Antidiabetic Attributes of Desert and Steppic Plants: A Review

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- oxidative stress
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- hypoglycemic effect

Abstract

The rapidly increasing incidence of diabetes mellitus is becoming a serious threat to mankind's health in all parts of the world. In fact, known cases reflect only part of the problem, as many diabetics, especially with type 2 diabetes, are unaware of their disease, which initially shows no definitive symptoms. Despite the great efforts invested in diabetes research, its prevalence continues to grow, while current medications do not cover all of the symptoms and complications of the disease. The present review highlights a plethora of studies focusing on the antidiabetic properties of desert and semidesert (steppic) plants, many of them being used for centuries in traditional medicine by Bedouins living in the arid zones of the Middle East and also by ethnic groups in other arid and semiarid parts of the world. The review concludes in summarizing the work done on the subject and also in pointing to the yet existing gaps in diabetes research of desert and steppic plants, and suggests directions for future exploration.

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Introduction

Diabetes mellitus is in a group of metabolic disorders having hyperglycemia as a common manifestation. It is a syndrome with both hereditary and environmental factors. Glycemia and diabetes are rising globally, driven both by population growth and ageing. The number of people with diabetes increased from 153 million in 1980 to 347 million in 2008 [1]. The greatest relative increase is expected to occur in Africa, followed by the Eastern Mediterranean and the Middle East [2]. The global health expenditure on diabetes has been expected to total at least USD 376 billion in 2010, rising to USD 490 billion in 3030 [3]. Diabetes is projected to become one of the world's main disablers and killers within the next 25 years [4].

Experimental diabetes in animals has provided considerable insight into the physiological and biochemical derangement of the diabetic state. Significant changes in lipid metabolism occur in diabetes as well as a profound alteration in the concentration and composition of lipids. In these cases, the lipid structural changes are clearly oxidative in nature [5]. In diabetes, increased lipid peroxidation is associated with hyperlipidemia [6]. Oxidative stress is, thus, produced under diabetic condition and is likely involved in the progression of pancreatic damage [7]. Despite the great strides made in the understanding and management of diabetes, the disease and its complications are increasingly unabated.

The role of oxidative stress and altered antioxidant levels in the pathogenesis of diabetic complications is well established [8]. Oxidative stress may have a common pathway linking diverse mechanisms for diabetes complications, such as vascular dysfunctions, nephropathy, neuropathy, and retinopathy. Apart from the initiation of lipid peroxidation, oxygen free radicals stimulate glycation of protein, inactivate enzymes and change the structure and function of collagen and other membranes, thereby playing a role in the long-term complications of diabetes [9]. Oxidative stress in diabetes coexists with a reduction in the antioxidant status and increase of the deleterious effects of free radicals [10]. Studies indicated that antioxidant intake may reduce the risk of developing type 2 diabetes [11]. Antioxidants were shown to reduce the risk of diabetes onset and improve glucose disposal and associated complications [12].

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Phenolic compounds (e.g., phenolic acids, flavonoids, quinones, and tannins) are natural antioxidants abundant in many desert and steppic plants. They function as terminators of free radical chains or as chelators of redox-active metal ions capable of catalyzing lipid peroxidation [13]. A positive linear correlation was found between the antioxidant activity (the capability to scavenge oxygen reactive species) and the total phenolic content in plants [14,15], suggesting that phenolic compounds contribute significantly to the antioxidant capacity of the investigated plant species. Direct correlation between the antioxidant property of medicinal plants and the latter's antidiabetic activity was found [16], and the relationship between the molecular structure of flavonoids and their radical-scavenging capability was shown [17].

Overproduction of reactive oxygen species (ROS) has been implicated in the causation of several acute diseases, such as liver cirrhosis, atherosclerosis, cancer, degenerative diseases, diabetes, and ageing. Therefore, compounds that can scavenge ROS have great potential in ameliorating or even stopping the processes leading to these diseases [18]. Antioxidants – ROS scavengers – thus play important roles in protecting the human body against the damage they cause.

Ethnic medicine uses mostly plants to fight diseases. The antidiabetic effects of medicinal mushrooms and their hypoglycemic mechanism have been reviewed [19]. Sugar control is thought to be linked to the action of substances like glycosides, alkaloids, terpenoids, tannins, and flavonoids contained in medicinal plants [4,19]. Generally, plant-based ethnic drugs and herbal formulations are less toxic and freer from side effects than their synthetic counterparts [20].

Being exposed to harsh environmental stress conditions, desert and steppic plants have developed unique survival systems based on phytochemicals of remarkable properties. Many of them not only protect the plant against the enhanced environmental oxidative stress conditions but are thought also to be capable of diminishing, or even preventing, deleterious oxidative processes in the human body, which are involved in the development of cancer, diabetes, and neurodegenerative diseases [21].

The high potential of desert and steppic plants in treating and preventing diabetes is reflected in Bedouin ethnic medicine. Although a systematic comparison between the antidiabetic attributes of desert and semidesert plants to those of plants growing under milder conditions has not yet been documented, those of the former could still be evaluated while observing the deleterious health effects due to the changes in the lifestyle of the Israeli Negev Bedouins in the last few decades. The transition has primarily been from traditional diet (local herbs, milk from sheep, goats, and camels nourished on natural pasture) to westernized food and has resulted in a dramatic increase in diabetes morbidity and mortality among the Bedouins [22,23]. Indeed, consumption of camel milk has traditionally been regarded by the Israeli Negev Bedouins as a sure remedy against diabetes, and its ethnic use, based on experience, has recently also been scientifically validated [24–26].

This review highlights the antidiabetic effects of extracts and pure components derived from desert and steppic (semidesert) plants in ethnic medicine and in research. **Table 1** summarizes the plants' antidiabetic bioactivities. **Fig. 1** exhibits the chemical structures of antidiabetic active components included in some of them.

Search Methodology

The purpose of this review article has been to provide the interested reader with a broad view, but not necessarily with complete literature coverage of the subject. Reference has been made only to plants growing mostly in arid and in semiarid zones, and used in traditional antidiabetic medicine. Others, which although being used against diabetes in ethnic medicine are basically temperate climate plants, such as *Inula viscosa*, for example, were not included.

Literature search has been focused on the experimental work done on the antidiabetic properties of plants traditionally used against diabetes by ethnic groups in different arid and semiarid zones of the world. The scientific search engine "SciFinder" was found to be an extremely usefull tool as it retrieves information from both MEDLINE and CAPLUS databases. In most cases, full articles were obtained and carefully gone through. In a few cases, only abstracts could be obtained. The essence of the experiments is given in the text with just a few experimental notes, such as the nature of solvent used for extraction, and the applied dosages, while ignoring experimental details.

Exploring the Antidiabetic Attributes of Desert and Steppic Plants

Artemisia judaica L. (Compositae) is an evergreen perennial shrub growing in the Israeli arid southern Arava and the southern Sinai desert and is commonly used in traditional Bedouin medicine. It was found that both water and alcoholic extracts of this plant significantly reduced blood glucose levels in experimentally diabetic rats, while no significant effect was detected in normal rats [27]. Phytochemical analysis of *A. judaica* revealed that it is a rich source of flavonoids, including apigenin (4′,5,7-trihydroxyflavone) and cirsirmaritin (**Fig. 1**). Indeed, the major bioactive compounds of defatted alcohol and water extracts of *A. judaica* were found to be flavonoids, compounds exhibiting strong antioxidant activities [28,29].

