Efficacy of Chinese herbal medicine for stroke modifiable risk factors: a systematic review

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Abstract

Background: The vast majority of stroke burden is attributable to its modifiable risk factors. This paper aimed to systematically summarise the evidence of Chinese herbal medicine (CHM) interventions on stroke modifiable risk factors for stroke prevention.

Methods: A literature search was conducted via the MEDLINE, CINAHL/EBSCO, SCOPUS, and Cochrane Database from 1996 to 2016. Randomised controlled trials or cross-over studies were included. Risk of bias was assessed according to the Cochrane Risk of Bias tool.

Results: A total of 46 trials (6895 participants) were identified regarding the use of CHM interventions in the management of stroke risk factors, including 12 trials for hypertension, 10 trials for diabetes, eight trials for hyperlipidemia, seven trials for impaired glucose tolerance, three trials for obesity, and six trials for combined risk factors. Amongst the included trials with diverse study design, an intervention of CHM as a supplement to biomedicine and/or a lifestyle intervention was found to be more effective in lowering blood pressure, decreasing blood glucose level, helping impaired glucose tolerance reverse to normal, and/or reducing body weight compared to CHM monotherapy. While no trial reported deaths amongst the CHM groups, some papers do report moderate adverse effects associated with CHM use. However, the findings of such beneficial effects of CHM should be interpreted with caution due to the heterogeneous set of complex CHM studied, the various control interventions employed, the use of different participants’ inclusion criteria, and low methodological quality across the published studies. The risk of bias of trials identified was largely unclear in the domains of selection bias and detection bias across the included studies.

Conclusion: This study showed substantial evidence of varied CHM interventions improving the stroke modifiable risk factors. More rigorous research examining the use of CHM products for sole or multiple major stroke risk factors are warranted.

Keywords: Chinese herbal medicine, Stroke, Risk factor, Prevention

Background

Stroke is the second foremost cause of mortality and a leading cause of serious disability worldwide [1]. The incidence of stroke continues to rise due to societal and lifestyle changes and an aging population [2]. More than 90% of the stroke burden is attributable to its modifiable risk factors such as high blood pressure, high fasting plasma glucose, and high total cholesterol [3]. These stroke risk factors are strongly inter-related and some of them are simultaneous shown as a combined risk factor in people with stroke with higher risk [4, 5]. Previous research has clearly demonstrated the benefits of treating risk factors such as hypertension, diabetes, hyperlipidemia, obesity, atrial fibrillation, or transient ischaemic attack (TIA) for reducing the prevalence of primary stroke [6, 7]. The treatments of major stroke modifiable risk factors are therefore crucial for informing stroke prevention.
strategies and helping achieve improved quality of life of people with those risk factors and lowered associated health care costs [3].

Chinese herbal medicine (CHM)—therapies and products made from any part of medicinal plants (e.g. leaves and roots) and some non-herb based components (e.g. shells and powdered fossil) [8]—has a history of more than 2500 years with a unique theory of diagnosis and treatment, and is considered a modality of complementary medicine in Western countries [9]. CHM has been increasingly used for a wide range of chronic diseases in China and elsewhere in the form of raw plant materials, powders, capsules, tablets and/or liquids [9–11].

Chinese herbal medicine is a field of health care that may offer potential for addressing related risk factors of stroke [12–14]. Many CHM interventions have long been used for the treatments of some stroke risk factors as individual diseases such as Type 2 diabetes [15], hypertension [8] and obesity [16]. However, the research evidence as to whether specific CHM therapies or products may be effective in reducing each individual or mixed major risk factors of stroke remains unclear. The aim of this systematic review is to assess and summarize the efficacy and safety of all relevant CHM interventions for people at greatest risk(s) of stroke.

Methods
Search strategy
Four key bibliographic databases—MEDLINE, CINAHL/EBSCO, SCOPUS, and Cochrane Database of Systematic Reviews—were searched in the systematic review. This review was designed and conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The stroke modifiable risk factors identified in this systematic review refer to high blood pressure (hypertension), high cholesterol (hyperlipidemia), irregular pulse (atrial fibrillation), TIA, high blood glucose (diabetes and impaired glucose tolerance (IGT)), and overweight (obesity). The literature search employed keyword and MeSH term searches for terms relevant to ‘CHM’ and terms regarding stroke risk factors (Table 1). The combination of the search results of CHM and stroke risk factors were identified for screening. To obtain all relevant articles, reference lists of published review papers were also reviewed via Google Scholar.

Study selection
The inclusion criteria of literature in the systematic review were: peer-reviewed English-language journal articles focusing upon randomized controlled trials (RCTs) or cross-over studies published in the past 20 years (1996–2016), and articles reporting primary data findings examining the efficacy and safety of any type of CHM interventions (e.g. decoction, capsule, granule, powder) on one or more major modifiable risk factors of stroke. Exclusion criteria were (1) published RCT protocols of this research area; (2) quasi- or pseudo-RCTs (3) studies focusing upon the efficacy and safety of CHM for treating stroke or post-stroke symptoms; (4) studies focusing upon the efficacy and safety of CHM for treating the complications of the stroke risk factors;

| Table 1 Search terms for the systematic review |
|-----------------------------------------------|
| Chinese herbal medicine OR Chinese herbal medicine [MeSH Term & Keyword] OR Chinese medicine [MeSH Term & Keyword] OR Chinese herbal* [Title/Abstract] OR Chinese herbal [Title/Abstract] |

**AND**

| Stroke risk factors | High blood pressure | Hypertension [MeSH Term & Keyword] OR Blood pressure [MeSH Terms & Keyword] OR Hypertens* [Title/Abstract] OR Prehypertens* [Title/Abstract] OR Systolic [Title/Abstract] OR Diastolic [Title/Abstract] OR |
|---------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------|
|                     | High cholesterol    | Cholesterol [MeSH Term & Keyword] OR Triglycerides [MeSH Term & Keyword] OR Dyslipidemia [MeSH Term & Keyword] OR Epicholesterol [Title/Abstract] OR HDL [Title/Abstract] OR LDL [Title/Abstract] OR Triglyceride* [Title/Abstract] OR Hyperlipidem* [Title/Abstract] OR Lipidem* [Title/Abstract] OR |
|                     | Irregular pulse     | Cardiac arrhythmias [MeSH Terms & Keyword] OR Atrial fibrillation [MeSH Terms & Keyword] OR Dysrhythmia* [Title/Abstract] OR Cardiac arrhythmia* [Title/Abstract] OR |
|                     | Transient ischaemic attack | Transient ischaemic attack [MeSH Terms & Keyword] OR Transient ischaemic attack* [Title/Abstract] OR |
|                     | High blood glucose  | Diabetes [MeSH Terms & Keyword] OR Mellitus [MeSH Terms & Keyword] OR Impaired glucose tolerance [MeSH Terms & Keyword] OR Diabet* [Title/Abstract] OR NIDDM [Title/Abstract] OR IDDM [Title/Abstract] OR T2DM [Title/Abstract] OR insulin* [Title/Abstract] OR Glucose [Title/Abstract] OR |
|                     | Overweight          | Obesity [MeSH Terms & Keyword] OR Overweight [MeSH Terms & Keyword] OR Metabolic syndrome [MeSH Terms & Keyword] OR Obes* [Title/Abstract] OR Adiposity [Title/Abstract] OR Adipos* [Title/Abstract] |

* Truncation, referring to all records that have those letters with any ending
(5) conference abstracts; and (6) publications without abstracts.

Data extraction

Titles and abstracts of all citations identified in the initial search were imported to Endnote (Version X7) and duplicates removed. Two of the authors screened all the titles/abstracts to identify articles meeting the inclusion and exclusion criteria independently. When consensus was not reached, the full texts of these unclear papers were retrieved and assessed by these two authors. Disagreements were discussed with a third author.

Data were extracted into a pre-determined table (Table 2) and checked for coverage and accuracy by two of the authors. Any differences in data extraction and interpretation were resolved through discussion amongst all authors. Table 2 includes detailed information on study recruitment, participant characteristics, intervention groups, results of primary outcome measures, study limitations, and CHM safety.

Quality assessment

Two authors independently assessed the methodological quality of the included studies using the Cochrane risk of bias criteria [17]. The characteristics of RCTs that might be related to selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias were evaluated. Disagreements regarding the risks of bias of some studies were resolved through discussion amongst these two authors (Table 3).

Results

The systematic review reported in this paper has been registered on the PROSPERO (International prospective register of systematic reviews, #CRD42017060107). The PRISMA flowchart of literature search and study/article selection has been shown in Fig. 1. A total of 2377 papers were identified (2374 via database searches and three additional papers via Google Scholar). After removing duplicates, a total of 2065 papers remained for review. From amongst these, 70 manuscripts were identified for full review following title and abstract screening. Further screening of the full texts identified 46 publications (reporting on 46 RCTs) as eligible for final inclusion in the systematic review. Twelve of the included articles report on the efficacy of CHM for hypertension (1340 participants), 10 for diabetes (2004 participants), eight for hyperlipidaemia (997 participants), seven for IGT (1805 participants), three for obesity (329 participants), and six for the combination of several stroke risk factors (420 participants). No manuscript reported on a trial investigating the efficacy of CHM interventions for the stroke risk factor of transient ischemic attack or atrial fibrillation as a primary outcome. The characteristics of included studies with regards to the CHM interventions for hypertension, diabetes, hyperlipidaemia, IGT, obesity, and combined stroke risk factors are summarized in Table 2.

