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, Google Scholar, 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 HbA1c, 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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Keywords: Diabetes mellitus; Plants; Iran; Randomized control trials

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-
Ranjarbar 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, HbA1c, and insulin resistance or sensitivity. The present data show that some of these plants included *Citrtullus colocynthus*, *Silybum marianum*, *Ipomoea betas* 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>
<thead>
<tr>
<th>Herb</th>
<th>Reference</th>
<th>Design</th>
<th>sample</th>
<th>intervention</th>
<th>control</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdalus L.</td>
<td>Lovejoy J C. et al. (2002)(34)</td>
<td>Randomized, double blind, cross over</td>
<td>30 T2D</td>
<td>HFA or LFA(containing 75-113g almond/day)*</td>
<td>HFC or LFC(without almond)*</td>
<td>4 weeks</td>
<td>No sig. changes in FBG &amp;HbA1C</td>
</tr>
<tr>
<td>(Almond)</td>
<td></td>
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<tr>
<td>Amygdalus L.</td>
<td>Li S C. et al. (2010)(35)</td>
<td>Randomized, cross over</td>
<td>20 T2D</td>
<td>Almond diet (60 g/day)</td>
<td>Control diet(National cholesterol Education program step 2)</td>
<td>4 weeks</td>
<td>Sig. Lower level of FBG&amp; fasting insulin &amp;insulin resistance</td>
</tr>
<tr>
<td>(Almond)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Allium sativum(Garlic)</td>
<td>Stiprija S et al. (1987)(36)</td>
<td>Double-blind.2 parallel groups</td>
<td>33 T2D</td>
<td>Garlic/700 mg/d (preparation unspecified);</td>
<td>Placebo</td>
<td>4 weeks</td>
<td>No change in FBG, PPG, insulin</td>
</tr>
<tr>
<td>Citrtullus colocynthis</td>
<td>Fallah-Hoseini H. et al. (2006)(24)</td>
<td>Randomized, placebo control.</td>
<td>50T2D</td>
<td>300 mg/day + antidiabetic drugs.</td>
<td>Placebo+ antidiabetic drugs</td>
<td>2 months</td>
<td>Sig. decrease FBG&amp; HbA1C</td>
</tr>
<tr>
<td><strong>Citrullus colocynthis</strong></td>
<td>Fallah-Hoseini H. et al. (2006)(25)</td>
<td>Randomized, placebo control</td>
<td>44T2 D</td>
<td>300 mg Citrullus/day</td>
<td>placebo</td>
<td>2 months</td>
<td>Sig. decrease FBG &amp; HbA1C</td>
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<tr>
<td><strong>Citrullus colocynthis</strong></td>
<td>Fallah-Hoseini H. et al. (2009)(26)</td>
<td>Randomized, double blind, placebo control</td>
<td>50 T2D on standard antidiabetic therapy</td>
<td>100mg /TDS fruit capsules</td>
<td>placebo</td>
<td>2 months</td>
<td>Sig. decrease HbA1c &amp; FBG</td>
</tr>
<tr>
<td><strong>Cuminum cyminum(cumin)</strong></td>
<td>Andallu B. et al. (2007)(37)</td>
<td>Randomized, controlled.</td>
<td>20 T2D</td>
<td>5 g Cumin seed powder/day</td>
<td>antidiabetic drugs</td>
<td>60 days</td>
<td>Sig. decrease FBG</td>
</tr>
<tr>
<td><strong>Ginkgo biloba</strong></td>
<td>Kudolo G B. et al. (2006)(38)</td>
<td>Randomized, double blind, placebo control</td>
<td>50 T2D on standard antidiabetic therapy</td>
<td>100mg /TDS fruit capsules</td>
<td>placebo</td>
<td>2 months</td>
<td>Sig. decrease HbA1c &amp; FBG</td>
</tr>
<tr>
<td><strong>Ipomoea betatas</strong></td>
<td>Ludvik B H. et al. (2002)(27)</td>
<td>Randomized, placebo control</td>
<td>18 T2D on diet</td>
<td>2, 4 g/day (LD&amp;HD)</td>
<td>Placebo</td>
<td>6 weeks</td>
<td>Improve insulin sensitivity, sig decrease FBG with HD Caiapo.</td>
</tr>
<tr>
<td><strong>Ipomoea betatas</strong></td>
<td>Ludvik B et al. (2004)(28)</td>
<td>Randomized, placebo-control.</td>
<td>61 T2D on diet</td>
<td>4g /day</td>
<td>placebo</td>
<td>12 weeks</td>
<td>Sig. decrease HbA1c, FBG,PPG</td>
</tr>
<tr>
<td><strong>Ocimum sanctum(Holy basil)</strong></td>
<td>Agrawal P. et al. (1996)(39)</td>
<td>Single-blind: Crossover</td>
<td>40 T2D on diet and/or OHA</td>
<td>Ocimum album fresh leaf; 2.5g powder</td>
<td>Fresh spinach leaf powder</td>
<td>4 weeks</td>
<td>Decrease FBG, PPG,urine glucose</td>
</tr>
<tr>
<td><strong>Opuntia streptacantha</strong></td>
<td>Frati AC. et al. (1990)(40)</td>
<td>Open-label: Crossover</td>
<td>14 T2D on diet and/or OHA</td>
<td>opuntia stems; 500 g</td>
<td>400 ml H2O Single dose</td>
<td>Decrease glucose, insulin</td>
<td></td>
</tr>
<tr>
<td><strong>Plantago ovata(Psyllium)</strong></td>
<td>Ziai S A. et al. (2005)(41)</td>
<td>Randomized, double blind, placebo control</td>
<td>49 T2D on diet and drug therapy</td>
<td>Psyllium husk fiber 5.1g/BD+ antidiabetic drugs</td>
<td>Placebo + antidiabetic drugs</td>
<td>8 weeks</td>
<td>Sig. decrease FBS, HbA,c</td>
</tr>
<tr>
<td><strong>Satureja khuzistanica</strong></td>
<td>Vosough-Ghanbari S. et al. (2010)(42)</td>
<td>Randomized, double blind, placebo control</td>
<td>21 T2D</td>
<td>250mg dried leaves tablet/day</td>
<td>placebo</td>
<td>60 days</td>
<td>No change in blood glucose</td>
</tr>
<tr>
<td><strong>Securigera Securidaca</strong></td>
<td>Fallah huseini H et al. (2006)(43)</td>
<td>Randomized , double blind, placebo control</td>
<td>70 T2D</td>
<td>1500mg /day + antidiabetic drugs</td>
<td>Placebo+ antidiabetic drugs</td>
<td>2 months</td>
<td>No sig. difference in blood glucose, HbA1c between groups</td>
</tr>
<tr>
<td><strong>Silybum marianum(silymarin)</strong></td>
<td>Fallah-Hoseini H. et al. (2004)(29)</td>
<td>Randomized, placebo control.</td>
<td>54 T2D</td>
<td>600 mg Silymarin /day+ antidiabetic drugs.</td>
<td>Placebo+ antidiabetic drugs.</td>
<td>4 months</td>
<td>Decrease FBG</td>
</tr>
<tr>
<td><strong>Silybum marianum (Silmarin)</strong></td>
<td>Fallah-Hoseini H. et al. (2006)(30)</td>
<td>Randomized, double blind, placebo control.</td>
<td>51 T2D</td>
<td>Silybum marianum seed extract 200mg/TDS+ antidiabetic drugs</td>
<td>Placebo + antidiabetic drugs</td>
<td>4 months</td>
<td>Sig. decrease HbA1c &amp; FBG between and within groups.</td>
</tr>
<tr>
<td><strong>Silymarin (Milk thistle)</strong></td>
<td>Velussi M. et al. (1997)(31)</td>
<td>Open-label; 2 parallel groups</td>
<td>60 T2D with cirrhosis; diet and insulin</td>
<td>Silymarin, 600mg</td>
<td>No treatment</td>
<td>12 months</td>
<td>Decrease FBG, mean BG, HbA1c, fasting insulin, insulin requierment</td>
</tr>
<tr>
<td><strong>Thea sinensis (green tea)</strong></td>
<td>Fukino Y. et al. (2008)(44)</td>
<td>Randomized cross over</td>
<td>60 borderline T2D</td>
<td>Green tea extract powder containing 544mg of poly phenols</td>
<td>observation</td>
<td>2*2 months</td>
<td>Sig decrease HbA1c, No sig. change in FBG</td>
</tr>
</tbody>
</table>
Antidiabetic plants of Iran

