A systematic review of Iranian medicinal plants useful in diabetes mellitus

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Abstract

Introduction: This review focuses on the efficacy and safety of Iranian medicinal plants found effective in the management of diabetes in humans and animals.
Material and methods: EMBASE, Scopus, PubMed, Web of Science, Google Scholar, and IranMedex databases were searched up to 8 October 2007. The search terms were "diabetes" and "plant", "herb", "traditional", and "natural" or "herbal medicine", limited to Iran. All of the human studies were included. Animal studies with the outcome of blood glucose or serum lipids, antioxidant effect, changes in hepatic enzymes, anti-inflammatory effect, or vascular activity in diabetes were included. Studies performed on cell lines, reviews and letters to editors were excluded. Blood glucose and serum lipids were the key outcomes.
Results: Twelve human studies were reviewed for efficacy of plants. These studies showed significant decrease in blood glucose after treatment with *Citrullus colocynthus* L., *Silybum marianum, Psyllium, Teucrium polium*, and Pomegranate. Thirty-one animal studies were included showing Walnut leaf, Coriander, Pomegranate, Garlic, *Satureja khuzestanica, Phlomis anisodonta, Trigonella foenum graecum*, Olive (*Olea europaea* L.), *Capsicum frutescens, Achillea santolina, Aloe vera, Salvia officinalis, Anathum graveolens, Teucrium polium, Urtica dioica, Morus nigra, Morus alba, Salvia lenifolia* benth leaf, and *Cynara scolymus* to be significantly effective in reduction of blood glucose.
Discussion: The present review indicates that some of these plants (*Citrullus colocynthus*, *Silybum marianum, Psyllium, Teucrium polium*, and Pomegranate) improve blood hyperglycemia in humans somewhat more effectively than standard chemical drugs used in diabetes. Some of these plants (Garlic, *Silybum marianum*, *Psyllium*, *Teucrium polium*, and Pomegranate) were found to have anti-hyperlipidaemic properties and thus can be supplemented in diabetes.
Conclusions: Special attention to these effective medicinal plants will lead us to obtain novel drugs in the management of diabetes mellitus.

Key words: diabetes mellitus, plant, herb, traditional, natural medicine, herbal medicine, Iran.

Introduction

The term diabetes mellitus describes several diseases of abnormal carbohydrate metabolism that are characterized by hyperglycaemia. It is associated with a relative or absolute impairment in insulin secretion, along with varying degrees of peripheral resistance to the action of insulin. Today about 2 565 500 people, equal to 6% of the population in the age group of 20-79 years, are suffering from diabetes mellitus in Iran; its prevalence is increasing as in other developing countries and is expected to reach 5 114 900 in 2025 [1].

For a very long time, plants have played an important role in the treatment of many diseases, especially in Eastern countries. The use of plants for treatment of diabetes has been common in the Iranian population too. These natural compounds are used by traditional herbalists for the management of diabetes in several parts of Iran [2]. There are enough reports on the positive effects of herbal medicines in the management of diabetes [3-45]. However, available herbal products have no clear statement of content or medically related information on the package labels, and they have not been validated or certified.

For various reasons, in recent years the popularity of alternative medicine has increased. Surveys conducted in Australia and the U.S. indicate that almost 48.5 and 34% of respondents respectively had used at least one form of unconventional therapy, including herbal medicine. The WHO has also recommended evaluation of effective plants for conditions such as diabetes for which there are few safe modern drugs [46]. This leads to increasing demand for herbal products with anti-diabetic activity and fewer side effects.

At the time being, some herbal preparations are used by diabetic patients in Iran, especially among unsuccessfully treated patients and those who are candidates for insulin therapy [2]. Most studies published in Iran have shown a statistically significant decrease in blood glucose but no there are no collective data and no systematic review has been performed yet.

This is the first review that focuses on the efficacy and safety of Iranian medicinal plants in the management of diabetes.

