

## **UC Davis**

### **UC Davis Previously Published Works**

#### **Title**

Chinese Herbal Medicine Versus Other Interventions in the Treatment of Type 2 Diabetes

#### **Permalink**

<https://escholarship.org/uc/item/1vk8d8rx>

#### **Authors**

Yu, Ao  
Adelson, David  
Mills, David

#### **Publication Date**

2018

#### **DOI**

10.1177/2515690x18781519

Peer reviewed



# Chinese Herbal Medicine Versus Other Interventions in the Treatment of Type 2 Diabetes: A Systematic Review of Randomized Controlled Trials

Ao Yu, MPH, BMed, BHSc, BHonHSc<sup>1</sup>, David Adelson, A.B, Ph.D.<sup>2</sup>,  
and David Mills, MBBS, FRACGP DA, PRACOG MD<sup>2</sup>

## Abstract

Diabetes affects 422 million people and directly caused 4.9 million deaths according to the global report on diabetes in 2014. Type 2 diabetes accounts for 90% of people with diabetes around the world. Chinese herbal medicine treatment for diabetes has more than 2000-year history in China. An increasing number of people around the world are trying to manage type 2 diabetes with Chinese herbal medicine. However, there is a lack of evidence to decide if Chinese herbal medicine is effective and safe when compared with other interventions for the treatment of type 2 diabetes. We identified 58 randomized controlled trials involving 6637 participants with type 2 diabetes with trial periods lasting from 8 weeks to 1 year (average 12 weeks). We extracted data following a predefined hierarchy. A total of 132 different Chinese herbal medicines were examined. We included studies comparing Chinese herbal medicine with other interventions and excluded trials that did not satisfy the inclusion criteria. We evaluated primary outcomes of trials in accordance with the *Cochrane Handbook for Systematic Reviews of Intervention*. Fifty-six out of 58 studies reported evidence that Chinese herbal medicines were effective at controlling blood sugar, insulin resistance, and traditional Chinese medicine clinical symptoms for patients with type 2 diabetes. And outcome variables are summarized. However, the evidence is limited because of the quality of the studies. Well-designed long-term studies with large samples and multiple centers as well as standardization and quality control will be required to determine if Chinese herbal medicine treatment is effective and safe for type 2 diabetes.

## Keywords

Chinese medicine, type 2 diabetes

Received November 16, 2017. Received revised April 20, 2018. Accepted for publication May 13, 2018.

## Introduction

### Description of the Condition

As a group of chronic metabolic diseases, diabetes mellitus was identified in 382 million people in 2013 worldwide and will affect almost 600 million by 2035 based on the prediction from the International Diabetes Foundation.<sup>1</sup> About 5.8% of the world population was diagnosed with diabetes in 2014.<sup>2</sup> Additionally, 1.5 million deaths were estimated as a direct result of diabetes in 2012,<sup>2</sup> and this number went up to 4.9 million in 2014 globally.<sup>3</sup> The World Health Organization predicts that diabetes will be the seventh leading cause of death in 2030.<sup>4</sup>

There are 2 main types of diabetes: type 1 diabetes and type 2 diabetes; gestational diabetes is a third form of diabetes.<sup>5</sup> Type 2 diabetes, which is also called non-insulin-dependent

or adult-onset diabetes, is described as a progressive condition where the body becomes resistant to insulin and is associated with multiple lifestyle risk factors.<sup>5</sup>

Diabetes, predominantly type 2 diabetes, has been recognized as one of the enormous health care challenges for the 21st century.<sup>1</sup> Ninety percent of the people with diabetes are recognized to have type 2 diabetes around the world.<sup>6</sup> There is

<sup>1</sup> Endeavour College of Natural Health, Adelaide, South Australia, Australia

<sup>2</sup> The University of Adelaide, Adelaide, South Australia, Australia

### Corresponding Author:

Ao Yu, Chinese Medicine Department, Endeavour College of Natural Health, 88 Currie Street, Adelaide, South Australia 5000, Australia.

Email: ao.yu@endeavour.edu.au



also an increasing prevalence of type 2 diabetes in children, adolescents, and young adults.<sup>1</sup>

The economic burden of diabetes is remarkable and estimated as US\$376 billion, which was 12% of all global health expenditure in 2010.<sup>1</sup> It is predicted to rise to between US\$490 and US\$893 billion by 2030.<sup>1</sup>

China has become the diabetes focus among all nations in the world; there were 98.4 million diabetes patients diagnosed in China in 2013 and this number will increase to 142.7 million in 2035.<sup>1</sup> A total of 1.3 million Chinese with diabetes died in 2011.<sup>7</sup> Direct health care expenditure of type 2 diabetes and its complications in China were estimated at US\$26 billion in 2007 and is expected to increase to US\$47.2 billion by 2030.<sup>1</sup>

### Description of Intervention

There is no cure for type 2 diabetes and the management is through the control of blood glucose level by diet and exercise alone or in combination with medications. These include pharmaceuticals that are mainly Western hypoglycemic drugs and complementary therapy. Traditional Chinese medicine (TCM) is becoming increasingly popular in Western countries as an alternative intervention for type 2 diabetes.<sup>8</sup>

Diabetes mellitus has been recognized since antiquity and TCM herbs have been used to treat diabetes in China for more than 2000 years.<sup>9</sup> Xiaoke (wasting-thirst) is an ancient term for diabetes, which was first recorded in *The Yellow Emperor's Classic of Internal Medicine*.<sup>10</sup> The recorded symptoms describe 3 increases and 1 decrease (polydipsia, polyphagia, polyuria, and weight loss) and probably equates to the term "diabetes" in Western medicine.<sup>10</sup>

The treatment of diabetes with Chinese herbs is according to syndrome differentiation based on Qi (vital energy) and blood, Zang-Fu (5 viscera and 6 bowels), and Yin-Yang (representing 2 opposite principles in the body) theory, which is different from Western medicine.<sup>11</sup>