Artemisia herba-alba Asso. (also called "white wormwood"; Compositae) is a dwarf perennial shrub growing in semiarid zones and in favorable niches in hot deserts of the Middle East, but also in semiarid zones of southern Europe and Asia. The aqueous extract of *A. herba-alba* was found to produce initial hyperglycemia, followed by hypoglycemia in normal and alloxan-treated rabbits and mice [30]. This plant has been widely used in Iraqi folk medicine for the treatment of diabetes mellitus. Oral administration of an aqueous extract of its aerial parts to normoglycemic and to alloxan-diabetic rabbits produced significant hypoglycemic activity, which proved to be consistent and time dependent [31].

Hydro-alcoholic extracts of *Centaurium erythraea* Rafn (Gentianaceae) and *A. herba-alba*, used in the traditional treatment of diabetes in north-eastern Algeria, were tested in mice with established type 2 diabetes induced with a standardized high-fat diet [32]. At 35 weeks, groups treated with *A. herba-alba* or with *C. erythraea* when compared to the high-fat diet control showed a significant reduction in mean fasting blood glucose concentration, triglyceride, total cholesterol, and serum insulin concentrations. The plant extracts also markedly reduced insulin resistance as compared to high-fat diet controls. Although *A. herba-alba* has already been shown to have antihyperglycemic and antihyperlipidemic effects, this research demonstrated for the first time

Table 1 Antidiabetic effects of desert and steppic plants.

Plant	Part of plant used/ type of extract	Target & antidiabetic effect	Administration route/ dosage	Reference
Achillea santolina	whole plant water-ethanol extract	Reduced activities of superoxide dismutase, catalase, and levels of pancreatic glutathione in STZ diabetic male Wistar albino rats; reduced blood glucose level and exhibited hypoglycemic activity in STZ diabetic rats.	oral/mL/rat/day (equivalent to 0.1 g plant powder per kg b. w. per day)	Yazdanparast et al., 2007 [61]
Aloe barbadensis (Aloe vera)	dried sap from leaf	Reduced fasting serum glucose levels in patients with non-insulin-dependent diabetes; induced hypoglycemia in alloxan-diabetic Swiss albino mice.	oral/humans: half a teaspoonful; mice: 0.5 g · kg^{-1} b. w.	Ghannam et al., 1986 [76]
	bitter principle from leaf extract	Produced hypoglycemic effect in alloxan-diabetic mice.	oral/5 mg · kg^{-1} b. w.	Ghannam et al., 1986 [76]; Ajabnoor, 1990 [77]
Aloe arbores- cence	polysaccharide fraction isolated from leaves	Lowered glucose levels in normal mice, and in alloxan-induced hyperglycemic mice.	oral/*ad libitum*	Hikino et al., 1986 [78]
Anabasis articulata	butyl alcohol extract of β-sitoglucoside saponin from aerial parts	Decreased glycemia in diabetic and non-diabetic mice.	oral/10 mg (dried butanolic extract) kg^{-1} b. w.	Kambouche et al., 2011 [68]
Artemisia herba-alba	plant's aqueous extract	Produced initial hyperglycemia, followed by hypoglycemia in normoglycemic and in alloxan-treated rabbits and mice.	oral/0.39 g (dry extract) kg^{-1} b. w.	Marrif et al., 1995 [30]
	aerial parts	Produced hypoglycemic activity to normoglycemic and to alloxan-diabetic rabbits.	oral/0.39 g (dry extract) kg^{-1} b. w.	Twaij, 1988 [31]
	hydro-alcoholic extract	Reduced mean fasting blood glucose, serum insulin concentrations, and insulin resistance in high-fat diet-induced diabetic rats.	oral/2 g (dry extract) kg^{-1} b. w.	Hamza et al., 2011 [32]
	aqueous extract of aerial parts	Reduced blood glucose level, prevented elevation of glycosylated hemoglobin level, exhibited hypoliposis effect and protected against body weight loss of diabetic rats and rabbits.	oral/0.39 g (dry extract) kg^{-1} b. w.	Al-Shamaony et al., 1994 [33]
		Lowered elevated blood sugar in patients with diabetes mellitus.		Al-Waili, 1986 [34]
	volatile oil from aerial parts	Decreased the high blood glucose level of alloxan-diabetic rats.	s. c. i./1350–1950 mg · kg^{-1} b. w.	Essway et al., 1995 [35]
Artemisia judaica		Reduced blood glucose level in experimentally diabetic rats but negligibly affected normal rats.	oral/0.25 g · kg^{-1} and 0.5 g · kg^{-1} b. w. for the water ext. and 0.5 g · kg^{-1} and 1 g · kg^{-1} b. w. for the alc. ext.	Nofal et al., 2009 [27]
Atriplex halimus	pressed juice, or water extract, or dialysate of the green leaves	Induced hypoglycemic effect in alloxan-diabetic albino rats.	oral	Aharonson et al., 1969 [70]
Balanites aegyptiaca	water extract of fruits	Decreased plasma glucose levels in diabetic male rats.	oral/3.6–9 g/week/rat	Morsy et al., 2010 [59]
Calotropis procera	dry latex from aerial parts	Caused dose-dependent decrease in blood glucose and an increase in the hepatic glycogen content in alloxan-induced diabetic rats; prevented loss of body weight in diabetic rats and brought down their daily water consumption to values comparable to normal rats.	oral/100–400 mg · g^{-1} b. w.	Roy et al., 2005 [62]
	water, petroleum ether, and ethanol extracts of leaves	Reduced blood glucose level, total cholesterol, phospholipids, low-density lipoprotein and very low-density lipoprotein and increased high-density lipoprotein in STZ-induced diabetic male Wister albino rats.	oral/250 mg (dry extract) kg^{-1} b. w.	Bhaskar and Sumant, 2009 [63]
Capparis spinosa	fruit	Decreased blood glucose level in STZ- and HFD-diabetic rats, normalizing it within 2 weeks of daily oral administration.	oral/20 mg (dry extract) kg^{-1} b. w.	Eddouks et al., 2004 [38]; Lemhadri et al., 2007 [39]
Caralluma sinaica	ethanol extract of aerial parts	Induced dose-dependent reduction in blood glucose levels in normal male albino rabbits, and brought to normal plasma glucose in STZ-induced diabetic rabbits.	oral/50–200 mg/kg b. w.	Habibuddin et al., 2008 [74]