Material and methods

The data sources EMBASE, Scopus, PubMed, Web of Science, Google Scholar, and IranMedex databases were searched up to 8th October 2007 for studies investigating medicinal plants in prevention and treatment of diabetes. The search terms were "diabetes" and "plant", "herb", "traditional", and "natural" or "herbal medicine", limited to Iran. The reference lists of articles were also reviewed for additional relevant studies.

Study selection

Inclusion criteria

All of the human studies with the key outcome of change in blood glucose or serum lipids in diabetic patients were included. Animal studies with the outcome of change in blood glucose, serum lipids, antioxidant parameters, hepatic enzymes, anti-inflammation, and vascular activity were also included.

Exclusion criteria

In vitro studies, review articles and letters to the editor were excluded. Unpublished data such as theses were not included. Studies published from countries other than Iran were excluded too. Two reviewers independently examined the title and abstract and references of each article to eliminate duplications, those published from countries other than Iran, and in vitro studies. The reviewers independently extracted data on the medicinal plant, dose, trial duration, sample size, outcome, results, and side effects.

Results

Human studies

Of publications identified in the initial database search, 12 trials on the efficacy of medicinal plants in diabetic patients were reviewed. Information from these clinical trials are summarized in Table I.

Blood glucose

The key outcome for anti-diabetic effects was reduction in blood glucose. These human studies showed a significant decrease in blood glucose after treatment with *Citrullus colocynthus* L., *Silybum marianum*, *Psyllium*, *Teucrium polium*, and Pomegranate [4, 6-12]. *Securigera securidaca* (1500 mg/day) had no benefit on improving glycaemic profile in type 2 diabetic patients [3]. *Salvia leriifolia* and *Morus nigra* had no hypoglycaemic effect but neuropathy and polyphagia became better during administration of the extracts [13, 14].

Serum lipids

Another key outcome in diabetes was reduction in serum lipids. In a before-after clinical trial, Garlic tablets significantly decreased total and LDL cholesterol levels in diabetic patients with hyperlipidaemia [5]. Improvement in lipid profile was shown by other medicinal plants including *Silybum marianum*, *Psyllium*, *Teucrium polium*, and Pomegranate [6-10, 12].

Side effects

The use of *Securigera securidaca* in the dose of 1500 mg in divided doses showed no gastrointestinal symptoms or liver and kidney abnormalities during two months of therapy [3]. Ten percent of patients treated with *Citrullus colocynthis* L. in the dose of 300 mg in three divided doses complained of mild diarrhoea [4]. No side effects were recorded with *Psyllium* (10 g/day) and an even better response to metformin was found [7, 9]. No adverse effects were reported for chronic use of *Silybum marianum* [6].

Animal studies

The details of the animal studies that investigated Iranian medicinal plants in animal diabetic models are summarized in Table II.