Hypertension

Eight RCTs were focused upon primary (essential) hypertension [18–25], one with isolated systolic [26], one with elder polarized hypertension [27], and two with hypertension and related cardiovascular diseases [28, 29]. Of the 12 RCTs on CHM for hypertension, 11 RCTs originated from China [18–22, 24–29]. Amongst the hypertension-focused RCTs, one RCT compared ‘CHM, biomedicine plus lifestyle’ intervention with ‘biomedicine plus lifestyle’ intervention [27] and showed significant decreased systolic blood pressure (SBP) before and after treatment of both intervention groups and a similar effect on controlling SBP between these two groups after treatment. Another two RCTs compared two different CHM interventions using different inclusion criteria of people with hypertension [19, 21]—these studies both reported a significant decrease of SBP and diastolic blood pressure (DBP) via all the CHM interventions examined with higher effective rate of treatments in the CHM groups than those in the control groups. Another three RCTs compared ‘CHM’ interventions with ‘biomedicine’ interventions and employed consistent inclusion criteria regarding SBP (140–179 mmHg) and DBP (90–109 mmHg) of participants, reporting a statistically significant decrease of SBP and DBP before and after treatment of both groups and a similar effect on controlling SBP and DBP between these two groups after treatment. Another two RCTs compared two different CHM interventions using different inclusion criteria—these studies both reported a significant decrease of SBP and diastolic blood pressure (DBP) via all the CHM interventions examined with higher effective rate of treatments in the CHM groups than those in the control groups. Another three RCTs compared ‘CHM, biomedicine plus lifestyle’ intervention with ‘biomedicine alone’ or ‘biomedicine plus placebo’ interventions [20, 23, 25, 26, 28, 29]. It is noteworthy that two of these six trials [20, 28] examined the efficacy of the same CHM products (Xuezhikang capsule) at different dose levels, demonstrating a significant decrease of SBP and DBP before and after treatment of both intervention groups and a similar effect on controlling SBP and DBP between these two groups after treatment. Another six RCTs compared ‘CHM plus biomedicine’ interventions with ‘biomedicine alone’ or ‘biomedicine plus placebo’ interventions [20, 23, 25, 26, 28, 29]. It is noteworthy that two of these six trials [20, 28] examined the efficacy of the same CHM products (Xuezhikang capsule) at different dose levels, demonstrating a significant decrease of SBP and DBP before and after treatment of both intervention groups and a similar effect on controlling SBP and DBP between these two groups after treatment. Also amongst these six RCTs, three were three-armed RCTs which compared either ‘CHM plus biomedicine’ intervention versus ‘biomedicine/no intervention,’ ‘CHM’ interventions versus ‘CHM plus biomedicine’ or ‘placebo plus biomedicine’ interventions, or two types of preparations of a ‘CHM plus biomedicine’ intervention versus ‘placebo plus biomedicine’ intervention [25, 26, 28], showing inconsistent findings.
| Author                                      | Country | Stroke risk factor | Study period      | Participants                                                                 | Intervention groups | Results                                                                 | Side effects | Limitations |
|---------------------------------------------|---------|--------------------|-------------------|-----------------------------------------------------------------------------|---------------------|-------------------------------------------------------------------------|--------------|-------------|
| Lin et al. [18]                             | China   | Hypertension       | Sep 2001–Sep 2002 | Sample size n = 102. CHM group n = 52, 41 males and 11 females; mean age: 55 years. Control group n = 50, 41 males and 9 females; mean age: 54 years. Inclusion criteria: SBP: 140–179 mmHg or DBP: 90–109 mmHg; TCM diagnosed for hyperactivity of the liver-yang syndrome. | Tianma gouteng decoction 150 ml/time, twice daily, 4 weeks. Nifedipine 10 mg/time, 3 times daily, 4 weeks. | Baseline balance Yes. Significantly decreased SBP and DBP of both CHM and control groups before and after treatment, without significant difference between these two groups after treatment. | No side effects | N/A         |
| Li [19]                                     | China   | Hypertension       | No information on study period | Sample size n = 72. CHM group n = 46, 18 males and 28 females; mean age: 54 years. Control group n = 26; 11 males and 15 females; mean age: 53 years. Both groups have cases with coronary heart disease, hyperlipemia, and diabetes. Inclusion criteria: SBP: 140–179 mmHg or DBP: 90–109 mmHg; TCM diagnosed for flaming-up of the liver-fire syndrome. | Huanglian fire-purging mixture 30 ml/time, twice daily, 4 weeks. Niuhuang Bolus 1–2 bolus/time, 2–3 times daily, 4 weeks. | Baseline balance Yes. An effective rate (return to the normal range of BP or ≥20 mmHg but not in the normal range) at 60.9% of hypertension in the CHM group and 15.4% in the control group. Significantly decreased cholesterol, TG, blood sugar of the CHM group before and after treatment, without significant difference compared to the control group after treatment. | No/CHM group: Vomiting and distension (n = 1), Slight abdominal pain and diarrhea (n = 3) | N/A         |
| Ye et al. [20]                              | China   | Hypertension       | Feb 2004–Dec 2004 | Sample size n = 55. CHM group n = 28. Control group n = 27. Inclusion criteria: SBP: 140–179 mmHg or DBP: 90–109 mmHg; normal LDL-C level; currently no antihypertensive medications or using antihypertensive medications for at least 16 months before screening. | Xuezhikang with Nifedipine 120 mg daily, 72 weeks. Placebo with Nifedipine 120 mg daily, 72 weeks. | Baseline balance Yes. No significant differences in BP between the CHM and placebo groups after treatment. 92.8% of the CHM group and 88.9% of the placebo group reached the target BP (<140/90 mmHg). | N/A          | N/A         |
| Author          | Country | Stroke risk factor | Study period                  | Participants                                                                 | Intervention groups                                                                                          | Results                                                                                       | Side effects | Limitations          |
|-----------------|---------|--------------------|-------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------|----------------------|
| Zhao et al.     | China   | Hypertension       | No information on study period | Sample size n = 79, CHM group n = 40, 17 males and 23 females; mean age: 52 years  
Control group n = 39, 18 males and 21 females; mean age: 52 years  
Inclusion criteria: SBP 140–159 mmHg or DBP 90–99 mmHg; no antihypertensive drugs or stopped taking antihypertensive drugs for 2 weeks; TCM diagnosed for stagnation of phlegm, blood stasis and hyperactivity of the liver-yang syndrome; age: 40–60 years | Yinyin Jiangya Yin 100 ml/time, twice daily, 15 days  
Formulas: Gouteng, Shijeming, Yimucao, Guija, Banxia, Zhike, et al.  
Tianma Gouteng Yin 100 ml/time, twice daily, 15 days  
Formulas: Tianma, Gouteng, Huangqin, Yejiaoteng, Fushen, Duzhong, et al. | Baseline balance  
Yes  
Significantly decreased SBP and DBP of both CHM and control groups before and after treatment; Significantly decreased SBP and DBP in the CHM group than those in the control group after treatment; The total effective rate at 95.0% of BP control in the CHM group, while 87.2% in the control group | No side effects | N/A |
| Zhong et al.    | China   | Hypertension       | Jan 2006–Dec 2008             | Sample size n = 57, CHM group n = 31, Control group n = 26  
Inclusion criteria: SBP 140–179 mmHg or DBP 90–109 mmHg; daytime BP > 135/85 mmHg or night-time BP > 120/70 mmHg; age: 18 years and older | Jiangya capsule with Nimodipine simulation (1 capsule simulation/time, 3 times daily) 4 capsules/time, 3 times daily, 4 weeks  
Formulas: Dilong, Nuxi, Hzzao, Tianma, Chuanxiong  
Control group 1: Integrative medicine 4 Jiangya capsule with 1 nimodipine capsule 3 times daily, 4 weeks  
Control group 2: Western medicine 4 Jiangya capsule simulation with 1 nimodipine capsule 3 times daily, 4 weeks | Baseline balance  
Yes  
Significantly decreased SBP and DBP in both CHM and control groups before and after treatment, without significant difference between these two groups after treatment | N/A | N/A |
| Yang et al.     | Taiwan  | Hypertension       | Sept 2008–Aug 2009            | Sample size n = 55, CHM group n = 30, Control group n = 25  
Inclusion criteria: sitting SBP ≥ 140 mmHg or sitting DBP ≥ 90 mmHg despite the conventional antihypertensive treatment; TCM diagnosed for hyperactivity of the liver-yang syndrome; age: 18–80 years | Fuling Danshen capsule 1000 mg/time, twice daily, 12 weeks  
Formulas: Gegen, Juhua, Danshen, Hongjingtian  
Placebo 12 weeks | Baseline balance  
Yes  
BP control rate (SBP < 140 mmHg and DBP < 90 mmHg) at 23.5% in the CHM group and 7.3% in the placebo group, More significant decrease of SBP in the CHM group than that of the placebo group after treatment | Mild side effects (e.g. diarrhea, fatigue, common cold) (CHM n = 13, Control n = 15) | Small sample size; Short study period |
Table 2 continued

