Antidiabetic Plants of Iran

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Abstract- To identify the antidiabetic plants of Iran, a systematic review of the published literature on the efficacy of Iranian medicinal plant for glucose control in patients with type 2 diabetes mellitus was conducted. We performed an electronic literature search of MEDLINE, Science Direct, Scopus, Proquest, Ebsco, Googlescholar, SID, Cochrane Library Database, from 1966 up to June 2010. The search terms were complementary and alternative medicine (CAM), diabetes mellitus, plant (herb), Iran, patient, glycemic control, clinical trial, RCT, natural or herbal medicine, hypoglycemic plants, and individual herb names from popular sources, or combination of these key words. Available Randomized Controlled Trials (RCT) published in English or Persian language examined effects of an herb (limited to Iran) on glycemic indexes in type 2 diabetic patients were included. Among all of the articles identified in the initial database search, 23 trials were RCT, examining herbs as potential therapy for type 2 diabetes mellitus. The key outcome for antidiabetic effect was changes in blood glucose or HbA_1 c, as well as improves in insulin sensitivity or resistance. Available data suggest that several antidiabetic plants of Iran need further study. Among the RCT studies, the best evidence in glycemic control was found in *Citrullus colocynthus, Ipomoea betatas, Silybum marianum* and *Trigonella foenum graecum*.

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Introduction

Diabetes is a serious global health issue, with type 2 diabetes mellitus (T2DM) accounting for approximately 90–95% of all cases (1). The recent rapid increase in the prevalence of T2DM is in part due to an ageing population but may also be attributed to an increase in the number of overweight and obese people.

The prevalence of T2DM ranges from 1.2% to 14.6% in Asia, 4.6% to 40% in the Middle East, and 1.3% to 14.5 % in Iran (2). The Middle East is expected to bear one of the world's greatest increases in the absolute burden of diabetes in the coming decades (3). Most of this increase is anticipated to affect the economically productive 45- to 64-year-old age segment in contrast with most developed countries, where the increase in diabetic patients will occur in those aged < 65 years (4).

Patients with T2DM are often required to undertake significant lifestyle and dietary changes in addition to prescription antidiabetes drug therapy (5). Inadequacies in current treatments for diabetes have led 2 to 3.6 million Americans to use complementary and alternative medicine (CAM) for diabetes treatment. Among different methods of CAM therapy, Most of the literature has focused on herbs or other dietary supplements. To date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these have received scientific and medical evaluation to assess their efficacy. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of T2DM (6).

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 (7).

There are some reviews that examined plants with hypoglycemic activity in humans, including clinical trials. Additionally, there have been several qualitative reviews reporting on selected supplements used in diabetes (8-16). Two prior reviews by Ernst *et al*. examined plants with hypoglycemic activity in human, including 5 RCTs (17,18). The most recent systematic review of Iranian plants for glycemic control by Hasani-

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Ranjbar *et al*. focused on Iranian medicinal plants found effective in diabetes in humans and animals. All of these studies were performed in Iran (19). Another systematic review of herbs for glycemic control by Yeh *et al.*, examined clinical studies that used human participant from database inception to May 2002 (20). To the best of our knowledge, there have been no comprehensive systematic review incorporating Iranian medicinal plants (some of these plants may grow in Iran and also in other countries), for glucose control among patients with T2DM. Our objective was to review and summarize the RCT studies (which may perform in Iran or other countries) on medicinal herbs of Iran for use in diabetes, to provide recommendations for future research and then propose guidelines that may aid practitioners in advising their patients.

Materials and Methods

We searched Medline, ScienceDirect, EMBASE, Scopus, ProQuest, Ebsco, Googlescholar, Cochrane Library Database since 1966 up to June 2010 using CAM, diabetes mellitus , plant (herb), Iran , patient, glycemic control, clinical trial, RCT, natural or herbal medicine, hypoglycemic plants, and individual herb names from popular sources, as keywords or combination of them. In addition, experts in the field were contacted to select studies that meet the criteria, and we also looked up references of key articles. We limited studies to those articles published in English or Persian and restricted our search to herbs (Iranian plants) in the basis of herbal books (21-23) for changes in glycemic indexes. We excluded trials that primarily examined diabetic complications such as neuropathy, nephropathy, or retinopathy. Studies in subjects with impaired glucose tolerance or those specifically at risk for diabetes (e.g., older, sedentary, obese individuals with a family history of diabetes and healthy individuals) were also excluded. Non-controlled, non-randomized, before-after trials, unpublished data, studies on type 1 diabetic patients and herbal component were excluded. All selected articles were studied by two reviewers to examine inclusion criteria and data extraction, including common and scientific names of herbs, study design, duration, sample size, control and outcome.