Table I. Human studies considering effects of plants in diabetes

Authors (year) [references]	Study	Target	Plant (scientific name)	Duration	Dose	Number (case/control)	Outcome
Fallah-Hoseini et al. (2006) [3]	RCT	DM2	*Securigera securidaca*	2 m	1500 mg/day + + standard therapy	35/35	no significant difference in blood glucose, HbA_{1c} and lipids between two groups
Fallah-Hoseini et al. (2006) [4]	RCT	DM2	*Citrullus colocynthis* L.	2 m	300 mg/day + + standard therapy	25/25	↓ blood glucose, ↓ HbA_{1c}, lipids → no change
Parastuei et al. (2006) [55]	before- -after clinical trail	DM2, hyper- lipidaemia*	Garlic tablet	6 w	900 mg/day	50	↓ blood glucose → no change, ↓ cholesterol, ↓ LDL, ↑ HDL, ↓ blood pressure
Fallah-Hoseini et al. (2006) [6]	RCT	DM2	*Silybum marianum*	4 m	600 mg/day + + standard therapy	25/26	↓ blood glucose, ↓ HbA_{1c}, ↓ cholesterol, ↓ TG, ↓ SGOT, ↓ SGPT
Ziai et al. (2005) [7]	RCT double-blind	DM2	*Psyllium*	8 w	10.2 g/day	27/22	↓ fasting blood glucose, ↓ HbA_{1c}, ↑ HDL
Esmailzadeh et al. (2004) [8]	before- -after	DM, hyperTG**, hypercho- lesterolaemia	Pomegranate juice	8 w	40 g/day	22	↓ cholesterol, ↓ LDL
Ziai et al. (2004) [9]	RCT double- -blind	DM2	*Psyllium*	8 w	10 g/day + + standard therapy	27/22	↓ fasting blood glucose, ↓ HbA_{1c}, ↑ HDL
Fallah-Hoseini et al. (2004) [10]	RCT	DM2, hyperli- pidaemia	*Silybum morianum*	4 m	600 mg + + standard therapy	29/25	↓ fasting blood glucose, ↓ LDL, ↓ cholesterol, ↓ TG, ↓ SGOT, ↓ SGPT
Fallah-Hoseini et al. (2006) [11]	RCT	DM2	*Citrullus colocynthis* L.	2 m	300 mg/day	22/22	↓ blood glucose, ↓ HbA_{1c}, glutathione, catalase, malondialdehyde and superoxidase dehydro- genase did not change
Karimi et al. (2000) [12]	comparison with gliben- clamide	DM2	*Teucrium polium*	6 w	125 mg/kg	24/19	↓ HbA_{1c} in both groups, ↓ cholesterol,↓ TG, ↓ body mass index only in plant group
Hosseinzadeh et al. (2001) [13]	crossover clinical trial	DM	*Salvia leriifolia*	1 w	5, 10, 20% decoction extract	10 patients in each group	no significant change in blood glucose in comparison to glibencla- mide but neuropathy and polyphagia improved
Khazaei et al. (2002) [14]	crossover clinical trial	DM	*Morus nigra* leaf	1 w	5, 10, 15% decoction extract	10 patients in each group	no significant change in blood glucose in comparison to gliben- clamide but neuropathy and diabetic symptoms improved

** cholesterol >220 mg/dl, ** cholesterol >5.2 mmol/l, triglyceride (TG) >2.3 mmol/l*
RCT – randomized control trial, DM – diabetes mellitus, m – month, w – week, d – day, ↓ – significant decrease, ↑ – significant increase, HDL – high density lipoprotein, LDL – low density lipoprotein, HbA_{1c} – hemoglobin 1c, SGOT – serum glutamic oxaloacetic transaminase, SGPT – serum glutamic pyruvic transaminase

Blood glucose

The key outcome for anti-diabetic drugs in animal studies was reduction in blood glucose. These animal studies showed that Walnut leaf, coriander, Pomegranate, Garlic, *Satureja khuzestanica*, *Phlomis anisodonta*, *Trigonella foenum graecum*, olive (*Olea europaea* L.), *Capsicum frutescens*, *Achillea santolina*, *Aloe vera*, *Salvia officinalis*, *Anathum graveolens*, *Teucrium polium*, *Urtica dioica*, *Morus nigra*, *Morus alba*, *Salvia lenifolia* benth leaf, and *Cynara scolymus* improve blood glucose of diabetic animals.

