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Full Length Research Paper

Herbs and herbal preparations for glycemic control in diabetes mellitus (a systematic review)

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To conduct an updated systematic review of the published literature to fined effective antihyperglycemic herbs and herbal preparations used in clinical trials for improving glycemic control in type 2 diabetes mellitus. We performed an electronic literature search of Medline, Science direct, Scopus, ProQuest, Ebsco, Googlescholar, and Cochrane Library Database, from January 2002 to June 2010. The key outcome for antidiabetic effect was changes in one or more parameters including FBG, PPG, and HbA1(c), as well as improve in insulin sensitivity or insulin resistance. Total clinical trials retrieved were 222, of which 38 were randomized controlled trial (RCT), examined single herbs or combination of herbs as potential therapy for type 2 diabetes mellitus. Of these 38 trials, the direction of the evidence for glycemic control was positive in 26 trials (68.4%). Several herbal medicine used in clinical trials had beneficial effects on glycemic control, but there is still insufficient evidence to draw definitive conclusion about the efficacy of herbs and herbal preparations for treatments of diabetic patients. Among the RCT studies, the good evidence in glycemic control was found in *Citrullus colocynthus, Ipomoea betatas,* and *Silybum marianum* although the sample size was low.

Key words: Diabetes mellitus, review, clinical trial, herb, plant, andomized controlled trial (RCT).

INTRODUCTION

Diabetes is a serious global health issue, with type 2 diabetes mellitus accounting for approximately 90 to 95% of all cases (Rodbard et al., 2007). The recent rapid increase in the prevalence of type 2 diabetes is in part due to an ageing population but may also be attributed to an increase in the number of overweight and obese people. It is estimated that approximately 6.6% of the world's population aged between 20 and 79 years will have diabetes in 2010, with this figure projected to increase to 7.8% by 2030 (Fakhoury et al., 2010) and prevalence of diabetes in people over 65 years of age will be 69% increase in developing countries (Wild et al., 2004). It is predicted that the developing countries will contribute 77.6% of the total number of diabetic patients in the world by the year 2030. The prevalence of type 2 diabetes mellitus 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 (Azimi nehzad et al., 2008). The disease causes substantial morbidity, mortality and long-term complications and remains an important risk factor for cardiovascular disease. It has been suggested that ineffective drug therapies, poor patient adherence to therapy and inadequate management regimens may all contribute to the increasing incidence of complications linked to the disease. Patients with type 2 diabetes are often required to undertake significant lifestyle and dietary changes in addition to prescription antidiabetes drug therapy (Fakhoury et al., 2010). Inadequacies in current treatments for diabetes have led 2 to 3.6 million Americans diabetic patients to use antihyperglycemic complementary and alternative medicine (CAM), despite of limited studies on their safety and efficacy. Several CAM practices and herbal remedies are promising for diabetes treatment, but further studies are needed in order to establish safety, efficacy and effective dosage (Dham et al., 2006). In a cross-sectional questionnaire survey involving 263 patients with diabetes mellitus with ages ranging from 28 to 80 years, the prevalence of CAM usage was 46% and the female /male ratio was 2:1. The

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main CAM used was bitter leaf (*V. amygdalina*), Aloe vera, garlic, and ginger (Ogbera et al., 2010). Medicinal plants are being looked up once again for the treatment of diabetes. Many modern pharmaceuticals used in conventional medicine today also have natural plant origins. Among them, Metformin was derived from the plant, *Galega officinalis* (Goat's Rue or French Lilac), which was a common traditional remedy for diabetes (Yeh et al., 2003). There is a need for conducting clinical research in herbal drugs and developing simple bioassays for biological standardization, pharmacological and toxicological evaluation. It is also important to establish the active components from these plant extracts. To date, over 400 plants reported in folk medicine for treatments of diabetes, 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 type 2 diabetes mellitus (Modak et al., 2007).

