REVIEW ARTICLE

Medicinal plants in the adjunctive treatment of patients with type-1 diabetes: a systematic review of randomized clinical trials

Farzaneh Barzkar[1] · Hamid Reza Baradaran[1] · Mohammad Ebrahim Khamseh[1] · Roya Vesal Azad[2] · Jalil Koohpayehzadeh[3] · Yousef Moradi[4]

Abstract

Propose This study aims to systematically review the randomized controlled trials that address the effectiveness and safety of herbal medicine in patients with type 1 diabetes.

Methods The Cochrane Library (latest issue); MEDLINE (until recent); EMBASE (until recent); AMED (Allied and Complementary Medicine Database) (until recent); and CINHAL (until recent) were searched electronically for the identification of trials until October 2019. Articles were initially screened based on title and abstract and then by full text by two independent authors. References of retrieved studies were hand-searched for further studies. Risk of bias was assessed according to the Cochrane handbook of systematic reviews of interventions. The results were summarized into GRADE (grading of recommendations, assessment, development and evaluation) tables. No meta-analysis was applicable as only one study was found for each intervention.

Results Four RCTs were finally included in the systematic review with an overall moderate quality of conduct and low quality of reporting. The sample sizes were very small. The results of these RCTs show that cinnamon pills and Berberine/Silymarine compound capsules may decrease blood glucose indices from baseline, while fenugreek seeds and fig leaf decoction do not show any statistically significant effect.

Conclusions The evidence is scarce and no recommendations can be made based on current evidence. Further trials with more rigorous methodology and stronger quality of reporting are needed to make conclusions.

Keywords Medicinal plants · Herbal medicine · Type-1 diabetes · Systematic review

Introduction

Diabetes mellitus is a chronic metabolic disorder that is marked by hyperglycemia resulting from defective insulin secretion, insulin action or both. Short-term complications include diabetic ketoacidosis and the nonketotic hyperosmolar syndrome. These complications are commonly categorized as microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (coronary artery disease, cerebrovascular disease, and peripheral vascular disease). Diabetes and its

✉ Hamid Reza Baradaran
   baradaran.hr@iums.ac.ir

   Farzaneh Barzkar
   barzkarfarzane@gmail.com

   Mohammad Ebrahim Khamseh
   khamseh.m@iums.ac.ir

   Roya Vesal Azad
   royavesal@yahoo.com

   Jalil Koohpayehzadeh
   jkoohpayezadeh@yahoo.com

   Yousef Moradi
   Yousefmoradi211@yahoo.com

[1] Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran

[2] School of Public Health, Iran University of Medical Sciences, Tehran, Iran

[3] Preventive Medicine and Public Health Research Center, Iran University of Medical Sciences, Tehran, Iran

[4] Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

complications are a major cause of morbidity and mortality worldwide. Many of the long-term complications can be prevented by appropriate blood glucose control [1, 2].

Type 1 diabetes mellitus is a clinical syndrome in which the destruction of the pancreatic islet -cells leads to progressive insulin deficiency and hyperglycemia that in turn result in microvascular complications such as retinopathy, nephropathy, and neuropathy as well as macrovascular complications like coronary heart disease [3–5]. It comprises about 5%–10% of all people with diabetes [6]. In contrast, type 2 diabetes is mainly caused by peripheral insulin resistance and a relative insulin deficiency which can be associated with nutrition and certain dietary elements [7, 8].

Insulin is the first-line treatment in patients with type 1 diabetes. However, insulin does not address the main pathological mechanism of type-1 diabetes which is immune-mediated beta-cell damage and insulin secretion; instead, it is a replacement for inadequate endogenous insulin [9–12]. Medicinal plants have historically been used and have been shown to be popular among patients with diabetes especially in Asian countries. At least about one third of patients with diabetes use herbal preparations as part of their treatment [13–19]. Several articles have reviewed these herbal preparations assumed to have antidiabetic properties focusing on their proposed mechanisms of action rather than reviewing the experimental evidence on their clinical effectiveness [20–23]. Systematic reviews are available that assess the therapeutic effectiveness of herbal medicine in type 2 diabetes [24, 25]. Nevertheless, the difference in pathogenesis and nature between type1 and type 2 diabetes warrants different management approaches in these patients. The experimental evidence for the effectiveness and safety of herbal interventions in type 1 diabetes has not been studied systematically. This study aims to systematically review the randomized controlled trials that address the effectiveness and safety of herbal medicine in patients with type 1 diabetes.

Methods

This systematic review was constructed according to the PRISMA guideline [26].

Eligibility criteria

Types of studies: Only randomized controlled trials were included in this systematic review.

Types of participants: Children and adults with type 1 diabetes were included. The diagnosis had to be established based on the appropriate criteria at the time the study was conducted.

Types of interventions: Any type of herbal medicines including extract from herbs, single herb or a compound of herbs alone or along with Insulin. No limitation was applied for the mode of administration or the method of preparation of the herbal medicine. Studies on medicinal herbs plus other therapies such as a holistic treatment, for example, herbs plus cupping or acupuncture, were excluded. The control intervention included placebo that should have been a drug without an effect on blood glucose levels.

Types of outcome measures

Primary outcomes: glycemic control (as measured by glycated hemoglobin levels (HbA1c) and fasting blood glucose levels); adverse events (for example liver toxicity, kidney damage).