continued

Table 1 *Continued*

Plant	Part of plant used/ type of extract	Target & antidiabetic effect	Administration route/ dosage	Reference
Chiliadenus iphionoides	ethanol extract of aerial parts	Increased insulin secretion in β cells and glucose uptake in adipocytes and skeletal myotubes. Displayed hypoglycemic activity in diabetic sand rats. (*Psammomys obesus*)	oral	Gorelick et al., 2011 [52]
	aqueous extract of aerial parts	Decreased blood glucose levels in diabetic and in nondiabetic rats.	oral	Afifi et al., 2011 [54]
Larrea tridentate (Creosote bush)	nordihydro-guaiaretic acid	Decreased concentration in plasma glucose of male mice without change in plasma insulin concentration, improved oral glucose tolerance and enhanced the ability of insulin to lower plasma glucose concentrations.		Luo et al., 1998 [82]
Moringa peregrina	aqueous and ethanol extracts of aerial parts	Induced antihyperglycemic effect on streptozotocin-induced diabetes in rats.	oral/25 mg · kg^{-1} b. w. i. p. i./50 mg · kg^{-1}b. w.	El-Alfy et al., 2011 [64]
Ochradenus baccatus		Initiated slow hypoglycemic activity in alloxanized rats.		Shabana et al., 1990 [51]
Opuntia streptacantha Lemaire	broiled nopal stems	Induced hypoglycemic effect in patients with non-insulin-dependent diabetes mellitus (NIDDM)	oral/500 g per person	Frati-Munari et al., 1988 [73]
Peganum harmala	essential oil	Ameliorated hyperglycemia-induced stress oxidative and hepatic dysfunction in diabetic rats.		Hamden et al., 2009 [60]
Plantago ovata	husk hot water extract	Suppressed rise in blood glucose after sucrose loading in control and diabetic rats; improved glucose tolerance in normal, type 1 and type 2 diabetic rats. Antihyperglycemic activity due to increased motility of the gastrointestinal tract.	oral/0.5 g · kg^{-1} b. w.	Hannan et al., 2006 [67]
Retama raetam	fruits methanol extract	Lowered blood glucose levels in STZ-diabetic rats.	oral/250 mg · kg^{-1} b. w.	Algandaby et al., 2010 [56]
	water extract of aerial parts	Induced hypoglycemic effect in STZ-diabetic rats.	oral/20 mg · kg^{-1} b. w.	Maghrani et al., 2003 [57]
	water extract of aerial parts	Displayed hypoglycemic activity in both normal and STZ-diabetic rats.	oral/10 mg · kg^{-1} b. w.	Maghrani et al., 2005 [58]
Terminalia chebula, Terminalia helerica, Emblica officinalis	methanol extract of aerial parts	Reduced blood sugar level in normal and in alloxan-treated diabetic rats.	oral/100 mg · kg^{-1} b. w. normal rats. 120 mg · g^{-1} b. w. alloxinated rats	Sabu and Kuttan, 2002 [16]
Teucrium polium	water – ethanol extract	Induced a decrease in glucose level and an increase in blood insulin level in STZ-diabetic rats.	oral/0.5 g (dry extract) kg^{-1} b.w	Yazdanparast et al., 2005 [43]
	water extract	Suppressed blood glucose levels; induced higher GSH levels along with enhanced CAT and SOD activities in pancreatic tissue; lowered serum NO, pancreatic MDA, PCO, and AOPP levels.	oral/0.5 g (dry extract) kg^{-1} b. w.	Ardestani et al., 2008 [45]
	ethanol extract	Demonstrated insulinotropic effect on INS-1E cells and a reduction of blood glucose levels in both normo- and hyperglycemic rats.	intragastric/125 mg (dry extract) kg^{-1} b. w.	Stefkov et al., 2011 [46]
Ziziphus spina-christi	leaf butyl alcohol extract	Reduced serum glucose level, liver phosphorylase, and glucose-6-phosphatase (G-6-pase) activities; increased serum pyruvate level and liver glycogen content and improved glucose utilization in STZ-diabetic rats.	oral/100 mg · kg^{-1} b. w.	Glombitza et al., 1994 [47]
	leaf water extract	Reduced blood glucose level, increased serum insulin and C-peptide levels, reduced elevated blood lactate level and elevated the reduced blood pyruvate content in STZ-diabetic rats.	oral/200 mg · kg^{-1} b. w.	Michel et al., 2011 [49]
	leaf butyl alcohol extract or pure christinin-A	Reduced serum glucose level and increased serum insulin level in nondiabetic control and in type 2, but not in type 1 diabetic rats.	oral/100 mg · kg^{-1} b. w.	Abdel-Zaher et al., 2005 [50]

b. w. = body weight; s. c. i.= subcutaneous injection; i. p. i. = intraperitoneal injection; alc. = alcohol

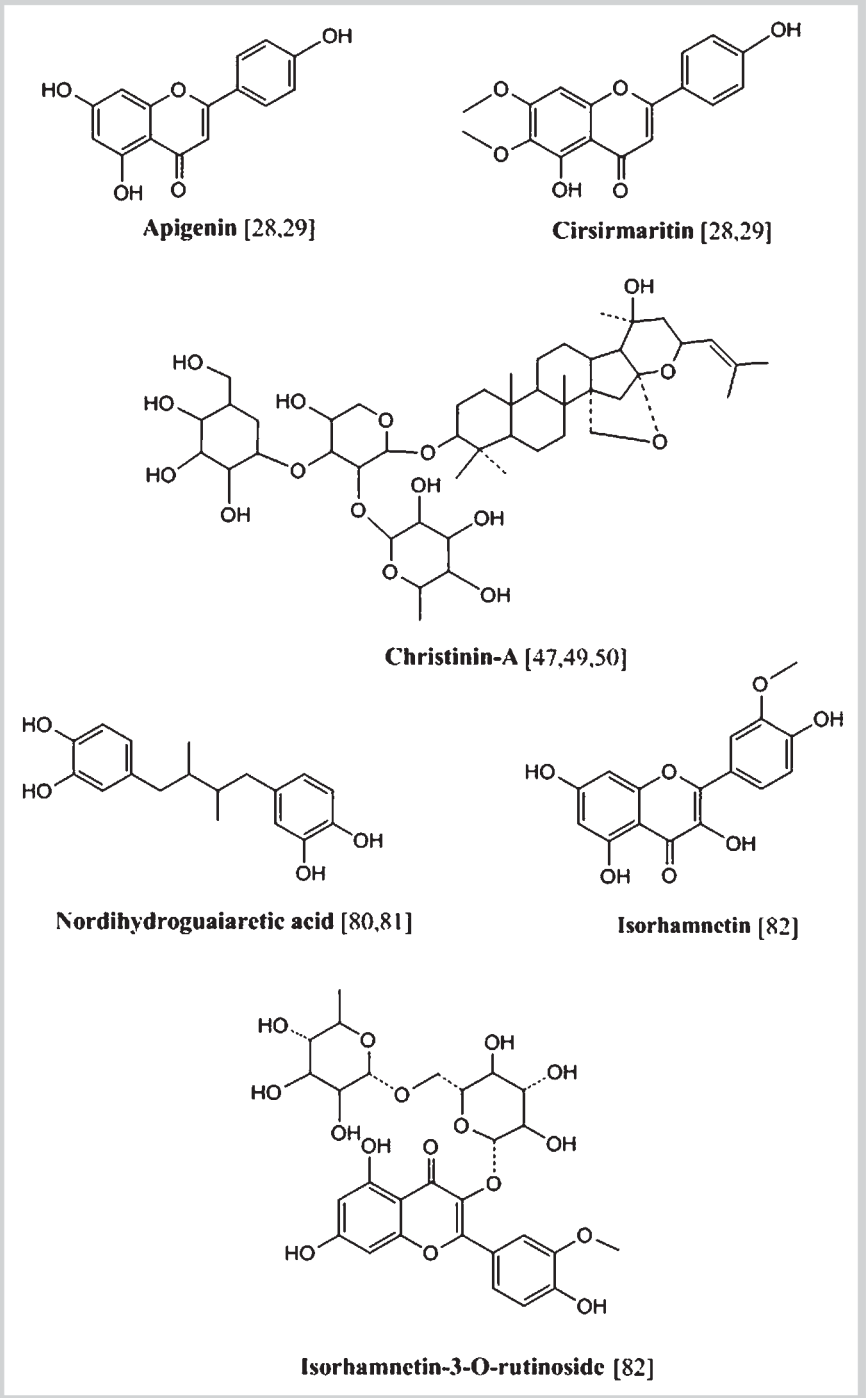

Fig. 1 Several antidiabetic compounds contained in desert and steppic plants.

the effect of this plant on established high-fat diet-induced diabetes.