| Author          | Country | Stroke risk factor | Participants | Intervention groups | Results | Side effects | Limitations               |
|-----------------|---------|--------------------|--------------|---------------------|---------|--------------|---------------------------|
| Tong et al.     | China   | (Mild to moderate) Hypertension | Sample size n = 219 | CHM group n = 106; 61 males and 45 females; mean age: 52 years | Jiang huo jing gan 1.70 ml/time, twice daily, 4 weeks | Baseline balance Yes | N/A | Short study period; No placebo group; Small sample size |
| China Mar 2010–Sep 2010 |         |                     |              | Control group n = 113; 62 males and 51 females; mean age: 52 years | Irbesartan 150 mg/time, once daily, 4 weeks |                |                |
|                 |         |                     |              | Inclusion criteria: SBP 140–180 mmHg or DBP 90–110 mmHg; age: 18–65 years; WC ≥ 85 cm (male)/80 cm (female); plus one of the following: (1) TG ≥ 1.7 mmol/l or have received antidyslipidemia treatment; (2) HDL-C < 0.9 mmol/l (male)/1.1 mmol/l (female), or have received the related treatment; (3) FPG ≥ 5.6 mmol/l, diagnosed Type 2 diabetes, or have received glycemic control treatment; (4) TCM diagnosed for liver and stomach damp-heat syndrome | Baseline balance Yes |        |                |
|                 |         |                     |              | Treatment group(s) | |                |                |
|                 |         |                     |              | Control group(s) | |        |                |
| Wu et al.       | China   | Primary Hypertension | Sample size n = 137 | CHM group 1 n = 45; 31 males and 14 females; mean age: 50 years | CHM group 1: Bushen Qinggan granule with amlodipine (5 mg/time, twice daily) Twice daily, 8 weeks | Baseline balance Yes | N/A | N/A |
| China Jan 2010–May 2012 |         |                     |              | CHM group 2 n = 47; 33 males and 14 females; mean age: 48 years | CHM group 2: Bushen Qinggan decoction with amlodipine (5 mg/time, twice daily) Twice daily, 8 weeks |                |                |
|                 |         |                     |              | Control group n = 45; 29 males and 16 females; mean age: 48 years | Placebo with amlodipine (5 mg/time, twice daily) Twice daily, 8 weeks |                |                |
|                 |         |                     |              | Inclusion criteria: diagnosed primary hypertension for at least 3 months prior to screening; age: 18–75 years; 24 h MBP ≥ 130/80 mmHg, MBP ≥ 135/85 mmHg during waking hours, or MBP ≥ 120/70 mmHg during sleeping hours, or SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg |                |                |                |
| Author          | Country          | Stroke risk factor | Participants                                                                 | Intervention groups                                                                 | Results                                                                 | Side effects                                                                 |
|-----------------|------------------|--------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Li et al. [26]  | China            | (Isolated systolic) Hypertension | Sample size n = 241; 98 males and 143 females; mean age 67 years              | During the intervention, no other antihypertensive drugs were used. Control group 1: Jiangya capsule with Nimodipine; Control group 2: CHM capsule with 1 nimodipine capsule 3 times daily. | Baseline balance Yes; Significantly decreased SBP in all three groups before and after treatment; More significant decrease of SBP in the control group 1 than that in the CHM group and control group 2, without significant difference between the CHM group and control group 2 after treatment | Stomach discomfort (CHM: n = 2; Control 2: n = 2); Facial flush and dizziness (Control 2: n = 1) |
| Chen et al. [27]| China            | Hypertension       | Sample size n = 125; CHM group n = 66; Control group n = 59                 | Diet, exercise, smoking/alcohol advices were provided; no other Western medicine affecting BP | Baseline balance Yes; Significantly decreased SBP and pulse pressure in the CHM group before and after treatment; Significantly decreased SBP in the control group before and after treatment; No significant difference of DBP between the two CHM capsule groups after treatment | Dizziness and weakness (CHM: n = 5; Control n = 4); Pretibial edema (CHM: n = 4; Control: n = 4); Facial flushing and headache (CHM: n = 4; Control: n = 4); Severe side effects (Control: n = 21) |
| Gong et al. [28]| China            | Hypertension with cardiac damage | Sample size n = 90; CHM group n = 32; 19 males and 13 females; mean age 59 years | Co-administered medications: aspirin, β-blockers, calcium antagonists, diuretics | Baseline balance Yes; Significantly decreased SBP, DBP in all three groups before and after treatment; More significant decrease of SBP, DBP, TO, LVMI in the CHM group and control group 1 than those in the control group 2 after treatment | Nausea and gastric discomfort (CHM: n = 3; Control 1: n = 1; Control 2: n = 2); Skin rash (Control: n = 1) |
| Author          | Country | Study period | Stroke risk factor                                | Participants | Intervention groups | Control group(s) | Results                                                                 | Side effects                                                                 | Limitations |
|-----------------|---------|--------------|--------------------------------------------------|--------------|--------------------|------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------|
| Xu et al.       | China   | Jan 2006–Apr 2006 | Hypertension, hypertension with diabetes, hypertension with coronary heart disease | Sample size n = 108; CHM group n = 55; Control group n = 53 | Qian Yang He Ji with antihypertensive angiotensin II receptor blocker therapy 35 ml/time, twice daily, 6 months | Antihypertensive angiotensin II receptor blocker No information of usage | Baseline balance Yes; Significantly decreased SBP, DBP, pulse pressure, cardioankle vascular index of both CHM and control groups before and after treatment; More significant decrease of SBP, DBP, cardioankle vascular index in the CHM group than those in the control group after treatment | CHM group serious side effects (n = 5)                                  | N/A         |
| Chao et al.     | China   | Sep 2006–Nov 2007 | Type 2 diabetes                                  | Sample size n = 43; age range 18–70; Inclusion criteria newly diagnosed Type 2 diabetes; FPG ≥ 7 mmol/l and/or OGTT 2hPG ≥ 11.1 mmol/l; BMI: 23–35 kg/m² with poor glucose level after a 1-month diet control (i.e., FPG: 7–10 mmol/l); no antidiabetic medications before | Diet and exercise advices were provided. During the intervention, no antidiabetic medications | Baseline balance Yes; Significantly decreased FPG, PPG, HbA1c, BMI in the CHM group before and after treatment, without significant difference between these two groups after treatment | Moderate constipation (CHM: n = 2; Placebo: n = 2) | N/A         |
| Ji et al. [31]  | China   | Dec 2007–Oct 2008 | Type 2 diabetes                                  | Sample size n = 627; (1) Drug naïve group, mean age: 54 years; CHM group n = 153; Control group n = 150; (2) Metformin group; mean age: 55 years; CHM group n = 164; Control group n = 160; Inclusion criteria diagnosed Type 2 diabetes; age: 21–70 years; BMI: 18–28 or 18–35 kg/m² using metformin at 750 mg/day (or more) for at least 3 months before screening; stable body weight within at least 3 months before screening; FPG: 7.0–13.0 mmol/l and HbA1c >7% | Diet and exercise advices were provided | Baseline balance Yes; In drug naïve group: Significant 38% lower any hypoglycemia rate and 4.1% lower mild hypoglycemic episode in the CHM group than those in the control group after treatment; In Metformin group: Significant 24% lower hypoglycemia rate in the CHM group than that in the control group, without significant difference between these two groups in the mild hypoglycemic episode after treatment; In both drug naïve group and Metformin groups, no significant difference of the rate of reducing HbA1c <6.5% between the CHM and control groups | Urinary tract infection; Upper respiratory tract infection; Elevated ALT/AST; Dyslipidemia | N/A         |
| Author            | Country | Stroke risk factor | Participants | Intervention groups | Results | Side effects | Limitations                  |
|-------------------|---------|--------------------|--------------|---------------------|---------|--------------|----------------------------|