The commonly recognized patterns of type 2 diabetes are Qi and Yin (body fluids) deficiency, heat, and stasis based on TCM theory. Qi and Yin deficiency patterns may occur in initial stages and result in the heat of tissues and blood stasis.<sup>12</sup> Alternatively, heat can occur earlier, or Yin deficiency and heat may present simultaneously for relatively longer duration, while stasis may happen at any stage.<sup>13</sup> Thus, frequently used herbal formulae can be categorized into 4 groups: Qi invigorating, Yin nourishing, heat clearing, and stasis-reducing (improving blood circulation).<sup>12</sup> The most frequently prescribed herbs are Membranous Milkvetch Root (Huang qi), Rehmannia Root (Di huang), Common Anemarrhena Rhizome (Zhi mu), and Danshen Root (Dan shen), which respectively belong to the above-mentioned groups.<sup>12</sup>

In China, government-owned health care delivery facilities are responsible for the treatment of most of patients and hospital delivery rates averaged 95% in 2011.<sup>14,15</sup> The private sector has grown more quickly than the public sector since the mid-1990s, especially in rural areas.<sup>14</sup> Diabetes in China is

mainly managed in public health care sectors as inpatient or outpatient services.<sup>16</sup>

### How TCM Works

TCM has its own theory for disease mechanism, diagnostic techniques, and therapeutic principles. Generally speaking, diseases are considered as interaction between both internal and external causes and result in disturbance of Qi and blood, Zang-Fu, and imbalance between Yin and Yang.<sup>17</sup> The diagnostic system in TCM is 4 examinations: inspection, listening/smelling, inquiry, and palpation.<sup>17</sup> Tongue inspection and pulse palpation are 2 unique diagnostic techniques of TCM compared with Western medicine. The discussion of treatment is based on syndrome differentiation. Syndrome differentiation is an approach to make a comprehensive analysis of the data collected from the 4 examinations and decide the diagnosis based on TCM theory.<sup>17</sup> The major differentiating methods are developed as follows: 8 guiding principles syndrome differentiation, disease-cause syndrome differentiation, syndrome differentiation of qi, blood and body fluids, Zang-Fu organ syndrome differentiation, 6-channel syndrome differentiation, defense-qi-nutrient-blood syndrome differentiation, and triple-burner syndrome differentiation.<sup>17</sup> The therapeutic philosophy and goals of TCM are focused on the overall functional state of the patient, which can differ from those in Western medicine.<sup>18</sup> Acupuncture and moxibustion, Chinese herbal medicine, Chinese dietary therapy, Chinese exercise therapy, and manual therapy are the 5 major branches of TCM treatment methods.<sup>17</sup>

TCM usually concentrates on holistic treatment of the patient instead of focusing on treating a single disease.<sup>18</sup> TCM formulae often contain large numbers of active ingredients that are suitable for regulating several crucial targets based on individualized treatment.<sup>18</sup> Thus, the action of Chinese herbal medicine is different due to the therapeutic principles and goals of TCM differing from those in Western medicine. And the measurement of intended effects of TCM herbs is also complicated compared to Western medicine, which primarily consists of single chemical compounds.<sup>18</sup>

Although many of the antihyperglycemic components of TCM herbs are unknown, Chang and colleagues summarized the chemistry and biological action of 40 extracts and compounds of plant origin.<sup>19</sup> The mechanism of action of these herbal medicines involves improving insulin sensitivity, stimulating insulin secretion, protecting pancreatic islet cells, and inhibiting intake of intestinal carbohydrates.<sup>12</sup>

### Adverse Effects of Chinese Herbal Medicine

It has been widely acknowledged that medicinal herbs are normally nontoxic, while the consumption of herbs still has risk due to incorrect prescribing, over dosage, improper preparation, erroneous substitution, adulteration with Western medicine, and inherent toxicity or contaminants.<sup>8,20</sup> The toxicity-related issues of herbal ingredients have been reported

earlier.<sup>8</sup> The most commonly seen TCM-dependent clinical complications are interactions between TCM herbs and conventional drugs taken for diabetes.<sup>8</sup> Another source of clinical concern is contamination of TCM preparations with impurities, heavy metals, or bacteria, and heavy metals have been reported before as the main poison associated with the use of TCM products.<sup>8</sup> Other causes of toxicity also involve intentional adulteration of TCM with bioactive additives such as corticosteroids, hormones, salicylates, or antihistamines.<sup>8</sup> Improper prescription of herbal formulae and preparation of herbs, which relate to the regulation of herbal medicine and Chinese herbal medicine practitioners, is a cryptic underlying risk factor. For example, if a doctor prescribed energy invigorating herbs rather than heat clearing herbs to a diabetic patient with body heat pattern, the symptoms could be worse in this patient. Identifying the active ingredients of herbs and their pharmacological mechanism of actions are both time consuming and financially expensive since one formula is often formed from many single herbs, and a single herb usually has multiple compounds. Besides, the real efficacy and toxicity of herbal agents are difficult to test using the current evaluation paradigm for single chemical compounds.<sup>18</sup>

### Why It Is Important to Conduct This Review

An increasing number of type 2 diabetes patients choose to manage their condition with TCM without consideration of the potential toxic effects of medicinal herbs.<sup>8</sup> There are limited studies in the English literature discussing both effectiveness and adverse effects of Chinese herbs used to treat type 2 diabetes. This review evaluated the evidence for effectiveness, explored adverse effects, and quality control according to the *Cochrane Handbook for Systematic Reviews of Interventions*, and also provides an English literature review of type 2 diabetes treatments with Chinese herbal medicines versus other interventions based on the original Chinese literature. In practice, it should also provide valuable information of study designs for future research into diabetes treatment with TCM herbal medicines.