Secondary outcomes: diabetes complications (for example, neuropathy, retinopathy, nephropathy, sexual dysfunction); health-related quality-of-life; all-cause mortality; costs.

Search and information sources

The Cochrane Library (latest issue); MEDLINE (until recent); EMBASE (until recent); AMED (Allied and Complementary Medicine Database) (until recent); Google Scholar and CINHAL (until recent) were searched electronically for the identification of trials. The sample search terms are presented in Table 1. Hawaiian herbal medicine was a search term because Hawaiian plant flora contain some of the most distinctive plant species in the world [1–3].

All related components of lipid profile including [Ketosis-Prone Diabetes Mellitus, Autoimmune Diabetes, Juvenile-Onset Diabetes Mellitus, Insulin-Dependent Diabetes Mellitus, Brittle Diabetes Mellitus and IDDM] added to searched queries based on scientific MeSH terms, EMTREE or the keywords. The results were limited to human subjects and refined for patients with type 1 diabetes. Reference Manager bibliographic software was used to manage searched citations. Duplicate entries were searched by considering the title of the published papers, authors, the year of publication, and specifications of the sources types. Based on a 2003 systematic review of herbal preparations for diabetes, another search was performed with additional search terms including all of the proposed herbal preparations [24]. Citation tracking was performed for all of the retrieved studies. Authors of relevant identified studies and other experts (authors of reviews) were contacted in order to obtain additional references, unpublished trials, or ongoing trials. We attempted to identify additional studies by searching the reference lists of

Table 1　PubMed search terms

((((“Type 1 Diabetes Mellitus”[tiab] OR (Diabetes Mellitus[tiab] AND Type I[tiab]) OR “Type 1 Diabetes”[tiab] OR (Diabetes[tiab] AND Type 1[tiab]) OR (Diabetes Mellitus[tiab] AND Ketosis-Prone[tiab]) OR (Diabetes Mellitus[tiab] AND Ketosis Prone[tiab]) OR “Ketosis-Prone Diabetes Mellitus”[tiab] OR (Diabetes[tiab] AND Autoimmune[tiab]) OR “Autoimmune Diabetes”[tiab] OR (Diabetes Mellitus[tiab] AND Juvenile-Onset[tiab]) OR (Diabetes Mellitus[tiab] AND Juvenile Onset[tiab]) OR “Juvenile-Onset Diabetes Mellitus” OR “Juvenile-Onset Diabetes” OR (Diabetes[tiab] AND Juvenile-Onset[tiab]) OR “Juvenile Onset Diabetes”[tiab] OR (Diabetes Mellitus[tiab] AND Insulin-Dependent[tiab]) OR (Diabetes Mellitus[tiab] AND Insulin Dependent[tiab]) OR “Insulin-Dependent Diabetes Mellitus”[tiab] OR IDDM OR “Insulin Dependent Diabetes Mellitus 1”[tiab] OR (Diabetes Mellitus[tiab] AND Brittle[tiab]) OR “Brittle Diabetes Mellitus”[tiab] OR (Diabetes Mellitus[tiab] AND Sudden-Onset[tiab]) OR (Diabetes Mellitus[tiab] AND Sudden Onset[tiab]) OR “Sudden-Onset Diabetes Mellitus”[tiab]) AND (Medicine[tiab] AND Herbal[tiab]) OR “Hawaiian Herbal Medicine”[tiab] OR “Hawaiian Herbal Medicines”[tiab] OR (Herbal Medicine[tiab] AND Hawaiian[tiab]) OR (Herbal Medicines[tiab] AND Hawaiian[tiab]) OR (medicinal[tiab] AND herb[tiab]) OR (medicinal[tiab] AND plant[tiab]) OR (medicinal[tiab] AND herbs[tiab]) OR (medicinal[tiab] AND plants[tiab]) OR (Medicine[tiab] AND Hawaiian Herbal[tiab]) OR (Medicines[tiab] AND Herbal[tiab]) OR Herbalism[tiab]) AND (“glycemic control”[tiab] OR “adverse events”[tiab] OR “diabetic complication”[tiab] OR “Fasting plasma glucose”[tiab] OR “glycated hemoglobin”[tiab] OR “Diabetes-Related Complications”[tiab] OR “Complications of Diabetes Mellitus”[tiab] OR “Diabetes Mellitus Complication”[tiab] OR “Life Quality”[tiab] OR “Health-Related Quality Of Life”[tiab] OR “Health Related Quality Of Life”[tiab] OR HRQOL[tiab] OR (Cost [tiab] AND Health Care[tiab]) OR “Health Care Cost”[tiab] OR “Health Costs”[tiab] OR “Healthcare Costs”[tiab] OR “Medical Care Costs”[tiab] OR “Treatment Costs”[tiab]))

included trials. A librarian in health sciences was involved in all the stages of the search.

Study selection

Two authors independently determined the studies for eligibility by scanning the title, abstract or both sections of all the retrieved records. All potentially relevant investigated as full text. Any differences in opinion were resolved by a third author. If resolving disagreement was not possible authors would be contacted for clarification (Fig. 1).

Data collection process

For studies that fulfilled our inclusion criteria, two authors independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see Characteristics of included studies). Any disagreements were resolved by discussion or, if required, by a third party. Any relevant missing information on the trial were sought from the original author(s) of the article, if required.