| Tong et al. [32]  | China   | Type 2 diabetes    | Sample size n = 480 CHM group n = 360 Control group n = 120 Inclusion criteria early diabetic status; BMI ≥ 24 kg/m²; HbA1c ≥ 7.0%; FPG 7.0–13.9 mmol/l or 2hPG > 11.1 mmol/l; age: 35–65 years | During the intervention, antihyperlipidaemia or antihypertensive drugs remain stable Tong-Bing-Ling-Wan 6 g/time, 3 times daily, 12 weeks Formulas Huangqin, Huangqian, Baishao, Chenpi, Dahuang | Baseline balance statistically different in HbA1c and 2hPG between groups Significantly decreased HbA1c, FPG, 2hPG and increased HOMA-β in both CHM and placebo groups before and after treatment; Significant higher proportion of the HbA1c reversed to normal (HbA1c ≤ 6.5%) in the CHM group (47.6%) than that in the placebo group (35.5%) after treatment; More significant decrease of HbA1c, FPG, 2hPG, body weight, BMI, WC and increase of HOMA-β in the CHM group than those in the placebo group after treatment | Mild side effects (CHM: n = 24; Placebo: n = 9); Transient slight ALT elevation (CHM: n = 2); Transient slight AST elevation (CHM: n = 2) | Short study period; No follow-up |
| Tu et al. [33]    | China   | No information on study period | Sample size n = 80 CHM group n = 41 Control group n = 39 Inclusion criteria diagnosed Type 2 diabetes; FPG 7.0–13.3 mmol/l or 2hPG 11.1–22.9 mmol/l; age: 18–70 years; normal renal function | Diet and exercise advices were provided Wumei Wan 3 packages daily, 12 weeks Formulas Huanglian, Huangbai, Ganjiang, Ginseng, Danggui, Huajiao, et al. | Baseline balance statistically different in gender between groups No significant difference of FPG, PPG, HbA1c between the CHM and control groups after treatment | Side effects (CHM: n = 1) | Short study period; Not double blind trial |
| Wu and Fan [34]   | China   | Type 2 diabetes    | Sample size n = 152 CHM group n = 76; 48 males and 28 females; age: 48–66 years Control group n = 76; 35 males and 41 females; age: 47–68 years Inclusion criteria diabetes symptoms and any plasma glucose ≥ 11.1 mmol/l; FPG ≥ 7.0 mmol/l; 2hPG ≥ 11.1 mmol/l during OGTT | Self-proposed Chinese herbal medicines with insulin 1 dose daily, 2 weeks Formulas Guijianyu, Zhimu, Gegen, Jineijin, Zexie, Ginseng, et al. | Baseline balance Yes Significant more 20% decrease of insulin use in the CHM group than that in the control group after treatment; Significant less treatment days and frequency of hypoglycaemia in the CHM group than those in the control group after treatment | N/A | N/A |
| Cai et al. [35]   | China   | No information on study period | Sample size n = 67 CHM group n = 37 Control group n = 30 Inclusion criteria diabetes course < 5 years, fasting serum glucose > 7.0 mmol/l and/or 11.1 mmol/l after meal | Diet and exercise advices were provided Lycium barbarum Polysaccharide capsule 300 mg/day, twice daily, 3 months Formulas Gouqi | Baseline balance Yes Significantly decreased serum glucose and increased insulinogenic index in the CHM group before and after treatment; Significantly increased HDL in the CHM group than that in the control group after treatment | No side effects | Small sample size; Short follow-up |
| Author          | Country | Type 2 diabetes | Study period | Sample size n | CHM group n | Control group n | Intervention groups | Results | Side effects | Limitations |
|-----------------|---------|------------------|--------------|---------------|-------------|------------------|---------------------|---------|--------------|-------------|
| Lian et al.     | China   | Type 2 diabetes | Apr 2013–Oct 2013 | 186           | 92          | 94               | Diet and exercise advices were provided | Jintaid with metformin (1500 mg/kg/day) 1 granule/time, 3 times daily, 12 weeks | Formulas Shuweicao, Yinyangghuo, Ginseng, Huangjing, Cangzhis, Kushen, et al. | Placebo with metformin (1500 mg/kg/day) 1 granule/time, 3 times daily, 12 weeks | Baseline balance Yes | N/A | Short study period; Small sample size |
| Zhang et al.    | China   | Type 2 diabetes | Jan 2011–Dec 2013 | 219; 112 males and 107 females; age 38–74 years | 109         | 110              | Shen-Qi-Formula with insulin injection (300 IU, twice daily before breakfast and dinner) 100 ml/time, 3 times daily, 12 weeks | Formulas Shengdi Huang, ZhiDahuang, Ginseng, Shanzhuyu, Shuweicao, et al. | Insulin injection 300 IU, twice daily before breakfast and dinner, 12 weeks | Baseline balance Yes | N/A | Transient hypoglycemia (Control: n = 1) |
| Hu et al.       | China   | Type 2 diabetes | No information on study period | 112           | 59          | 53               | Diet and exercise advices were provided | Jianyutangkong tablet with Metformin (1.5 g/time, 3 times daily, 26 weeks | Formulas Cuiwujia, Zhimu, Guijiayu | Placebo with Metformin 1.5 g/time, 3 times daily, 26 weeks | Baseline balance Yes | No side effects | Small sample size; No group without lifestyle intervention; Almost 25% participants lost from both groups |
| Author | Country | Stroke risk factor | Participants | Intervention groups | Results | Side effects | Limitations |
|--------|---------|-------------------|-------------|---------------------|---------|------------|-------------|
| Li et al. [39] | China | Type 2 diabetes | Sample size n = 38 | During the intervention, metformin remains stable | Baseline balance; Yes | Gastrointestinal side effects; Lower in the CHM group than control group | Short study period; Small sample size; Missing data of BMI in follow-up period |
|       | Jun 2014–Dec 2014 | | CHM group n = 23; Control group n = 15 | Mulberry twig alkaloid tablet with Acarbose placebo (50 mg/time, 3 times daily); 50 mg-100 mg/time, 3 times daily; 24 weeks | | | |
|       | | | Inclusion criteria diagnosed Type 2 diabetes; not on a regimen of antidiabetic medical treatment at least 3 months before screening or on a regimen of antidiabetic treatment no more than 3 months at any time in the past, or on a stable regimen of metformin monotherapy for at least 8 weeks; age: 18–70 years; HbA1c: 7.0–10.0%; FPG ≤ 13 mmol/l; BMI: 19–30 kg/m² | Formulas: Sangshi | | | |
| Wang et al. [40] | China | Hyperlipidemia | Sample size n = 446 | During the intervention, no medications affecting serum lipids | Baseline balance; Yes | CHM group: Heartburn; Flatulence; Dizziness; Exacerbation of preexisting stomachache | N/A |
| No information on study period | | | CHM group n = 324; 188 males and 136 females; mean age: 56 years; Control group n = 122; 73 males and 49 females; mean age: 56 years | Monascus purpureus rice preparation 3 tablets (600 mg)/time; twice daily, 8 weeks | | | |
|       | | | Inclusion criteria: serum TC ≥ 5.95 mmol/l; LDL-C ≥ 3.41 mmol/l, or TG: 2.26-4.52 mmol/l; HDL-C ≤ 1.04 mmol/l (male)/1.16 mmol/l (female); no medication for hyperlipidemia for more than 4 weeks and received dietary advice for 2–4 weeks | Formulas: Red yeast rice; Jiaogulan 3 tablets (600 mg)/time; twice daily, 8 weeks; Formulas: Jiaogulan | | | |
|       | | | Formulas: Sangshen, Sangshen, Jiaogulan | | | | |
| Author        | Country | Stroke risk factor | Participants                                                                 | Intervention groups                                                                 | Results                                                                 | Side effects                      | Limitations |
|--------------|---------|-------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------|-----------------------------------|-------------|
| Yang et al.  | China   | Hyperlipidemia    | Sample size n = 96 CHM group n = 56; 31 males and 25 females; mean age: 69 years   | During the intervention, no other drugs Dangshen Jueming granules 24 g/time, twice daily, Xuezhikang capsules 0.8 g/time, 3 times daily | Baseline balance Yes Significantly decreased TC, LDL-C in both CHM and control groups before and after treatment; Significantly decreased TG in the CHM group before and after treatment; More significant decrease of TC, LDL-C in the CHM group than those in the control group after treatment | No side effects                  | N/A         |
| Ai et al.    | China   | Hyperlipidemia    | Sample size n = 60 CHM group n = 30 Control group n = 30 Inclusion criteria BMI < 35 kg/m²; TC ≥ 5.72 mmol/l and TG > 4.52 mmol/l; age: 18 years and older | During the intervention, no other lipid-modulating drugs Danshen Jueming granules twice daily, Pravastatin 10 mg/time, once daily, 6 weeks | Baseline balance statistically different in the serum TG level between groups Significantly decreased in the TC, LDL-C in both CHM and control groups before and after treatment; More significant decrease of TC, LDL-C in the control group than those in the CHM group after treatment | Diarrhea (CHM n = 8); Myalgia and epigastric discomfort (Control n = 2) | N/A         |
| Xu et al.    | China   | Hyperlipidemia    | Sample size n = 77 CHM group n = 37; 17 males and 20 females; mean age: 59 years   | During the intervention, no drugs affecting the blood lipid metabolism Antihyperlipidemic decoction 150 ml/time, twice daily, 8 weeks, Zhinbiticose 1030 mg/time, 3 times daily, 8 weeks | Baseline balance Yes Significantly decreased TC, TG, LDL-C, BMI in the CHM group and significantly decreased LDL-C, BMI in the control group, before and after treatment; More significant decrease of TC, TG in the CHM group than those in the control group after treatment; Significantly lower recurrence rate in the CHM group than that in the control group after treatment | No side effects                  | N/A         |