## Methods

### Criteria for Considering Studies for This Review

We did a systematic review and assessed the primary outcomes according to the *Cochrane Handbook for Systematic Review of Interventions*.

### Types of Studies

Randomized controlled clinical trials with a minimum treatment period of 8 weeks were included in this review. Only studies in the English and Chinese literature were used in this review.

### Types of Participants

Adults diagnosed with type 2 diabetes mellitus based on documented diagnostic criteria were included. WHO 1999, WHO 2007, ADA

1999, ADA 2003, China 1994, China 2007 and China 2012 were used as the benchmark for type 2 diabetes in the inclusion criterion. Only studies of type 2 diabetes with Chinese herbal medicine treatment were studied. The review included studies only if participants' intervention duration was 8 weeks or more. Trials involving type 2 diabetes treatment with acupuncture or other TCM modalities (alone or combined with Chinese herbal medicine) were excluded.

### Types of Interventions

Chinese herbal medicines including a compounded herbal formula or individualized prescriptions by Chinese medicine practitioner(s), patent herbs, single herb, Chinese herbal medicines combined with pharmacological intervention, and other intervention including diet control, exercise therapy, and diabetes education, regardless of the dose, method of dosing, or duration of administration were compared with other treatments (mainly pharmacological intervention). The following comparisons were included:

1. Chinese herbal medicines combined with other pharmaceuticals versus other pharmaceuticals (mainly Western medicines)
2. Chinese herbal medicines alone versus other pharmaceuticals (mainly Western medicines)
3. Chinese herbal medicines (alone or combined with other interventions or other pharmaceuticals) versus placebo
4. Chinese herbal medicines combined with other pharmaceuticals versus Chinese herbal medicines versus pharmaceuticals alone
5. Chinese herbal medicines alone versus pharmaceuticals versus other interventions (including diabetes education, diet control, and exercise therapy)

### Types of Outcome Measures

#### Effectiveness of Intervention.

- Glycemic control: glycated hemoglobin levels (HbA1C) and blood glucose levels (fasting blood glucose [FBG] or 2-hour postprandial blood glucose [2hPBG])
- Blood lipid profiles: total cholesterol [TC], triglycerides [TG], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C]
- Weight or body mass index (BMI)
- Insulin resistance levels (HOMA-IR or ISI)
- TCM clinical symptom score

Scoring of TCM symptoms is a method of evaluating the symptoms of diabetes including dry throat and mouth, lack of strength, polyphagia, polydipsia, polyuria, shortness of breath, vexing heat in the chest, palms and soles, palpitation, insomnia, and so on.

#### Adverse Outcomes.

- Routine blood and urine test
- Liver and kidney function test
- Electrocardiography (ECG)
- Clinical symptoms of adverse effects

## Timing of Outcome Assessment

Studies with possible effective treatment duration from 8 weeks to 1 year were included for analysis.

## Search Methods for Identification of Studies

The following resources were searched to identify trials:

- The Cochrane Library (Wiley Online Library)
- Web of Science
- PubMed
- Google Scholar
- The University of Adelaide Library Research
- China Academic Journals Full-text Database (Basic Search)
- China Dissertation Database
- China Knowledge Resource Integrated (CNKI) Database
- Baker Heart and Diabetes Institute

We conducted extensive and ongoing electronic searches in the above-described databases from 2004 until April 2016. All authors screened search results and identified the full texts of all relevant trials reports. We also detected additional keywords of relevance during any of electronic or other searches by modifying the search strategies to incorporate the search terms. Studies published in English and Chinese were included. We searched other resources as well, such as reference lists of relevant trials and reviews from published studies and used personal communication from the National Resource Centre for Chinese Materia Medica for identification of additional relevant studies. We did not search unpublished literature (the studies that have not been published due to negative results and the studies that were not peer reviewed).

## Data Collection and Analysis

**Selection of Studies.** The abstract, title, or both of every record retrieved were scanned by the authors to determine the studies to be assessed further. The full texts of all potentially relevant articles was studied, and inclusion in this review was based on the following criteria:

- Compared Chinese herbal medicines (alone or combined with other intervention or other pharmaceuticals) with other pharmaceuticals (alone or combined with other intervention), placebo or other intervention (including diet control, exercise therapy and diabetes education) as treatment for type 2 diabetes
- Included patients with type 2 diabetes mellitus; excluded pre-type 2 diabetes, diabetes complications
- Excluded herb extracts, Chinese herbal medicine combined with acupuncture and Tui Na (traditional Chinese medicine remedial massage) treatment, comparison of different forms of Chinese herbs
- Assessed more than one relevant outcome
- Used random allocation to the comparison groups
- Study duration not less than 8 weeks

Where information was ambiguous or missing in the article or there was differences of opinion, the decision to include the trial was resolved by consensus. Authors of relevant identified studies and experts in relevant fields were contacted in order to

obtain additional references. In addition, we contacted the agency responsible for the regulation of reviewed Chinese herbal medicines—National Resource Centre for Chinese Materia Medica and China Academy of Chinese Medical Science—in order to retrieve information on published herb trials.

## Data Extraction and Management

For studies that fulfilled the inclusion criteria, data of the relevant population, intervention, and outcome characteristics were abstracted by using standard data extraction templates (for details, see “Table 2: Characteristics of Included Studies,” available as supplemental material in the online version of the article); any questions were resolved by discussion between the authors, referring back to the original article. When necessary, additional information was sought from the authors of the primary studies.

## Assessment of Risk of Bias in Included Studies

We assessed the risk of bias for each included study based on the criteria outlined in the *Cochrane Handbook for Systematic Review of Interventions*. Any uncertainty was resolved by discussion between the 3 authors. The details of risk of bias are listed in “Table 2: Characteristics of Included Studies” (available in the online version of the article).