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 (Pandey et al., 1995; O'Connell, 2001; Shane-Mc Whorter, 2001; Mooradian et al., 1994; Bailey and Day, 1989; Chitwood, 1999; Morelli and Zoorob, 2000; Berman et al., 1999; Gori and Campbell, 1998). Two prior reviews by Ernst examined plants with hypoglycemic activity in humans, including 5 RCTs (Ernst, 1996, 1997). The most recent systematic review of herbs for glycemic control by Yeh et al. (2003) examined clinical studies that used human participants from database inception, to May 2002 (Yeh et al., 2003). There have been no comprehensive systematic reviews in the last 10 years incorporating herbs and herbal products, for glucose control among patients with diabetes. Our objective was to review and summarize the literature on herbal remedies used for diabetes may be useful to practitioners in advising their patients, and to provide recommendations for future research.

RESEARCH DESIGN AND METHODS

We searched Medline, Science direct, Scopus, ProQuest, Ebsco, Googlescholar, Cochrane Library Database from January 2002 to June 2010 using CAM, diabetes mellitus , plant (herb) patient, glycemic control , clinical trial, RCT, natural or herbal medicine, hypoglycemic, plants and individual herb names from popular sources, as keywords.

Included criteria

Randomized control trials which evaluate hypoglycemic effect of single herb or herbal preparations in type 2 diabetic patients were included. The most common outcomes measures encountered in RCT studies including FBG, PPG, HbA1(c), as well as improve in insulin sensitivity or insulin resistance. We limited studies to those articles published in English or Persian and restricted our search to herbs and herbal preparations for changes in glycemic indexes.

Excluded criteria

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 (older, sedentary, obese individuals with a family history of diabetes) were also excluded. Non-controlled, non-randomized, before-after trials, unpublished data, studies on type 1 diabetes mellitus 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, control and outcome.

RESULTS

A total of 222 human trials of herbs and herbal preparation for treatments of diabetic patients were founded. Most trials examined herbs or herbal preparations as an adjunct to conventional treatment with diet and /or medication. The most common outcome measures encountered in these studies were fasting and postprandial blood glucose, Hb A1(C) and insulin resistance or sensitivity.

The present data showed that some of these plants including *C. colocynthus, S. marianum* and I*. betatas* are effective in reducing blood glucose (Fallah Huseini et al., 2004, 2006 and 2009; Ludvik et al., 2003 and 2004), in type II diabetic patients (All of the controlled clinical trials suggested efficacy of these plants). All RCTs on herbal preparations showed significant effects on type 2 diabetes patients. In some reviews on Cinnamon and *Momordica charantia* more than 50% of the RCTs reported no significant change in blood glucose in diabetic patients (Dugoua et al., 2007; Baker et al., 2008; Ooi et al., 2010; Leng et al., 2009).

Among 38 RCTs were found examining single herb or combination herb formulas, 26 (68.4%) had positive effect on glycemic control in type 2 diabetic patients. Of these 26 trials, 10(38.4%) were reduced FBG or PPG as well as HbA1(C), 3 (11.5%) trials reduced HbA1(C) and 7(26.9%) trials were effective in blood glucose lowering without effect on Hb A1(C). However, 6 (23.1%) of these positive trials improve insulin resistance or sensitivity and/or reduction in BG or Hb A1(C), but 12 RCTs did not have a significant effect on glycemic control and 10 (26.3%) of RCTs had small sample size (less than 20 in each group) (Tables 1 and 2).

Single herbs for glycemic control

Table 1 presents 34 controlled clinical trials of single herbs for glycemic control in patients with diabetes. Among the single herbs studied, the good evidence in glycemic control was found in *Citrullus colocynthus, Ipomoea betatas,* and *Silybum marianum*.

Table 1. RCT studies of single herbs for glycemic control.