**Inclusion criteria**
- TC > 5.7 mmol/l and/or TG > 1.7 mmol/l; TCM diagnosed for phlegm-damp and blood stasis syndrome
- **Baseline balance**
- **Side effects**
- **Limitations**
### Table 2 continued

| Author and Country | Stroke risk factor | Study period | Participants | Intervention groups | Results | Side effects | Limitations |
|--------------------|--------------------|--------------|--------------|---------------------|---------|--------------|-------------|
| Hu et al. [44]     | Hyperlipidemia     | Hong Kong    | No information on study period | CHM group n = 20; 6 males and 14 females; mean age: 58 years; Control group n = 20; 10 males and 10 females; mean age: 55 years | A multiherb formula 4 capsules in the morning and 4 capsules in the evening, 12 weeks | Baseline balance statistically different in the LDL-C level between groups; More significant decrease of LDL-C in the CHM group than that in the placebo group after treatment; No significant difference of LDL-C in the CHM group before and after treatment | CHM group n = 11, including one stomach upset; Placebo group n = 12, including one acid reflux | Not balanced baseline data of the two groups; Small sample size; Lack of consideration of the different types of dyslipidemia |
| Moriarty et al. [45] | Hyperlipidemia     | USA and China | Apr 2011–Aug 2012 | CHM group 1 n = 36; 6 males and 30 females; mean age: 58 years; CHM group 2 n = 42; 13 males and 29 females; mean age: 56 years; Control group n = 38; 11 males and 27 females; mean age: 56 years | During the intervention, no lipid-lowering drugs, investigational agent, medications promoting weight loss, agents affecting lipid metabolism | Baseline balance Yes; Significantly decreased LDL-C in both two CHM groups before and after treatment, without significant difference between these two groups after treatment; The total effective rates at about 48% of LDL-C by ≥ 30% in the two CHM groups before and after treatment, without significant difference between these two groups | CHM groups 1, 2 n = 5, not CHM-related side effects (thyroid cancer, pulmonary embolism, fractured leg); Placebo group n = 3 | Not representative data; More females than males; Short treatment period |
| Heber et al. [46]  | Hyperlipidemia     | USA          | No information on study period | CHM group n = 83; 46 males and 37 females; age: 34–78 years | Diet advice were provided | Baseline balance Yes; Significantly decreased TC, TG, LDL-C in the CHM group before and after treatment; More significant decrease of TC, LDL-C in the CHM group than those in the placebo-group after treatment | Placebo group; Rash (n = 1); Concurrent development of pneumonia (n = 1) | N/A |
| Author          | Country          | Study period                  | Stroke risk factor | Participants                                                                                      | Intervention groups                                                                                           | Results                                                                                                         | Side effects                             | Limitations                                      |
|-----------------|------------------|-------------------------------|--------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------|-------------------------------------------------|
| Lin et al.      | Taiwan           | Dec 2001–Jan 2003             | Hyperlipidemia     | CHM group n = 39; 23 males and 16 females; mean age: 46 years                                    | Diet advices were provided: *Monascus purpureus* Went rice 1 capsule (600 mg)/time, twice daily, 8 weeks       | Baseline balance: Yes; Significantly decreased TC, TG, LDL-C in the CHM group before and after treatment; More significant decrease of TC, TG, LDL-C in the CHM group than those in the placebo group after treatment | CHM group: Drug-related side effects (n = 6) | No record of diets of the participants          |
| Wei et al.      | China            | Mar 2006–Sep 2007             | Impaired glucose   | CHM group n = 70; 31 males and 39 females; mean age: 51 years                                   | Tang No. 1 granule with IGT knowledge education 2 packets/time, twice daily, 6 months                         | Baseline balance: Yes; Significantly decreased FPG, 2hPG, HbA1c, HOMA-IR in the CHM group before and after treatment; More significant decrease of FPG, 2hPG, HbA1c, TG, HOMA-IR in the CHM group than those in the control group after treatment; More patients with IGT reversed to normal in the CHM group (19.1%) than that in the control group (3.1%) | No side effects                           | N/A                                             |
| Gao et al.      | China            | No information on study period | Impaired glucose   | CHM group n = 255; 110 males and 145 females; mean age: 49 years                                | Co-administered medications: calcium antagonists, a blockers or ACE antagonists, or β-blockers or thiazide for hypertension control | Baseline balance: Yes; Significantly decreased 2hPG, HbA1c, BMI, FIN, HOMA-IR in the CHM group before and after treatment; More significant decrease of FPG, 2hPG, HbA1c, FIN, HOMA-IR in the CHM group than those in the control group after treatment; More patients with IGT reversed to normal in the CHM group (29.1%) than those in the control group (13.6%) after treatment; Lower risk of IGT patients progressing to Type 2 diabetes in the CHM group (22.2%) than that in the placebo group (43.9%) | Mild abdominal distension (CHM: n = 4; Control: n = 3) | Small sample size; Short follow-up            |
Table 2 continued

| Author | Country | Stroke risk factor | Participants | Intervention groups | Results | Side effects | Limitations |
|--------|---------|--------------------|--------------|---------------------|---------|--------------|-------------|
| Fang et al. | China | No information on study period | Sample size n = 514 | CHM group n = 257; 136 males and 121 females; mean age: 55 years | Baseline balance | Gastrointestinal reactions were the most common side effects | Short follow-up; No consensus about efficacy of the CHM approach |
| Lian et al. | China | Impaired glucose tolerance | Sample size n = 420 | CHM group n = 210; 98 males and 112 females; mean age: 53 years | More patients with IGT reversed to normal in the CHM group (63.1%) than that in the control group (46.6%); Lower risk of IGT patients progressing to Type 2 diabetes in the CHM group (18.2%) than that in the placebo group (29.3%) | Short study period; No data on plasma insulin and HbA1c; Small sample size |
| Huang et al. | China | Impaired glucose tolerance | Sample size n = 120 | CHM group n = 60; 31 males and 29 females; mean age: 52 years | Significantly decreased 2hPG, HbA1c, HOMA-IR, TG in the CHM group before and after treatment; More significant decrease of 2hPG, HbA1c, HOMA-IR, TG in the CHM group than those in the control group after treatment; More patients with IGT reversed to normal in the CHM group (58.3%) than that in the control group (26.7%); Lower risk of IGT patients progressing to Type 2 diabetes in the CHM group (16.7%) than that in the placebo group (31.7%) | No severe side effects | Small sample size; Short follow-up; Insufficient outcome measures |
| Author          | Country | Stroke risk factor | Study period | Participants | Intervention groups | Results | Side effects | Limitations                        |
|-----------------|---------|--------------------|--------------|--------------|---------------------|---------|--------------|-------------------------------------|
| Shi et al.      | China   | Impaired glucose tolerance | Apr 2014–Oct 2014 | Sample size: n = 61 | CHM group: n = 32; 17 males and 15 females; mean age: 47 years | Diet, exercise, smoking/alcohol consumption advices were provided; no other CHM products with similar function | Baseline balance Yes | Gastrointestinal reactions (n = 2) | Short study period; Small sample size |
| Grant et al.    | Australia | Impaired glucose tolerance | Jun 2007–Dec 2009 | Sample size: n = 71 | CHM group: n = 39; 15 males and 24 females; mean age: 58 years | Jingtang Xiaozhi 3 capsules/time, 3 times daily, 16 weeks | Baseline balance Yes | CHM group moderate dizziness (n = 1) | Short study period; Small sample size |
| Pan et al.      | China   | Obesity             | Jul 2003–Aug 2003 | Sample size: n = 78 | CHM group: n = 40, 18 males and 22 females; mean age: 41 years | Dietary powder 1 package (9 g)/time, twice daily, 7 weeks | Baseline balance Yes | Irritability (CHM: n = 1; Placebo: n = 1); Nausea (CHM: n = 2; Placebo: n = 1); Constipation (Placebo: n = 2) | N/A |
| Zhou et al.     | China   | Obesity             | May 2010–Feb 2011 | Sample size: n = 134 | CHM group: n = 70, 31 males and 39 females; mean age: 40 years | Xin-Ju-Xiao-Gao-Fang (full-dose) 170 ml decoction/time, twice daily, 24 weeks | Baseline balance Yes | Minor side effects (e.g. skin rash) (CHM: n = 4; Control: n = 3) | Short study period; No follow-up; No true placebo group |
| Author          | Country | Study period | Stroke risk factor               | Participants                                                                 | Intervention groups                                                                 | Results                                                                                           | Side effects | Limitations |
|-----------------|---------|--------------|----------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------|-------------|
| Lenon et al. [57] | Australia | No information on study period | Obesity                         | Sample size n = 117; CHM group n = 59; 10 males and 49 females; mean age: 39 years; Control group n = 58; 10 males and 48 females; mean age: 40 years | During the intervention, no other medications for obesity management | Chinese herbal medicine formula RCM-104; 4 capsules/time, 3 times daily, 12 weeks | Baseline balance | Nausea (CHM: n = 4); Headache (CHM: n = 9); Decrease of appetite (Placebo: n = 2) | N/A          |
| Hioki et al. [58] | Japan | No information on study period | Obesity and impaired glucose tolerance | Sample size n = 81; mean age: 54 years; CHM group n = 41; Control group n = 40 | Diet and exercise advice were provided | Bofu-tsusho-san 3 times daily, 24 weeks | Baseline balance | N/A          |
| Gao & Hu [59] | China | No information on study period | Type 2 diabetes and hyperlipidemia | Sample size n = 80; CHM group n = 40; 22 males and 18 females; mean age: 59 years; Control group n = 40; 20 males and 20 females; mean age: 59 years | During the intervention, hypoglycemic agents remained stable | Taizhi’an capsule with Simvastatin 10 mg daily, 0.9 g/time, 3 times daily, 12 weeks | Baseline balance | CHM group: Loose bowels (n = 3) | N/A          |
| Poppel et al. [60] | Netherlands | May 2012 – Mar 2013 | Hyperlipidemia and hypertension | Sample size n = 20; 14 males and 6 females; mean age: 58 years; CHM group n = 9; Control group n = 11 | During the intervention, no other medications for hypertension management | Danshen capsules 4 capsules (500 mg)/time, 3 time daily, 4 weeks | Baseline balance | CHM group: Headache (n = 5); Dizziness (n = 3); Change in stool frequency (n = 3); Flatulence (n = 2); Peripheral facial nerve paralysis (n = 1) | N/A          |
| Author       | Country | Stroke risk factor                  | Participants                                                                 | Intervention groups                                                                 | Results                                                                 | Side effects | Limitations |
|-------------|---------|-------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------|-------------|
| Chu et al.  | China   | Metabolic syndrome                 | Sample size n = 90. CHM group n = 60, 28 males and 32 females, mean age: 51 years; Control group n = 30, 13 males and 17 females, mean age: 50 years | Diet and exercise advices were provided; During the intervention, no other CHM with hypoglycemic, lipid-lowering and antihypertensive effects | Baseline balance: Yes Significant decrease of BMI, waist-to-hip ratio, TC, TG, LDL-C, 2hPG and increased HDL-C in the CHM group before and after treatment; More significant decrease of BMI, TG, TC, LDL-C, 2hPG and increase of HDL-C in the CHM group than those in the placebo group after treatment | CHM group: Diarrhea (n = 1) | N/A         |
| Chen et al. | China   | Hypertension and metabolic syndrome | Sample size n = 43. CHM group n = 22, 14 males and 8 females, mean age: 49 years; Control group n = 21, 14 males and 7 females, mean age: 49 years | Diet and exercise intervention were provided | Baseline balance: Yes Significantly decreased body weight, WC, BMI, FPG, 2hPG, FIN, HOMA-IR, SBP, DBP, daytime SBP, daytime DBP, nighttime SBP in the CHM group before and after treatment; More significant decrease of WC, waist-to-hip ratio, 2hPG, HOMA-IR, FIN, SBP, DBP, daytime SBP and DBP than those in the placebo group after treatment | CHM group: Skin allergy (n = 2) | N/A         |
| Author          | Country | Stroke risk factor | Participants | Intervention groups | Results | Side effects | Limitations                      |
|-----------------|---------|--------------------|--------------|---------------------|---------|--------------|----------------------------------|
| Azushima et al. | Japan   | Hypertension and obesity | Sample size: n = 106 CHM group n = 54; 28 males and 26 females; mean age: 59 years | Diet and exercise advice were provided | Baseline balance: Yes. | CHM group: Gastric irritation (n = 1); Constipation (n = 1); Elevation of serum hepatic enzyme level (n = 1) | Not a double-blinded placebo-controlled study; Short study period |
|                 |         |                    |              | Bofu-tusho-san with Antihypertensive therapy 2.5 g/time, once daily, 24 weeks | Antihypertensive therapy No further information | More significant decrease of daytime SBP, body weight, BMI in the CHM group than those in the control group after treatment |