## Results

### Description of Studies

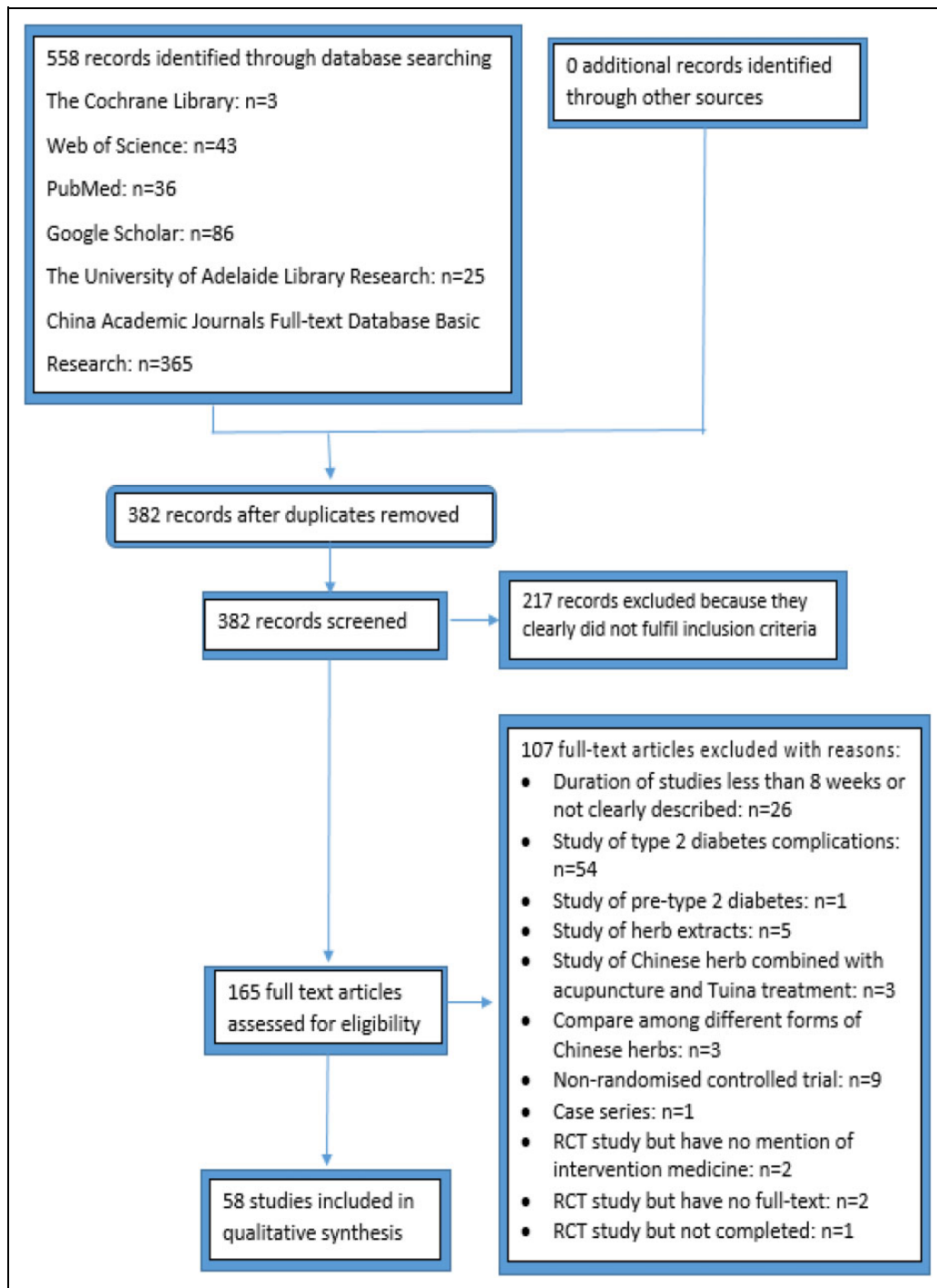
558 clinical trials of type 2 diabetes with Chinese herbal medicine treatment were identified, and 165 full-text articles were eligible for detailed review. 58 studies were included and 107 studies excluded based on the above-mentioned criteria.

### Results of the Search

A total of 558 references were identified by initial database searching up to April 8, 2016. 382 potentially eligible studies were kept for further assessment after duplicates were removed. 217 studies were excluded because they clearly did not fulfil the inclusion criteria. Full-text articles were explored for clarification if the title and abstract did not provide clear information. 165 full-text articles were assessed for eligibility. 58 full-text articles were included in our qualitative synthesis, and 107 full-text articles were excluded. The reasons for exclusion are listed in Figure 1 and “Table 3: Characteristics of Excluded Studies” (available in the online version of the article). Further investigation of the full articles retrieved included 5 studies that were initially excluded, and 9 studies were excluded that were initially included. An adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart of study selections is shown in Figure 1.

### Included Studies

58 trials were included for effectiveness and safety assessment and risk of bias analysis. For more information, see “Table 2:



**Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection.

Characteristics of Included Studies” (available in the online version of the article).

### Study Design

All the included studies stated they were randomized controlled clinical trials, but only 13 trials reported the details of randomization methods, and 3 trials (Ji 2013; Chao 2009; Tong

2013) provided very detailed information of the randomization methods. 1 trial (Ji 2013) had 4 arms (see Supplemental Materials for details of the studies).

### Participants

All the study participants were hospital patients diagnosed with type 2 diabetes mellitus that were either receiving or not

receiving treatment before the study commenced. 55 studies were carried out in a single study center, mainly different provincial and municipal hospitals of main cities in mainland China. 3 trials (Chao 2009; Tong 2013; Ji 2013) were carried out in multiple study centers, with 2 studies using 2 and 10 centers, respectively, in China, and the other study using 20 centers (19 participant centers in China and 1 participant center in Queensland, Australia). See Supplemental Materials for details of the studies.