Results

From all of publications identified in the initial database search, 23 trials were Randomized Controlled Trial (RCT), examined herbs as potential therapy for type 2 diabetes mellitus. Most trials examined herbs as an adjunct to conventional treatment with diet and /or medication. 18 (78%) out of these 23 RCTs, have positive effect on diabetic patients. The most common outcome measures encountered in these studies were fasting and postprandial blood glucose, HbA_1 c, and insulin resistance or sensitivity. The present data show that some of these plants included *Cittrullus colocynthus, Silybum marianum, Ipomoea betatas* and Fenugreek are really effective in reducing blood glucose (24-33) in diabetic patients (All of the controlled clinical trials suggested efficacy of these plants). Information from these clinical trials is summarized in table 1.

Table 1. RCT studies of herbs for glycemic control

Herb	Reference	Design	sample	intervention	control	Duration	Outcome
Amygdalus L. (Almond)	Lovejoy J C. *et al*. (2002)(34)	Randomized, double blind, cross over	30 T 2D	HFA or LFA(containing 75-113g almond/day)*	HFC or LFC(without almond)*	4 weeks	No sig. changes in FBG &HbA1C
Amygdalus L. (Almond)	Li S C. *et al.* (2010)(35)	Randomized, cross over	20 T2D	Almond diet (60 g/day)	Control diet(National cholesterol Education program step 2)	4 weeks	Sig. Lower level of FBG& fasting insulin &insulin resistance
Allium sativum(Garlic)	Stiprija S *et al.* (1987)(36)	Double-blind,2 parallel groups	33 T2D, diet alone	Garlic:700 mg/d (preparation unspecified);	Placebo	4 weeks	No change in FBG, PPG, insulin
Citrullus colocynthis	Fallah-Hoseini H. *et al.* (2006)(24)	Randomized, placebo control.	50T2D	300 mg/day + antidiabetic drugs.	Placebo+ antidiabetic drugs	2 months	Sig. decrease FBG& HbA1C

Citrullus colocynthis	Fallah-Hoseini H. *et al.* (2006)(25)	Randomized, placebo control.	44T2 D	300 mg Citrullus/day	placebo	2 months	Sig. decrease FBG& HbA1C
Citrullus colocynthis	Fallah-Hoseini H. *et al.* (2009)(26)	Randomized, double blind, placebo control	50 T2D ,on standard antidiabetic therapy	100mg /TDS fruit capsules	placebo	2 months	Sig. decrease HbA_1c & FBG
Cuminum cyminum(cumin)	Andallu B. *et al.* (2007)(37)	Randomized, controlled.	20 T2D	5 g Cumin seed powder/day	antidiabetic drugs	60 days	Sig. decrease FBG
Ginkgo biloba	Kudolo G B. *et al.* (2006)(38)	Randomized, double blind, placebo control, cross over	8 T2D	120 mg Ginkgo extract /day	placebo	3 months	No sig. change in insulin resistance
Ipomoea betatas	Ludvik B H. *et al.* (2002)(27)	Randomized, placebo control	18 T2D on diet	2, 4 g/day (LD&HD)	Placebo	6 weeks	Improve insulin sensitivity, sig decrease FBG with HD Caiapo.
Ipomoea betatas	Ludvik B. *et al.* (2004)(28)	Randomized, placebo-control.	61 T2D on diet	4g /day	placebo	12 weeks	Sig. decrease HbA_1 c, FBG,PPG
Ocimum sanctum(Holy basil)	Agrawal P. *et al.* (1996)(39)	Single-blind: Crossover	40 T2D on diet and/or OHA	Ocimum album fresh leaf; 2.5g powder	Fresh spinach leaf powder	4 weeks	Decrease FBG, PPG.urine glucose
Opuntia streptacantha)	Frati AC. *et al.* (1990)(40)	Open-label: Crossover	14 T2D on diet and/or OHA	opuntia stems; 500 g	400 ml H_2o	Single dose	Decrease glucose, insulin
Plantago ovata(Psyllium)	Ziai S A. *et al.* (2005)(41)	Randomized, double blind, placebo control.	49 T2D on diet and drug therapy	Psyllium husk fiber 5.1g/BD+ antidiabetic drugs	Placebo + antidiabetic drugs	8 weeks	Sig. decrease FBS, HA_1c
Satureja khuzistanica	Vosough-Ghanbari S. *et al.* (2010)(42)	Randomized, double blind, placebo control.	21 T2D	250mg dried leaves tablet/day	placebo	60 days	No change in blood glucose
Securigera Securidaca	Fallah huseini H *et al.* (2006)(43)	Randomized , double blind, placebo control.	70 T2D	1500mg /day + antidiabetic drugs	Placebo+ antidiabetic drugs	2 months	No sig. difference in blood glucose, HbA_1 c between groups
Silybum morianum(silymarin)	Fallah-Hoseini H. *et al.* (2004)(29)	Randomized, placebo control.	54 T2D	600 mg Silymarin /day+ antidiabetic drugs.	Placebo+ antidiabetic drugs.	4 months	Decrease FBG
Silybum marianum (Silymarin)	Fallah-Hoseini H. *et al.* (2006)(30)	Randomized, double blind, placebo control.	51 T2D	Silybum marianum seed extract 200mg/TDS+ antidiabetic drugs	Placebo + antidiabetic drugs	4 months	Sig. decrease HbA_1c & FBG between and within groups.
Silymarin (Milk thistle)	Velussi M. *et al.* (1997)(31)	Open-lable; 2 parallel groups	60 T2D with cirrhosis; diet and insulin	Silymarin, 600mg	No treatment	12 months	Decrease FBG, mean BG, HbA1c, fasting insulin, insulin requierment
Thea sinensis (green tea)	Fukino Y. *et al.* (2008)(44)	Randomized cross over	60 borderline T2D	Green tea extract powder containing 544mg of poly phenols	observation	2*2 months	Sig decrease HbA_1 c, No sig. change in FBG