A study assessed the efficacy and toxicity of *A. herba-alba* [33]. Feeding diabetic rats and rabbits with 0.39 g/kg body weight of the aqueous extract of the aerial parts of the plant for 2–4 weeks resulted in a significant reduction in blood glucose levels, prevented elevation of glycosylated hemoglobin levels, led to hypoliposis and protected against body weight loss of the diabetic animals.

Fifteen patients with diabetes mellitus treated with *A. herba-alba* extract showed a considerable lowering of elevated blood sugar, while 14 out of the 15 patients had good remission of diabetic symptoms. No side effects were recorded during or after treatment with the plant extract [34].

Mice treated with the volatile oil of *A. herba-alba* showed significant hypoglycemia, and the high blood glucose levels of alloxan-treated diabetic rats significantly decreased subsequent to injecting the oily extract [35].

The genus *Capparis* (Capparidaceae or Capparaceae) includes more than 250 species and has a wide distribution, particularly covering the Atlantic coasts from the Canary Islands and Morocco to the Black Sea and Armenia [36]. The species *Capparis spinosa* L. is a semiarid, drought tolerant perennial shrub, largely distributed throughout the Mediterranean Sea basin. In Israel, a variant, *Capparis spinosa* L. var. *arvensis* Zohary, is found throughout the

arid part of the country, the southern Jordan Valley, Judean Desert, Negev, and Arava, growing on poor stony lands in wadies and canyons [37]. In Arab and Bedouin traditional medicine different parts of the plant have been used for treating rheumatism, women infertility, open wounds, respiratory diseases, and diabetes. The aqueous extract of the fruit of this plant was found to produce a significant decrease in blood glucose level in streptozotocin (STZ)-diabetic rats [38] and in high-fat diet (HFD) diabetic rats [39], normalizing blood glucose levels within 2 weeks of daily oral administration. Treating nondiabetic rats with the plant's extract did not result in significant changes in blood glucose levels. No changes were observed in basal plasma insulin concentrations following treatment with this plant in either normal or STZ-diabetic rats, suggesting that the underlying mechanism of its pharmacological activity is independent of insulin secretion.

Teucrium polium L. (syn. *Teucrium capitatum* L.; Lamiaceae) is a wild-growing Mediterranean and West Irano-Turanian perennial, a plant belonging to the semiarid and arid climates of the Middle East, North Africa, south-western Asia, and southern Europe [40]. As a medicinal plant, it has been used for more than 2000 years. Traditionally, *T. polium* has been used for treating different pathological conditions, such as gastrointestinal disorders, inflammations, diabetes, and rheumatism. In Arab and Bedouin traditional medicine, *T. polium* has been primarily applied in treating abdominal pain, indigestion, diabetes, liver diseases, and hypertension [41]. During the past 40 years, different classes of compounds have been isolated from various parts of this plant, the main groups of which are terpenoids and flavonoids. These compounds possess a broad spectrum of pharmacological effects, including antioxidant, anticancer, anti-inflammatory, hypoglycemic, hepatoprotective, hypolipidemic, antibacterial, and antifungal activities [42].

The aqueous extract of the dried aerial parts of *T. polium* has traditionally been used in southern Iran. The local claimed hypoglycemic effect of this plant was validated through administering the crude extract to STZ-diabetic rats. Compared to untreated diabetic rats, the glucose level in the treated rats was decreased by 64%, and an increase of almost 160% was observed in the blood insulin level. *In vitro* investigation using isolated rat Langerhans islets indicated that the crude aqueous extract of *T. polium* is capable of enhancing insulin secretion by almost 135% following a one dose treatment at a high glucose concentration, suggesting that a regenerative process of the islets of Langerhans in the *T. polium*-treated diabetic rats has occurred [43]. In another study, Gharaibeh et al. suggested that the hypoglycemic activity of aqueous extracts derived from *T. polium* is due to the enhancement of peripheral metabolism of glucose rather than an increase in insulin release [44].

Rats treated with *T. polium* extract had significantly higher glutathione (GSH) levels, along with enhanced catalase (CAT) and superoxide dismutase (SOD) activities in the pancreatic tissue. In addition to suppressed blood glucose levels, serum nitric oxide (NO), pancreatic malondialdehyde (MDA), protein carbonyl content (PCO), and advanced oxidation carbonyl products (AOPP) levels were all lower in the diabetic rats treated with the *T. polium* extract as compared with untreated counterparts [45].

The insulinotropic and antihyperglycemic effects of the ethanol extract of *T. polium* from the Republic of Macedonia, a plant traditionally used in that country to treat diabetes, were also investigated [46]. The dried extract showed a distinct *in vitro* insulinotropic effect on INS-1E cells at 500 µg/mL. An oral administration of the extract to both normal and hyperglycemic rats lowered blood glucose levels of both groups by 35%.

Ziziphus spina-christi (L.) Willd. (Christ's thorn jujube; Rhamnaceae) is an evergreen tree of Sudanese origin native to northern and tropical Africa, and southern and western Asia. In Israel it grows in valleys up to an elevation of 500 m. It is also found in moist wadies in the Israeli hot Judean Desert and Arava. *Z. spina-christi* is a plant commonly used in Egyptian and Middle East traditional medicine for the treatment of various ailments [47, 48]. A study investigated the effect of the butyl alcohol extract of leaves of this plant and that of christinin-A (**Fig. 1**), its principal saponin glycoside, in normal and STZ-induced diabetic rats [47]. In normal rats, treatment for one and four weeks produced insignificant changes in all studied parameters. However, in diabetic rats, both treatments significantly reduced serum glucose levels, liver phosphorylase, and glucose-6-phosphatase (G-6-pase) activities and significantly increased serum pyruvate levels and liver glycogen content after 4 weeks of treatment. A marked improvement was noticed in glucose utilization in diabetic rats in both cases. Serum insulin and pancreatic cyclic adenosine monophosphate (cAMP) levels showed a significant increase in diabetic rats treated with the extract, suggesting an improvement of the pancreas function.

Additional study showed that the antihyperglycemic potencies of leaf extracts of *Z. spina-christi* on STZ-induced diabetic rats depend on seasonal variation, and that leaves should preferably be collected from June to October [49]. This study showed that oral administration of *Z. spina-christi* leaf extract reduced the blood glucose level with a significant increase in serum insulin and in C-peptide levels. The extracts reduced the elevated blood lactate level and elevated the reduced blood pyruvate content of diabetic rats. In line with the amelioration of the diabetic state, *Z. spina-christi* extract, both plain and formulated, restored liver and muscle glycogen content, together with a significant decrease of hepatic glucose-6-phosphatase and enhanced the activities of glucose-6-phosphate dehydrogenase. *In vitro* tests marked a dose-dependent inhibitory activity of *Z. spina-christi* extract against α-amylase enzyme with an IC_{50} at 0.3 mg/mL. This work showed that *Z. spina-christi* leaf extract improves glucose utilization in diabetic rats by increasing insulin secretion, which may be due to both saponin and polyphenols contents, and controls hyperglycemia through the attenuation of meal-derived glucose absorption, attributed to the total polyphenols content.