### Diagnosis

The diagnostic criteria for type 2 diabetes mellitus were mainly based on WHO criteria (43 trials by criteria in 1999, 1 trial by 2007, 2 trials without specification), and 3 trials used the criteria of ADA (1 trial by 1999, 1 trial by 2003, and 1 trial without specification). 4 trials used their diagnostic criteria based on textbook criteria, and 5 trials had no specification.

### Interventions and Comparisons

42 trials compared combined Chinese herbal medicines and other pharmaceuticals with other pharmaceutical. Ten trials compared Chinese herbal medicines with other pharmaceuticals. 4 trials compared Chinese herbal medicines with placebo; 2 trials compared 3 groups (one compared Chinese herbal medicines combined with pharmaceuticals to other pharmaceuticals or to Chinese herbal medicines; the other compared Chinese herbal medicines to pharmaceuticals or to other interventions). Only 1 trial was a multiple-armed study that compared Chinese herbal medicines combined with pharmaceuticals to other pharmaceutical between a drug naïve group and drug group. Most trials tested various Chinese herbal medicines including individual prescriptions modified from classical formulae. 3 trials only tested a single Chinese herb: Huanglian (*Coptidis Rhizoma*) or Wuweizi (*Fructus Schisandrae*).

The formulae of Chinese herbal medicines were different in each study. All recorded formulae, individual formulae, and patent herbal formulae were included in the studies and the basic composition consisted of the 132 common Chinese herbal medicines; for more details, see “Table 4: List of Chinese Herbal Medicines Used as Treatment for Type 2 Diabetes” (available in the online version of the article). Pharmaceuticals included commonly used hypoglycemic Western medicines such as metformin, sulfonylureas (glibenclamide, glimepiride, and glipizide),  $\alpha$ -glucosidase inhibitor (acarbose), thiazolidinediones (rosiglitazone), and insulin. Other interventions mainly included diet control, exercise therapy, diabetes health education, and other lifestyle changes.

### Follow-up

All of the 58 included trials followed-up the participants until the end of the treatment. 24 trials studied and/or reported the adverse effects of the intervention.

### Publication Details

See “Table 2: Characteristics of Included Studies” for detailed information (available in the online version of the article).

### Risk of Bias in Included Studies

Most participants in included studies were mainly Chinese recruited from TCM hospitals, which led to selection bias because the results might not be applicable to the general population. A general conclusion cannot be drawn because the sample might not be representative of the whole population.

In addition, there was insufficient information to make a formal assessment; most included studies were at an unclear risk of bias for nearly all of the “Risk of Bias” domains apart from attrition bias. See “Table 2: Characteristics of Included Studies” for more information.

### Allocation

42 included studies reported that the participants were randomly divided into 2 groups for respective treatments without giving further details. 11 included studies reported a further randomization method: “By using random number table method.” Moreover, 2 trials mention “by random file number method.” Only 3 trials reported a detailed randomization method, “Statistics Analysis System software was used to randomly divide the subjects,”<sup>21</sup> or “randomization was performed centrally and was concealed and stratified in blocks of four,”<sup>22</sup> or “randomization and blinding were conducted by personnel who did not participate in data acquisition and evaluation. A computer program was used to generate the subject assignment; each subject was given a unique number and this number was used throughout the trial.”<sup>23</sup> In addition, all 16 of these trials were assessed as having a low risk of selection bias.

### Blinding

53 studies were assessed as unclear for performance bias and detection bias because no information on blinding of participants and personnel or outcome assessors was provided in the trial reports. Only 5 studies reported detailed information of blinding methods: “double-blinded and placebo-controlled” or “All investigators were blinded from the study drug assignment, in which only a randomization code was disclosed. Unblinding was conducted only after all study data were collected.” Moreover, all 5 of these trials were assessed as having a low risk of performance bias and detection bias.

### Incomplete Outcome Data

All 58 studies were assessed as having a low risk of attrition bias. After checking the total number of participants and the patients included in each intervention group, there were no missing data in 53 studies. There were exclusions or losses to follow-up reported in 5 included studies. 1 trial lost follow-up in both groups before the start of the study. 2 trials

had missing outcome data balanced in numbers and with similar reasons for missing data across groups. Another trial had missing outcome data balanced in numbers across groups for no reported reason. The last one had missing outcome data balanced in numbers across intervention groups, and the proportion of missing data compared with the observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate.<sup>24</sup>

### Selective Reporting

54 studies were assessed as having an unclear risk of reporting bias since their protocols were not available. 4 had clear protocols and were assessed as having a low risk of reporting bias.

### Other Potential Sources of Bias

All 58 studies were assessed as unclear risk of other potential bias. All included studies followed-up the participants until the end of treatment. Most of studies reported that there was no significant difference among the groups before the interventions, and were considered to have good baseline similarity. However, other aspects of bias were still unclear, as most studies did not clearly report how diabetes had been controlled, and for how long, before the studies.

### Effects of Interventions

58 studies with 6637 patients diagnosed with type 2 diabetes were included in the review. All included studies compared Chinese herbal medicine with other interventions (pharmaceuticals, diet control, and exercise therapy and health education). 5 comparisons and summary of findings are available in Supplemental Table 1 (available in the online version of the article).

### Discussion

This review aimed to evaluate the effectiveness and safety of Chinese herbal medicine as a treatment for type 2 diabetes mellitus. The therapeutic effects of Chinese herbal medicine on the control of glycosylated hemoglobin and glycemic level, insulin resistant level, and TCM clinical symptoms score have been studied and reported mostly inside China, and very few English language studies were found outside of China. This research included 55 studies from the Chinese literature and 3 studies from the English literature (58 studies involving 6637 type 2 diabetes patients in total). All included studies from the Chinese literature were translated into English and incorporated in "Table 2: Characteristics of Included Studies" (available in the online version of the article). There were 5 different comparisons with 132 herbal medicines involved in the 58 trials with trial periods lasting from 8 weeks to 1 year. Meta-analysis was not performed in this review because there was a mix of comparisons of different treatments, the outcomes were too diverse in most of the included studies, and bias was present in most of the individual studies.<sup>24</sup> There was no picture of

general statistics for average change rate of primary outcomes in this review because insufficient information was available in many included studies to generate this summary. This is the same reason that no meta-analysis was included in this review.