Trigonella foenum graecum (Fenugreek)	Bawadi HA. *et al.* (2009)(32)	RCT	160 T_2D,	2.5 g FG seed, 5 g FG seed	placebo	Single dose	Sig. decrease PPG in 5g FG group
Trigonella foenum (Fenugreek)	Sharma RD. *et al.* (1990)(33)	Randomized Crossover	15 T2D on diet and OHA	Defatted fenugreek seed powder; 100 g/day in bread	No treatment	10 days	Decrease FBG, PPG, postprandial insulin
Trigonella foenum (Fenugreek)	Sharma RD. *et al.* (1990)(33)	Randomized Crossover	5 T2D on diet and OHA	Defatted fenugreek seed powder; 100 g/day in bread	No treatment	20 days	Decrease FBG, PPG, insulin
vaccinum arctostaphylos (Blueberry)	Abidov,M. *et al.* (2006)(45)	Randomized, placebo control	42 T2D	300mg/TDS+ antidiabetic drugs	Placebo + antidiabetic drug	4 weeks	Sig. decrease FBG

*HFA(high-fat, high-almond; 37% total fat, 10% from almonds), LFA(low-fat, high-almond; 25% total fat,10% from almond), HFC(high-fat control; 37% total fat, 10% from olive or canola oil), LFC(low f- fat control; 25%total fat, 10% from olive or canola oil.

T_2D - Type 2 Diabetes mellitus, Sig - significant (P value<0.05), OHA - oral hypoglycemic agents, FBG -fasting blood glucose, PPG- postprandial glucose, HbA1c- glycosylated hemoglobin, BG-blood glucose

Discussion

In Iran, there are multiple plants that are unofficially taken by diabetic patients (46). In this systematic review, 23 RCTs of antidiabetic plants (plants that grow in Iran and may also grow in other countries) were studied. Among these RCTs, 18 trials showed effectiveness of herbs on T2DM versus 5 trials which showed no significant effect of herbs in type 2 diabetic patients. The present data show that some of these plants including *Cittrullus colocynthus, Silybum marianum, Ipomoea betatas* and Fenugreek have effectiveness in reducing blood glucose. Previous review of Iranian plants (until 2008) only focuses on studies which were performed by Iranian investigators on Iranian plants (19). This study provides a list of RCT studies performed in Iran or other countries on Iranian medicinal plants with effects on glycemic indexes in type2 diabetic patients, although these are still insufficient to decide about hypoglycemic effects of herbs and we need more RCTs with greater sample size and then meta analysis of high quality RCTs of each herb. It is notable that the hypoglycemic effect of these herbal medicines can interfere with hypoglycemic drugs and insulin, which are standard treatments for diabetic patients, but in some cases these patients take it without informing their physicians. This type of herbal therapy may lead to drug interaction of false and unstable blood glucose level monitoring. Therefore, physicians should have adequate knowledge about hypoglycemic herbal medicines to be prepared how to manage patients who are at risk. Any consumption of medicinal plants must be under the supervision of physicians. There are many plants in traditional medicine of Iran which have been used for treatment of diabetes. In recent years, experimental works in rats and humans approved antidiabetic effect of some of these plants. Despite significant anti diabetic effects of some of medicinal plants reported in this literature, clinical studies did not continue to evaluate long term efficacy and safety of these plants, so there are still insufficient evidences to decide definitely about efficacy and safety of these herbal remedies and this review suggest investigators to continue RCT studies on Iranian herbs and herbal preparation which used as antidiabetic treatment in traditional medicine of Iran.

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