First International Journal of Andrology
ANDROLOGIA

REVIEW ARTICLE

Chinese herb formulae for treatment of erectile dysfunction: a systematic review of randomised controlled clinical trials

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Keywords
Chinese traditional medicine—erectile dysfunction—systematic review

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Accepted: December 19, 2012

doi: 10.1111/and.12074

Summary

To assess the beneficial and adverse effects of orally therapies of Chinese herb formulae (CHF) for erectile dysfunction (ED), four electronic databases were searched until 23 June 2012. Randomised clinical trials testing CHF or combined with Western medicine therapy (WMT) against placebo, another different CHF and WMT were included. Study selection, data extraction, assessing of bias risk and data analysis were conducted according to the Cochrane handbook. Twenty-one randomised controlled clinical trials (involving 2253 patients) were included, and the bias risks were not low. Funnel plots of comparing CHF to another CHF on the clinical comprehensive effectiveness were asymmetrical. The compositions of CHF used were greatly complex. The analyses showed that some CHF or combined with WMT had significant effects on cure rate, total clinical effective rates, IIEF-5 scores, erectile quality scores, erection angles of penis and recovery times of erection compared with the controls. Eight trials reported mild adverse drug reactions, mostly involving gastrointestinal symptoms. It was concluded that some therapies of CHF may be more effective than the controls for treatment of ED. However, because of the generally not low risks of bias, CHF are not recommended for ED. Further research that demonstrates their mechanisms of action and meaningful efficacies must be carried out by rigorously designed, randomised controlled trials.

Introduction

Erectile dysfunction (ED) has been defined as the persistent or recurrent inability, for at least 3 months duration, to achieve and/or maintain an erection sufficient to permit satisfactory sexual performance (NIH, 1993; Montague *et al.*, 1996). Epidemiological data have shown a high prevalence and incidence of ED.

In developed countries, the Massachusetts Male Aging Study reported an overall prevalence of 52% ED in non-institutionalised 40- to 70-year-old men in the Boston area (Wespes *et al.*, 2012). In the Cologne study of men aged 30–80 years, the prevalence of ED was 19.2% (Braun *et al.*, 2000). In the National Health and Social Life Survey, the prevalence of sexual dysfunctions (not specifically ED) was 31% (Laumann *et al.*, 1999). The incidence rate (new cases per 1000 men annually) of ED was 26% in the Massachusetts Male Aging Study (Johannes *et al.*, 2000), 65.6% (mean follow-up of 2 years) in the Brazilian study (Moreira *et al.*, 2003) and 19.2% (mean follow-up of 4.2 years) in the Dutch study (Schouten *et al.*, 2005). In Asian countries, the prevalence of ED for men aged 20–86 years was found to be 28.3% (Jiang & Zhu, 2006), and another study in the Shanghai area of China suggested that the incidence of ED in 40- to 70-year-old men was 73.1% and 86.3% in men aged $\geq$70 years (Leng *et al.*, 2000). Current data have also confirmed that the prevalence of ED mounts with increasing age and the presence of comorbid medical conditions. Ayta *et al.* (1999) estimated a prevalence of approximately 322 million men with ED in 2025, with the largest increases occurring in the developing world. First and last, although the data in these studies varied from 19.2% to 86.3% – differences can be explained by inconsistencies in methodology and in the ages and socio-economic status of the populations studied -, the existing epidemiological data have all shown a high prevalence and incidence of ED worldwide.

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Regardless of the fact that it is a benign disorder, ED affects physical and psychosocial health and has a significant impact on the quality of life of sufferers and their partners and families (Feldman *et al.*, 1994). ED has taken on increasing importance with respect to its socioeconomic impact. Besides its medical comorbidity associations, ED is recognised to adversely affect quality of life, decrease occupational productivity and increase healthcare resource utilisation (Krane *et al.*, 1989; Litwin *et al.*, 1998). ED can be included among a host of urologic diseases having a substantial financial burden on the public. Nationally, total charges for treatment of ED in the United States in 2006 were approximated $ 556 million (Litwin & Saigal, 2012).

Advances in basic and clinical research during the past two decades have led to the development of several new treatment options for ED, including new pharmacological agents for intracavernous, intra-urethral and, more recently, oral use, especially inhibitors of phosphodiesterase-5 (PDE5) (Brock *et al.*, 2002; Goldstein *et al.*, 2002; Hellstrom *et al.*, 2003) and penile prosthesis implantation. Although considerable advances have been made, the ideal treatment of ED has not been identified (Montague *et al.*, 2012).

Traditional Chinese medicine (TCM) has been used widely for more than 2000 years to enhance sexual function and to treat sexual dysfunction, including ED. As one category of alternative therapies, TCM has its unique theories for concepts of aetiology, systems of diagnosis and treatment, which are vital to their practice. In other words, based on differentiation of syndromes ('Zheng' in Chinese pinyin), there are different types of syndromes in the same disease, so, there is so-called 'treating the same disease with different methods (namely "syndrome differentiation and treatment")', which means a variety of therapy in TCM for the treatment of the same disease. TCM follows a specific theoretical and methodological pathway, and the treatments for ED are different from those of the Western medicine therapy (WMT) and phytotherapy. Chinese herb formula based on the guidance of TCM theory consists typically of complex prescriptions of a combination of several herbs. In summary, the mechanism of the traditional Chinese description may be tonifying kidney, activating blood, soothing liver and dredging collaterals (Wang & Lu, 1999). The characteristics of such flexible and diversified therapy in TCM show the advantages of individualised therapy according to the personalised disease condition.

Currently, many controlled trials have been completed investigating interventions with Chinese herb formulae (CHF) used alone or integrated with Western medicine therapies as an alternative and effective method for the treatment of ED in China. Effectiveness was reported in clinical studies ranging from case reports and case series to controlled observational studies and randomised clinical trials. The movement towards alternative medicines in this field actually gained momentum over the past decade with the emergence of effective oral therapy in the form of PDE-5 inhibitors, which created avenues for producing PDE5 inhibitor-like counterfeit and imitation substances and promoting regulatory agency unapproved products in general (Burnett AL, 2010). However, the quality of these trials and the evidence for their effects have not been assessed systematically; indeed, the true efficacies of CHF remain uncertain in the absence of evidenced benefit from rigorous meta-analysis or systematic review. The effectiveness of such treatment needs to be reviewed systematically and appraised critically to inform the current medical practice and direct further research for new treatment regimens. Chinese herb formula for ED is considered collectively in this review as a special experimental treatment.

Methods

Database and search strategies

A systematic search was conducted in four databases including PubMed (1946-2012.6.23), Embase (1947-2012.6.23), Chinese Biomedical Literature Database (1978-2012.6.23) and China Dissertation Database (1980-2012.6.23). All of those searches ended until June 23 2012. We used the following search terms: 'ED', 'impotence', 'medicine, Chinese traditional' and 'drugs, Chinese herbal'. Various combinations of the terms were used, depending on the database searched. The bibliographies of included trials were also searched for thorough references, irrespective of languages.

Inclusion criteria

All parallel randomised controlled clinical trials (RCCT) of the Chinese herb formula based on the guidance of TCM theories including decoction, pills, capsule, tablet and oral liquid compared with placebo, the other different CHF and WMT in adult patients with ED were included. RCCTs combined CHF with WMT or basic treatment (BT) compared with WMT or BT alone was included as well. There were no restrictions on population characteristics, language and publication type.

Outcome measures included the clinical comprehensive effect (cure rate, CR; total clinical effective rate, TCER), improvement of the international index of erectile function (IIEF-5) scores, TCM symptom complex (TCM-SC) score, erection angle of penis and recovery time of erection. Adverse drug reactions (ADR) were also included in

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the outcome measurement. Nonrandomised evaluations, pharmacokinetic studies, CHF that were nonorally administered in trials, animal or laboratory studies and general reviews were excluded, and duplicate publications reporting on the same groups of participants were also excluded.

Data extraction and bias risk assessing

Two authors (Guobing Xiong and Bo Li) extracted the data from the included trials independently, based on the inclusion and exclusion criteria outlined above. Any remaining disagreement was resolved by consensus among the four authors. The extracted data were entered into an electronic database. The bias risk was assessed using a revised tool of the recommended approach by Cochrane handbook for systematic reviews of interventions (Version 5.1.0) (Higgins *et al.*, 2011a,b). In this handbook, it was categorised into low, unclear or high risk of bias according to a judgement about risk of bias for each important outcome within the included trial from a description of the support for that judgement (Higgins *et al.*, 2011a,b). This revised tool included ten domains of bias: (i) proportionality of baseline data; (ii) calculation of sample size; (iii) sequence generation; (iv) allocation concealment; (v) blinding of participants and personnel; (vi) blinding of outcome assessors; (vi) incomplete outcome data; (vii) selective outcome reporting; (ix) statement of the proper statistical method; and (x) intention-to-treat analysis.

The summary assessments of the bias risks for each important outcome (across domains) within and across studies referred to the Cochrane handbook recommended standards (Higgins *et al.*, 2011a,b). The overall risks were also rated in three categories: low risk of bias (most information is from studies at low risk of bias, we defined 'most information' as $\geq$5 items and the followings were same); unclear risk of bias (most information is from studies at low or unclear risk of bias); and high risk of bias (the proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results).