Notes: 2hPG: 2-hour postprandial glucose, BP: blood pressure, BMI: body mass index, DBP: diastolic blood pressure, FIN: fasting plasma insulin, FPG: fasting plasma glucose, HbA1c: glycated hemoglobin, HC: hip circumferences, HDL: high-density lipoprotein, HDL-C: high-density lipoprotein cholesterol, HOMA-β: homeostatic model assessment β-cell function, HOMA-IR: homeostatic model assessment insulin resistance, IGT: impaired glucose tolerance, LDL-C: low-density lipoprotein cholesterol, LVMI: left ventricular mass index, MBP: mean blood pressure, OGTT: oral glucose tolerance test, PPG: postprandial plasma glucose, SBP: systolic blood pressure, TC: total cholesterol, TG: triglyceride, TO: original heart rate, WC: waist circumference.
| Author, Country, Publication year | Stroke risk factor | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|----------------------------------|-------------------|---------------------------|------------------------|----------------------------------------|-------------------------------|-------------------------|-----------------|------------|
| Lin et al. [18], China, 2004     | (Primary) Hypertension | Unclear                    | Unclear                | High risk                             | Unclear                      | Low risk                | Unclear         | Unclear    |
| Li [19], China, 2005             | (Primary) Hypertension | Unclear                    | Unclear                | High risk                             | Unclear                      | Unclear                | Unclear         | Unclear    |
| Ye et al. [20], China, 2009      | (Primary) Hypertension | Unclear                    | Unclear                | Low risk                              | Low risk                     | Unclear                | Low risk        | Unclear    |
| Zhao et al. [21], China, 2010    | (Primary) Hypertension | Unclear                    | Unclear                | Low risk                              | Unclear                      | Low risk                | Unclear         | Unclear    |
| Zhong et al. [22], China, 2011   | (Primary) Hypertension | Low risk                   | High risk              | High risk                             | Unclear                      | Low risk                | Low risk        | Unclear    |
| Yang et al. [23], Taiwan, 2012  | (Uncontrolled primary) Hypertension | Low risk | Unclear                | High risk                             | Low risk                     | Unclear                | Low risk        | High risk  |
| Tong et al. [24], China, 2013    | Hypertension        | Low risk                   | High risk              | High risk                             | Low risk                     | Unclear                | Low risk        | Unclear    |
| Wu et al. [25], China, 2014      | (Primary) Hypertension | Low risk                   | Low risk               | Unclear                               | Low risk                     | Low risk                | Low risk        | Unclear    |
| Li et al. [26], China, 2010      | (Isolated systolic) Hypertension | Low risk | Unclear                | Low risk                             | Unclear                      | High risk                | Unclear         | Unclear    |
| Chen et al. [27], China, 2012    | (Polarized) Hypertension | Low risk                   | Unclear                | High risk                             | Unclear                      | Unclear                | Unclear         | High risk  |
| Gong et al. [28], China, 2010    | Hypertension with cardiac damage | Unclear | Unclear                | High risk                             | Unclear                      | Low risk                | Unclear         | Unclear    |
| Xu et al. [29], China, 2013      | Hypertension, hypertension with diabetes, hypertension with coronary heart disease | Unclear | Unclear                | High risk                             | Unclear                      | Unclear                | Unclear         | Low risk   |
| Chao et al. [30], China, 2009    | Type 2 diabetes      | Low risk                   | Low risk               | Low risk                             | Low risk                     | Low risk                | Unclear         | Unclear    |
| Ji et al. [31], China, 2013      | Type 2 diabetes      | Low risk                   | Low risk               | High risk                             | Low risk                     | Low risk                | Unclear         | Unclear    |
| Tong et al. [32], China, 2013    | Type 2 diabetes      | Low risk                   | Low risk               | Unclear                               | Low risk                     | High risk                | Unclear         | Unclear    |
| Tu et al. [33], China, 2013      | Type 2 diabetes      | Low risk                   | Low risk               | High risk                             | Unclear                      | Low risk                | Unclear         | Unclear    |
| Wu & Fan [34], China, 2014       | Type 2 diabetes      | Unclear                    | High risk              | Unclear                               | Unclear                      | Unclear                | Unclear         | Unclear    |
Table 3 continued

