake by skeletal muscle cells in an AMPK-dependent manner [204], thus significantly reducing high-fat and high-sucrose diet-induced body weight gain, abdominal fat accumulation, and the development of hyperglycemia, hyperinsulinemia, and hyperleptinemia in C57BL/6J mice [211] |

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**Table 1** Selected plants indigenous to Jordan used for the treatment of diabetes in folk medicine. *(continued)*

| No. | – Species<br>– Preparation Method<br>– References of ethnopharmacological indications | Reported phytoconstituents | Reported antidiabetic efficacy and/or action mechanism |
|---|---|---|---|
| 26 | **Rutaceae**<br>*C. sinensis* (L.) Osbeck (decoction of peels [69]) | Phenolics: chlorogenic acid, luteolin, myricetin, naringenin, *p*-coumaric acid, and quercetin; and flavonoids – mainly hesperidine [215, 216]. Flavanones [217]. Cyclic monoterpene, DL-limonene [218]. Ascorbic acid [219] | Maximum glucose lowering and antiperoxidative activities in alloxan diabetic mice [220]. Antithyroidal, hypoglycemic, and insulin stimulatory properties, suggesting its potential to ameliorate both hyperthyroidism and diabetes mellitus [221]. Significant decrease in fasting glucose levels in the overweight treatment group of osteoarthritis patients [222]. Lack of α-glucosidase inhibitory effects [223]. Selective inhibition of aldose reductase [224] and reduction of advanced glycation end products and $H_2O_2$ induced oxidative stress in human adipocytes [225] |
| 27 | **Rutaceae**<br>*Ruta chalepensis* L. (decoction of leaves, buds, roots [49]) | Alkaloids, flavonoids, coumarins, tannins, volatile oil, sterols and/or triterpenes [226], and rutin, a flavone glycoside [227] | None |
| 28 | **Umbelliferae**<br>*Coriandrum sativum* L. (decoction of seeds [18, 56]) | Polyacetylenes [228]. 1-*O*-*β*-D-glucopyranoside, 3-*O*-*β*-D-glucopyranoside, 4-*O*-*β*-D-glucopyranoside, 1-*O*-*β*-D-fructofuranoside, 3-*O*-*β*-D-fructofuranoside, 4-*O*-*β*-D-fructofuranoside, 1-*O*-*β*-D-(6-*O*-4-hydroxybenzoyl)-glucopyranoside, and 1-*O*-*β*-D-(6-*O*-4-methoxybenzoyl)-glucopyranoside of 2-C-methyl-D-erythritol [229]. Monoterpenoids, glycosides, monoterpenoid glucoside sulfates, and aromatic compound glycosides [230] | Antihyperglycemic, insulin-releasing, and insulin-like activity [231, 232] |
| 29 | **Umbelliferae**<br>*Cuminum cyminum* L. (dry fruits [18]) | Monoterpenoid glucosides [233]. Sesquiterpene lactone glucosides and alkyl glycosides [234]. A flavonoid glycoside; 3′,5-dihydroxyflavone 7-*O*-*β*-D-galacturonide 4′-*O*-*β*-D-glucopyranoside [235]. Cuminlaldehyde, γ-terpinene, o-cymene, *β*-pinene, 2-caren-10-al, trans-carveol, and myrtenal [236] | Antihyperglycemic effect [237] comparable to glibenclamide and inhibition of advanced glycation end products formation in STZ-diabetic rats [238]. Aldose reductase and α-glucosidase inhibition [239] |
| 30 | **Umbelliferae**<br>*Eryngium creticum* Lam. (decoction of aerial parts [100]) | A unique *n*-propyl sesquiterpene [240] | Hypoglycemic effects [241] in rat models. Favorable acute antihyperglycemic trend in starch-fed rats despite the lack of *in vitro* inhibitory activity of α-amylase and α-glucosidase [23] |

shown in relation to their medicinal use reflects a striking diversity of species and uses, as well as their importance in popular plant therapy. Pharmacologic and therapeutic evaluation of the selected plants in this review explicitly substantiates the ethnopharmacological practices in Jordan. These traditions could pave the way for future phytochemical and pharmacological studies, thereby contributing to alternative therapeutic strategies to available drugs with undesirable adverse effects or those lacking in satisfactory efficacy or safety.

## Supporting information

In **Table 1S** of the Supporting information, the up-to-date reported pharmacological activities of the selected medicinal plants with claimed antidiabetic propensities are discussed. On the other hand, ● **Table 1** includes the reported antidiabetic efficacy and/or action mechanism of the same selection of medicinal plants.

## Conflict of Interest

▼

The authors declare none.

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