Data synthesis

The statistical package of REVMAN 5.1.7 (The Nordic Cochrane Centre, 2011), which was provided by the Nordic Cochrane Centre, was used to analyse the collected data. Dichotomous data were presented as risk ratio (RR) and continuous outcomes as mean difference (MD), both with 95% confidence interval (CI). Meta-analyses were only conducted where the studies were considered to be sufficiently homogenous and in the absence of significant methodological, clinical or statistical heterogeneities. The statistical heterogeneity was presented as significant when *I* square (I^2) was over 50% or $P < 0.1$. Random effect model was used for the meta-analysis if there was significant heterogeneity ($I^2 \geq 50\%$), and fixed-effect model was used when the heterogeneity was not significant ($I^2 < 50\%$).

For dichotomous outcomes, patients with incomplete or missing data were included in the 'worst-case scenario' analysis by counting these patients in the treatment group as treatment failures and those in the control group as responders. Publication bias was explored via a funnel plot analysis with REVMAN 5.1.7 and the Egger's test (Egger *et al.*, 1997) quantitatively with the statistical package of R version 2.15.2 (R Core Team, 2012).

Results

Search flow

See Fig. 1. According to the predefined search strategy, 315 potentially relevant studies were screened out for further identification. By reading the titles and abstracts, 242 studies that were obviously ineligible were excluded, including review articles, case reports, animal or experimental studies, nonrandomised trials, nonorally administered CHF in trial groups, qualitative researches, diagnostic tests and repetitions.

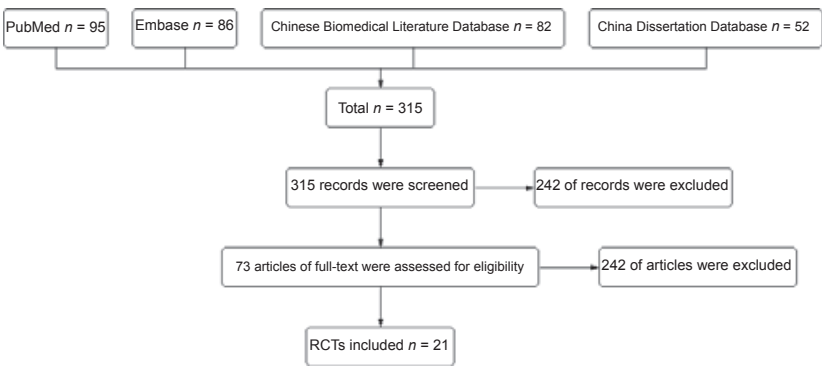

Fig. 1 Diagram of the study selection flow.

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Seventy-three studies with full-text papers were further retrieved, but the full texts of two of 73 studies were not obtained. After the full-text reading of 71 studies, six studies were excluded because of interventions in trial groups where the phytotherapies lacked guidance of classic TCM theories, seven studies were excluded due to duplicated publication, 11 studies were excluded as a result of interventions in trial groups that did not receive CHF and were not orally medicated. Eighteen studies were ruled out because the compositions of CHF in trial groups were obviously heterogeneous, eight trials were excluded as seven of them were non-RCCTs and one was an economic evaluation. Thus, 21 RCCTs (Guo *et al.*, 1999; Wang *et al.*, 1999, 2004; Hu *et al.*, 2004; Jie, 2004; Gong *et al.*, 2005; Lu *et al.*, 2005; Xue, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Xu & Hu, 2006; Cao *et al.*, 2009; Chen *et al.*, 2009; Lu *et al.*, 2009; Wu *et al.*, 2005; Sun, 2009; Wang & Wang, 2009; Hu & Lu, 2010; Zhang, 2010; Zhao & Sun, 2011) were included for systematic review.

Description of included trials

The characteristics of 21 randomised trials are summarised in Table 1. A total of 2253 adult patients with ED were involved. The sample size varied from 11 to 200 participants, with an average of 107 patients per study. There was a wide variation in the age of subjects (20–66 years old). Twenty studies were published in Chinese and one in English (Guo *et al.*, 1999). All participants were Chinese people.

Nineteen trials (Guo *et al.*, 1999; Wang *et al.*, 1999, 2004; Hu *et al.*, 2004; Gong *et al.*, 2005; Lu *et al.*, 2005, 2009; Wu *et al.*, 2005; Xue, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Xu & Hu, 2006; Cao *et al.*, 2009; Chen *et al.*, 2009; Sun, 2009; Wang & Wang, 2009; Hu & Lu, 2010; Zhang, 2010) specified four categories of diagnostic criteria, including The Guiding Principle for Clinical Research on Traditional Chinese Medicine New Drugs issued by the Ministry of Health of People's Republic of China, The Chinese Guideline for Diagnosis and Treatment of Male Erectile Dysfunction issued by the Chinese Medical Association, the 5-item version of the International Index of Erectile Function Scoring System (IIEF-5) and various criteria from the Chinese version of medical professional books or textbooks. Nine trials (Guo *et al.*, 1999; Wang *et al.*, 1999, 2004; Hu *et al.*, 2004; Lu *et al.*, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Cao *et al.*, 2009) made clear diagnoses of functional ED. Thirteen studies (Wang *et al.*, 1999, 2004; Hu *et al.*, 2004; Jie, 2004; Xue, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Xu & Hu, 2006; Cao *et al.*, 2009; Chen *et al.*, 2009; Lu *et al.*, 2009; Hu & Lu, 2010) made clear statements of the exclusion criteria. No study reported use of the calculation of sample size. All studies stated syndrome differentiation of TCM, but only 11 trials (Guo *et al.*, 1999; Wang *et al.*, 2004; Wu *et al.*, 2005; Xue, 2005; Ying & Xu, 2005; Wang, 2006; Chen *et al.*, 2009; Sun, 2009; Wang & Wang, 2009; Hu & Lu, 2010; Zhang, 2010) declared definite diagnosis basis according to the classic TCM theory.

The interventions included various Chinese herbal drug prescriptions based on the guidance of TCM theory, namely 'syndrome differentiation and treatment'. The CHF included decoction (Guo *et al.*, 1999; Hu *et al.*, 2004; Lu *et al.*, 2005, 2009; Ying & Xu, 2005; Xu & Hu, 2006; Cao *et al.*, 2009; Chen *et al.*, 2009; Wang & Wang, 2009; Hu & Lu, 2010; Zhang, 2010; Zhao & Sun, 2011), tablet (Xue, 2005; Liu, 2006), pill (Jie, 2004; Gong *et al.*, 2005; Wang, 2006; Sun, 2009), capsule (Wang *et al.*, 2004) and oral liquid (Wang *et al.*, 1999; Wu *et al.*, 2005) administered through oral approaches or combined with antihypertensive treatment (Xue, 2005), hypoglycaemic treatments (Cao *et al.*, 2009; Hu & Lu, 2010; Zhang, 2010) or WMT (Xu & Hu, 2006; Chen *et al.*, 2009). The controls included placebo (Wang *et al.*, 2004), WMT (Guo *et al.*, 1999; Lu *et al.*, 2005, 2009; Xu & Hu, 2006; Zhao & Sun, 2011), BT (Xue, 2005; Cao *et al.*, 2009; Chen *et al.*, 2009; Hu & Lu, 2010), WMT plus BT (Zhang, 2010) or the other CHF (Guo *et al.*, 1999; Wang *et al.*, 1999, 2004; Hu *et al.*, 2004; Jie, 2004; Gong *et al.*, 2005; Wu *et al.*, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Sun, 2009; Wang & Wang, 2009). Only six trials (Guo *et al.*, 1999; Lu *et al.*, 2005, 2009; Xu & Hu, 2006; Chen *et al.*, 2009; Zhao & Sun, 2011) investigated CHF versus WMT, and the other CHF were the controls in 12 studies (Guo *et al.*, 1999; Wang *et al.*, 1999, 2004; Hu *et al.*, 2004; Jie, 2004; Gong *et al.*, 2005; Wu *et al.*, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Sun, 2009; Wang & Wang, 2009). In only one study (Wang *et al.*, 2004), the control was placebo. The total treatment duration ranged from 4 days (Wang *et al.*, 1999) to 3 months (Jie, 2004; Sun, 2009). Informed consents were obtained from participants in only three trials (Wang *et al.*, 2004; Cao *et al.*, 2009; Chen *et al.*, 2009). Only three studies (Wang *et al.*, 2004; Gong *et al.*, 2005; Chen *et al.*, 2009) reported the average follow-up of 3 months. The detailed variable compositions of CHF are presented in Table 2.

Except for one trial (Xue, 2005) which did not state the judgement criterion of clinical comprehensive effect, the other 20 trials had clear judgement criteria, which could be classified into four categories, included the national standards (The Guiding Principle of New Drugs Clinical Research of TCM issued by the Ministry of Health of P.R.C., The Criteria of Diagnosis and Therapeutic Effect of TCM Diseases issued by the State Administration of Traditional Chinese Medicine of P.R.C.) for seven studies (Wang *et al.*, 2004; Lu *et al.*, 2005; Ying &

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Table 1 Characteristics of 21 included randomised trials