| Author, Country, Publication year | Stroke risk factor       | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|-----------------------------------|--------------------------|-----------------------------|------------------------|----------------------------------------|-------------------------------|------------------------|---------------------|-----------|
| Cai et al. [35], China, 2015      | Type 2 diabetes          | Low risk                    | Unclear                | Low risk                               | Unclear                       | Low risk               | Low risk            | Unclear   |
| Lian et al. [36], China, 2015     | Type 2 diabetes          | Low risk                    | Low risk               | Low risk                               | Low risk                       | Low risk               | Low risk            | Unclear   |
| Zhang et al. [37], China, 2015    | Type 2 diabetes          | Low risk                    | Low risk               | High risk                              | Unclear                       | Low risk               | Low risk            | Unclear   |
| Hu et al. [38], China, 2016       | Type 2 diabetes          | Low risk                    | High risk              | Low risk                               | Low risk                       | High risk              | Low risk            | Unclear   |
| Li et al. [39], China, 2016       | Type 2 diabetes          | Low risk                    | Low risk               | Low risk                               | Low risk                       | Low risk               | Low risk            | Unclear   |
| Wang et al. [40], China, 1997     | Hyperlipidemia           | Low risk                    | Unclear                | High risk                              | Low risk                       | Low risk               | Low risk            | Unclear   |
| Yang et al. [41], China, 2006     | Hyperlipidemia           | Unclear                     | Unclear                | Unclear                                | Unclear                       | Unclear               | Unclear            | High risk |
| Ai et al. [42], China, 2009       | Hyperlipidemia           | High risk                   | High risk              | High risk                              | High risk                      | Unclear               | Low risk            | High risk |
| Xu et al. [43], China, 2009       | Hyperlipidemia           | Unclear                     | High risk              | Unclear                                | Unclear                       | Unclear               | Unclear            | Unclear   |
| Hu et al. [44], Hong Kong, 2014   | Hyperlipidemia           | Low risk                    | Low risk               | Low risk                               | Unclear                       | Low risk               | Low risk            | High risk |
| Moriarty et al. [45], USA & China, 2014 | Hyperlipidemia         | Low risk                    | Low risk               | Low risk                               | Unclear                       | Low risk               | Low risk            | Unclear   |
| Heber et al. [46], USA, 1999      | Hyperlipidemia           | Unclear                     | Low risk               | Unclear                                | Unclear                       | Low risk               | Low risk            | High risk |
| Lin et al. [47], Taiwan, 2005     | Hyperlipidemia           | High risk                   | Unclear                | Low risk                               | Low risk                       | Low risk               | Low risk            | High risk |
| Wei et al. [48], China, 2008      | Impaired glucose tolerance | High risk                  | Unclear                | High risk                              | Unclear                       | Low risk               | Unclear            | Unclear   |
| Gao et al. [49], China, 2013      | Impaired glucose tolerance | Low risk                   | Unclear                | High risk                              | Unclear                       | Low risk               | Low risk            | Unclear   |
| Fang et al. [50], China, 2014     | Impaired glucose tolerance | Unclear                    | High risk              | Unclear                                | Unclear                       | Low risk               | Low risk            | Unclear   |
| Lian et al. [51], China, 2014     | Impaired glucose tolerance | Low risk                   | Low risk               | Low risk                               | Low risk                       | Low risk               | Low risk            | Unclear   |
| Huang et al. [52], China, 2016    | Impaired glucose tolerance | Low risk                   | High risk              | Unclear                                | Unclear                       | Low risk               | Low risk            | Unclear   |
| Shi et al. [53], China, 2016      | Impaired glucose tolerance | Low risk                   | High risk              | Unclear                                | High risk                      | Low risk               | Low risk            | Unclear   |
| Author, Country, Publication year | Stroke risk factor                              | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|----------------------------------|-------------------------------------------------|----------------------------|------------------------|----------------------------------------|-------------------------------|------------------------|---------------------|------------|
| Grant et al. [54], Australia, 2013 | Impaired glucose tolerance                      | Low risk                  | Low risk               | Low risk                               | Low risk                     | Low risk               | Unclear            | High risk |
| Pan et al. [55], China, 2005     | Obesity                                         | Low risk                  | Unclear                | Low risk                               | Unclear                      | Low risk               | Unclear            | High risk |
| Zhou et al. [56], China, 2014    | Obesity                                         | Low risk                  | Unclear                | Low risk                               | Unclear                      | Unclear                | Low risk           | Unclear   |
| Lenon et al. [57], Australia, 2012 | Obesity                                         | Unclear                   | Low risk               | Low risk                               | Unclear                      | Low risk               | Unclear            | Unclear   |
| Hioki et al. [58], Japan, 2004   | Obesity and impaired glucose tolerance          | Low risk                  | High risk              | Low risk                               | Unclear                      | Unclear                | Low risk           | High risk |
| Gao & Hu [59], China, 2006       | Type 2 diabetes and hyperlipidemia              | Unclear                   | High risk              | Unclear                                | Low risk                     | Low risk               | Unclear            | Unclear   |
| Poppel et al. [60], Netherlands, 2015 | Hyperlipidemia and hypertension            | High risk                 | Unclear                | Low risk                               | Unclear                      | Low risk               | Low risk           | High risk |
| Chu et al. [61], China, 2011     | Metabolic syndrome                             | High risk                 | Unclear                | Low risk                               | Unclear                      | Low risk               | Unclear            |                      |
| Chen et al. [62], China, 2013    | Hypertension and metabolic syndrome            | Low risk                  | Unclear                | Low risk                               | Unclear                      | High risk              | Low risk           | Unclear   |
| Azushima et al. [63], Japan, 2015 | Hypertension and obesity                      | Low risk                  | Unclear                | High risk                               | Low risk                     | Low risk               | Low risk           | High risk |
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with regards to the decrease of SBP or DBP amongst the three groups after treatment. Gouteng (钩藤) [18, 19, 21, 24, 25, 29] and Tianma (天麻) [18, 22, 25–27] were the most frequently used Chinese herbs in the hypertension-focused RCTs included, and all the CHM interventions using Gouteng and/or Tianma reported significant pre-post effectiveness regarding the decrease of SBP (and/or DBP) level. Also, Gouteng was the principal CHM formula constituent amongst four out of six hypertension-focused RCTs presenting between-group effectiveness of the investigated CHM interventions on the decrease of SBP (and/or DBP) levels compared to control interventions [21, 24, 25, 29]. In addition, the sample size of hypertension-focused RCTs ranged from 55 to 219. Six hypertension-focused RCTs did not provide the age and gender profile of the participants in either CHM group or control group [20, 22, 23, 26, 27, 29]. The duration of the hypertension-focused trials ranged from 2 weeks to 24 months, with the majority of trials conducted between 4 and 12 weeks.

Eight hypertension-focused RCTs reported safety-related information and no deaths were noted [18, 19, 21, 23, 26–29]. One trial reported five cases of serious side effects of the ‘CHM plus biomedicine’ intervention group [29]. One trial (sample: 55) reported 13 mild side effects in the ‘placebo plus biomedicine’ control group [23]. Only two of the papers reporting results from hypertension-focused RCTs listed any study limitations including small sample size and short study period [23, 24]. As for risk of bias in the hypertension-focused RCTs, three papers provided information on the allocation concealment [22, 24,
25] and four on the blinding of outcome assessment [20, 23–25]. Additionally, only three trials reported double-blinding of participants and personnel involved [20, 21, 26].

Diabetes
All of the 10 included diabetes-focused RCTs were focusing upon patients diagnosed with Type 2 diabetes mellitus and all these RCTs were conducted in China [30–39]. Amongst the 10 RCTs examining the efficacy of CHM on controlling the glucose level of patients with diabetes, four RCTs compared ‘CHM’ intervention to ‘placebo’ [32], ‘CHM plus biomedicine’ intervention to ‘placebo plus biomedicine’ intervention [39], and further, ‘CHM plus lifestyle’ intervention to ‘placebo plus lifestyle’ intervention [30, 35]. These four trials indicated more significant decreased glucose level [e.g. fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), glycated hemoglobin (HbA1c)] by using CHM products when compared to the placebos after treatment, while this significant between-group variance in the decrease of glucose level showed no statistical significance when both CHM interventions and placebos were used concurrently with biomedicine or lifestyle intervention. Also amongst these 10 diabetes-focused RCTs, ‘CHM plus biomedicine’ intervention was compared to ‘biomedicine’ intervention, showing a more significant decrease of insulin usage by the CHM plus biomedicine treatment after treatment [34]. Also, after treatment, ‘CHM, biomedicine plus lifestyle’ interventions were found to achieve a more significant decrease of FPG, HbA1c, or hypoglycemia when compared to either ‘biomedicine plus lifestyle’ intervention [31, 37] or ‘placebo, biomedicine plus lifestyle’ intervention [36, 38]. Of the nine diabetes-focused RCTs providing CHM formulas, Huanglian (黄连) was the most common Chinese herb [30, 32–34, 36], followed by Ginseng (人参) [33, 34, 36, 37], Shanzhuyu (山茱萸) [34, 36, 37], Dahuang (大黄) [32, 34, 37], and Huangqi (黄芪) [30, 34, 37]. The CHM interventions examined in three out of five diabetes-focused RCTs, showing significant between-group effectiveness on the decrease of glucose level, indicated that the combination of these five commonly used Chinese herbs played a vital role for the efficacy of type 2 diabetes management [34, 36, 37]. All diabetes-focused RCTs defined inclusion criteria of diabetes based on different FPG, 2hPG, and/or HbA1c levels, and all the tested CHM products used in these RCTs were different. The sample size of the diabetes-focused RCTs ranged from 43 to 627. Only one RCT provided the age and gender profile of participants in the CHM and control groups [35]. The duration of the trials ranged from 2 weeks to 12 months, with the majority of trials conducted between 3–12 months.

Hyperlipidemia
Half of the eight RCTs on CHM for the treatment of hyperlipidemia originated from China [40–43]. Amongst the hyperlipidemia-focused RCTs, two compared ‘CHM’ interventions with ‘biomedicine’ interventions [42, 43], two compared different ‘CHM’ interventions [40, 41], two compared ‘CHM’ interventions with ‘placebos’ [44, 45] and two compared ‘CHM plus lifestyle’ interventions with ‘placebo plus lifestyle’ interventions [46, 47]. Although the inclusion criteria of people with hyperlipidemia shown in the included hyperlipidemia-focused RCTs are limited to the total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and/or body mass index (BMI) levels, the threshold value of these indices are diverse across the RCTs. It is worth noting that Monascus purpureus rice preparation (Xuezhi-kang capsule in Chinese) of which the main ingredient is red yeast rice, was tested in four hyperlipidemia-focused RCTs [40, 45–47]. The effects of the red yeast rice products are not consistent across these four RCTs. When the ‘red yeast rice product plus lifestyle’ intervention was compared with ‘placebo plus lifestyle’ intervention, a more significant decrease of TC and LDL-C was found in the red yeast rice product group after treatment. However, there was no significant improvement in TC or LDL-C amongst those receiving the red yeast rice product alone when compared to placebo alone. Amongst the rest four hyperlipidemia-focused RCTs, Danshen (丹参) [41–43], Juemingzi (沢明子) [41–43], Zexie (澤泄) [41, 43, 44], and/or Shanzha (山楂) [41, 43, 44] were the main constituents of the CHM formulas examined and three of these trials reported the significant between-group
The effects of CHM interventions are consistent through the inclusion criteria and CHM products, the results on IGT-focused RCTs are different. Despite the variation in the age and gender profile of the participants in CHM and control groups [42, 46]. The duration of the trials ranged from 6 weeks to 12 months while one trial did not specify the study period.

All hyperlipidemia-focused RCTs reported safety-related information and no deaths were noted. Three trials specified their side effects in the CHM intervention groups, including heartburn/flatulence [40], diarrhea [42], and stomach upset [40, 44]. Three hyperlipidemia-focused RCTs reported their study limitations including small sample size, lack of balanced baseline data between the CHM and control groups and no record of the participants’ dietary control [44, 45, 47]. As for risk of bias of the hyperlipidemia-focused RCTs, five trials did not use the random sequence generation method [41–43, 46, 47], only two trials specified the appropriate allocation concealment [44, 45], and six trials failed to employ the blinding of outcome assessment [41–46].