Herb	Reference	Design	Sample	Intervention	Control	Duration	Outcome
Agaricus Blazei Murill (ABM)	Hsu et al., 2007	Randomized, double-blind, placebo control	72 T2D , on OHA	1500 mg/day (ABM extract)	placebo	12 week	Sig. decrease insulin resistance
Amorphophallus konjac	Chen et al., 2003	Randomized, double blind crossover	22 T2D	Konjac glucomannan (KGM) 3.6 g/day + antidiabetic drugs	Placebo + antidiabetic drugs	2 * 28 days	Sig. decrease FBG
Amygdalus L. (Almond)	Lovejoy et al. 2002	Randomized, double blind, crossover.	30 T 2D	HFA or LFA(containing 75-113 g almond/day)*	HFC or LFC(without almond)*	4 week	No sig. changes in FBG &HbA1C
Amygdalus L. (Almond)	Li et al., 2011	Randomized, cross over	20 T2D	Almond diet (60 g/day)	Control diet (National cholesterol Education program step 2)	4 week	Sig. Lower level of FBG& fasting insulin &insulin resistance
Cinnamomum aromaticum (Cassia cinnamon)	Khan et al., 2003	Randomized, placebo control.	60 T2D	1,3,6 g Cassia cinnamon / day	Placebo	40 day	Sig. decrease BG
Cinnamomum aromaticum (Cassia cinnamon)	Blevins et al., 2007	Randomized, placebo control.	58 T2D	1 g Cinnamon /day	Placebo	3 month	No sig. change in FBG, HbA_1(c) or insulin levels.
Cinnamomum aromaticum (Cassia cinnamon)	Mang et al., 2006	Randomized, placebo control, double blind.	79 T2D on OHA	3 g Cinnamon extract/ day	Placebo	4 month	decrease FBG No sig change in HbA1C.
Cinnamomum aromaticum (Cassia cinnamon)	Suppapitiporn et al., 2006	Randomized, single blind, placebo control.	60 T2D	1.5g/d Cinnamon cassia powder+ OHA	Placebo + OHD	12 week	No sig. difference between groups
Citrullus colocynthis	Fallah Huseini et al., 2006	Randomized, placebo control.	50T2D	300 mg /day + antidiabetic drugs.	Placebo+ antidiabetic drugs	2 month	Sig. decrease FBG& HbA1C
Citrullus colocynthis	Fallah Huseini et al., 2006	Randomized, placebo control.	44T2 D	300 mg Cittrullus/day	Placebo	2 month	Sig. decrease FBG& HbA1C
Citrullus colocynthis	Fallah Huseini et al., 2009	Randomized, double blind, placebo control	50 type2, on standard antidiabetic therapy	100 mg /TDS fruit capsules	Placebo	2 month	Sig. decrease HbA_1c & FBG

Table 1. Condt.