Included trials	Sample	Age (years) Trial/ Control	Diagnostic criteria	Informed Consent	Intervention			Follow-up	Outcome measure
					Trial	Control	Duration		
Guo *et al.*, 1999;	141	≥20	Guiding principle of new drug clinical research of TCM, CUA Guidelines	Unclear	Tonifying kidney and activating blood formula, 1 agent/d, Tid	Other Chinese herbs: Shen-bao oral liquid, Tid	30 days	Unclear	CR, TCER
Wang *et al.*, 1999;	82	28–60/25–60	Surgery	Unclear	Life-saving kidney qi decoction, 20 ml, Tid	Other Chinese herbs: Wu zi yan zong pill, 9 g, Tid	4 days	Unclear	TCER
Hu *et al.*, 2004;	81	42.01 ± 15.04/ 41.02 ± 14.08	IIEF-5 score	Unclear	Tonifying kidney, dredging collaterals and sooth liver formula, 150 ml, Bid	Other Chinese herbs: San bian capsule, 2 grans, Tid	30 days	Unclear	TCER
Jie, 2004;	80	46.6 ± 16.5/ 44.9 ± 14	Unclear	Unclear	Tonifying kidney and soothing liver pill, 9 g, Bid	Other Chinese herbs: Golden cabinet's kidney qi pill, 9 g, Bid	3 months	Unclear	TCER, IIEF-5 score, ADR
Wang *et al.*, 2004;	500	20–60	Guiding principle of new drug clinical research of TCM	Yes	Soothing liver and replenishing yang capsule, 1.2 g, Tid (double blinding) or Soothing liver and replenishing yang capsule, 1.2 g, Tid	Placebo, 1.2 g Tid, (double blinding) or Other Chinese herbs: Compact yang and tonifying kidney capsule, 1.2 g, Tid (double blinding)	4 weeks	3 months*	TCER, erection angle of penis, recovery time of erection, ADR
Gong *et al.*, 2005;	107	23–65 (43.3)/ 22–66 (41.6)	IIEF-5 score	Unclear	Tonifying kidney and soothing liver pill, 9 g, Bid	Other Chinese herbs: Golden cabinet's kidney qi pill, 9 g, Bid	15 days	3 months	TCER
Lu *et al.*, 2005;	85	23–45 (28.3)/ 23–44 (24.8)	IIEF-5 score, nocturnal penile tumescence test (NPTT)	Unclear	Relieving depression and treating flaccidity decoction, 1 agent/d, Bid	Western medicine therapy: Yohimbine hydrochloride tablets, 5.4 mg, Tid	1 month	Unclear	TCER
Wu *et al.*, 2005;	60	42.86 ± 9.62/ 42.33 ± 10.17	Wang Q's Clinical Medicine Serial	Unclear	Tonifying kidney and supplementing essence decoction, 10 ml, Bid	Other Chinese herbs: Securing kidney decoction, 10 ml, Bid	60 days	Unclear	TCER, the improvement of TCM syndrome, ADR
Xue, 2005;	32	48.52 ± 10.11/ 50.91 ± 9.92	Guiding principle of new drug clinical research of TCM, CUA Guidelines	Unclear	Tonifying kidney and replenishing heart formula, 4 tablets, Tid plus BT (antihypertensive treatment)	Basic treatment (BT)	8 weeks	Unclear	IEF-5 score, ADR

(*Continued*)

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Table 1 (*Continued*)

Included trials	Sample	Age (years) Trial/ Control	Diagnostic criteria	Informed Consent	Intervention			Follow-up	Outcome measure
					Trial	Control	Duration		
Ying & Xu, 2005;	60	38.96 ± 11.53/ 41.7 ± 10.96	Guiding principle of new drug clinical research of TCM, IIEF-5 score	Unclear	Two rehmannia-turtle shell decocted pill, 15 g, Tid	Other Chinese herbs: Zhuang yang fu chun ling formula, 1.5 g, Tid	30 days	Unclear	TCER, IIEF-5 score
Liu, 2006;	252	37 ± 1.58/ 38 ± 1.13	Sexual medicine	Unclear	Regenerating essence and assisting yang formula, 5 tablets, Bid	Other Chinese herbs: Shen-bao oral liquid, Tid	2 months	Unclear	TCER, ADR
Wang, 2006;	80	36.09 ± 10.42/ 36.43 ± 10.24	Guiding principle of new drug clinical research of TCM	Unclear	Tonifying kidney and soothing liver pill, 9 g, Bid	Other Chinese herbs: Xian le xiong capsule, 2 grans, Tid	1 month	Unclear	TCER, EQS, ADR
Xu & Hu, 2006;	80	Unclear	IIEF-5 score, NPTT	Unclear	Enhancing masculinity and treating flaccidity decoction, 200 ml, Bid plus Vardenafil hydrochloride tablets, 10 mg, PRN	Western medicine therapy: Vardenafil hydrochloride tablets, 10 mg, PRN	2 months	Unclear	CR, TCER, the improvement of TCM syndrome
Chen *et al.*, 2009;	128	36.5 ± 15.2/ 32.2 ± 12.3/ 31.2 ± 11.3	Guiding principle of new drug clinical research of TCM	Yes	Resolving phlegm and dredging collaterals decoction, 1 agent/d plus Simvastatin tablets, 20 mg, QN or Resolving phlegm and dredging collaterals decoction, 1 agent/d	Western medicine therapy: Simvastatin tablets, 20 mg, QN	2 months	3 months	CR, TCER, IIEF-5 score, erectile quality score, erection angle of penis, ADR
Cao *et al.*, 2009;	63	30–49 (40.5)/ 30–46 (39.2)	IIEF-5 score	Yes	Replenishing qi and nourishing yin formula, 1 agent/d, QD plus BT (hypoglycaemic treatment)	Basic treatment	12 weeks	Unclear	TCER, IIEF-5 score, ADR
Lu *et al.*, 2009;	32	44.42 ± 4.18/ 42.65 ± 3.62	IIEF-5 score	Unclear	Soothing liver, tonifying kidney and activating blood formula, 150 ml, Bid	Western medicine therapy: Bromocriptine, 2.5 mg, Bid	1 month	Unclear	TCER, IIEF-5 score, ADR

(*Continued*)

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Table 1 (*Continued*)

Included trials	Sample	Age (years) Trial/ Control	Diagnostic criteria	Informed Consent	Intervention			Follow-up	Outcome measure
					Trial	Control	Duration		
Sun, 2009;	100	Unclear	Guiding principle of new drug clinical research of TCM	Unclear	Tonifying kidney and supporting body pill, 6 g, Tid	Other Chinese herbs: Guifudihuang pill, 8 grains, Tid	3 months	Unclear	CR, TCER
Wang & Wang, 2009;	91	45.3 ± 3.8/ 45.1 ± 3.9	Criteria of diagnosis and therapeutic effect of TCM diseases	Unclear	Dispelling stasis and treating flaccidity formula, 1 agent/d, Bid	Other Chinese herbs: Right-Restoring Pill, 1 agent/d, Bid	30 days	Unclear	CR, TCER
Hu & Lu, 2010;	72	26–63 (50.1)/ 28–60,(49.8)	Guiding principle of new drug clinical research of TCM	Unclear	Activating blood, resolving depression and treating flaccidity decoction, 1 agent/d, Bid plus BT (hypoglycaemic treatment)	Basic treatment	8 weeks	Unclear	CR, TCER
Zhang, 2010;	50	27–52 (39.2)/ 28–55 (38.5)	Criteria of diagnosis and therapeutic effect of TCM diseases	Unclear	Revised Right-Restoring Pill, 100 ml Bid plus BT (hypoglycaemic treatment)	Western medicine therapy: Methycobal, 0.5 mg, Tid plus BT	2 months	Unclear	CR, TCER
Zhao & Sun, 2011	77	28–68	Unclear	Unclear	Lu-zhong warming kidney decoction, 1 agent/d, Tid	Western medicine therapy: Andriol, 500 mg, QD	5 weeks	Unclear	CR, TCER

ADR, adverse drug reactions; CR, cure rate; TCER, total clinical effective rate; TCM, traditional Chinese medicine.
*Only 105 of clinically cured patients had been followed-up.

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Table 2 Compositions of Chinese herb formulae