Abdel-Zaher et al. studied the effect of butyl alcohol extract of the leaves of *Z. spina-christi* and its major saponin glycoside, christinin-A, on serum glucose and insulin levels in nondiabetic controls, type 1 and type 2 diabetic rats [50]. They found that treatment either with 100 mg/kg extract, or with christinin-A alone, reduced the serum glucose level and increased the serum insulin level of nondiabetic control and in type 2 diabetic rats, but not of type 1 diabetic rats. Similar effects were obtained with the butyl alcohol extract and with christinin-A. Pretreatment of nondiabetic control and type 2 diabetic rats, either with butyl alcohol extract or with christinin-A, enhanced the glucose lowering and insulinotropic effects of glibenclamide, a sulfonylurea antidiabetic drug used for the treatment of type 2 diabetes. It was also found that treating rats with 100 mg/kg butyl alcohol extract for 3 months produced no functional or structural disturbances in the liver and kidney and no hematological changes. These results point to the leaves of *Z. spina-christi* as a safe alternative to lower blood glucose. The safe insulinotropic and subsequent hypoglyce-

mic effects of *Z. spina-christi* leaves could be due to a sulfonylurea-like activity.

The hypoglycemic effect of 31 plants from different Egyptian localities was tested [51]. Twenty-one plant extracts were given orally to normal rats, and fifteen were tested on fasting and alloxanized rats. The results were compared with a standard oral hypoglycemic drug [DAONIL® tablets; Daonil (INN), also known as glyburide (USAN), a second-generation sulfonylurea antidiabetic agent] used as a positive control. Eight plants exhibited persistent hypoglycemic effects, while transient hypoglycemic effects appeared in response to the administration of four other plants. Among the fifteen plant extracts tested on alloxanized diabetic rats, only four showed hypoglycemic effects more potent than those of the administered dose of DAONIL® tablets. These were *Matthiola livida* (Delile) DC. (Brassicaceae), *Salvia aegyptiaca* L. (Lamiaceae), and *Arthrocnemum glaucum* Ung.-Sternb. (Chenopodiaceae). *S. aegyptiaca* also induced the hypoglycemic effect in fasting alloxanized diabetic rats.

C. iphionoides (Boiss. & Blanche) Brullo (syn. *Varthemia iphionoides* Boiss.; Compositae) is a small aromatic shrub, an herbaceous perennial hemicryptophyte distributed in the Mediterranean woodlands and shrub-steppes, deserts and extreme deserts, and is used traditionally in the treatment of diabetes mellitus. The ethanol extract of the aerial parts of *C. iphionoides* increased insulin secretion in β cells as well as glucose uptake in adipocytes and skeletal myotubes. The extract also displayed hypoglycemic activity in diabetic sand rats (*Psammomys obesus*) [52].

Various extracts of the aerial parts of *C. iphionoides* were investigated for their radical scavenging, antioxidative, and porcine pancreas α-amylase inhibitory activities [53]. Ethanol and water extracts showed a pronounced 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging activity, with inhibition of about 90% at a concentration of 100 µg/mL, and α-amylase inhibitory activity of about 70% at a concentration of 200 µg/mL by the 2-chloro-4-nitrophenyl α-maltotrioside (CNP-G3) degradation method.

Aqueous extract of the aerial parts of *C. iphionoides* decreased blood glucose by 70% after one hour in STZ-treated rats and also lowered blood glucose in normal rats 4 hours after treatment [54].

The effect of *C. iphionoides* was evaluated *in vitro* and *in vivo* on enzymatic starch digestion [55]. The results confirmed that *C. iphionoides* could be considered a potential candidate for therapeutic modulation of impaired fasting glycemia, impaired glucose tolerance, and type 2 diabetes.

Retama raetam (Forssk.) Webb & Berthel (Fabaceae) is a phanerophyte shrub distributed in the Mediterranean woodlands and shrublands, semi-steppe shrublands, shrub-steppes, deserts, and extreme deserts. The fruits of *R. raetam* are used in Saudi traditional medicine for the treatment of diabetes. A study evaluating the potential and mechanisms of the antidiabetic activity of *R. raetam* methanol extract in STZ-induced diabetic rats showed that the extract neither altered glucose uptake by rat isolated psoas muscle nor the activity of hepatic microsomal glucose-6-phosphatase [56]. The methanol extract of *R. raetam* improved STZ-induced diabetes in rats due to stimulating pancreatic insulin release and the reduction of intestinal glucose absorption.

The effect of the aqueous extract of the leaves of *R. raetam* on blood glucose levels was investigated in fasting normal and streptozotocin-induced diabetic rats after single and repeated oral administration [57]. The aqueous extract of *R. raetam* at a dose of 20 mg/kg significantly reduced the blood glucose in normal rats 6 hours after a single oral administration and two weeks after repeated oral administration. This hypoglycemic effect was more pronounced in STZ-diabetic rats. The extract had no effect on basal plasma insulin levels, indicating an extra-pancreatic mechanism. The aqueous extract of *R. raetam* thus possesses a significant hypoglycemic effect in both normal and STZ-diabetic rats.

An additional study of the hypoglycemic activity of the aqueous extract of the aerial parts of *R. raetam* in normal and in STZ-diabetic rats following intravenous injection indicated a significant decrease in blood glucose levels in normal rats and an even more marked decrease in diabetic rats [58]. The results suggested that the hypoglycemic effect is due to an extra-pancreatic action of the extract since the basal plasma insulin concentrations remained constant. The aqueous extract perfusion of *R. raetam* caused a potent inhibition of renal glucose reabsorption. This effect indicated at least one mechanism that could explain the observed hypoglycemic activity of this plant in both normal and diabetic rats.

Balanites aegyptiaca (L.) Delile (Balanitaceae) is a multibranched, spiny shrub or tree up to l0 m high, native to Africa, the Arabian Peninsula, and adjacent parts of the Middle East. Within Africa it ranges from Mauritania in the west to Somalia in the east and from Egypt southwards to Zimbabwe. It is a highly drought-tolerant evergreen desert plant species, having a wide ecological distribution, but prefers open woodlands and savannahs. The fruit of a *B. aegyptiaca* species grown naturally at radioactive places in the Wadi El-Gemal area, Egypt, exhibited potential antidiabetic and hypolipidemic capabilities [59].

Peganum harmala L. (Syrian rue; Nitrariaceae) is a perennial shrub with fleshy spikey-looking leaves, growing up to 0.8 m tall. It is native to the eastern Mediterranean region and extends up to India. It can be found in diverse climates, ranging from Mediterranean to steppes and deserts. In Israel, it is distributed mainly throughout the arid and semiarid northern Negev. Treatment of diabetic rats with the essential oil of *P. harmala* ameliorated hyperglycemia-induced stress, and oxidative and hepatic dysfunction. Administration of the oil to diabetic rats initiated antidiabetic and antioxidant activities through the decrease in the plasmatic glucose level, an increase in hepatic SOD, CAT, and glutathione peroxidase activities, and a concomitant reduction in glutathione and glycogen contents compared to untreated diabetic rats [60].