### Summary of Main Results

**Effectiveness.** The general results suggested that Chinese herbal medicines used alone or in combination with other Western hypoglycemic agents or lifestyle changes was associated with a decrease of glycosylated hemoglobin and blood glycemic level, blood lipid profiles, BMI, and TCM clinical symptom score. However, there was no clear description of how insulin resistance was measured. 14 trials recruited type 2 diabetes patients with insulin resistance and used a combination of Chinese herbal medicine with other pharmaceuticals or lifestyle interventions. The outcomes were associated with Chinese herbal medicine enhancing the therapeutic effects of other pharmaceuticals by improving insulin sensitivity in the treatment of type 2 diabetes.

42 trials showed statistically significant improvement of blood glucose control by Chinese herbal medicines combined with Western hypoglycemic agents compared to Western medicine alone for type 2 diabetes. 34 of the 42 trials indicated improvement with statistical significance in both glycosylated hemoglobin and glycemic control. 39 studies reported glycosylated hemoglobin decreases, and the range of reduction was 0.02% to 2.81% for 34 trials and 0.2 to 1.6 mmol/L for 5 trials. 42 studies mentioned glycemic level decreases with 37 trials reporting measurable details: the range of reduction was 0.02 to 1.75 mmol/L for fasting plasma glucose (37 trials) and -0.2 to 7.2 mmol/L for postprandial plasma glucose (33 trials). Except for one case of asymptomatic type 2 diabetes, 41 of the 42 trials showed improvement of TCM clinical symptoms. 19 trials measured TCM symptoms scores of diabetes with the range of reduction from 12% to 80%, indicating statistically significant improvement. 26 studies included blood lipid profiles and 5 studies included BMI along with blood glycemic level as primary outcomes. Most of these studies reported no statistically significant difference with blood lipid profiles changes between 2 groups. 20 studies measured insulin resistance level along with blood glycemic level as primary outcomes.

10 trials claimed improvement of glycemic control by Chinese herbal medicines, alone or in combination with lifestyle interventions compared to Western medicine for type 2 diabetes. 8 of the 10 trials indicated statistically significant effectiveness. 7 of 10 trials showed both glycosylated hemoglobin and glycemic control improvement. The range of glycemic level reduction was 0.19 to 2.4 mmol/L for fasting plasma glucose and 0.33 to 2.3 mmol/L for postprandial plasma glucose. 5 studies reported glycosylated hemoglobin reduction with a range variation of 0.1% to 0.4%. All 10 trials showed improvement of TCM clinical symptoms, with 7 trials indicating statistically significant improvement of TCM clinical symptoms score. The range of reduction is from 15% to 70%.



4 trials showed improvement at glycemic control of Chinese herbal medicines alone or in combination with other lifestyle interventions compared to placebo for type 2 diabetes, with statistical significance for 2 of 4 trials. The range of the glycosylated hemoglobin reduction was 0.1% to 0.4%, the range of glycemic level reduction was 0.1 to 0.3 mmol/L for fasting plasma glucose, and 0.2 to 1.1 mmol/L for postprandial plasma glucose. All 4 trials claimed TCM symptom improvement but only 2 trials had statistically significant (35% and 67%).

For 2 trials with comparisons of 3 groups, effectiveness could not be evaluated based on the available data (one study only reported effectiveness in the combination group compared to single Chinese herbal medicine group and Western medicine group; another study reported the effectiveness in 2 treatment groups compared to the no treatment group).

Most studies had average study durations of 8 to 12 weeks, which was too short to assess effectiveness in relation to glycosylated hemoglobin and glycemic level control.

**Adverse Effects.** Chinese herbal medicines are generally regarded as safe to treat type 2 diabetes if used properly, and this is supported by a long history of clinical practice. However, all medicines are associated with some risks and there is no exception for Chinese herbal medicine. The adverse effects related to type 2 diabetes treatment with Chinese herbal medicines might be attributable to incorrect prescription, over dosage, improper preparation, erroneous substitution, adulteration with Western medicine, and inherent toxicity or contaminants.<sup>20</sup> However, there was lack of universal reference for scientific evidence to assess the safety of this intervention, and the data related to the adverse effects of Chinese herbal medicine were insufficient. In addition, the chemical components of Chinese herbal medicines are more complex than in Western medicine, and each formula usually contains several herbs with each herb usually having multiple potentially active ingredients.

22 clinical trials out of the 58 included studies reported adverse effects such as nausea, vomiting, bloating, diarrhea, or other stomach discomfort along with hypoglycemic episodes. 19 trials out of 22 reported the examination details for identifying adverse effects and certainly had no safety assessment comparable with Western medicines. 3 trials out of 22 reported no adverse effects observed and they did not mention if and what kinds of examinations were performed for identifying the adverse effects. There was no information reported in terms of adverse effects in the other 36 included studies. There were no information reported of any serious adverse outcomes or deaths in the 58 included trials.

**Overall Completeness and Applicability of Evidence.** There were 3 main approaches of intervention for type 2 diabetes in all included studies: pharmaceutical treatment, Chinese herbal medicine, and lifestyle (diet and exercise) control. In this review, all of these treatments were included for analysis. The results suggest that Chinese herbal medicines combined with other interventions (diet control, exercise therapy, and pharmaceuticals) were more effective than pharmaceuticals but with a

major limitation (selection bias of patients recruitment). Most clinical trials were not well designed, and the overall quality of the studies was hard to determine because of the limited information reported in the studies. Overall, the quality of evidence was unsatisfactory and the risk of bias was unclear due to insufficient available information from most included studies. Most participants were from the Chinese population and recruited from TCM hospitals, and this could influence the applicability of the interventions to other populations. This is a major source of bias.