Included trials	Formulations	Compositions
Guo *et al.*, 1999;	Decoction	*Herba Epimedii*, *Radix Rehmanniae Praeparata*, *Radix Pseudostellariae*, *Fructus Lycii*, *Rhizoma Chuanxiong*, *Radix et Rhizoma Salviae Miltiorrhizae*, *Semen Juglandis*, *Radix et Rhizoma Notoginseng*
Wang *et al.*, 1999;	Oral liquid	Chinese patent medicine: *Radix Rehmanniae Praeparata*, *Fructus Lycii*, *Semen Cuscutae*, *Herba Epimedii*, *Radix Morindae Officinalis*, *Semen Allii Tuberosi*, *Cortex Moutan* and so on
Hu *et al.*, 2004;	Decoction	Chinese patent medicine: *Herba Epimedii*, *Scolopendra*, *Fructus Tribuli* and so on
Jie, 2004;	Pill	*Radix Rehmanniae* 30 g, *Rhizoma Dioscoreae* 30 g, *Fructus Corni* 15 g, *Rhizoma Alismatis* 10 g, *Poria* 10 g, *Cortex Moutan* 10 g, *Cortex Cinnamomi* 10 g, *Radix Aconiti Lateralis Praeparata* 10 g, *Radix Bupleuri* 10 g, *Radix Angelicae Sinensis* 10 g, *Radix Paeoniae Alba* 10 g, *Rhizoma Atractylodis Macrocephalae* 10 g, *Radix et Rhizoma Glycyrrhizae Praeparata cum Melle* 6 g, *Herba Menthae* 6 g, *Radix et Rhizoma Ginseng* 10 g, *Squama Manitis* 10 g, *Scolopendra* 10 g, *Hippocampus* 10 g
Wang *et al.*, 2004;	Capsule	Chinese patent medicine: *Fructus Tribuli*, *Radix Bupleuri, Nidus Vespae*, *Fructus Cnidii* and so on
Gong *et al.*, 2005;	Pill	Chinese patent medicine: *Radix Rehmanniae Praeparata*, *Rhizoma Dioscoreae*, *Fructus Corni*, *Fructus Lycii*, *Poria*, *Herba Cistanches*, *Herba Epimedii*, *Radix Angelicae Sinensis*, *Radix Paeoniae Alba*, *Radix Bupleuri*, *Radix Curcumae*, *Scolopendra*, *Radix et Rhizoma Glycyrrhizae* and so on
Lu *et al.*, 2005;	Decoction	Chinese patent medicine: *Radix Bupleuri* 10 g, *Radix Angelicae Sinensis* 15 g, *Radix Paeoniae Alba* 15 g, *Radix Curcumae* 10 g, *Herba Epimedii* 30 g, *Scolopendra* 2, *Nidus Vespae* 15 g, *Semen Astragali Complanati* 30 g, *Herba Pyrolae* 15 g, *Semen Allii Tuberosi* 15 g, *Fructus Tribuli* 15 g and so on
Wu *et al.*, 2005;	Oral liquid	Chinese patent medicine
Xue, 2005;	Tablet	Chinese patent medicine: *Herba Epimedii*, *Semen Plantaginis* and so on
Ying & Xu, 2005;	Decoction	Chinese patent medicine: *Radix Rehmanniae*, *Radix Rehmanniae Praeparata*, *Carapax Trionycis*, *Fructus Lycii*, *Fructus Schisandrae Chinensis*, *Semen Cuscutae*, *Poria*, *Cortex Moutan*, *Radix et Rhizoma Salviae Miltiorrhizae* and so on
Liu, 2006;	Tablet	Chinese patent medicine: *Herba Epimedii* 15 g, *Placenta Hominis* 18 g, *Peni et Testes Canitis* 15 g, *Cornu Cervi Pantotrichum* 12 g, *Radix Morindae Officinalis* 12 g, *Rhizoma Curculiginis* 12 g, *Herba Cistanches* 12 g, *Radix et Rhizoma Ginseng* 20 g, *Radix Bupleuri* 15 g, *Rhizoma Cimicifugae* 12 g, *Rhizoma Chuanxiong* 12 g, *Fructus Tribuli* 12 g and so on
Wang, 2006;	Pill	Chinese patent medicine: *Radix* Bupleuri, *Radix Paeoniae Alba*, *Rhizoma Curculiginis*, *Herba Epimedii*, *Radix Rehmanniae Praeparata*, *Radix et* Rhizoma *Salviae Miltiorrhizae*, *Scolopendra* and so on
Xu & Hu, 2006;	Decoction	*Herba Epimedii* 15 g, *Radix Rehmanniae Praeparata* 15 g, *Rhizoma Curculiginis* 15 g, *Herba* Cynomorii 15 g, *Fructus Lycii* 15 g, *Semen Cuscutae* 15 g, *Radix Curcumae* 15 g, *Colla Cornus Cervi* 24 g, *Radix Codonopsis* 15 g, Radix *Morindae Officinalis* 12 g, *Radix Angelicae Sinensis* 10 g, *Rhizoma Chuanxiong* 10 g, *Semen Juglandis* 10 g, *Flos Carthami* 10 g, *Radix et Rhizoma Salviae Miltiorrhizae* 10 g,*Scolopendra* 3 g, *Radix et Rhizoma Glycyrrhizae Praeparata cum Melle* 6 g
Chen *et al.*, 2009;	Decoction	*Pericarpium Citri Reticulatae* 15 g, *Rhizoma Pinelliae* 15 g, *Poria* 15 g, *Rhizoma Atractylodis* 15 g, *Cortex Magnoliae Officinalis* 15 g, *Pericarpium Arecae* 15 g, *Fructus Liquidambaris* 15 g,*Scolopendra* 10 g, *Hirudo* 10 g, *Pheretima* 20 g, *Radix et Rhizoma Glycyrrhizae* 5 g
Cao *et al.*, 2009;	Decoction	*Radix Astragali* 30 g, *Radix Codonopsis* 30 g, *Fructus Schisandrae Chinensis* 6 g, *Radix Ophiopogonis* 10 g, *Rhizoma Anemarrhenae* 10 g, *Radix Rehmanniae* 10 g, *Radix Polygoni Multiflori* 10 g, *Herba Leonuri* 10 g, *Radix Angelicae Sinensis* 10 g, *Herba Epimedii* 15 g, *Cortex Cinnamomi* 3 g, *Scolopendra* 2 g, *Herba Ephedrae* 3 g
Lu *et al.*, 2009;	Decoction	*Radix Bupleuri* 10 g, *Fructus Aurantii* 10 g, *Rhizoma Chuanxiong* 10 g, *Pericarpium Citri Reticulatae* 10 g, *Rhizoma Cyperi* 15 g, *Radix Paeoniae Alba* 15 g, *Fructus Tribuli* 15 g, *Radix et Rhizoma Salviae Miltiorrhizae* 15 g,*Scolopendra* 6 g, *Nidus Vespae* 6 g, *Radix Rehmanniae Praeparata* 20 g,*Fructus Corni* 10 g, *Colla Cornus Cervi* (melt and take drenched) 10 g, *Herba Epimedii* 10 g, *Semen Cuscutae* 15 g, *Radix et Rhizoma Glycyrrhizae* 6 g
Sun, 2009;	Pill	*Radix Rehmanniae Praeparata*, Herba *Cistanches*, *Radix Morindae Officinalis*, *Fructus Corni*, *Fructus Lycii*, *Herba Epimedii*, *Fructus Ligustri Lucidi*, *Fructus Psoraleae*, *Fructus Rosae Laevigatae*, *Semen Euryales*, *Radix Astragali*, *Radix Codonopsis*, *Rhizoma Dioscoreae*, *Cortex Eucommiae*, *Herba Taxilli*, *Radix Angelicae Sinensis*, *Rhizoma Chuanxiong*, *Radix et Rhizoma Salviae Miltiorrhizae*, *Radix Paeoniae Alba*, *Flos Carthami*, *Radix et Rhizoma Notoginseng*, *Radix et Rhizoma Glycyrrhizae*

(*Continued*)

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Table 2 (*Continued*)

Included trials	Formulations	Compositions
Wang & Wang, 2009;	Decoction	*Radix Angelicae Sinensis* 15 g, *Radix et Rhizoma Salviae Miltiorrhizae* 10 g, *Rhizoma Chuanxiong* 10 g, *Radix Achyranthis Bidentatae* 12 g, *Flos Carthami* 6 g, *Hirudo* 3 g, *Tabanus* 3 g, *Herba Leonuri* 20 g, *Rhizoma Polygonati* 10 g, *Semen Ziziphi Spinosae* 12 g, *Radix Bupleuri* 10 g, *Rhizoma Cyperi* 6 g
Hu & Lu, 2010;	Decoction	*Fructus Tribuli* 15 g, *Fructus Aurantii* 10 g, *Radix Curcumae* 10 g, *Rhizoma Chuanxiong* 10 g, *Radix et Rhizoma Salviae Miltiorrhizae* 15 g, *Radix Angelicae Sinensis* 15 g, *Ramulus Cinnamomi* 10 g, *Scolopendra* 10 g, *Herba Epimedii* 10 g, *Semen Cuscutae* 15 g, *Herba Cynomorii* 10 g
Zhang, 2010;	Decoction	*Radix Rehmanniae Praeparata* 30 g, *Rhizoma Dioscoreae* 20 g, *Fructus Corni* 15 g, *Fructus Lycii* 15 g,*Colla Cornus Cervi* 10 g, *Semen Cuscutae* 15 g, *Cortex Eucommiae* 15 g, *Radix Angelicae Sinensis* 10 g, *Cortex Cinnamomi* 10 g, *Radix Aconiti Lateralis Praeparata* 7.5 g, *Scolopendra* 20 g, *Radix Paeoniae Alba* 20 g, *Radix et Rhizoma Glycyrrhizae* 7.5 g
Zhao & Sun, 2011	Decoction	*Cornu Cervi Pantotrichum* 15 g, *Herba Epimedii* 15 g, *Fructus Cnidii* 15 g, *Semen Allii Tuberosi* 15 g, *Radix Rehmanniae Praeparata* 15 g, *Cortex Eucommiae* 15 g, *Radix Rhizoma Curculiginis* 15 g, *Radix Morindae Officinalis* 15 g, *Semen Cuscutae* 15 g, *Herba Epimedii* 15 g, *Nidus Vespae* 15 g

Xu, 2005; Liu, 2006; Wang, 2006; Wang & Wang, 2009; Zhang, 2010), the Chinese version of urological professional academic writings for two studies (Wu *et al.*, 2005; Wang & Wang, 2009), the IIEF-5 scores for three studies (Jie, 2004; Cao *et al.*, 2009; Chen *et al.*, 2009) and other criteria formulated by researchers for the rest of trials. The outcome measure methods included the IIEF-5, clinical symptoms, rate of successful intercourse, erectile quality score, erectile function scale, erectile angle of penis and TCM syndrome. Ten studies (Guo *et al.*, 1999; Wang *et al.*, 1999, 2004; Jie, 2004; Gong *et al.*, 2005; Liu, 2006; Wang, 2006; Cao *et al.*, 2009; Chen *et al.*, 2009; Lu *et al.*, 2009) stated that side effects were evaluated by clinical symptoms, ADR, three conventional laboratory tests, electrocardiographic examination and liver and kidney function tests. Nine trials (Guo *et al.*, 1999; Hu *et al.*, 2004; Wang *et al.*, 2004; Wu *et al.*, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Xu & Hu, 2006; Lu *et al.*, 2009) used four classes to evaluate treatment effects including cure, significantly effective, effective, ineffective, while 11 trials (Wang *et al.*, 1999; Jie, 2004; Gong *et al.*, 2005; Lu *et al.*, 2005; Cao *et al.*, 2009; Chen *et al.*, 2009; Sun, 2009; Wang & Wang, 2009; Hu & Lu, 2010; Zhang, 2010; Zhao & Sun, 2011) used three classes (except of cure or significant) according to the score reducing rate.