Quality assessment

Quality of reporting was assessed using CONSORT and its specific extension for herbal interventions. The Cochrane Risk of Bias tool was used to assess risk of bias within studies. Special issues regarding cross-over design in 2 of the trials were addressed according to the Cochrane handbook of systematic reviews. Two authors assessed risk of bias within each trial independently. Any disagreement was resolved by consensus and by consultation of a third party in case of persistent disagreement. The GRADE (Grading of recommendations, Assessment, Dissemination, and Evaluation) approach was used to assess quality of evidence for all study outcomes in summary of findings tables.

Summary measures

Results of each individual study were extracted based on predetermined characteristics and outcomes as defined by the study protocol. These templates included Study ID/year, Study Design, Target population, age range, Mean baseline BMI, Mean number of years since the diagnosis of DM1, Sample size, Number of Drop-outs, Baseline insulin regimen, Study duration, Description of Intervention, and Description of comparison. Mean differences were used to analyze the effect sizes of continuous outcomes. The effect sizes for dichotomous data were expressed in terms of relative risks or odds ratio.
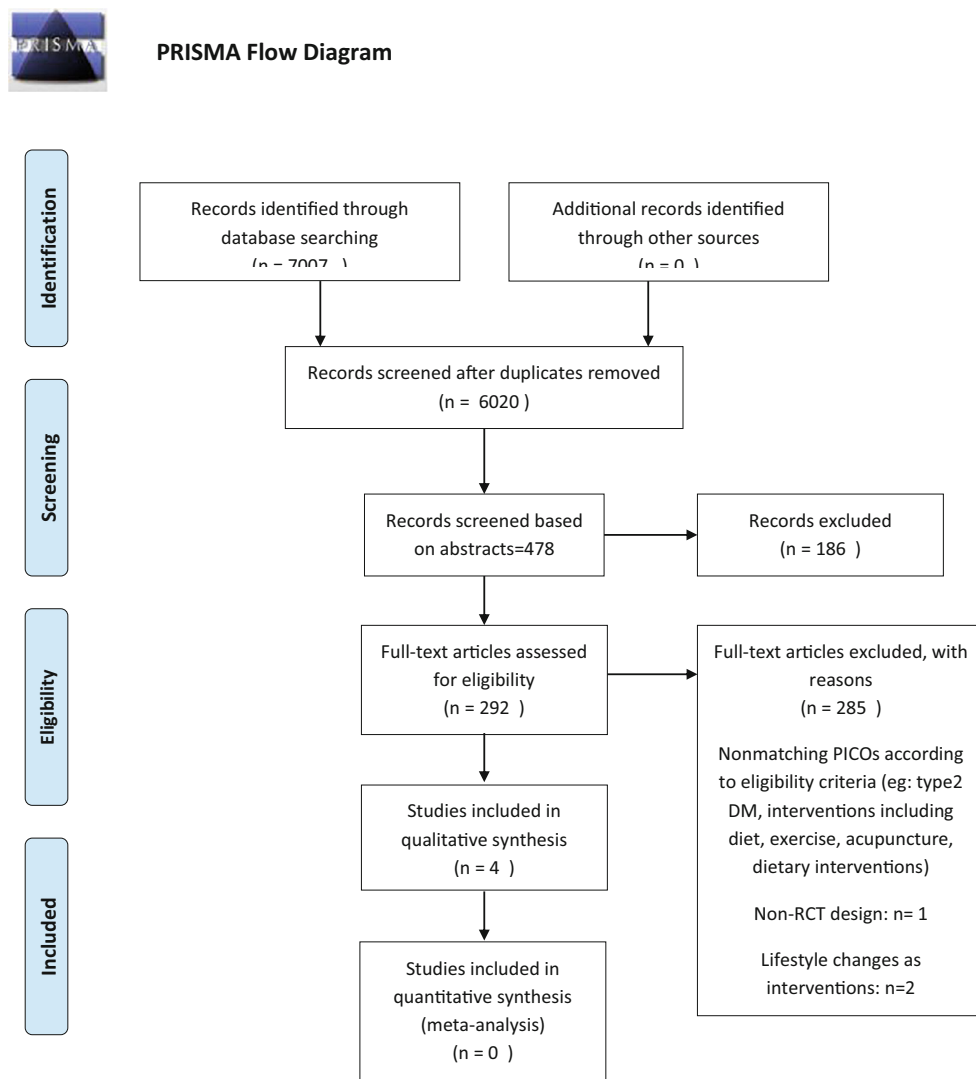
How does the review differ from the protocol?

The search strategy was changed to include a secondary search that included the list of proposed medicinal plants used in the treatment of type-1 diabetes. The length of follow up was not limited to the predetermined protocol because of the scarcity of trials in the field and that this limitation would result in even fewer studies being included and reviewed. The outcome measures that are finally reported here were also extended according to the retrieved studies. The included studies did not have a sufficient description of their diagnostic criteria. No studies had long-term follow-up and thus our predetermined secondary outcomes were not assessable in any of the studies.