Achillea santolina L. (Compositae) is a 0.3 m high perennial shrub, growing on loess soils in the semiarid central northern Negev in Israel. This plant is used by Bedouin traditional healers as a hypoglycemic agent. The protective effect against pancreatic damage of the hydro-ethanol extract of the plant's aerial parts was tested on STZ-treated diabetic rats [61]. Following oral administration of the extract, a significant reduction in the activities of SOD, CAT, and pancreatic GSH levels was observed in the diabetic rats, compared to control subjects. Extract of *A. santolina* reduced blood glucose level, serum NO, pancreatic MDA, PCO, and AOPP. CAT and SOD activities decreased by diabetic conditions were significantly increased in diabetic rats treated with the extract, manifesting the high hypoglycemic activity of *A. santolina*, an attribute probably resulting from its antioxidative potential [61].

A. santolina L., *Pistacia atlantica* Desf. (Anacardiaceae), *Rheum ribes* L. (Polygonaceae), *Sarcopoterium spinosum* L. Spach (Rosaceae), and *T. polium* L. have traditionally been used as herbal antidiabetic medicines. The *in vitro* and *in vivo* effects of water extracts of these plants were tested [55]. Compared to acarbose (IC_{50} = 1.2 µg/mL), water extracts of *P. atlantica, R. ribes*, and *S.*

spinosum exerted significant dose-dependent dual inhibition of α-amylase and α-glucosidase in the *in vitro* enzymatic starch digestion bioassay, with IC_{50} values of 46.98, 58.9, and 49.9 mg/mL, respectively. Comparable *in vivo* results were obtained for starch-fed rats exhibiting significant acute postprandial anti-hyperglycemic efficacies. While the extracts of *A. santolina* and *T. polium* lacked any favorable *in vitro* anti-α-amylase and anti-α-glucosidase effect, other modes of action can possibly explain their substantial acute anti-hyperglycemic activities in starch-treated rats. Except for *P. atlantica* extracts, none of the investigated extracts qualified for improving the glucose intolerance in fasting rats on glucose loading. *P. atlantica, R. ribes*, and *S. spinosum* are potential candidates for amelioration/management of type 2 diabetes.

Calotropis procera (Aiton) W.T. Aiton (Asclepiadaceae), also called Sodom apple, is a flowering plant growing in North Africa, tropical Africa, western Asia, south Asia, and Indochina. It is a soft-wooded, evergreen perennial shrub found in the hot oasis around the Dead Sea and in the Jordan Valley. It is a plant tolerant to drought and salt. The dry latex of *C. procera*, collected from its aerial parts and mixed with normal saline, was evaluated for its antioxidant and anti-hyperglycemic effects against alloxan-treated diabetic rats [62]. Daily oral administration of the dry latex produced a dose-dependent decrease in the blood glucose and an increase in the hepatic glycogen content. It also prevented the loss of body weight in diabetic rats and brought down the daily water consumption to values comparable to normal rats. The latex also increased the hepatic level of glutathione and the level of endogenous antioxidants, SOD and CAT, while bringing down the levels of thiobarbituric acid-reactive substances (TBARS) in the alloxan-induced diabetic rats. It was found that the efficacy of the dry latex as an antioxidant, and as an antidiabetic agent, was comparable to the standard antidiabetic drug, glibenclamide. Water, petroleum ether, and ethanol extracts of the leaves of *C. procera* were tested for their anti-hyperglycemic effect on STZ-induced diabetic Wister albino rats [63]. The three extracts significantly reduced the blood glucose level, total cholesterol, phospholipids, low-density (LDL), and very low-density lipoprotein (VLDL) in the treated diabetic rats and concomitantly increased the high-density lipoprotein (HDL), indicating the recovery of their lipid metabolism. This investigation established pharmacological evidence supporting the folkloric claim of the antidiabetic attributes of this plant.

Moringa peregrina (Forssk.) Fiori (Moringaceae Martinov) is a wild plant growing in the eastern desert mountains of Egypt. The aqueous and ethanol extracts of this plant were found to exert a significant anti-hyperglycemic effect on STZ-induced diabetic rats [64].

Plantago ovata Forssk. (Plantaginaceae) is a plant growing in semiarid regions of India, Iran, northern Africa, and Pakistan. It has been traditionally used for constipation, diarrhea, hemorrhoids, irritable bowel syndrome, weight loss, obesity, high cholesterol, and diabetes [65]. A patent deals with a functional powdered beverage containing the seed powder of this plant as the effective component, capable of preventing adult diseases including diabetes [66].

Administration of the husk extract of *P. ovata* significantly improved glucose tolerance in normal, type 1, and type 2 diabetic rats [67]. When orally administered with sucrose solution, the extract suppressed postprandial blood glucose and retarded the small intestinal absorption without inducing the influx of sucrose into the large intestine. It significantly reduced glucose absorption in the gut during *in situ* perfusion of the small intestine to nondiabetic rats. The extract did not stimulate insulin secretion in perfused rat pancreas, isolated rat islets, or clonal β cells. Neither did it affect glucose transport in 3 T3 adipocytes. The suggested mechanism for the reduction of hyperglycemia is *via* the inhibition of intestinal glucose absorption and enhancement of motility.

Anabasis articulata Moq. (Amaranthaceae) is a Saharo-Arabian shrub growing in wadies and flat lands of the extreme deserts of Israel, Jordan, and Sinai. Water extracts of this plant are used in traditional medicine for the treatment of diabetes. An oral administration of butyl alcohol extract of β-sitoglucoside saponin obtained from *A. articulata* to diabetic mice decreased glycemia to 20.09% ($p < 0.05$) six hours after administration, practically restoring to normal the blood glucose level of the diabetic mice. The results obtained indicated an antidiabetic action like a reference compound, glibenclamide [68].

A. articulata is used in Algerian traditional medicine as a remedy for diabetes [67]. The administration of the aqueous extract of the aerial part of this plant to alloxan-treated diabetic mice remarkably decreased glycemia (to nearly 30%) 6 hours after administration. The aqueous extract contain alkaloid and saponin, but only the latter furnish the active component responsible for restoring normal blood glucose levels [69].

Atriplex halimus L. (salt bush; Amaranthaceae) is a halophyte native to Europe and Northern Africa, including the Sahara in Morocco. It grows in all parts of Israel on salty lands, in the Judean Desert, Jordan Valley, and along the Mediterranean coast. The leaves of this plant are the main feeding source for the sand rat. When these rats are fed with high-caloric diets, they develop diabetes which can be reversed by the addition of *A. halimus* leaves [70]. Alloxan-diabetic albino rats showed a significant hypoglycemic effect when fed with either pressed juice or water extract, or dialysate of the green leaves of this plant, but with no decrease in appetite [70]. *A. halimus* showed an insulin potentiating effect in an animal model for diabetes and obesity [71]. Another study showed the effectiveness of *A. halimus* extract against type 2 diabetic patients [72]. Indeed, tisane (herbal tea) prepared from the leaves of this plant is traditionally used by Bedouins in Israel for treating diabetes [37].