Table II. Animal studies considering effects of plants in diabetes

Authors (year) [references]	Target	Scientific name	Dose/day	Duration	Other groups	Effect
Jelodar et al. (2007) [15]	alloxan-induced diabetic rats	*Walnut leaf*, *Coriander*, *Pomegranate*	60 g/kg	15 d	no treatment diabetic rats	↓ blood glucose, ↑ B-cells and percent of islets size
Eidi et al. (2006) [16]	STZ-induced diabetic rats	*Trigonella foeum graecum*	0.1-0.25-0.5 g/kg	14 d	healthy and glibenclamide-treated diabetic rats	decreased SGOT and SGPT in diabetic rats but not in healthy rats
Jelodar et al. (2005) [17]	alloxan-induced diabetic rats	*Fenugreek*, *Onion*, and *Garlic*	12.5%/w	15 d	healthy and untreated diabetic rats	only Garlic: ↓ blood glucose and ↑ B-cells mass
Abdolahi et al. (2003) [18]	STZ-induced diabetic and diet-induced hyperlipidaemic rats	*Satureja khuzestanica*	500-1000 ppm/oral	15 d	healthy rats	↓ blood glucose, ↓ TG, stimulatory effect on reproduction
Sarkhail et al. (2007) [19]	STZ-induced diabetic rats	*Phlomis anisodonta*	100-200-400 mg/kg/oral	10 d	untreated diabetic rats	↓ fasting blood glucose, ↑ insulin, prevented weight loss, ↑hepatic antioxidant enzymes
Roghani et al. (2006) [20]	STZ-induced diabetic rats	*Trigonella feonum graelum*	200 mg/kg/ip	2 m	healthy and diabetic rats without treatment	enhanced vascular activity
Roghani et al. (2006) [21]	STZ-induced diabetic rats	*Quercetin*	0.1 μM	8 w	healthy and diabetic rats without treatment	dose-dependent vasorelaxation in aortic ring
Morshedi et al. (2006) [22]	STZ-induced diabetic rats	*Kombuchatia*	25-50-75-100% solution	15 d	healthy and diabetic rats without treatment	↑ weight in test groups in comparison to control groups that had significant weight loss
Zahedi et al. (2006) [23]	STZ-induced diabetic rats	*Trigonella foenum graecum*	–	3 d	untreated diabetic and insulin-treated	↓ blood glucose, ↓ water intake, ↑ liver glycogen
Eidi et al. (2004) [24]	STZ-induced diabetic rats	*Olive* (*Olea europaea* L.)	0.1-0.25-0.5 g/kg/oral	14 d	healthy and glibenclamide-treated diabetic rats	↓ blood glucose, ↑ insulin, hypoglycaemic effect was greater than glibenclamide
Roghani et al. (2004) [25]	STZ-induced diabetic rats	*Capsicum frutescens*	ratio of 1/15 food/oral	4 w	healthy and pepper-treated healthy rats and untreated diabetic rats	↓ blood glucose in 2 w, ↓ TG in 4 w, no change in cholesterol
Yazdanparast et al. (2007) [26]	STZ-induced diabetic rats	*Achillea santolina*	0.1 g/kg/oral	30 d	untreated diabetic rats	↓ blood glucose, ↓ serum NO, ↓ malondialdehyde, ↓ protein carbonyl, ↓ advanced oxidation protein products
Eidi et al. (2005) [27]	STZ-induced diabetic rats	*Garlic* (*Allium sativum* L.)	0.1-0.25-0.5 g/kg/oral	14 d	healthy and glibenclamide-treated diabetic rats	↓ blood glucose, ↓ cholesterol, ↓ TG, ↑ insulin, Garlic was more effective than glibenclamide
Jadidoleslami et al. (2006) [28]	STZ-induced diabetic rats	*Aloe vera*	100-200-300-400 mg/kg	4 w	healthy and glibenclamide-treated diabetic rats	↓ blood glucose in 400 mg/kg, ↓ cholesterol, ↓ TG, ↓ LDL in all dose groups, HDL unchanged

Table II. Animal studies considering effects of plants in diabetes – cont.