Results

Study selection

Among 7007 search results initially retrieved, 6006 remained after removing duplicates. 478 Studies were assessed for eligibility based on their titles and abstracts. Two-hundred-and-ninety-two studies that were assessed based on their full-texts,

Fig. 1 PRISMA Flow diagram

PRISMA Flow Diagram

Identification

Records identified through database searching (n = 7007)

Additional records identified through other sources (n = 0)

Screening

Records screened after duplicates removed (n = 6020)

Records screened based on abstracts=478

Records excluded (n = 186)

Eligibility

Full-text articles assessed for eligibility (n = 292)

Full-text articles excluded, with reasons (n = 285)

Nonmatching PICOs according to eligibility criteria (eg: type2 DM, interventions including diet, exercise, acupuncture, dietary interventions)

Non-RCT design: n= 1

Lifestyle changes as interventions: n=2

Included

Studies included in qualitative synthesis (n = 4)

Studies included in quantitative synthesis (meta-analysis) (n = 0)

many studies were excluded because they included patients with type 2 diabetes. Two studies were excluded as they assessed the role of exercise and dietary interventions in patients with type1 diabetes rather than specific herbal medications [27, 28]. One clinical trial was excluded as it had used a metabolomics approach and did not assess our predetermined outcomes. Eventually, four studies were included to the systematic review.

Study characteristics

Only four studies met the criteria to be included to this systematic review; these included RCTs aimed to evaluate the effect of a) *Cinnamomum zeylanicum*(cinnamon*)* pills, b) *Ficus carica* (fig)leaf decoction, c) *Berberis aristata/Sylibum marianum* capsules, and d) *Trigonella foenum-graecum(fenugreek)* powder added to local bread, in glycemic control among patients with type 1 diabetes mellitus in comparison to control groups.

The studies included different patient age groups; The study on cinnamon included 72 adolescents (mean age: 14 ± 1.4 years) [29], the study on fenugreek included 10 adults(mean age: 22.7 ± 2.7 years) [30], the Berberis/ Sylibum trial included 85 adults with type-1 diabetes(mean age: 29.8 ± 7.2) [31], and the Fig-leaf study included 10 patients with type-1 diabetes(mean age:29 ± 2.2) [29].The trial length and design varied among the studies. The study characteristics are presented in detail in Table 2.

Risk of bias assessment

The risk of bias varied significantly from unclear, and low to high. The quality of reporting was suboptimal. This was especially a concern since they did not have sufficient description of their methods including their methods of randomization and sequence generation, as well as blinding which made it difficult for the researchers to draw clear judgements about risk of bias.

Table 2 Table of Study Characteristics

Study ID/year	Study Design	Target population	Mean baseline BMI	Mean number of years since the diagnosis of DM1	Sample size	Drop-out	Baseline insulin regimen	Study duration	Intervention	Comparison	Outcome measures
Serraclara, {Serraclara, 1998 #79}1998	Randomized controlled trial(RCT)-cross-over design	Adults, Mean age: 29 ± 2.2 years	Not reported	9 ± 6.3 years	10	2	two daily doses of subcutaneous insulin	1 month per intervention (total 2 months)	Fig-leaf decoction	Non-sweet commercial tea	7 day/week glycemic profiles, Post-prandial glucose (2 h-pp) c-peptide Glycated hemoglobin (Hb A1c) Episodes of clinical hypogly-caemia Total daily insulin intake
ALTSCHULER, {Altschuler, 2007 #80} 2007	Double blind-RCT	Adolescents, Mean age: 14.7± 1.4	Not reported	7.1 ±4.6 years	72	15	Basal/bolus	90 days	Cinnamon pills	Placebo (lactose) pills	A1C, total daily insulin intake, adverse events
Sharma, {Sharma, 1990 #78}1990	Randomized controlled trial- cross-over design	Mean age: 22.7±2.7 Age range: [12–37]	17±0.97	7 years	10	0	Fixed dose of insulin not sufficient to control BS+ 40-50 g increase in daily carbohydrate intake	20 days(total)/ two ten-day periods for each group	Fenugreek powder added to local bread	No Fenugreek powder	Oral glucose tolerance test 24-h urinary glucose Areas under the glucose and insulin concentration curves
Derosa, {Derosa, 2016 #57}	Double-blind Randomized placebo controlled trial	Adults ≥18 years old Mean age: 29.8 ± 7.2	22.6 ± 1.8	15.1 ± 2.8 years	85	4	Meal-time rapid-acting insulin analogs with or without basal log-acting insulin analogs	6-months	Berberis aristata/Sylibum marianum 588/105 mg, 1 tablet at lunch and 1 tablet at dinner, for six months	identical, opaque, white capsules(placebo)	Reduction of insulin dose necessary to reach adequate glycemic control Glycated hemoglobin (Hb A1c) Fasting plasma glucose (FPG), Post-prandial glucose (PPG),

Three studies had unclear risk of bias in random sequence generation due to inadequate reporting of randomization methods [29, 30, 32]. Two studies had unclear risk of bias in allocation concealment [30, 31]. Two studies had high risk of bias in blinding of participants due to the distinguishable nature and appearance of their interventions from the controls. [30, 32] One study had a high rate of drop-outs, but this was unlikely to affect its results as the researchers had appropriately used an intention-to-treat analysis [29]. Outcome data were reported completely in all of the studies except one which had an inadequate reporting of adverse effects; Risk of selective reporting was unclear for two studies since protocols were not available [29, 30], and high for one study which was suspected of inadequate reporting of adverse effects. [31]

A high risk of bias was suspected in two of the studies regarding the special issues concerning use of herbal interventions, the plant accreditation and details of preparation of the intervention [30, 32].

One study used lactose pills (which contain glucose) as placebo which could potentially affect the results. Because of the opposite direction of the results of the study relative to the perceived bias, the risk of bias from this issue is perceived as low [30].