**Impaired glucose tolerance**

The seven RCTs on CHM for the treatment of IGT originated from China (n = 6) [48–53] and Australia (n = 1) [54]. Amongst the IGT-focused RCTs, one compared ‘CHM’ with ‘placebo’ [54], five compared ‘CHM plus lifestyle’ interventions with ‘lifestyle’ interventions alone [48–50, 52, 53], and one compared ‘CHM plus lifestyle’ intervention with ‘placebo plus lifestyle’ intervention [51]. The inclusion criteria regarding the 2hPG level remain stable (7.8–11.0 mmol/l) while the FPG level is either <7.0 or >7.0 mmol/l across all the IGT-focused RCTs. As for risk of bias of the hyperlipidemia-focused RCTs, five trials did not use the random sequence generation method [41–43, 46, 47], only two trials specified the appropriate allocation concealment [44, 45], and six trials failed to employ the blinding of outcome assessment [41–46].

**Obesity**

Two RCTs on CHM for the treatment of obesity originated from China [55, 56] and one from Australia [57]. The three obesity-focused trials compared different CHM products with their placebos. BMI is the key indicator of the inclusion criteria of all obesity-focused RCTs included. However, the threshold value of BMI was set differently across these trials. Amongst the obesity-focused RCTs, CHM products all showed more decrease of body weight than placebos after treatment. *Green tea* (绿茶) [55, 57] and *Juemingzi* (決明子) [56, 57] were the Chinese herbs included in two CHM formulas amongst these three obesity-focused trials. The sample size of the obesity-focused RCTs ranged from 78 to 134 and all these RCTs provided the age and gender profile of participants in the CHM and placebo groups. There were 115 males and 214 females across all the obesity-focused RCTs with a mean age of 40 years, ranging from 39 to 41 years. The duration of the obesity-focused trials ranged from 7 weeks to 6 months.

All obesity-focused RCTs reported safety-related information and no death were noted. CHM interventions were reported more side effects than the placebos, including nausea, headache, and skin rash. One obesity-focused RCT indicated the study limitations including short study period, no follow-up period, and no true placebo group [56]. As for risk of bias of the obesity-focused RCTs, all trials reported the double-blinding of participants and personnel while these trials failed to provide any details of the blinding of outcome assessment.

**Combined stroke risk factors**

Six RCTs exploring the efficacy of CHM on one or more of the stroke risk factors were identified in the systematic review. Specifically, one trial examined the ‘CHM
plus lifestyle’ intervention for the treatment of ‘IGT and obesity’ compared to ‘placebo plus lifestyle’ intervention, showing significant efficacy on both IGT and obesity before and after treatment and a significant effect on obesity control between groups after treatment [58]; Two trials examined the ‘CHM plus biomedicine’ interventions for the treatment of ‘diabetes and hyperlipidemia’ and ‘hypertension and hyperlipidemia’ compared to the ‘biomedicine’ intervention [59] and ‘placebo plus biomedicine’ intervention [60], respectively—both of these studies found similar effect on the combined stroke risk factors between groups after treatment. Moreover, three trials examined the ‘CHM, biomedicine plus lifestyle’ interventions for the treatment of ‘metabolic syndrome’ [61], ‘hypertension and metabolic syndrome’ [62], and ‘hypertension and obesity’ [63] compared to the ‘biomedicine plus lifestyle’ interventions with or without placebo, respectively, indicating significant effects on all included stroke risk factors by the CHM interventions compared to the control groups after treatment. Except the Bofu-tsusho-san (防风通圣散) used in two trials, all the other CHM interventions involved exploring a combination of multiple stroke risk factors were different and therefore it is unable to report the commonly used Chinese herbs which are vital for the efficacy of combined stroke risk factors across these six RCTs. The sample size of the RCTs focused upon combined stroke risk factors ranged from 20 to 106, and two of these RCTs failed to provide the age and gender profile of participants in the CHM and control groups [58, 60]. The duration of the RCTs exploring the combined stroke risk factors ranged from 4 to 6 months.

All RCTs focusing upon combined stroke risk factors reported safety-related information and no deaths were noted. Five out of these six RCTs reported that side effects only occurred in the CHM group [58, 60–63] including headache, dizziness, gastrointestinal reactions, and skin allergy. Only two RCTs focusing upon combined stroke risk factors identified their study limitations [60, 63], including failure to double-blind the RCT, short study period and carry-over effect. As for risk of bias of the RCTs focusing upon combined stroke risk factors, no trial reported appropriate allocation concealment and blinding of outcome assessment, and two trials were found to have a high risk of bias regarding the random sequence generation [60, 61].

**Discussion**

This paper reports the first comprehensive systematic review of the literature concerning the use of CHM amongst people at greatest risk(s) of stroke. A number of significant findings from our review are important for future evidence-based planning and priority setting for research in stroke prevention.

Our analyses show some positive efficacy and safety evidence of varied CHM interventions in lowering high blood pressure, high blood glucose, high cholesterol, high body BMI and a combination of multiple stroke risk factors. Importantly, our findings indicate that, compared to biomedicine alone/lifestyle modification alone/biomedicine plus lifestyle intervention, CHM monotherapy may be not sufficient enough for people to obtain their treatment goals when treating hypertension, diabetes, and hyperlipidemia, while an intervention of CHM as a supplement to biomedicine and/or a lifestyle intervention is more effective in lowering the levels of SBP/DBP, glucose, BMI, TC, 2hPG, and/or HbA1c. These findings from our review are in line with previous systematic reviews on CHM for cardiovascular diseases [12–14]. In addition, the evidence reported in the papers included with regards to the successful reversion from elevated blood glucose level to normal by using CHM interventions suggests that some CHM products, in combination with a lifestyle intervention, could be considered a potential effective therapeutic regimen for IGT, and these findings are consistent with a Cochrane review on CHM for IGT published in 2009 [13]. Although many RCTs identified in our review demonstrate the therapeutic benefits of CHM in people with a number of stroke risk factors, there is a lack of replicable evidence on CHM use in combined stroke risk factors. It is worth noting that a CHM product (red yeast rice preparation), a medicinal food [64], has been used several times not only for the management of hypertension but also for hyperlipidemia. However, the control interventions of all RCTs examining the efficacy of this rice preparation are different. Therefore, no trial included in our review paper has tested exactly the same CHM and control interventions for the treatment of any stroke risk factor(s).

Our findings show a large variation in the sample size and study period across the included RCTs. The potential risks of bias have been reported in the domains of allocation concealment, the blinding of participants and personnel, and/or the blinding of outcome assessment in the included RCTs. Most included trials have reported their safety information. No serious adverse events were noted although some studies showed some moderate side effects in the CHM groups.

Stroke risk factors vary by ethnic groups and such disparities may influence the etiology of stroke and the implementation of stroke prevention programs [65]. Nevertheless, the majority of studies on CHM use for stroke risk factors included in this review were conducted in China on Chinese populations. As such, the results shown in our review paper may not always be directly
applicable to populations at risk of stroke in other countries beyond China. Furthermore, CHM is often composed of a number of herbs and is prescribed based on the unique Chinese medicine theory—syndrome differentiation. The replicability of these trial designs without Chinese medicine practitioners is therefore difficult.

There are some limitations to our systematic review that should be mentioned. Generalisability of the results from this systematic review is limited. Meanwhile, the overall ‘unclear’ reporting of research methodology in the included RCTs may limit the quality of the results reported in this review. In addition, our review was restricted to English peer-reviewed journal articles.

Conclusion
Although the findings in this systematic review with regards to the effect of CHM for stroke modifiable risk factors should be interpreted with caution, the potential therapeutic benefits of CHM as a treatment—particularly in combination with biomedicine and/or lifestyle intervention—for different stroke risk factors needs to be further examined by conducting rigorous trials. Future research should be designed and implemented with adequate sample size, detailed reporting of the allocation concealment method, sufficient application of double-blinding with an adequate placebo and blinding of outcome assessment, and long-term follow-up in different countries. Moreover, it is important for future research on this topic to pay attention to potential drug-herb interactions as a major safety issue in trial design when participants need to take one or more co-administered biomedicine as well as CHM products.

Abbreviations
2hPG: 2-hour postprandial glucose; BMI: body mass index; BP: blood pressure; CHM: Chinese herbal medicine; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; HC: hip circumference; HDL: high-density lipoprotein; HDL-C: high-density lipoprotein cholesterol; HOMA-β: homeostatic model assessment β-cell function; HOMA-IR: homeostatic model assessment insulin resistance; IGT: impaired glucose tolerance; LDL-C: low-density lipoprotein cholesterol; LVMi: left ventricular mass index; MBP: mean blood pressure; OGTT: oral glucose tolerance test; PPG: postprandial plasma glucose; RCT: randomized controlled trial; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride; TIA: transient ischaemic attack; TO: original heart rate; WC: waist circumference.

Authors’ contributions
DS designed the study. WP, CF and JF conducted the literature search. WP and RL extracted and interpreted the data. WP drafted the manuscript and prepared tables and figures. JA and DS contributed to the critical revisions of the manuscript. All authors read and approved the final manuscript.

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