Opuntia, also known as nopales or paddle cactus, is a genus in the cactus family, Cactaceae. Currently, only prickly pears are included in this genus of about 200 species distributed throughout most of the Americas. Prickly pear species are found in abundance in Mexico, especially in the central and western regions. They are also found in the western United States, in arid regions in the Northwest, throughout the mid- and lower elevations of the Rocky Mountains, such as in the state of Colorado, where species such as *Opuntia phaeacantha, Opuntia polyacantha,* and others, become dominant. The hypoglycemic effect of *Opuntia streptacantha* Lemaire was tested, showing that the stems of this plant induce a hypoglycemic effect in patients with non-insulin-dependent diabetes mellitus (NIDDM) [73].

Caralluma sinaica (Decne.) A. Berger (Apocynaceae) is a plant distributed in the deserts and dry steppes of the Middle East. In Israel, it grows near the Dead Sea and in the southern Negev. Native people in the Asir region in Saudi Arabia are reported to chew this plant as a hypoglycemic herb [74]. The utility of *C. sinaica* in diabetes mellitus was examined by testing its effect on an STZ-induced diabetic model and oral glucose tolerance [74]. Administration of an ethanol/water extract of the aerial part of *C. sinaica* to normal rabbits caused a significant decrease in glucose level, while in diabetic rabbits, the plasma glucose was brought to al-

most normal. Administration of either *C. sinaica* or glibenclamide blocked the rise of glucose caused by the STZ. The STZ-induced lowering of glycogen content of the liver and muscle was reversed by both *C. sinaica* and glibenclimide. STZ induced a significant increase in renal glycogen content, which was brought almost back to normal by the *C. sinaica* extract. Compared with the glibenclamide treatment, the blood glucose lowering effect was more pronounced for diabetic rabbits given *C. sinaica*. The above effects could explain the basis for the ethnic use of this plant in managing diabetes mellitus.

The genus *Aloe* comprises small to large evergreen perennials with fleshy, sword to lance-shaped leaves. This genus contains about 400 species, native to sub-Saharan Africa, the Saudi Arabian Peninsula, and to many islands of the western Indian Ocean. However, the majority are desert plants inhabiting the deserts of South Africa. The dried sap of *Aloe barbadensis* Mill. (syn. *Aloe vera*; Xanthorrhoeaceae) is one of several traditional remedies used for diabetes in the Arabian Peninsula [75]. It caused a sustained lowering of blood sugar levels in patients [76], while a similar effect was obtained in alloxan-induced diabetic mice, suggesting that the hypoglycemic effect of plants of the *Aloe* genus may be mediated through stimulating synthesis and/or the release of insulin from Langerhans beta-cells [77].

Polysaccharide fractions from water extracts of whole leaves of *Aloe arborescence* Mill. reduced the glucose levels in normal mice. Two polysaccharides (glycans) were separated from the water extract of the leaves of this plant and described as arboran A and arboran B. Both were found to produce marked hypoglycemic effects in normal and in alloxan-induced hyperglycemic mice [78].

Surveys of Antidiabetic Desert and Semidesert Plants by Ethnic Medicine

The high concentration of radical scavenging compounds in many desert and semidesert plants make them potential candidates as a source for antidiabetic drugs, which, in many cases were also proved by ethnic medicine. In the following are some examples:

Methanol extracts of *Terminalia chebula* Retz. (Combretaceae) and *Emblica officinalis* Gaertn. (Euphorbiaceae), extensively used in Indian traditional medicine and known to strongly inhibit lipid peroxidation, significantly reduced the blood sugar level in normal and alloxan-treated diabetic rats, suggesting a relationship between the antidiabetic activity and the antioxidant capability of the plants [15].

Surveying ethnomedicinal plants in the Errachidia province in south-eastern Morocco has brought to light 64 medicinal plants belonging to 33 families, of which 45 are regularly being used by the local population for treating diabetes. In this region, the most frequently used plants to treat diabetes include arid zone plants, such as *P. harmala* and *A. herba-alba* [79].

Phytotherapy is widely adopted in Morocco. A survey was undertaken in different parts of oriental Morocco, aiming at selecting the main medicinal plants used in traditional medicine to treat arterial hypertension and diabetes [80]. For diabetes, 41 plants were cited, of which the most frequently used were *Trigonella foenum-graecum* L. (Leguminosae), *Globularia alypum* L. (Globulariaceae), *Artemisia herba alba* Asso. (Compositae), *Citrullus colocynthis* (L.) Schrad. (Cucurbitaceae), and *Tetraclinis articulata* Benth (Cupressaceae).

An extensive ethnobotanical survey (130 informants) of the medicinal plants of Israel revealed 16 species being traditionally used for hypoglycemic treatments. The list includes desert and semi-desert plants like *Achillea fragrantissima* (Forssk.) Sch. Bip, *A. halimus, C. spinosa*, and *T. polium* [37].

Antidiabetic Compounds Derived From Desert and Semidesert Plants

Larrea tridentate (Sessa & Moc. Ex DC.) Coville (Zygophyllaceae) (creosote bush) is the most common plant in the Northern Chihuahuan Desert, particularly in the border zone of the southern USA and northern Mexico, thriving in nearly every habitat in the desert. Creosote bush is used to treat a variety of illnesses including infertility, rheumatism, arthritis, diabetes, gallbladder and kidney stones, pain and inflammation [81]. Nordihydroguaiaretic acid (**Fig. 1**), a potent antioxidant and a well-known lipoxygenase inhibitor isolated from creosote bush, is the primary product extracted from it. It is a naturally occurring lignin, believed to reduce cell damage caused by free radicals. Under the free-radical theory of ageing, it is speculated to be responsible for the bush's long life. During the past 100 years, extensive research has demonstrated that nordihydroguaiaretic acid and its synthetic analogs are potentially useful in treating diseases related to cancers, diabetes, viral and bacterial infections, as well as inflammation [81].

The ability of masoprocol (a form of nordihydroguaiaretic acid derived from creosote bush) was evaluated in NIDDM mouse models for its ability to lower blood glucose [82]. Following oral administration of masoprocol, the plasma glucose concentration fell in male C57BL/ks-*db/db* or C57BL/6J-*ob/ob* mice. This decline was achieved without any change in plasma insulin concentration. In addition, oral glucose tolerance improved, and the ability of insulin to lower plasma glucose concentrations was accentuated in the masoprocol-treated db/db mice. These data raise the possibility that masoprocol, or other lipoxygenase inhibitors, represent a new approach to the pharmacological treatment of type 2 diabetes.

An aqueous extract of the mesocarp of the fruits of *B. aegyptiaca* exhibited a prominent antidiabetic activity by oral administration in STZ-induced diabetic mice. From one of the active fractions of this extract, two new steroidal saponins were isolated, and their structures were determined as 26-O-*β*-D-glucopyranosyl-(25R)-furost-5-ene-3*β*,22,26-triol 3-O-[*α*-L-rhamnopyranosyl-(1 → 2)]-[*β*-D-xylopyranosyl-(1 → 3)]-[*α*-L-rhamnopyranosyl-(1 → 4)]-*β*-D-glucopyranoside and its 22-Me ether. In addition, 2 known saponins, 26-O-*β*-D-glucopyranosyl-(25R)-furost-5-ene-3*β*,22,26-triol 3-O-(2,4-di-O-*α*-L-rhamnopyranosyl)-*β*-D-glucopyranoside and its methyl ether analog were isolated and identified. From the ethanol extract of the epicarps, 2 known flavonol glycosides, isorhamnetin-3-O-robinobioside and isorhamnetin-3-O-rutinoside, were isolated and identified. Although the individual saponins did not show antidiabetic activity, combined treatment with the saponins resulted in significant activity [83].