There was a concern regarding one of the studies' choice of HbA1C as an outcome in the study with a cross-over design and a one-month intervention. This study did not have a wash-out period. This concern was based on the fact that HbA1C is describe to assess the state of glycemic control in the past three months. Thus, it is difficult to ascertain whether the results at the end of the 2-month period are due to the second intervention alone or the combination of the first and the second intervention.

Risk of bias within each study is presented in Fig. 2.

Results of individual studies

The four included studies evaluated the effects of four different herbal interventions. Three of the four studies showed statistically significant effects for the interventions. The results of individual studies are presented in Table 3.

Summary of findings and effectiveness of treatments

The quality of the evidence regarding the use of fenugreek in patients with type 1 diabetes was low to very low for all of the outcomes. Only one trial was retrieved which assessed 20 patients. Patients in the fenugreek group had a significantly increased mean urinary glucose and fasting plasma glucose after 10 days. However, Indices showing glucose tolerance were slightly improved in the group of patients taking fenugreek. There were six patients in the fenugreek group experiencing minor gastrointestinal adverse effects compared

to no people in the placebo group. More details are presented in Table 3. [30]

One trial compared the effects of oral fig leaf decoction with placebo in patients with type 1 diabetes. The quality of evidence differed between outcomes and is presented in Table 3. There was no statistically significant difference in Hb A1C and fasting plasma glucose between the group taking oral fig leaf decoction and the placebo group. Glucose tolerance improved significantly in the group of patients taking oral fig leaf in comparison to placebo. Although the rate of hypoglycemia did not differ between groups, the insulin dosage had been reduced to prevent such an event [32].

The overall quality of evidence for the use of cinnamon in type 1 diabetes is low based on a single RCT including 57 patients. The effect of cinnamon on HbA1c was not statistically significant. The change in insulin dosage varied among participants and was not statistically different either. Neither was the number of hypoglycemic episodes [29].

One randomized trial examined the effect of *B. aristata/S. marianum* combination on glycemic control and adverse events in type-1 diabetes. There is moderate certainty that *B. aristata/S. marianum* pills may slightly improve fasting plasma glucose. The degree of certainty is low for evidence regarding the effect of this herbal preparation on glycated hemoglobin, postprandial glycemia, and adverse effects. In addition, although these outcomes were statistically improved from baseline, the difference in improvement from baseline was not significantly different between groups [31].

The findings were summarized into GRADE tables as presented below (Tables 3).

Discussion

This systematic review aimed to evaluate the efficacy of herbal medicine as a complementary treatment for type 1 diabetes. We found only four randomized studies which used fenugreek, cinnamon, oral fig leaf decoction, and Berberine-Silymarine compound.

Although the mechanism of fenugreek (*Trigonella. f*) action in humans is not understood, animal studies have revealed the ability of dietary fiber including fenugreek seeds to delay gastric emptying, and suppress release of gastric inhibitory peptides and insulinotropic hormones. In another study, fenugreek oil was shown to restore a normal architecture of pancreas and kidney in comparison with the control group in alloxan-induced diabetic rats [33]. Although several studies showed a hypoglycemic effect for Fenugreek, the majority of these studies were carried out in animals and in people with type 2 diabetes and cannot be applied clinically for patients with type 1 diabetes. The only published randomized study for the