Risk assessing of bias

Bias risk assessing of the included 21 randomised trials is summarised in Table 3. Only three (Xue, 2005; Ying & Xu, 2005 Wang, 2006) of the 21 trials (14.29%) were evaluated as low risks of biases, the rest were evaluated as unclear or high bias risks.

None of the 21 studies reported sample size calculation. Except for two studies (Guo *et al.*, 1999; Lu *et al.*, 2009), the others reported the baseline data and showed no statistically significant difference between trial and control groups. Seven studies (Xue, 2005; Ying & Xu, 2005; Wang, 2006; Xu & Hu, 2006; Cao *et al.*, 2009; Chen *et al.*, 2009; Lu *et al.*, 2009) employed blinding procedures of random number tables, but only one trial (Xue, 2005) used opaque envelopes to conceal allocation. Five trials (Jie, 2004; Wang *et al.*, 2004; Xue, 2005; Ying & Xu, 2005; Wang, 2006) employed a blinding procedure, four of them using blinding of participants and one (Wang *et al.*, 2004) employing double blinding of participants and personnel. Three studies (Wang *et al.*, 2004; Xue, 2005; Cao *et al.*, 2009) reported incomplete outcome data (missing outcome data unbalanced in numbers across intervention groups, with different reasons for missing data across groups). The adverse effects of CHF were defined as key outcomes in the review, but only eight trials (Jie, 2004; Wang *et al.*, 2004; Wu *et al.*, 2005; Xue, 2005; Liu, 2006; Wang, 2006; Chen *et al.*, 2009; Lu *et al.*, 2009) stated the outcome data of ADR, so the others were considered as selective outcome reporting. The statistical methods applied in only two studies (Liu, 2006; Sun, 2009) were unclear. Three of the 21 trials (Wang *et al.*, 2004; Xue, 2005; Cao *et al.*, 2009) did not use per-protocol analysis.

Three trials (Wang *et al.*, 2004; Xue, 2005 Cao *et al.*, 2009) reported withdrawals, and only three trials (Wang *et al.*, 2004; Gong *et al.*, 2005; Chen *et al.*, 2009) mentioned follow-up for incomplete patient data.

Effects of interventions

Cure rate

See Table 4. A total of 17 trials (Guo *et al.*, 1999; Hu *et al.*, 2004; Jie, 2004; Wang *et al.*, 2004; Lu *et al.*, 2005, 2009; Wu *et al.*, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Xu & Hu, 2006; Chen *et al.*, 2009; Sun, 2009; Wang & Wang, 2009; Hu & Lu, 2010; Zhang, 2010; Zhao &

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Table 3 Risks of bias of included studies

	Bias risks assessing of ten domains in included studies										
Included trials	Calculation of sample size	Balance of baseline data	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Proper statistics method	Intention-to-treatment analysis	Total bias risk assessing
Guo *et al.*, 1999;	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Wang *et al.*, 1999;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Hu *et al.*, 2004;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Jie, 2004;	No	Yes	Unclear	Unclear	Single blind[a]	Unclear	Unclear	No	Yes	Unclear	Unclear
Wang *et al.*, 2004;	No	Yes	Unclear	Unclear	Double blinding[b]	Unclear	Yes	No	Yes	No	Unclear
Gong *et al.*, 2005;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Lu *et al.*, 2005;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Wu *et al.*, 2005;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	No	Yes	Unclear	Unclear
Xue, 2005;	No	Yes	Table of random number	Yes	Single blind[a]	Unclear	Yes	No	Yes	No	Low
Ying & Xu, 2005;	No	Yes	Table of random number	Unclear	Single blind[a]	Unclear	Unclear	Yes	Yes	Unclear	Low
Liu, 2006;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear
Wang, 2006;	No	Yes	Table of random number	Unclear	Single blind[a]	Unclear	Unclear	No	Yes	Unclear	Low
Xu & Hu, 2006;	No	Yes	Table of random number	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Chen *et al.*, 2009;	No	Yes	Table of random number	Unclear	Unclear	Unclear	Unclear	No	Yes	Unclear	Unclear
Cao *et al.*, 2009;	No	Yes	Table of random number	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	High
Lu *et al.*, 2009;	No	Unclear	Table of random number	Unclear	Unclear	Unclear	Unclear	No	Yes	Unclear	Unclear
Sun, 2009;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Wang & Wang, 2009;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Hu & Lu, 2010;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Zhang, 2010;	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Zhao & Sun, 2011	No	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear

[a]Blinding of participants.
[b]Double blinding in three centres and blinding of participants and personnel.

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Table 4 Analyses of clinical comprehensive effect

Included trials	Risk of bias	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)	*P*-value
The cure rate					
CHF versus Placebo					
Soothing liver and replenishing yang capsule (double blinding) versus placebo (Wang *et al.*, 2004)	Unclear	34/100	0/100	69.00 (4.29, 1110.17)	0.003
Soothing liver and replenishing yang capsule (nonblinding) versus placebo (Wang *et al.*, 2004)	Unclear	60/200	0/100	60.80 (3.80, 973.17)	0.004
CHF versus WMT					
Relieving depression and treating flaccidity decoction versus Yohimbine (Lu *et al.*, 2005)	Unclear	17/50	6/35	1.98 (0.87, 4.52)	0.10
Soothing liver, tonifying kidney and activating blood formula versus Bromocriptine (Lu *et al.*, 2009)	Unclear	4/16	1/16	4.00 (0.50, 31.98)	0.19
Resolving phlegm and dredging collaterals formula versus Simvastatin (Chen *et al.*, 2009)	Unclear	9/32	2/32	4.50 (1.05, 19.22)	0.04
Lu-zhong warming kidney decoction versus Andriol (Zhao & Sun, 2011)	Unclear	14/39	9/38	1.52 (0.75, 3.08)	0.25
CHF plus BT versus BT only					
Activating blood, resolving depression and treating flaccidity decoction plus BT versus BT (Hu & Lu, 2010)	Unclear	6/36	0/36	13.00 (0.76, 222.53)	0.08
CHF plus BT versus WMT plus BT					
Revised Right-Restoring Pill plus BT versus Methycobal plus BT (Zhang, 2010)	Unclear	15/26	11/24	1.26 (0.73, 2.17)	0.41
CHF plus WMT versus WMT only					
Enhancing masculinity and treating flaccidity decoction plus Vardenafil versus Vardenafil (Xu & Hu, 2006)	Unclear	8/40	4/40	2.00 (0.65, 6.11)	0.22
Resolving phlegm and dredging collaterals decoction plus Simvastatin versus Simvastatin (Chen *et al.*, 2009)	Unclear	23/64	2/32	5.75 (1.44, 22.88)	0.01
CHF versus another CHF					
Tonifying kidney and activating blood formula versus Shen-bao oral liquid (Guo *et al.*, 1999)	Unclear	23/103	5/38	1.70 (0.70, 4.14)	0.25
Soothing liver and replenishing yang capsule (double blinding) versus Compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	34/100	11/100	3.09 (1.66, 5.75)	0.0004
Soothing liver and replenishing yang capsule (nonblinding) versus Compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	60/200	11/100	2.73 (1.50, 4.95)	0.001
Tonifying kidney, dredging collaterals and sooth liver formula versus San bian capsule (Hu *et al.*, 2004)	Unclear	11/41	7/40	1.53 (0.66, 3.56)	0.32
Tonifying kidney and supplementing essence decoction (improvement of TCM-SC) versus Securing kidney decoction (Wu *et al.*, 2005)	Unclear	8/30	6/30	1.33 (0.53,3.38)	0.54
Two rehmannia-turtle shell decocted pill versus Zhuang yang fu chun ling formula (Ying & Xu, 2005)	Low	9/30	4/30	2.25 (0.78, 6.52)	0.14
Tonifying kidney and supplementing essence decoction versus securing kidney decoction (Hu *et al.*, 2004)	Unclear	7/30	6/30	1.17 (0.44, 3.06)	0.75
Tonifying kidney and soothing liver formula versus Xian le xiong capsule (Wang, 2006)	Low	12/40	4/40	3.00 (1.06,8.52)	0.04
Regenerating essence and assisting yang formula versus Shen-bao oral liquid (Liu, 2006)	Unclear	87/168	12/84	3.63 (2.10, 6.24)	<0.00001
Tonifying kidney and supporting body pill versus Gui fu di huang pill (Sun, 2009)	Unclear	27/60	14/40	1.29 (0.77, 2.13)	0.02
Dispelling stasis and treating flaccidity formula versus right-restoring pill (Wang & Wang, 2009)	Unclear	35/52	16/39	1.64 (1.08, 2.50)	0.33
The total clinical effective rate					
CHF versus Placebo					
Soothing liver and replenishing yang capsule (double blinding) versus placebo (Wang *et al.*, 2004)	Unclear	88/100	21/100	4.19 (2.85, 6.17)	<0.00001
Soothing liver and replenishing yang capsule (nonblinding) versus placebo (Wang *et al.*, 2004)	Unclear	81/100	21/100	3.86 (2.61, 5.71)	<0.00001

(*Continued*)

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Table 4 (*Continued*)