Authors (year) [references]	Target	Scientific name	Dose/day	Duration	Other groups	Effect
Afshari et al. (2006) [29]	STZ-induced diabetic rats	*Ginger*	5% in food	8 w	healthy and untreated diabetic rats	↓ lipid peroxidation, ↑ antioxidant activity
Reza et al. (2006) [30]	hypercholesterolaemic male rats	*Persian Walnut*	5% (1 g oil/g weight) 7.5% (1.5 g oil/g weight) 10% (2 g oil/g weight)	8 w	untreated diabetic rats	↓ TG (14%), ↓ LDL (11%), ↓ VLDL (12%)
Fatehi et al. (2005) [31]	STZ-induced diabetic rats, cotton pellets-induced inflammation	*Ginger root* (*Zingiber officinale*)	100-200-400 mg/100 ml water	4 d	placebo-treated and indomethacin group	anti-inflammatory effect of ginger was less than indomethacin
Eidi et al. (2005) [32]	STZ-induced diabetic rats	*Salvia officinalis* L.	0.042-0.125-0.2-0.4 ml/kg/oil/ip	1-3-5 h	healthy and placebo treated	↓ blood glucose in 3 h but no effect on insulin
Madani et al. (2005) [33]	alloxan-induced diabetic rats	*Anathum graveolens*	300 mg/kg/ip	48 h	healthy and untreated diabetic rats	↓ blood glucose, ↓ cholesterol, ↓ TG, ↓ LDL, ↓ VLDL, ↑ HDL
Yazdanpanat et al. (2005) [34]	STZ-induced diabetic rats	*Teucrium polium*	–	6 w	untreated diabetic rats	↓ blood glucose 64%, ↓ bilirubin 35%, ↓ SGOT 48%, ↓ SGPT 30%, ↑ serum insulin 160%
Baluchnejad et al. (2003) [35]	STZ-induced diabetic rats	*Garlic*	100 mg/kg/day	8 w	–	prevention of abnormal thoracic aorta contractility
Farzami et al. (2003) [36]	STZ-induced diabetic rats	*Urtica dioica leave*	–	30-120 min	healthy	↓ glucose, ↑ insulin
Hosseinzadeh et al. (2002) [37]	alloxan-induced diabetic mice	*Securigera securidaca*	–	–	healthy and glibenclamide treated	↓ glucose in a mechanism different from that of glibenclamide
Hosseinzadeh et al. (1999) [38]	alloxan-induced diabetic mice	*Morus nigra*, *Morus alba*	500 g/kg	7 d	healthy and glucose-induced hyperglycaemia	↓ blood glucose
Shahraki et al. (2007) [39]	STZ-induced diabetic rats	*Teucrium polium*	50 mg/kg	30 d	untreated diabetic rats	↓ blood glucose but ↑ TG, ↑ cholesterol, ↑ LDL, ↑ SGOT, ↑ SGPT
Saeb et al. (1994) [40]	alloxan-induced diabetic rats	*Coriander*, *Walnut*, *Fenugreek*, *Garlic*, *Celery*, *Coriander seed*, *Lemon*, *Madder*, *Pomegranate*, *Carrot*, *Onion*, *Fumotory*	–	15 d	–	no significant difference in CPK and arginase observed among the negative, positive and experimental groups
Hosseinzadeh et al. (1998) [41]	alloxan-induced diabetic rats	*Salvia lenifolia benth* leaf and seed	2 g/kg	–	healthy	↓ blood glucose by leaf extract

Table II. Animal studies considering effects of plants in diabetes – cont.

Authors (year) [references]	Target	Scientific name	Dose/day	Duration	Other groups	Effect
Chandra et al. (2004) [42]	type I diabetic rats	Garlic (*Allium sativum*), Neem (*Azadirachta indica*), Tulsi (*Ocimum sanctum*), Bitter gourd (*Momordica charantia*)	–	–	healthy and insulin-treated diabetic rats and glibenclamide treated	↓ blood glucose, ↑ antioxidant enzymes, ↑ metal ions
Arzi et al. (2001) [43]	STZ-induced diabetic rats	*Morus alba*	150-200-300-350 mg/kg	maximum (blood glucose in 75 min)	healthy and glibenclamide-treated diabetic rats	↓ blood glucose in normal and treated rats but not in glibenclamide group
Roghani et al. (2004) [44]	STZ-induced diabetic rats	*Artemisia dracunculus* (Tarragon)	6.25% in food	1 m	healthy and untreated diabetic rats	no decrease in blood glucose, ↓ TG by tarragon
Mahmoodabadi et al. (2006) [45]	alloxan-induced diabetic rats	*Cynara scolymus*	300 mg/kg	48 h	placebo and alloxan-induced diabetic rats and glibenclamide-treated	↓ blood glucose, ↓ cholesterol, ↓ TG, ↓ LDL, ↓ VLDL, ↑ HDL as compared to placebo