Fig. 2 Risk of bias within the studies
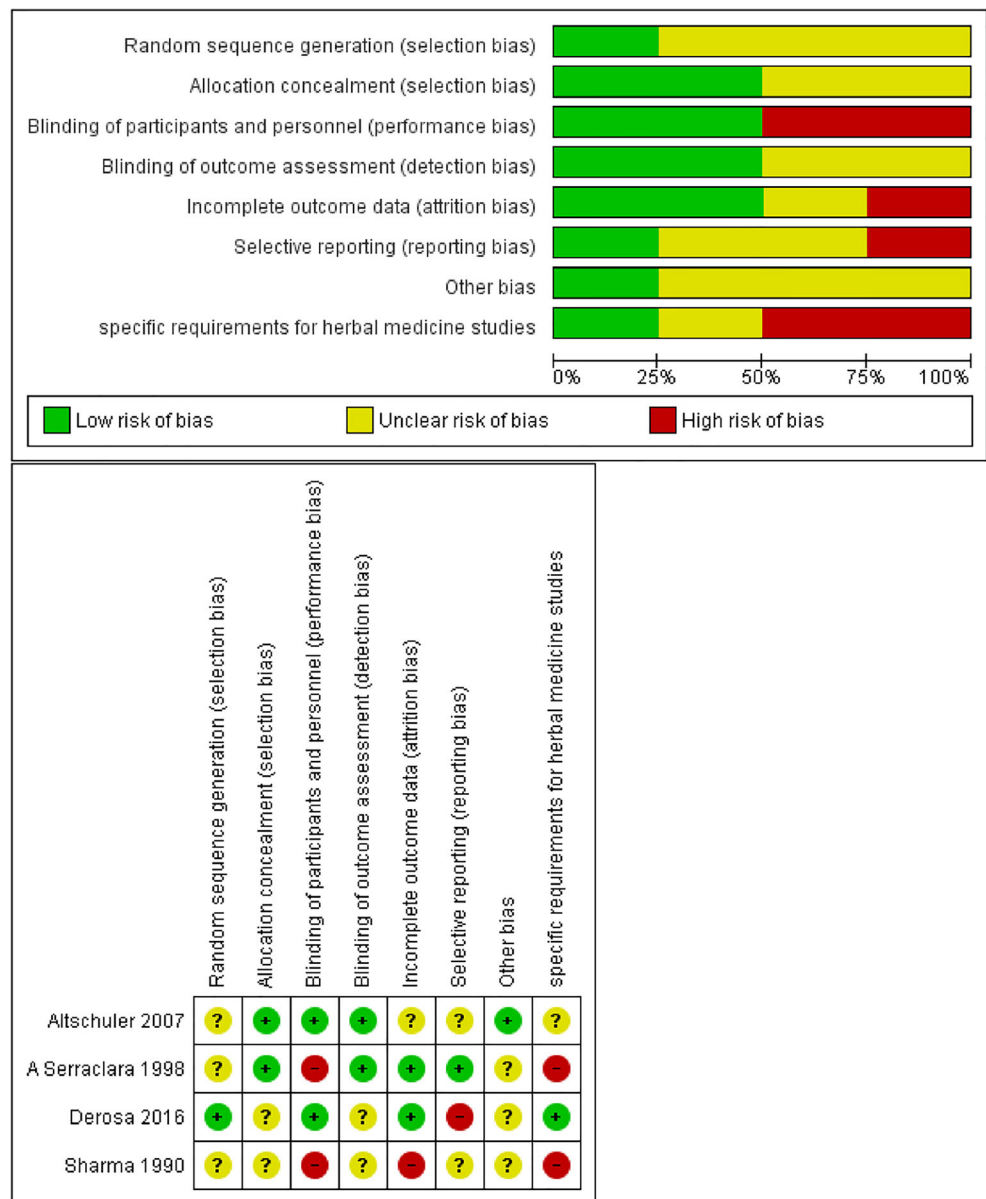
efficacy of fenugreek in humans, only showed a significant effect on fasting plasma glucose levels; however, the mechanism of potential effect in humans with type one diabetes cannot be inferred yet and the only human trial on patients with type one diabetes did not show significant positive effects on glycemic control.

Cinnamon (*Cinnamomum. z*) is one of the oldest herbal plants, a widely used spice that is postulated to improve glucose control by promoting phosphorylation of insulin receptor tyrosine kinase which increases insulin sensitivity. In addition, cinnamon extracts have been implicated in the production of transcription factors that modify insulin resistance through possible modulation of GLUT4 transporters which mobilize glucose into the cell. In animal models of type 1 diabetes, a hot water extract of cinnamon has been shown to exert insulin

independent catabolic effects on serum glucose via upregulation of mitochondrial uncoupling protein-1(UCP-1) in brown adipose tissue in streptozocin-induced type-1 diabetes in rats [34]. In another study, it showed insulinotropic activity comparable to glibenclamide in rat models of type 1 diabetes and cultured pancreatic beta cell lines [35]. Several studies in people with type 2 diabetes show that cinnamon reduces fasting blood glucose levels but has no effect on other glycemic parameters or markers of insulin resistance; the studies have significant heterogeneity which limits their direct clinical application [36]. The only randomized study in humans which was included in this review had low quality and did not show a significant effect for cinnamon on glycemic control in patients with type 1 diabetes [29]. This may be due to the small sample size, different pathogenic mechanisms between type 1 and

Table 3 GRADE summary of findings tables

Summary of findings:

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1 g cinnamon tablets compared to lactose tablets for patients with type 1 diabetes

Patient or population: patients with type 1 diabetes

Setting:

Intervention: 1 g cinnamon tablets

Comparison: lactose tablets

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
change in HbA1c № of participants: 57 (1 RCT)	-	The mean change in HbA1c was **0**	-	mean **0.3 higher** (0.1 lower to 0.7 higher) a	⊕⊕◯◯ LOW b,c,d	The evidence suggests that 1 g cinnamon tablets results in little to no difference in change in HbA1c.
Insulin dose (insulin dose) assessed with: unit/day follow up: mean 90 days № of participants: 57 (1 RCT)	-		-	mean **2.9 more** (5.8 fewer to 11.6 more)	⊕⊕◯◯ LOW b,c,d,e	1 g cinnamon tablets may not have a significant effect on reducing insulin dose.
Hypoglycemic episodes/14 days assessed with: (mg/dl ≤80) follow up: mean 14 days № of participants: 57 (1 RCT)	**39** (-13 to 123)	Low			⊕⊕◯◯ LOW c,d	1 g cinnamon tablets probably result in a slight increase in risk of hypoglycemic episodes/14 days. However there is significant uncertainty regarding the possibility and magnitude of the effect of this outcome.
		0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)		

Summary of findings:

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty	What happens
			Difference		

*****The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

type 2 diabetes, and the inadequate duration of the only available study to detect any possible effect. Another possible reason may be the relatively lower doses-1 g/day used in this study in comparison with studies in type 2 diabetes that have used up to 6 g/day of cinnamon [37–39]; Nevertheless, the direction of the results of this trial-although not significant- is towards a harmful effect of cinnamon and higher doses could probably increase this difference toward a significant level rather than show a benefit for cinnamon [29].