Included trials	Risk of bias	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)	*P*-value
CHF versus WMT					
Relieving depression and treating flaccidity decoction versus Yohimbine (Lu *et al.*, 2005)	Unclear	46/50	20/35	1.61 (1.19, 2.17)	0.002
Resolving phlegm and dredging collaterals decoction versus Simvastatin (Chen *et al.*, 2009)	Unclear	25/32	18/32	1.39 (0.97, 1.98)	0.07
Soothing liver, tonifying kidney and activating blood formula versus Bromocriptine (Lu *et al.*, 2009)	Unclear	14/16	7/16	2.00 (1.11, 3.59)	0.02
Lu-zhong warming kidney decoction versus Andriol (Zhao & Sun, 2011)	Unclear	35/39	30/38	1.17 (0.93, 1.38)	0.20
CHF plus BT versus BT only					
Tonifying kidney and replenishing heart formula plus BT versus BT (Xue, 2005)	Low	19/21	8/11	1.24 (0.84, 1.83)	0.27
Replenishing qi and nourishing yin formula plus BT versus BT (Cao *et al.*, 2009)	High	30/40	11/23	1.57 (0.99, 2.49)	0.06
Activating blood, resolving depression and treating flaccidity decoction plus BT versus BT (Hu & Lu, 2010)	Unclear	32/36	18/36	1.78 (1.26, 2.51)	0.001
CHF plus BT versus WMT plus BT					
Revised right-restoring pill plus BT versus Methycobal plus BT (Zhang, 2010)	Unclear	24/26	16/24	1.38 (1.02, 1.88)	0.04
CHF plus WMT versus WMT only					
Enhancing masculinity and treating flaccidity decoction plus Vardenafil versus Vardenafil (Xu & Hu, 2006)	Unclear	33/40	25/40	1.32 (1.00, 1.75)	0.05
Resolving phlegm and dredging collaterals decoction plus Simvastatin versus Simvastatin (Chen *et al.*, 2009)	Unclear	53/64	18/32	1.47 (1.06, 2.04)	0.02
CHF versus another CHF					
Tonifying kidney and activating blood formula versus Shen-bao oral liquid (Guo *et al.*, 1999)	Unclear	87/103	23/38	1.40 (1.07, 1.83)	0.02
Life-saving kidney qi decoction versus Wu zi yan zong pill (Wang *et al.*, 1999)	Unclear	46/50	12/32	2.45 (1.56, 3.87)	0.0001
Kidney-supplementing and liver-soothing pill versus golden cabinet's kidney qi pill (Jie, 2004)	Unclear	31/40	21/40	1.48 (1.05, 2.07)	0.02
Tonifying kidney, dredging collaterals and sooth liver formula versus San bian capsule (Hu *et al.*, 2004)	Unclear	33/41	29/40	1.11 (0.87, 1.42)	0.40
Soothing liver and replenishing yang capsule (double blinding) versus Compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	88/100	60/100	1.47 (1.23, 1.75)	<0.00001
Soothing liver and replenishing yang capsule (nonblinding) versus Compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	181/200	60/100	1.51 (1.28, 1.78)	<0.00001
Tonifying kidney and soothing liver pill versus golden cabinet's kidney qi pill (Jie, 2004)	Unclear	45/64	23/43	1.31 (0.95, 1.81)	0.09
Two rehmannia-turtle shell decocted pill versus Zhuang yang fu chun ling formula (Ying & Xu, 2005)	Low	25/30	22/30	1.14 (0.87, 1.49)	0.35
Tonifying kidney and supplementing essence decoction (improvement of TCM-SC) versus securing kidney decoction (Wu *et al.*, 2005)	Unclear	29/30	28/30	1.04 (0.92, 1.16)	0.55
Tonifying kidney and supplementing essence decoction versus securing kidney decoction (Wu *et al.*, 2005)	Unclear	29/30	28/30	1.04 (0.92, 1.16)	0.55
Kidney-Boosting and liver-soothing pill versus Xian le xiong capsule (Wang, 2006)	Low	36/40	24/40	1.50 (1.14, 1.97)	0.004
Regenerating essence and assisting yang formula versus Shen-bao oral liquid (Liu, 2006)	Unclear	166/168	73/84	1.14 (1.04, 1.24)	0.003
Tonifying kidney and supporting body pill versus Gui fu di huang pill (Sun, 2009)	Unclear	41/60	27/40	1.01 (0.77, 1.33)	0.93
Dispelling stasis and treating flaccidity formula versus right-restoring pill (Wang & Wang, 2009)	Unclear	48/52	31/39	1.16 (0.97, 1.39)	0.10
'Worst-case scenario' analysis					
Cure rate of CHF versus control					

(*Continued*)

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Table 4 (*Continued*)

Included trials	Risk of bias	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)	*P*-value
Soothing liver and replenishing yang capsule (double blinding) versus placebo (Wang *et al.*, 2004)	Unclear	34/102	5/101	6.73 (2.74, 16.52)	<0.0001
Soothing liver and replenishing yang capsule (double blinding) versus compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	34/102	12/101	2.81 (1.54, 5.10)	0.0007
Soothing liver and replenishing yang capsule (nonblinding) versus placebo (Wang *et al.*, 2004)	Unclear	60/205	5/101	5.91 (2.45, 14.26)	<0.0001
Soothing liver and replenishing yang capsule (nonblinding) versus compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	60/205	12/101	2.46 (1.39, 4.37)	0.002
The total clinical effective rate of CHF versus control					
Soothing liver and replenishing yang capsule (double blinding) versus placebo (Wang *et al.*, 2004)	Unclear	88/102	22/101	3.96 (2.72, 5.78)	<0.00001
Soothing liver and replenishing yang capsule (double blinding) versus compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	88/102	61/101	1.43 (1.20, 1.70)	<0.0001
Soothing liver and replenishing yang capsule (nonblinding) versus placebo (Wang *et al.*, 2004)	Unclear	181/205	22/101	4.05 (2.79, 5.89)	<0.00001
Soothing liver and replenishing yang capsule (nonblinding) versus compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	181/205	61/101	1.46 (1.24, 1.73)	<0.00001
Tonifying kidney and replenishing heart formula plus BT versus BT (Xue, 2005)	Low	19/24	8/12	1.06 (0.72, 1.55)	0.78
Replenishing qi and nourishing yin formula plus BT versus BT (Cao *et al.*, 2009)	High	30/42	11/28	1.25 (0.86, 1.82)	0.24

BT, basic treatment; CHF, Chinese herb formulae; TCM-SC, TCM symptom complex; WMT, Western medicine therapy.

Sun, 2011) used the CR to evaluate the outcome, but the efficacy standards were heterogeneous.

One multi-centre trial (Wang *et al.*, 2004) compared CHF with placebo. Either in double-blinding or nonblinding trials, soothing liver and replenishing yang capsules showed significant effects on CRs [RR60.80, 95% CI (3.80, 973.17), $P = 0.004$; RR69.00, 95% CI (4.29, 1110.17), $P = 0.003$; respectively] compared with placebos.

Four trials (Lu *et al.*, 2005, 2009; Chen *et al.*, 2009; Zhao & Sun, 2011) compared CHF with WMT. Three trials relieving depression and treating flaccidity decoction versus Yohimbine hydrochloride tablet (Lu *et al.*, 2005), soothing liver, tonifying kidney and activating blood formula versus bromocriptine tablet, and Lu-zhong warming kidney decoction versus Andriol tablet (Zhao & Sun, 2011), All showed no significant effects on CRs [RR1.98, 95% CI (0.87, 4.52), $P = 0.10$; RR4.00, 65% CI (0.50, 31.98), $P = 0.19$; RR4.50, 95% CI (1.05, 19.22), $P = 0.04$; RR1.52, 95% CI (0.75, 3.08), $P = 0.25$; respectively]. But resolving phlegm and dredging collaterals decoction showed a significant effect on CR [RR4.50, 95% CI (1.05, 19.22), $P = 0.04$] compared with Simvastatin tablet (Chen *et al.*, 2009).

One trial (Hu & Lu, 2010) compared CHF plus BT with BT only. Activating blood, resolving depression and treating flaccidity decoction plus hypoglycaemic treatment showed no significant effect on CR [RR13.00, 95% CI (0.76, 222.53), $P = 0.08$] compared with hypoglycaemic treatment only.

One trial (Zhang, 2010) compared CHF plus BT with WMT plus BT. Revised right-restoring pill plus hypoglycaemic treatment showed no significant effect on CR [RR1.26, 95% CI (0.73, 2.17), $P = 0.41$] compared with Methycobal tablet plus hypoglycaemic treatment.

Two trials (Xu & Hu, 2006; Chen *et al.*, 2009) compared CHF plus WMT with WNT only. Enhancing masculinity and treating flaccidity decoction plus Vardenafil hydrochloride tablet showed no significant effect on CR [RR2.00, 95% CI (0.65, 6.11), $P = 0.22$] compared with Vardenafil hydrochloride tablet (Xu & Hu, 2006). However, resolving phlegm and dredging collaterals decoction plus Simvastatin tablet showed a significant effect on CR [RR5.75, 95% CI (1.44, 22.88), $P = 0.01$] compared with Simvastatin tablet only (Chen *et al.*, 2009).

Nine trials (Guo *et al.*, 1999; Hu *et al.*, 2004; Wang *et al.*, 2004; Wu *et al.*, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Sun, 2009; Wang & Wang, 2009) compared CHF with another CHF. In 4 of these trials (Wang *et al.*, 2004; Liu, 2006; Wang, 2006; Sun, 2009), soothing liver and replenishing yang capsule (double blinding) versus compact yang and tonifying kidney capsule (double blinding) (Wang *et al.*, 2004), soothing liver and replenishing yang capsule (nonblinding) versus compact yang and tonifying kidney capsule (double blinding) (Wang *et al.*, 2004), tonifying kidney and soothing liver formula

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versus Xian le xiong capsule (Wang, 2006), regenerating essence and assisting yang formula versus Shen-bao oral liquid (Liu, 2006) and tonifying kidney and supporting body pill versus Gui fu di huang pill (Sun, 2009) all showed significant effects on CRs [RR3.09, 65% CI (1.66, 5.75), $P = 0.0004$; RR2.73, 95% CI (1.50, 4.95), $P = 0.001$; RR3.00, 95% CI (1.06, 8.52), $P = 0.04$; RR3.63, 95% CI (2.10, 6.24), $P < 0.00001$; RR1.29, 95% CI (0.77, 2.13), $P = 0.02$; respectively].