An invention deals with a novel method for the treatment of diabetes mellitus (type 1, impaired glucose tolerance [IGT], and type 2) by administering a therapeutically effective amount of one or both *α*-glucosidase inhibitors, namely, paniculoside IV and ent-16,17-dihydroxy-(−)-kauran-19-oic acid, to humans and animals [84]. Diterpenes isolated from the desert plant *Pulicaria undulata* (L.) C.A. Mey (Compositae) were identified as paniculoside IV and

ent-16,17-dihydroxy-(−)-kauran-19-oic acid, both demonstrating α-glucosidase inhibiting activity.

Discussion

The review highlights the effects of extracts of desert and steppic plants on various parameters of diabetes including unveiling potential biochemical pathways involved. Several plant extracts influence the content of free radicals and antioxidants in treated animals, suggesting that the levels of free radicals and antioxidants are associated with the diabetic state. For example, the extract of *A. santolina*, in addition to reducing blood glucose level in diabetic rats, lead to an increase of catalase (CAT) and superoxide dismutase (SOD), whose activities used to be decreased by diabetic conditions [61]. Similarly, *Calotropis procera* extracts, in addition to reducing blood glucose and increasing hepatic glycogen content, also lead to an increased hepatic level of glutathione, the level of endogenous antioxidants, SOD and CAT in diabetic rats [62].

The involvement of glutathione and glutathione-related enzymes was suggested as the mechanism of action of natural antioxidant compounds [85]. Recent studies suggested that there are consistent structure–function relationships that affect bioavailability, antioxidant capacity, and the ability to induce antioxidant/detoxifying enzymes [86–88].

Flavonoids probably also function in reducing glucose levels in diabetic animals, as suggested by the case of *Artemisia judaica*, known to be a rich source of flavonoids and very effective in reducing blood glucose levels in experimentally diabetic rats [27]. Diabetic rats treated with extracts of *T. polium*, known to contain terpenoids and flavonoids that possess hypoglycemic effects, showed changes in various biochemical parameters related to diabetes apart from a reduced glucose level, such as serum nitric oxide (NO), pancreatic malondialdehyde (MDA), protein carbonyl content (PCO), and advanced oxidation carbonyl products (AOPP) levels [44]. The hypoglycemic activity of *C. iphionoides* Boiss is accompanied by radical-scavenging activity, suggesting that reducing radical levels contribute to better blood sugar levels [52].

The improvement of diabetes parameters by plant extracts is associated with an improvement in the lipid state, as hyperlipidemia and the oxidised forms of glycated lipids enhance insulin resistance. For example, treatment of diabetic rats with extracts of *C. procera* not only improved sugar levels in the treated diabetic animals [62,63], but also reduced total cholesterol, phospholipids, low-density (LDL) and very low-density lipoprotein (VLDL), and increased the levels of high-density lipoprotein (HDL). Extract of *A. herba-alba* produced significant hypoglycemic activity in rabbits associated with reducing triglyceride, total cholesterol, and serum insulin concentrations. In term of mechanism, it prevented the elevation of glycosylated hemoglobin levels. Preclinical studies with patients with diabetes mellitus showed that treatment with *A. herba-alba* extract caused considerable lowering of elevated blood sugar and remission of diabetic symptoms [30,34,35].

Several studies presented in this review pointed to the possible mode of action of the plant extract or its active moiety. For example, *Z. spina-christi* extract contains antidiabetes activity in the form of its principal saponin glycoside christinin-A. Apart from reducing serum glucose levels, liver phosphorylase, glucose-6-phosphatase (G-6-pase) activities, and elevated blood lactate, it significantly increased serum pyruvate levels, liver glycogen content, serum insulin, C-peptide levels, and pancreatic cyclic adenosine monophosphate (cAMP) levels in diabetic rats [47,48]. The hypoglycemic activity of *C. iphionoides* Boiss extract in diabetic rats can be attributed to its direct effect on insulin secretion from β cells, glucose uptake by adipocytes, and skeletal myotubes [52]. Intravenous injection of *R. raetam* extract, apart from leading to decreased blood glucose levels in diabetic rats, also inhibited renal glucose reabsorption [57], and the administration of an ethanol/water extract of the aerial part of *C. sinaica* improved renal glycogen content in rat models [74]. One of the complications in diabetes patients is deterioration in renal function; identification of plant materials that will inhibit/delay such complications is very important.

It is important to mention that some of the plant extracts reviewed here were used traditionally by local communities in the desert and were found to be effective in the treatment of diabetes symptoms in human patients. Arab and Bedouin communities use herbal tea made of *C. spinosa* to treat patients with diabetes, and this tradition can be supported by the results of the experiment that showed that diabetic rats that consumed aqueous extract of the fruit of *C. spinosa* presented reduced glucose levels in the blood. Interestingly, herbal tea prepared from the leaves of *A. halimus* is used in folk medicine by Bedouins of the desert in Israel for treating diabetes [70,71]. Treatment of an animal model for diabetes and obesity with *A. halimus* extract showed a significant hypoglycemic effect with no decrease in appetite, supporting the beneficial ethnic use of this plant against diabetes in human patients.

We suggest to perform preclinical studies with patients with diabetes with several of the above-mentioned plants.

In summary, the ever increasing prevalence of the two types of diabetics in Western society could be attributed to environmental factors and to lifestyle. Thus, targeting both, meaning adopting the prevention approach, seems to be the preferred approach to cope with the problem. Current research of diabetes, as also clearly reflected in this review, focuses mainly on curing the disease.

The use of extracts of plant sources, and particularly those derived from desert and steppic plants, to treat patients with diabetes, has been shown to achieve a positive outcome. However, little efforts have as yet been directed to exploring toxicity and side effects in desert and steppic plants. Also little work was performed to investigate the action of isolated pure bioactive components derived from these plants, comparing their therapeutic activity, toxicity, and side effects to those of the crude extracts from which they were derived. Not much effort has yet been directed to clinical studies of these plants.

Owing to the accumulated traditional knowledge, desert and steppic plants used from time immemorial to prevent and cure diabetes are natural candidates for in-depth exploration. Prominent candidates mentioned in this review are *A. judaica, A. herba-alba, Z. spina-christi, C. iphionoides, T. polium*, and *C. spinosa* (particularly the evergreen var. *aravensis* growing on arid lands in the southern part of Israel, Jordan, and the Sinai desert). However, we also suggest other plants, not known to be of traditional use but still found to exhibit positive results in the laboratory, as candidates for in-depth exploration. Investigating the therapeutic effects of extract mixtures derived from several plants, each known to be endowed with antidiabetic properties, may become an interesting challenge too.

Supporting information

High-resolution pictures of some Judean Desert plants used in ethnic anti-diabetes medicine and in diabetes research are available as Supporting Information.

Conflict of Interest

▼

The authors have no conflicts of interest.

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