Ficus. c belongs to the Moraceae family which is popularly called "figs" and has been used for diabetes among other ailments since ancient times [40]. The *Ficus* species contain bioactive metabolites such as phenolic acids, flavonoids, coumarins, vitamin E, sterols*, glycosides, tannins, alkaloids, and triterpenoids* [41–43]. Several in-vivo animal studies have shown the beneficial effects of these compounds on insulin secretion and blood glucose [41, 43–47]. One study showed that fig leaf extract may inhibit beta cell apoptosis in mice via

Table 3   (continued)

Summary of findings:

Fenugreek seeds compared to no fenugreek seeds for patients with type 1 diabetes

Patient or population: patients with type 1 diabetes

Setting:

Intervention: fenugreek seeds

Comparison: no fenugreek seeds

Outcome	Relative effect	Anticipated absolute effects (95% CI)			Certainty	What happens
№ of participants (studies)	(95% CI)			Difference		
Fasting Plasma Glucose follow up: 10 days № of participants: 20 (1 RCT)	-	The mean fasting Plasma Glucose was **15.1** mmol/liter	-	mean **4.2 mmol/liter lower** (6.73 lower to 1.67 lower)	⊕⊕◯◯ LOW [a,b]	Fenugreek seeds may result in a reduction in fasting plasma glucose.
Post-prandial Serum Glucose(2hpp) № of participants: 20 (1 RCT)	-	The mean post-prandial Serum Glucose(2hpp) was **22.33** mmol/liter	-	mean **1.22 mmol/liter higher** (0.04 lower to 1.8 higher)	⊕◯◯◯ VERY LOW [a,b,c]	Fenugreek seeds have little to no effect on h-hour-post-prandial serum glucose but the evidence is very uncertain.
24-hr Urinary Glucose follow up: 10 days № of participants: 20 (1 RCT)	-	The mean 24-hr Urinary Glucose was **363** mmol	-	mean **196 mmol lower** (99.47 lower to 292.43 lower)	⊕◯◯◯ VERY LOW [b,c,d]	Fenugreek seeds may decrease 24-hr urinary glucose but the evidence is very uncertain.
Adverse Effects follow up: 10 days № of participants: 20 (1 RCT) [e]	4 Patients reported mild gatrointestinal disturbance such as diarrhea and flatulance during the 3-4 days afer initiation of the period they were on the fenugreek diet.				⊕◯◯◯ VERY LOW [a,b,f]	The evidence is very uncertain about the effect of fenugreek seeds on the rate of adverse effects.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

inhibition of the AMPK/JNK/caspase-3 signaling pathway and its anti-oxidant properties [48]. Other proposed mechanisms of effect based on experimental evidence include decreased intestinal glucose absorption, affecting glucose homeostasis, and enhancement of glucose uptake by the skeletal muscle [40]. A recent RCT showed beneficial effects of two fig fruit extracts on glycemic and insulinemic indices in healthy adults [49]. The only randomized trial in the literature did not show significant effects of oral fig leaf decoction on blood glucose in patients with type-1 diabetes. However, the results were statistically significant for its effect on insulin resistance [32].

Berberine is an alkaloid isolated from the roots, rhizomes, and stem barks of many plants including *B. aristata*. In traditional Eastern medicine, it has been used to treat diabetes, inflammation, and infections for more than 1000 years. It has two distinct modes of action acting paradoxically on different mechanisms involved in diabetes pathophysiology. It has been shown that it increases insulin sensitivity and consequently reduces blood insulin levels in patients with type 2 diabetes. On the other hand, in type 1 diabetes and more advanced stages of type 2 diabetes where poor beta cell function is involved, it is able to increase insulin secretion via promoting beta cell regeneration, insulin expression, antioxidant enzyme activity, and decreasing lipid peroxidation [31, 50–55]. These effects have been studied in a few trials on patients with type 2 diabetes the results of which are consistent with the findings from animal studies [52–55]. Silymarine is the powder extract from seeds from a plant called *S. marianum* which is from the *Asteracea*(sunflower) family [56]. It has been proposed to have independent antidiabetic effects and has also been shown to increase the bioavailability and effectiveness of *B. aristata* extract when used in combination [51–57].

Table 3 (continued)

Summary of findings:

Oral fig-leaf decoction compared to bitter commercial tea for patients with type 1 diabetes mellitus
Patient or population: patients with type 1 diabetes mellitus

Setting:

Intervention: oral fig-leaf decoction

Comparison: bitter commercial tea

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty	What happens
			Difference		
Fasting plasma glucose (FPG) № of participants: 20 (1 RCT)	-	The mean fasting plasma glucose was **0**	mean **1.15 lower** (1.75 lower to 0.08 higher) [a]	⊕◯◯◯ VERY LOW [b,c,d]	The evidence is very uncertain about the effect of oral fig-leaf decoction on fasting plasma glucose.
Glycated Hemoglobin (Hb A1c) assessed with: HPLC follow up: 3 months № of participants: 20 (1 RCT)	-	The mean glycated Hemoglobin was **7**	mean **0.1 lower** (0.95 lower to 0.8 higher) [a]	⊕◯◯◯ VERY LOW [b,c,d,e]	The evidence is very uncertain about the effect of oral fig-leaf decoction on glycated Hemoglobin.
1hour-post-prandial glucose(1hpp) (GTT) № of participants: 20 (1 RCT)	-	The mean 1hour-post-prandial glucose(1hpp) was **293.7** mg/dl	mean **2.2 mg/dl lower** (2.6 lower to 0.59 lower) [f]	⊕⊕◯◯ LOW [b,c,d]	The amall and low-quality evidence suggests that oral fig-leaf decoction results in little to no clinically significant difference in 1hour-post-prandial glucose(1hpp).
Number of Hypoglycemia Events № of participants: 20 (1 RCT)	"Although no significant increase in hypoglycemia was found, the total insulin doses were decreased during the study according to their glycemic profiles in order to avoid this complication."			⊕◯◯◯ VERY LOW [b,c,d,g]	The evidence is very uncertain about the effect of oral fig-leaf decoction on number of Hypoglycemia Events.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

However, these effects have only partially been addressed in the only randomized study on patients with type 1 diabetes which showed a small but statistically significant reduction in daily insulin dose from baseline and in comparison to controls for patients receiving a combination of *Berbesris asristata/ Silybum marianum*.