In contrast, in the other 5 (Guo *et al.*, 1999; Hu *et al.*, 2004; Wu *et al.*, 2005; Ying & Xu, 2005; Wang & Wang, 2009), tonifying kidney and activating blood formula versus Shen-bao oral liquid (Guo *et al.*, 1999), tonifying kidney, dredging collaterals and sooth liver formula versus San bian capsule (Hu *et al.*, 2004), tonifying kidney and supplementing essence decoction (improvement of TCM-SC) versus securing kidney decoction (Wu *et al.*, 2005), two rehmannia-turtle shell decocted pill versus Zhuang yang fu chun ling formula (Ying & Xu, 2005), tonifying kidney and supplementing essence decoction versus securing kidney decoction (Wu *et al.*, 2005) and dispelling stasis and treating flaccidity formula versus right-restoring pill (Wang & Wang, 2009) all showed no significant effects on CRs [RR1.70, 95% CI (0.70, 4.14), $P = 0.25$; RR1.53, 65% CI (0.66, 3.56), $P = 0.32$; RR1.33, 95% CI (0.53, 3.38), $P = 0.54$; RR2.25, 95% CI (0.78, 6.52), $P = 0.14$; RR1.17, 95% CI (0.44, 3.06), $P = 0.75$; RR1.64, 95% CI (1.08, 2.50), $P = 0.33$; respectively].

Total clinical effective rate

See Table 4. All the 21 trials used the TCER to evaluate the outcome, but the efficacy standards were not the same. One multi-centre trial (Wang *et al.*, 2004) compared CHF with placebo. Either in double-blinding or non-blinding trials, soothing liver and replenishing yang capsules showed significant effects on TCERs [RR4.19, 95% CI (2.85, 6.17), $P < 0.00001$; RR3.86, 95% CI (2.61, 5.71), $P < 0.00001$; respectively] compared with placebo.

Four trials (Lu *et al.*, 2005, 2009; Chen *et al.*, 2009; Zhao & Sun, 2011) compared CHF with WMT. Two trials with relieving depression and treating flaccidity decoction versus Yohimbine hydrochloride tablet (Lu *et al.*, 2005) and soothing liver, tonifying kidney and activating blood formula versus Bromocriptine tablet (Lu *et al.*, 2009) showed significant effects on TCERs [RR1.61, 95% CI (1.19, 2.17), $P = 0.002$; RR2.00, 65% CI (1.11, 3.59), $P = 0.02$; respectively]. The other two trials, resolving phlegm and dredging collaterals decoction versus Simvastatin tablet (Chen *et al.*, 2009) and Lu-zhong warming kidney decoction versus Andriol tablet (Zhao & Sun, 2011) showed no significant effects on TCERs yet [RR1.39, 95% CI (0.97, 1.98), $P = 0.07$; RR1.17, 65% CI (0.93, 1.38), $P = 0.20$; respectively].

Three trials (Xue, 2005; Cao *et al.*, 2009; Hu & Lu, 2010) compared CHF plus BT with BT only treatment. Two trials, tonifying kidney and replenishing heart formula plus antihypertension treatment (Xue, 2005) and replenishing qi and nourishing yin formula plus hypoglycaemic treatment (Cao *et al.*, 2009) showed no significant effects on TCERs [RR1.24, 95% CI (0.84, 1.83), $P = 0.27$; RR1.57, 95% CI (0.99, 2.49), $P = 0.06$; respectively] compared with BTs only. However, another trial, activating blood, resolving depression and treating flaccidity decoction plus hypoglycaemic treatment versus hypoglycaemic treatment only (Hu & Lu, 2010) showed significant effect on TCER [RR1.78, 65% CI (1.26, 2.51), $P = 0.001$].

One trial (Zhang, 2010) compared CHF plus BT with WMT plus BT. Revised right-restoring pill plus hypoglycaemic treatment showed a significant effect on TCER [RR1.38, 95% CI (1.02, 1.88), $P = 0.04$] compared with Methycobal tablet plus hypoglycaemic treatment.

Two trials (Xu & Hu, 2006; Chen *et al.*, 2009) compared CHF plus WMT with WMT only treated. Enhancing masculinity and treating flaccidity decoction plus Vardenafil hydrochloride tablet showed no significant effect on TCER [RR1.32, 95% CI (1.00, 1.75), $P = 0.05$] compared with Vardenafil hydrochloride tablet (Xu & Hu, 2006). However, resolving phlegm and dredging collaterals decoction plus Simvastatin tablet showed a significant effect on TCER [RR1.47, 95% CI (1.06, 2.04), $P = 0.02$] compared with Simvastatin tablet only (Chen *et al.*, 2009).

Twelve trials (Guo *et al.*, 1999; Wang *et al.*, 1999, 2004; Hu *et al.*, 2004; Jie, 2004; Gong *et al.*, 2005; Wu *et al.*, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Sun, 2009; Wang & Wang, 2009;) compared CHF group with another CHF. Six of these (Guo *et al.*, 1999; Wang *et al.*, 1999, 2004; Jie, 2004; Liu, 2006; Wang, 2006) with tonifying kidney and activating blood formula versus Shen-bao oral liquid (Guo *et al.*, 1999), life-saving kidney qi decoction versus Wu zi yan zong pill (Wang *et al.*, 1999), kidney-supplementing and liver-soothing pill versus golden cabinet's kidney qi pill (Jie, 2004), soothing liver and replenishing yang capsule (double blinding) versus compact yang and tonifying kidney capsule (Wang *et al.*, 2004), Soothing liver and replenishing yang capsule (nonblinding) versus compact yang and tonifying kidney capsule (Wang *et al.*, 2004), kidney-boosting and liver-soothing pill versus Xian le xiong capsule (Wang, 2006) and regenerating essence and assisting yang formula versus Shen-bao oral liquid (Liu, 2006) all showed significant effects on TCERs [RR1.40, 95% CI (1.07, 1.83), $P = 0.02$; RR2.45, 65% CI (1.56, 3.87), $P = 0.0001$; RR1.48, 95% CI

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(1.05, 2.07), $P = 0.02$; RR1.47, 95% CI (1.23, 1.75), $P < 0.00001$; RR1.51, 95% CI (1.28, 1.78), $P < 0.00001$; RR1.50, 95% CI (1.14, 1.97), $P = 0.004$; RR1.14, 95% CI (1.04, 1.24), $P = 0.003$; respectively].

However, the other six trials (Hu *et al.*, 2004; Gong *et al.*, 2005; Wu *et al.*, 2005; Ying & Xu, 2005; Sun, 2009; Wang & Wang, 2009) tonifying kidney, dredging collaterals and sooth liver formula versus San bian capsule (Hu *et al.*, 2004), tonifying kidney and soothing liver pill versus golden cabinet's kidney qi pill (Gong *et al.*, 2005), two rehmannia-turtle shell decocted pill versus Zhuang yang fu chun ling formula (Ying & Xu, 2005), tonifying kidney and supplementing essence decoction (improvement of TCM-SC) versus securing kidney decoction (Wu *et al.*, 2005), tonifying kidney and supplementing essence decoction versus securing kidney decoction (Wu *et al.*, 2005), tonifying kidney and supporting body pill versus Gui fu di huang pill (Sun, 2009) and dispelling stasis and treating flaccidity formula versus right-restoring pill (Wang & Wang, 2009) all showed no significant effects on TCERs [RR1.11, 95% CI (0.87, 1.42), $P = 0.40$; RR1.31, 65% CI (0.95, 1.81), $P = 0.09$; RR1.14, 95% CI (0.87, 1.49), $P = 0.35$; RR1.04, 95% CI (0.92, 1.16), $P = 0.55$; RR1.04, 95% CI (0.92, 1.16), $P = 0.55$; RR1.01, 95% CI (0.77, 1.33), $P = 0.93$; RR1.16, 95% CI (0.97, 1.39), $P = 0.10$; respectively].

Improvement of IIEF-5 score

See Table 5. A total of five trials (Xue, 2005; Ying & Xu, 2005; Cao *et al.*, 2009; Chen *et al.*, 2009; Lu *et al.*, 2009) used improvements of the IIEF-5 score to evaluate the outcome.