### Quality of Methodology

The general methodological quality of all selected trials was unsatisfactory based on international standards for a well-conducted randomized controlled trial. All selected trials reported important demographic information and mentioned that no significant difference was found between intervention groups on baseline data at recruitment. Most studies provided detailed information with baseline data before the recruitment of the study. However, in terms of randomization, allocation, and concealment methods, only 3 studies provided sufficient details. 13 trials reported limited details of randomization and allocation concealment method. The remaining 42 trials only generally mentioned that randomization applied in their studies without details of the randomization, allocation, and concealment methods. Only 5 studies reported detailed information of blinding methods. However, blinding is difficult with respect to Chinese medicine due to its taste. Furthermore, most studies that did not mention blinding might have avoided blinding because the patients were expected to receive only Chinese herbal treatment rather than Western medicines or placebo since they had decided to see a traditional Chinese medicine practitioner.

### Study Design

Most of the included studies provided information regarding the hypothesis to be tested, the baseline information of participants, their recruitment criteria, WHO diagnosis criteria of type 2 diabetes mellitus, and diagnosis criteria by Chinese medicine theory, clear information on study and control groups, the details of intervention medicines and treatment methods, the duration of intervention, and the proper outcome measurements. However, only 22 clinical trials out of 58 reported adverse effects, with 19 trials reporting the examination details for adverse effects. Most trials did not report potential side effects as a study outcome. Adverse effects of Chinese herbal medicines may have been neglected in most clinical studies due to various reasons mentioned above. Meta-analysis could not be performed due to the limited information with respect to study medicines and the different Chinese herbs used in each study. Furthermore, there were only 4 placebo-controlled trials, which were insufficient to draw any conclusion with respect to the effectiveness and safety of Chinese herbal medicine for treating type 2 diabetes mellitus.

## Result Report and Analysis

No exclusion or losses were reported in most of the included trials, but the number of participants remained the same at the beginning and the endpoint of studies. So apart from 5 trials that reported lost follow-up data, all remaining 53 trials were assumed to have had no dropouts by checking the numbers of participants from the beginning and the end of the study. The 5 studies that reported the incomplete data were assessed as low risk based on the Cochrane Collaboration's tool for assessing risk of bias.<sup>24</sup> The protocol of most included studies was not described in sufficient detail, so it was not possible to carry out a meta-analysis.

## Conclusions of the Included Studies

All studies reported the therapeutic effects of the interventions, but only 2 studies published outside of China recorded their limitations in the discussion section of the trial report. The approach to treating type 2 diabetes may differ according to TCM syndrome differentiation. Many herbal formulae were slightly modified compared to the classical prescription depending on individual clinical presentation. Most studies described formulae with multiple herbs and only 3 studies reported single herb usage. Therefore, the conclusion with respect to effectiveness in this review is only in general terms but not for specific formulae or individual Chinese herbal medicines.

All selected studies were eligible for this review but the overall quality of the methodology was inconclusive and unsatisfactory. The evidence of included studies was insufficient, so the risk of bias of included studies was unclear. In addition, the evidence of safety of Chinese herbal medicines as a treatment for type 2 diabetes was inadequate due to the variation in studies and methodology. Well-designed clinical trials with standard criteria are required for the study of safety of Chinese herbal medicines.

## Potential Biases in the Review Process

We tried to include all relevant studies on type 2 diabetes treatment with Chinese herbal medicine. Most full-text articles were in Chinese with only English abstracts. However, not all literature are in all database. Some database could not be accessed due to location and language limitation, as some Chinese databases are not accessible from Australia. It is also impossible to avoid publication bias, as negative studies were not reported. Alternatively, some articles were published but not peer reviewed. Meta-analysis could not be conducted due to the reason mentioned above.

Systematic bias could be possible since most of the included studies did not provide detailed protocol of administration of treatment and assessment of outcomes but only simply reported that randomization was performed for allocation of intervention groups. Selection bias could not be avoided since most study participants were Chinese recruited from TCM hospitals. Blinding of participants and personnel processes were described with detailed information in most included studies.

In terms of duration of intervention, only 2 studies lasted 4 months, 5 studies lasted 6 months, 1 study 48 weeks, and 1 study 1 year. Most trials reported end-of-treatment outcomes ranging from 8 to 12 weeks, which was too short to address long-term effectiveness and toxicity of the herbs. In particular, for Chinese herbal medicine, there is a lack of information about the half-life of plant secondary metabolites to test long-term effectiveness and adverse effects, making it problematic to determine if Chinese herbal medicine could be an effective and safe treatment for type 2 diabetes. Effectiveness and safety issues should be a future research emphasis for Chinese herbal medicine used to treat chronic diseases such as type 2 diabetes.

## Agreements and Disagreements With Other Studies or Reviews

The findings in this review related to effectiveness of Chinese herbal medicines to treat type 2 diabetes are similar to the conclusion of previous systematic reviews. The only previous Cochrane systematic review on Chinese herbal medicine to treat type 2 diabetes was in 2004 by Liu and others.<sup>11</sup> Liu and colleagues analyzed the effects of 66 randomized trials of 69 herbs involving 8302 patients with type 2 diabetes. The conclusion was that herbal medicines were effective on blood glucose control in people with type 2 diabetes mellitus. Nevertheless, there was no mention of any adverse effects related to type 2 diabetes with Chinese herbal medicine treatment.