Coccinia cordifolia	Kuriyan et al., 2008	Randomized, double blind, placebo control	60 newly diagnosed T2D	Two 500 mg cap/day	Placebo	90 days	Sig. decrease the FBG & PPG& HbA1c
Cuminum cyminum (cumin)	Andallu and Ramaya, et al., 2007	Randomized, controlled.	20 T2D	5 g Cumin seed powder/day	Antidiabetic drugs	60 day	Sig. decrease FBG
Ganoderma lucidum	Wang et al., 2008	Randomized, double-blind placebo control	46 T2D	Dry extract of G.l 3000 mg + OHA	Placebo + OHA	12 week	No sig. changes in FBG & HbA1C.
Ginkgo biloba	Kudolo et al., 2006	Randomized, double blind, placebo control, cross over	8 T2D	120 mg Ginkgo extract /day as a single dose	Placebo	3 month	No sig. change in insulin resistance
Gynostemma pentaphyllum	Huyen et al., 2010	Randomized, placebo control.	24 T2D	6g /day G. penta phylum tea	Placebo tea	12 week	Sig. decrease FBG&HbA1C& insulin resistance
Ipomoea batatas (Caiapo)	Ludvik et al., 2003	Randomized, placebo control	18 T2D on diet	2, 4 g/day Caiapo(LD&HD)	Placebo	6 week	Improve insulin sensitivity, sig decrease FBG with HD Caiapo.
Ipomoea betatas (Caiopo)	Ludvik et al., 2004	Randomized, placebo-control	61 T2D on diet	4 g Caipo/day	Placebo	12 week	Sig. decrease HbA1 c, FBG, PPG
Momordica charantia	John et al., 2003	Randomized, placebo control.	50 T2D	2 tab/TDS (each contain 1 g of dried fruit) + antidiabetic drugs	Placebo + antidiabetic drugs	4 week	No sig. change in FBG&PPS in both groups.
Momordica charantia	Dans et al., 2007	Randomized, double blind, placebo control.	40 newly diagnosed T2D	2 cap/TDS M. charantia ap. + antidiabetic drugs	Placebo + antidiabetic drugs	3 month	No sig. change in HbA1c & FBG
Nigella sativa	Qidwai et al., 2009	Randomized, double-blind controlled trial	123 Diabetics patient	1 g twice daily	Placebo (calcuim lactate)	6 week	Results were not significant
Plantago ovate (Psyllium)	Ziai et al., 2005	Randomized, double blind, placebo control	49 type2 on diet and drug therapy	Psyllium husk fiber 5.1g/BD+ antidiabetic drugs	Placebo + antidiabetic drugs	8 week	Sig. decrease FBS, HA1c
Pinus maritima (French maritime pine bark) or Pycnogenol	Liu et al., 2004	Randomized, Double blind, placebo control.	77 T2D	100 mg Pycnogenol + antidiabetic drugs	Placebo+ antidiabetic drugs	12 week	Sig. decrease PG& HbA1c

Table 1. Condt.

Salacia oblonga	Williams et al., 2007	Randomized, double blind, crossover	66 T2D	240 or 480 mg salacia extract + control meal	Control meal (620 kcal)	180 min	Decrease acute glycemia & insulinemia with Both doses.
Satureja khuzetanica	Vosough-Ghanbari et al., 2010	Randomized, Double blind, placebo control.	21 T2D	250 mg dried leaves tablet/day	Placebo	60 day	No change in blood glucose.
Securigera Securidaca	Fallah Huseini et al., 2006	Randomized, double blind, placebo control.	70 T2D	1500 mg /day + antidiabetic drugs	Placebo+ antidiabetic drugs	2 month	No sig. difference in blood glucose, HbA1(c) between groups
Silybum morianum (silymarin)	Fallah Huseini et al., 1383	Randomized, placebo control.	54 T2D	600 mg Silymarin /day+ antidiabetic drugs.	Placebo+ antidiabetic drugs.	4 month	Sig. decrease FBG
Silybum marianum (Silymarin)	Fallah Huseini et al., 2006	Randomized, double blind, placebo control	51 T2D	Silybum marianum seed extract 200 mg/TDS+ antidiabetic drugs	Placebo + antidiabetic drugs	4 month	Sig. decrease HbA1c & FBG
Stevia rebaudiana Bertoni(SrB)	Gregersen et al., 2004	Cross over.	12 T2D	1 g (S rB) single dose	1 g maize starch	240 minute	Sig. reduction of incremental area under the glucose response curve& increase insulinogenic index.
Syzygium cumini	Teixeira et al., 2006	Randomized, double blind, double dummy.	27 T2D	-Tea of leaves of S.cumini (2 g/day)+ placebo tab	-Placebo tea + glyburide (5mg twice a day) or placebo tea+ placebo tab	28 days	No sig. change in FBG
Thea sinensis *(green tea)*	Fukino et al., 2008	Cross Over	60 borderline T2D	Green tea extract powder containing 544 mg of poly phenols	Observation	2*2 month	Sig decrease HbA1(c) , No sig. change in FBG
Trigonella foenum graecum (Fenugreek)	Bawadi et al., 2009	RCT	160 T2D, 3 group	2.5 g FG seed, 5 g FG seed,	Placebo	Single dose	Sig. decrease PPG in 5 g FG group
Tinospora crispa	Sangsuwan et al., 2004	Randomized, double blind, placebo control.	40 T2D on OHA	1 g/TDS Tinospora crispa powder+ OHA	Placebo + OHA	6 month	No sig. changes in FBG&HbA1c& Insulin between groups and within groups.