<table>
<thead>
<tr>
<th>Plant</th>
<th>Authors (Year)</th>
<th>Design</th>
<th>Details</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigonella foenum graecum</td>
<td>Bawadi HA, et al. (2009)</td>
<td>RCT</td>
<td>160 T2D, 2.5 g FG seed, 5 g FG seed, placebo</td>
<td>Single dose, Sig. decrease PPG in 5g FG group</td>
</tr>
<tr>
<td>Trigonella foenum</td>
<td>Sharma RD, et al. (1990)</td>
<td>Randomized Crossover</td>
<td>15 T2D on diet and OHA, Defatted fenugreek seed powder; 100 g/day in bread, No treatment</td>
<td>10 days, Decrease FBG, PPG, postprandial insulin</td>
</tr>
<tr>
<td>Vaccinium arctostaphylos</td>
<td>Abidov, M, et al. (2006)</td>
<td>Randomized, placebo control</td>
<td>42 T2D, 300mg/TDS+ antidiabetic drugs, Placebo + antidiabetic drug</td>
<td>4 weeks, Sig. decrease FBG</td>
</tr>
</tbody>
</table>

*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. T2D - Type 2 Diabetes mellitus, Sig - significant (*P* value<0.05 ), OHA - oral hypoglycemic agents, FBG -fasting blood glucose, PPG- postprandial glucose, HbA1c- glycylated 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 Citrullus 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.

**References**