## Conclusions

### Implications for Practice

A combination of Chinese herbal medicine and other pharmaceuticals (mainly Western hypoglycemic agents) might be more effective than pharmaceuticals in terms of glycosylated hemoglobin, glycemia, and control of insulin resistance level in type 2 diabetes mellitus. However, there was limited evidence to assess the effectiveness of Chinese herbal medicine alone for treating type 2 diabetes (only 10 trials with small sample size). The quality of evidence (data of study duration and outcome) is insufficient to fully evaluate the effectiveness and adverse effects of the intervention.

### Implications for Research

Long-term well-designed studies are required to compare Chinese herbal medicines alone with pharmaceutical alone or placebo before drawing any conclusion about the effectiveness and safety of type 2 diabetes treatment with Chinese herbal medicine. We suggest undertaking high-quality clinical trials with multiple centers (large samples) and publication in English as a way to rectify this. Adequate randomization methods need to be applied and clearly reported. Clear information should be provided about the management methods and their duration before the study, along with other baseline characteristics for the recruitment of patients. Evaluation of

effectiveness must be more clearly specified and focused on glycosylated hemoglobin and glycemic control.

We suggest standardization and quality controls to assess effectiveness and safety of Chinese herbal medicine for type 2 diabetes treatment. Future studies should address safety issues by not only reporting adverse effects but also supplying details of toxicity tests for type 2 diabetes patients. With respect to TCM assessment and treatment variation based on syndrome differentiation, we suggest recruiting the same category of type 2 diabetes patients and treatment with similar Chinese herbal medicines in future studies in order to reduce the information bias of studies as much as possible. We recommend multiple-center trials with type 2 diabetes patients recruited from different sources (such as patients outside hospitals, patients outside China, etc) in order to avoid selection bias.

### Authors' Note

The work was carried out at the University of Adelaide with regular meetings of the three authors.

### Author Contributions

Ao Yu - wrote the first draft of the manuscript, analyzed the data and contributed to major revision. David Adelson and David Mills - contributed to major revision, equally provided the support and mentorship necessary for the success of the work.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The University of Adelaide.

### Ethical Approval

None required.

### Supplemental Material

Supplementary material for this article is available online. The list of abbreviations is also available in supplementary material.

### References

- Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol*. 2014;2:56–64.
- Krug EG. Trends in diabetes: sounding the alarm. *Lancet*. 2016; 387:1485–1486.
- International Diabetes Foundation. *IDF Diabetes Atlas*. 7th ed. Brussels, Belgium: International Diabetes Foundation; 2015.
- Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3:e442.
- World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1, Diagnosis and Classification of Diabetes Mellitus*. Geneva, Switzerland: World Health Organization; 1999.
- Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539–553.
- Scully T. Diabetes in numbers. *Nature*. 2012;485:S2–S3.
- Youns M, Hoheisel JD, Efferth T. Toxicogenomics for the prediction of toxicity related to herbs from traditional Chinese medicine. *Planta Med*. 2010;76:2019–2025.
- Cheng JT. Review: drug therapy in Chinese traditional medicine. *J Clin Pharmacol*. 2000;40:445–450.
- Zhang H, Tan C, Wang H, Xue S, Wang M. Study on the history of traditional Chinese medicine to treat diabetes. *Eur J Integr Med*. 2010;2:41–46.
- Liu JP, Zhang M, Wang WY, Grimsgaard S. Chinese herbal medicines for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2004;(3):CD003642.
- Xie W, Zhao Y, Zhang Y. Traditional Chinese medicines in treatment of patients with type 2 diabetes mellitus. *Evid Based Complement Alternat Med*. 2011;2011:726723.
- Peng B. *Traditional Chinese Internal Medicine*. 2nd ed. Beijing, China: People's Medical Publishing House; 2007:516.
- Eggleston K, Ling L, Qingyue M, Lindelow M, Wagstaff A. Health service delivery in China: a literature review. *Health Econ*. 2008;17:149–165.
- Meng Q, Xu L, Zhang Y, et al. Trends in access to health services and financial protection in China between 2003 and 2011: a cross-sectional study. *Lancet*. 2012;379:805–814.
- Pan C, Yang W, Jia W, Weng J, Tian H. Management of Chinese patients with type 2 diabetes, 1998–2006: the Diabcare-China surveys. *Curr Med Res Opin*. 2009;25:39–45.
- Zhu B, Wang H. *Diagnostics of Traditional Chinese Medicine (International Acupuncture Textbooks)*. 1st ed. Philadelphia, PA: Singing Dragon; 2010.
- Jiang WY. Therapeutic wisdom in traditional Chinese medicine: a perspective from modern science. *Trends Pharmacol Sci*. 2005; 26:558–563.
- Chang CLT, Lin Y, Bartolome AP, Chen Y, Chiu S, Yang W. Herbal therapies for type 2 diabetes mellitus: chemistry, biology, and potential application of selected plants and compounds. *Evid Based Complement Alternat Med*. 2013;2013:378657.
- Zhao HL, Tong PCY, Chan JCN. Traditional Chinese medicine in the treatment of diabetes. In: Bantle JP, Slama G, eds. *Nutritional Management of Diabetes Mellitus and Dysmetabolic Syndrome*. Vol 11. Basel, Switzerland: Nestle Nutrition Institute/Karger; 2006:15–29.
- Ji L, Tong X, Wang H, et al. Efficacy and safety of traditional Chinese medicine for diabetes: a double-blind, randomised, controlled trial. *PLoS One*. 2013;8:e56703.
- Chao M, Zou D, Zhang Y, et al. Improving insulin resistance with traditional Chinese medicine in type 2 diabetic patients. *Endocrine*. 2009;36:268–274.
- Tong X, Wu S, Lian F, et al. The safety and effectiveness of TM81, a Chinese herbal medicine, in the treatment of type 2 diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Obes Metab*. 2013;15:448–454.
- Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Vol 5. Hoboken, NJ: John Wiley; 2008.