Table 1. Condt.

*Vaccinum arctostaphylosl (*Blueberry)	Abidov et al., 2006	Randomized, placebo contro.	42 T2D	300 mg/TDS+ antidiabetic drugs	Placebo + antidiabetic drugs	4 week	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 oil0.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 1c, BG-blood glucose

C. colocynthus

C. colocynthis (L.) Schrad is a member of the Cucurbitaceae family and is used traditionally as an antidiabetic medication. It is also used as a natural laxative in several Asian countries (Ziyyat et al., 1997). *C. colocynthis* grows widely in Asia, especially East Asian countries. One of the RCT studies for evaluating antidiabetic effect of this herb was conducted in 50 type II diabetic patients (aged 40 to 65 years). Two groups of 25 each under standard antidiabetic therapy, received 100 mg *C. colocynthis* fruit capsules or placebos three times a day, respectively for 2 months. The results showed a significant decrease in HbA1c and fasting blood glucose levels in *C. colocynthis* treated patients *(*Fallah Huseini et al., 2009*)*.

In another studies (n=44, n=50) compared 2 month' use of 300 mg of fruit capsule of *C. colocynthus* with placebo in patients with type 2 diabetes. The available evidence for *C. colocynthus* in diabetes suggests a possible hypoglycemic effect .Further information and higher quality clinical trials are needed to further investigate this plant in glycemic control (Fallah Huseini et al., 2006).

S. marianum (Milk thistle)

S. marianum is referred to as holy thistle, Marian thistle, Mary thistle, Our Lady's thistle, St. Mary thistle, wild artichoke, Mariendistel (German), and Chardon-Marie (French) (Samer et al., 2009). *S. marianum*, commonly known as 'milk thistle' (Family: Asteraceae/Compositae) is one of the oldest and thoroughly researched plants in the treatment of liver diseases. The plant itself grows as a stout thistle in rocky soils with large purple flowering heads. The leaves are characterized by milky veins, from which the plant derives its name (Pradhan and Girish, 2006).

The one available clinical trial examined type 2 diabetic patients (n = 51) using a 200 mg silymarin tablet three times a day before meals day and the control group (26 patients) received a placebo tablet three times a day before meals for 4 months. The results showed a significant decrease in HbA1c, FBS, total cholesterol, LDL, triglyceride SGOT and SGPT levels in silymarin treated patients compared with placebo as well as with values at the beginning of the study in each group (Fallah Huseini et al., 2006). In another RCT study, prescribing silymarin tablet in 54 type 2 diabetic patients cause decrease in blood glucose and HbA1c as well as reduction of triglyceride and SGOT and SGPT. These studies, suggest a potential effect of *S. marianum* in glycemic control, however, further large clinical trial investigation is required (Fallah Huseini et al., 1383).