Limitations

The studies in this systematic review were of short duration and thus many patient-important outcomes such as the rate of diabetes complications were not addressed. Safety of these interventions cannot be assessed because adverse outcomes have not been reported adequately in the included studies. In addition, most of the studies evaluated patients with well-controlled diabetes and without complications which may not be representative of all patients with type-1 diabetes. There is special concern for use of these herbs in pregnant women with diabetes due to potential risk of toxicity and scarcity of evidence.

Although every attempt was made to include the names of all the commonly proposed plants in the search terms, the diversity of the medicinal herbs traditionally proposed for use in diabetes makes it difficult to ensure a comprehensive literature search that will retrieve all the possible RCTs.

There are too few randomized clinical trials addressing the use of medicinal plants in the management of type-1 diabetes. A meta-analysis could not be done because the herbal preparations(interventions) varied among the few included studies and no series of studies evaluated the effect of the same plant on the study outcomes.

Conclusions

There is insufficient evidence to draw conclusions about the efficacy of fenugreek, Berberine/Silymarine compound

Table 3 (continued)

Summary of findings:

Berberis aristata/Sylibum marianum compared to Placebo for patients with type 1 diabetes?

Patient or population: patients with type 1 diabetes?

Setting: Outpatient

Intervention: Berberis aristata/Sylibum marianum 588/105 mg one tablet at lunch one tablet at dinner

Comparison: Placebo

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty	What happens
			Difference		
Fasting plasma glucose (FPG) follow up: mean 6 months № of participants: 85 (1 RCT)	-	The mean fasting plasma glucose was **-3.5** mg/dl	MD **20.7 mg/dl lower** (25.92 lower to 15.48 lower)	⊕⊕⊕◯ MODERATE a	Berberis aristata/Sylibum marianum 588/105 mg one tablet at lunch one tablet at dinner likely reduces fasting plasma glucose slightly.
Glycated Hemoglobin (Hb A1C) follow up: mean 6 months № of participants: 85 (1 RCT)	-	The mean reduction in glycated Hemoglobin from baseline was **-0.1** %	MD **0.5 % lower** (0.64 lower to 0.36 lower)	⊕⊕◯◯ LOW a	The evidence suggests that berberis aristata/Sylibum marianum 588/105 mg one tablet at lunch one tablet at dinner results in little to no clinically significant change in glycated Hemoglobin. However, the evidence background is too small and of low quality for a firm judgement to be made.
Postprandial Glucose (PPG) follow up: mean 6 months № of participants: 85 (1 RCT)	-	The mean postprandial Glucose reduction from baseline was **2.4** mg/dL	MD **20.9 mg/dL reduction from baseline higher** (11.9 higher to 29.8 higher)	⊕⊕◯◯ LOW a,b,d	Berberis aristata/Sylibum marianum 588/105 mg one tablet at lunch one tablet at dinner may increase postprandial Glucose slightly. However, the effect may not be clinically significant.

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty	What happens
			Difference		
Adverse effects follow up: mean 6 months № of participants: (1 RCT)	No significant variations of parameters including liver and kidney function were recorded.			⊕⊕◯◯ LOW b,c	The evidence suggests that berberis aristata/Sylibum marianum 588/105 mg one tablet at lunch one tablet at dinner does not increase/reduce adverse effects.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

capsule, oral fig leaf decoction and cinnamon for glycemic control in type 1 diabetes. In addition, the evidence is inconclusive regarding the optimal doses and methods of preparations of these herbs and their safety in these patients.

There is insufficient evidence to support the use of medicinal plants in patients with type 1 diabetes. We suggest that more robust randomized studies be conducted in this field that measure more clinically-important outcomes such as real-time continuous glucose monitoring and long-term diabetes-related adverse effects, cover longer follow-ups and address outcome measures that better clarify the pharmacodynamics and the pharmacokinetics of commonly used medicinal herbs.

Authors' contributions HRB, MEK and JK Conceived and designed this study. FB, YM and RVA searched and retrieved all information. FB, YM and HRB conducted the risk of bias assessment and evaluation of study results. All authors contributed to writing the manuscript. All the authors read and approved the final manuscript.

Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interests The authors declare that they have no conflict of interests.

Abbreviation *MEDLINE,* Medical Literature Analysis and Retrieval System Online,; *AMED,* Allied and Complementary Medicine Database,; *Embase,* Excerpta Medica Database,; *CONSORT,* Consolidated Standards of Reporting Trials,; *CINAHL,* Cumulative Index of Nursing and Allied Health Literature,; *BMI,* Body Mass Index,; *DM,* Diabetes Mellitus.

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