** m – month, w – week, d – day, ↓ – significant decrease, ↑ – significant increase, HDL – high density lipoprotein, LDL – low density lipoprotein, TG – triglycerides, VLDL – very low density lipoprotein, SGOT – serum glutamic oxaloacetic transaminase, SGPT – serum glutamic pyruvic transaminase*

Serum lipids

Improvement in lipid profile was shown by some medicinal plants including *Satureja khuzestanica*, *Capsicum frutescens*, Garlic, *Aloe vera*, *Anathum graveolens*, *Persian Walnut*, tarragon, and *Cynara scolymus*. In one study, *Teucrium polium* in a dose of 50 mg/kg increased blood lipid levels [39].

Discussion

In Iran, there are multiple plants that are unofficially taken by diabetic patients [2]. The present data show that some of these plants (*Citrullus colocynthus* L., *Silybum marianum*, *Psyllium*, *Teucrium polium*, and Pomegranate) are really effective in reducing blood glucose in diabetic patients [4, 6-12]. Animal studies have also shown that some natural plants are even more effective than currently used chemical drugs in diabetic animals [24, 27]. Special attention to these natural compounds seems necessary to search for novel therapeutic agents. Some of these plants have shown a significant hypoglycaemic effect in animals but not in humans (e.g. Garlic, *Salvia leriifolia*, *Morus nigra*, and *Securigera securidaca*) [3, 5, 13, 14, 17, 27, 35, 37, 41]. This controversy seems to be due to inappropriately designed clinical trials; it thus remains to be elucidated by further examinations in diabetic patients.

It is notable that the hypoglycaemic effect of these herbal medicines can interfere with hypoglycaemic drugs and insulin, which are standard treatments for diabetic patients. Most physicians advise their patients to avoid herbal medicine, but in some cases the diabetic patients take it without informing their physicians [2]. This type of herbal therapy may lead to drug interaction or false and unstable blood glucose level monitoring [2]. Therefore, physicians should have adequate knowledge about herbal medicines effective in blood glucose to be prepared how to manage patients who are at risk. Any consumption of medicinal plants must be under the supervision of physicians.

Some of these plants (Garlic, *Silybum marianum*, *Psyllium*, *Teucrium polium*, and Pomegranate) had anti-hyperlipidaemic properties and this reduction in serum lipids was statistically significant. Of course there were two controversial reports about *Teucrium polium* affecting blood lipid profile [12, 39], which needs to be proved by further studies. The medicinal plants with lipid-lowering potential can better be supplemented to standard therapy of diabetic patients. Investigation of other clinical trials in different parts of the world can help us to recommend a proper dose for diabetic patients. For some of these plants (Garlic and Pomegranate), proper randomized controlled trials are needed show their benefit in diabetic patients.

Induction of insulin release is the mechanism of action for some medicinal plants, including *Phlomis* *anisodonta*, olive (*Olea europaea* L.), Garlic, *Teucrium polium*, and *Urtica dioica* [19, 24, 27, 34, 36]. In addition, density of islets in pancreatic tissue, percent of beta cells and islets size increased significantly in rats treated with Walnut leaf and Garlic [15, 17].

It has been suggested that enhanced production of free radicals and oxidative stress are central events to the development of diabetic complications. Use of antioxidants reduces oxidative stress and alleviates diabetic complications [47]. Most of the tested medicinal plants (e.g. *Achillea santolina*, *Phlomis anisodonta*, ginger) have shown antioxidant effects [19, 26, 29]. Further studies in diabetic animal models and also diabetic patients should be better focused on those Iranian herbal medicines that have been found to have adequate antioxidant effects in humans and some tested in disease models other than diabetes [48-60].

In conclusion, any consumption of medicinal plants must be under the supervision of physicians. Some natural plants are more effective than currently used chemical drugs in diabetic patients [24, 27]. Special attention to these natural compounds would open a new approach for novel therapeutic agents.

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