I. betatas

Sweet potato or *I. batatas* (L.) was an important food crop whose production ranks the seventh in global market. The aerial part of the sweet potato is used as vegetable and the underground part is used as food or raw material in industry. Chinese people used it also as herb to promote the production of body fluid, haemostasis and apocenosis for centuries (Yin et al., 2008). The extract of white-skinned sweet potato (*I. betatas) called caiapo.* Two randomized controlled trials, both from the same investigator group, in patients with type 2 diabetes (n=61 and n = 18) have reported significant lowering effects on blood glucose with *caiapo.* In one of these RCT trials A total of 18 male type 2 diabetic patients treated by diet alone were randomized to receive placebo or 2 (low dose) or 4 g (high dose) caiapo (four tablets each containing 168 or 336 mg powdered white-skinned sweet potato, respectively) before breakfast, lunch, and dinner for 6 weeks. This pilot study shows beneficial effects of high-dose caiapo on plasma glucose and total as well as LDL cholesterol levels in patients with type 2 diabetes. These effects relate to a decrease in insulin resistance (Ludvik et al., 2003). In another trial, 61 type 2 diabetic patients treated by diet were given 4 g Caiapo or placebo once daily for 12 weeks. After treatment with Caiapo, HbA_{1c} decreased significantly (P < 0.001) from 7.21 ± 0.15 to 6.68 ± 0.14%, and Fasting blood glucose levels decreased (P < 0.001) in the Caiapo group (143.7 ± 1.9 vs. 128.5 ± 1.7 mg/dl) and did not change in the placebo group (Ludvik et al., 2004). These studies confirm the beneficial effects of Caiapo on plasma glucose as well as cholesterol level in patients with type 2 diabetes. However, further investigation in RCTs is required.

Table 2. RCT studies of combination herbs for glycemic control.

Herbal preparation	Reference	Design	sample	intervention	control	Duration	Outcome
Ayurvedic protocol MA 471	Elder et al., 2006	Randomized control trial	60 patient with HbA1c value between 6 &8	Exercise, Ayurvedic diet meditation instruction and MA 471	Standard diabet education	6 month	Significant improvement in HbA1c, fasting glucose
Kothala himbutu tea	Jayawardena et al., 2005	Double –blind randomized placebo controlled cross over study	51 type 2 Diabetes	Standard preparation of herbal tea or placebo	Placebo	6 month	Sig decrease in HbA_1(c)
Pancreas Tonic	Hsia et al., 2004	randomized double blind placebo controlled study	47 type 2 diabetes ≥ 1 year with a baseline HbA_1c between 10.0% to 12.0%	2 cap/TDS	placebo	3 month	Significantly improved HbA_1c in subject with baseline HbA_1c between 10% to 12%
TCM	Chao et al., 2009	Randomized double blind placebo controlled study	43 newly diagnosed type 2 diabetic patients.	3 mg of a mixture of plants .	placebo	3 month	Decrease in FBG and HbA1c in TCM group.

Combination of herbs for glycemic control

Table 2 presents the controlled clinical trials of multiple herbs combinations for glycemic control in patients with type 2 diabetes.

Ayurvedic protocols for glycemic control

For some 3000 years the traditional medical practice of Ayurvedic has been used in India and has since found acceptance in other parts of Asia as well as the West. It has therapeutic benefits for numerous conditions, including diabetes mellitus, through a combination of approaches such as diet, exercise, herbs, massage and meditation (on the basis of folklore medicine).

Pancreas tonic

It is a botanical mixture, currently available in North America as a dietary supplement marketed under the trade names Pancrease tonic or antibetic. Pancrease tonic is an herbal mixture of 10 herbal extracts as shown in Table 3.

A variety of preclinical's studies, using *in vitro* or *in vivo* models, have suggested that most of the components of this mixture possess antidiabetic properties (Hsia et al., 2004). Hsia et al. (2004) in a double-blind, placebo-controlled-3-month study in type 2 diabetic patients, reported that, therapy with Pancreas Tonic capsule 3 times a day for 3 month significantly lowers HbA_1c in those type 2 diabetic subject with a baseline HbA_1c level between 10.0 to 12.0%.

Ayurvedic protocol MA 471

This dietary supplement contains the herbs *Phylanthus niruri*, *Arjuna myrobalan*, *Eniconstema littlorale*, as well as bael fruit (*Aegle marmelos*), and black berry. In a clinical study conducted by Elder et al. (2006), the feasibility and clinical impact of this Ayurvedic preparation along with exercise, an Ayurvedic diet and meditation instruction, were determined in newly diagnosed type 2 diabetic patients (ns60) with HbA_1c value between 6 and 8%. In this study Ayurvedic herb supplement (MA 471) for 6 month statistically significant improved HbA_1c

Table 3. Composition of pancrease tonic.

Ingredient	%Dry weight
Aegle marmelose (leaves)	30
Pterocarpus marsupium(heartwood)	30
Syzigium cumini (fruit)	10
Momordica charantia (seeds)	7
Gymnema sylvestre (leaves)	5
Trigonella foenum graecum (seeds)	5
Azadirachta indica (seeds)	5
Ficus racemosa	5
Tinospora cordifolia (stem)	2
Cinnamum tamala (leaves)	1

(p=0.006), fasting glucose (p=0.001), total cholesterol (p=0.05) and LDL cholesterol (p=0.04) (Elder et al., 2006).

Kothala Himbutu tea

Kothala Himbutu is an Ayurvedic herbal tea containing *Salacia reticulata*, *Pterocarpus marsopium* Roxb, *Cinnamomum Zeylonicum* Blume, *Artocarpus heterophyllus* Lam and *Tinospora cordifolia*. In a randomized double – blind clinical trial, Jayawardena et al. investigated the effects of Kothala Himbutu tea over a 6 month period in patients with type 2 diabetes mellitus. The HbA_1c at the end of study was significantly lower than placebo. The authors concluded that Kothala Himbutu tea is an effective and safe treatment for type 2 diabetic patients (Jayawardena et al., 2005).

Herbal preparation in traditional Chinese medicine

Traditional Chinese Medicine (TCM) encompasses a system of healing that has origins over 2000 years old. Since the introduction of the 2 X 2 factorial design studies comparing the effects of TCM versus placebo and sulfonylurea (Vray and Attalli, 1995), the TCM has been used in China for several years. In a randomized, double-blind, and placebo controlled trial the efficacy of TCM on insulin sensitivity in newly diagnosed type 2 diabetic patients were reported (Chao et al., 2009). The TCM was composed of three plants: Coptis chinensis, Astragalus membrane sceus, and Lonicera Japanica.

In this study, 43 subjects with type 2 diabetes were enrolled. After 3 months treatment with TCM (3 mg of a mixture of plants in powder from with 50 mg of *Coptis chinensis*, 30 mg of *Astragalus mambranesceus*, and 120 mg of *Lonicera japonica*), glucose disposal rate increased from 5.12 to 6.37 mg $kg^{-1}min^{-1}$, showing a significant change compared to both initial level and that of placebo group. This result showed that insulin resistance was improved in the early period in TCM treatment. TCM also had a moderate glucose-lowering effect by reducing fasting and post prandial plasma glucose levels, as well as HbA_1c (Chao et al., 2009).

DISCUSSION

In this systematic review, 222 clinical trials investigating the effects of antidiabetic plants on diabetic patients were found. Of these studies 38 were RCTs examining 25 herbs and 4 herbal preparations. Among these CTs, 26 trials showed effectiveness of herbs or herbal preparations on type 2 diabetes mellitus versus 12 trials which showed no significant effects. In previous systematic review of clinical trials on antihyperglycemic herbs or supplements, 42 RCTs were reported until May 2002 (Yeh et al., 2003). The present systematic review indicated that clinical trials on some of the herbs such as Silymarine, Fenugreek, Bitter gourd and coccinia, reported in previous review, have been continued in recent years (Bawadi et al., 2009; Fallah Huseini et al., 2006; Dans et al., 2007). However, further clinical trials on some of the herbs like *Artocarpus heterophyllus* or *Ficus carica* which previously have shown beneficial effect in diabetic patients (Yeh et al., 2003), have not been continued..

Conclusion

As interest in the benefit of medicinal herbs for management of diabetes increases, it will become increasingly important to monitor the progress of the clinical literature. The present study provides a list of herbs which affect glycemic indexes in type 2 diabetic patients, although these data are insufficient to decide about their hypoglycemic effects. In this systematic literature search we observed some low quality studies. Even some studies with significant effects on blood glucose did not continue to evaluate long term efficacy,

so there are still insufficient evidences to decide definitely about efficacy and safety of these herbal remedies.

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