Two trials (Chen *et al.*, 2009; Lu *et al.*, 2009) compared CHF with WMT. Resolving phlegm and dredging collaterals decoction versus Simvastatin tablet (Chen *et al.*, 2009) and Soothing liver, tonifying kidney and activating blood formula versus Bromocriptine tablet (Lu

Table 5 Analysis of erectile function-related scores

Included trials	Risk of bias	MD (95% CI)	*P*-value
Improvement of IIEF-5 score			
Resolving phlegm and dredging collaterals decoction versus Simvastatin (Chen *et al.*, 2009)	Unclear	4.10 (3.62, 4.58)	<0.00001
Soothing liver, tonifying kidney and activating blood formula versus Bromocriptine (Lu *et al.*, 2009)	Unclear	2.87 (1.66, 4.08)	<0.00001
Tonifying kidney and replenishing heart formula plus BT versus BT (Xue, 2005)	Low	5.15 (3.85, 6.45)	<0.00001
Replenishing qi and nourishing yin formula plus BT versus BT (Cao *et al.*, 2009)	High	5.31 (4.20, 6.42)	<0.00001
Resolving phlegm and dredging collaterals decoction plus Simvastatin versus Simvastatin (Cao *et al.*, 2009)	High	4.52 (4.08, 4.96)	<0.00001
Two rehmannia-turtle shell decocted pill versus Zhuang yang fu chun ling formula (Ying & Xu, 2005)	Low	2.57 (1.71, 3.43)	<0.00001
Improvement of erectile quality score			
Resolving phlegm and dredging collaterals decoction versus Simvastatin (Cao *et al.*, 2009)	High	31.11 (30.04, 32.18)	<0.00001
Resolving phlegm and dredging collaterals decoction plus Simvastatin versus Simvastatin (Cao *et al.*, 2009)	High	35.4 (34.24, 36.56)	<0.00001
Improvement of TCM-SC score			
Tonifying kidney and supplementing essence decoction versus securing kidney decoction (Wu *et al.*, 2005)	Unclear	1.16 (−1.08, 3.40)	0.31
Improvement of erection angle of penis			
Resolving phlegm and dredging collaterals decoction versus Simvastatin tablets (Chen *et al.*, 2009)	Unclear	13.08 (12.24, 13.92)	<0.00001
Resolving phlegm and dredging collaterals decoction plus Simvastatin versus Simvastatin (Chen *et al.*, 2009)	Unclear	21.02 (20.24, 21.80)	<0.00001
Recovery time of erection			
Soothing liver and replenishing yang capsule (double blinding) versus placebo (Wang *et al.*, 2004)	Unclear	−9.8 (−10.55, −9.05)	<0.00001
Soothing liver and replenishing yang capsule (nonblinding) versus placebo (Wang *et al.*, 2004)	Unclear	−10.3 (−11.00, −9.60)	<0.00001
Soothing liver and replenishing yang capsule (double blinding) versus compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	−4.8 (−5.42, −4.18)	<0.00001
Soothing liver and replenishing yang capsule (nonblinding) versus compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	Unclear	−5.3 (−5.86, −4.74)	<0.00001

BT, basic treatment; CI, confidence interval; TCM, Traditional Chinese medicine; TCM-SC, TCM symptom complex.

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et al., 2009) showed significant effects on the improvement of the IIEF-5 score [MD4.10, 95% CI (3.62, 4.58), $P < 0.00001$; MD2.87, 95% CI (1.66, 4.08), $P < 0.00001$; respectively].

Two trials (Xue, 2005; Cao *et al.*, 2009) compared CHF plus BT group with BT only treatment. Tonifying kidney and replenishing heart formula plus antihypertension treatment (Xue, 2005) and replenishing qi and nourishing yin formula plus hypoglycaemic treatment (Cao *et al.*, 2009) showed significant effects on the improvement of the IIEF-5 score [MD5.15, 95% CI (3.85, 6.45), $P < 0.00001$; RR5.31, 95% CI (4.20, 6.42), $P < 0.00001$; respectively] compared with BT only.

One trial (Cao *et al.*, 2009) compared CHF plus WMT with WMT only treatment. Resolving phlegm and dredging collaterals decoction plus Simvastatin tablet showed a significant effect on the improvement of the IIEF-5 score [MD4.52, 95% CI (4.08, 4.96), $P < 0.00001$] compared with Simvastatin tablet only.

One trial (Ying & Xu, 2005) compared CHF group with another CHF. Two rehmannia-turtle shell decocted pill showed a significant effect on the improvement of the IIEF-5 score [MD2.57, 95% CI (1.71, 3.43), $P < 0.00001$] compared with Zhuang yang fu chun ling formula.

Improvement of erectile quality score

See Table 5. Only one trial (Cao *et al.*, 2009) resolving phlegm and dredging collaterals decoction plus Simvastatin tablet showed significant effects on the improvement of the erectile quality score [MD31.11, 65% CI (30.04, 32.18), $P < 0.00001$; MD35.4, 95% CI (34.24, 36.56), $P < 0.00001$; respectively] compared with Simvastatin tablet only.

Improvement of TCM-SC score

See Table 5. Only one trial (Wu *et al.*, 2005) compared CHF with another CHF. Tonifying kidney and supplementing essence decoction showed no significant effect on the improvement for score of TCM-SC score [MD1.16, 95% CI (−1.08, 3.40), $P = 0.31$] compared with securing kidney decoction.

Improvement of erection angle of penis

See Table 5. Only one trial (Chen *et al.*, 2009) resolving phlegm and dredging collaterals decoction or plus Simvastatin tablet showed significant effects on the improvement of erection angle of penis [MD13.08, 95% CI (12.24, 13.92), $P < 0.0000$; MD21.02, 95% CI (20.24, 21.80), $P < 0.00001$; respectively] compared with Simvastatin tablets only.

Recovery time for erection

See Table 5. Only one multi-centre trial (Wang *et al.*, 2004) compared CHF with placebo, either in double blinding or nonblinding trials, soothing liver and replenishing yang capsule showed less recovery times of erection [MD-9.8, 95% CI (−10.55, −9.05), $P < 0.00001$; MD-10.3, 95% CI (−11.00, −9.60), $P < 0.00001$; respectively] compared with placebo. Furthermore, either in double-blinding or non-blinding arms, the same intervention also shows the same effects [MD-5.3, 95% CI (−5.86, −4.74), $P < 0.00001$; MD-4.8, 95% CI (−5.42, −4.18), $P < 0.00001$; respectively] compared with compact yang and tonifying kidney capsule.

'Worst-case scenario' analysis

See Table 4. Based on the number of withdrawals reported in three trials (Wang *et al.*, 2004; Xue, 2005; Cao *et al.*, 2009), 'worst-case scenario' analyses for these outcomes including all patient withdrawals and lost-to-follow-up as treatment failure in trial groups and responder in control groups were performed.

Assessing the outcomes of CR, soothing liver and replenishing yang capsule (double-blinding and nonblinding arms) still kept the effect sizes and directions, showed significant effects [RR6.73, 95% CI (2.74, 16.52), $P < 0.0001$; RR5.91, 95% CI (2.45, 14.26), $P < 0.0001$; respectively] compared with placebo (Wang *et al.*, 2004). As for TCER, the same interventions still kept the effect sizes and directions [RR3.96, 95% CI (2.72, 5.78), $P < 0.00001$; RR4.05, 95% CI (2.79, 5.89), $P < 0.00001$; respectively] compared with compact yang and tonifying kidney capsules (Wang *et al.*, 2004).

Assessing the outcomes of TCER, soothing liver and replenishing yang capsule (double-blinding and nonblinding arms) (Wang *et al.*, 2004) still kept the effect sizes and directions, showed significant effects on [RR2.81, 95% CI (1.54, 5.10), $P = 0.0007$; RR2.46, 95% CI (1.39, 4.37), $P = 0.002$; respectively] compare with placeboes. Moreover, the same interventions kept the effect sizes and directions [RR1.43, 95% CI (1.20, 1.70), $P < 0.0001$; RR1.46, 95% CI (1.24, 1.73), $P < 0.00001$; respectively] compared with compact yang and tonifying kidney capsules (Wang *et al.*, 2004) as well.

Tonifying kidney and replenishing heart formula plus antihypertension treatment (Xue, 2005) and replenishing qi and nourishing yin formula plus hypoglycaemic treatment (Cao *et al.*, 2009) still kept the effect sizes and directions, showed no effects on the TCERs [RR1.06, 95% CI (0.72, 1.55), $P = 0.78$; RR1.25, 95% CI (0.86, 1.82), $P = 0.24$; respectively] compared with BTs only.

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Adverse effects

See Table 6. Eight of the 21 trials (Jie, 2004; Wang *et al.*, 2004; Wu *et al.*, 2005; Xue, 2005; Liu, 2006; Wang, 2006; Chen *et al.*, 2009; Lu *et al.*, 2009) stated ADR outcomes, two of which (Xue, 2005; Liu, 2006) were unclear and most frequently involved were gastrointestinal symptoms. Only one of these eight trials (Jie, 2004) in terms of anepithymia, tonifying kidney and soothing liver pill versus golden cabinet's kidney qi pill showed less cases of this adverse effect [RR0.33, 95% CI (0.12, 0.95), $P = 0.04$]. In the same trial, the differences of the cases of dry mouth and constipation between two arms showed no statistical significance [RR0.75, 95% CI (0.49, 1.15), $P = 0.19$; RR0.43, 95% CI (0.18, 1.00), $P = 0.05$; respectively]. Two trials (Xue, 2005; Lu *et al.*, 2009) reported adverse effects in two arms unclearly. In addition, the other five of eight trials reported no ADRs in two arms.

Publication bias

See Figs 2 and 3. On visual inspection, the funnel plot of trials (Guo *et al.*, 1999; Hu *et al.*, 2004; Wang *et al.*, 2004; Wu *et al.*, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Sun, 2009; Wang & Wang, 2009;) comparing CHF to control other CHF on the CR with binary outcomes was symmetrical around a single peak, and the symmetry was also validated by Egger's test ($P = 0.96$).

However, the funnel plot of comparison (Guo *et al.*, 1999; Wang *et al.*, 1999, 2004; Hu *et al.*, 2004; Jie, 2004; Gong *et al.*, 2005; Wu *et al.*, 2005; Ying & Xu, 2005; Liu, 2006; Wang, 2006; Sun, 2009; Wang & Wang, 2009) on the clinical total effective rate was asymmetrical on visual inspection, and this asymmetry was almost the same in Egger's regression analysis ($P = 0.03$).

Discussion

Every year there are lots of clinical trials testing Chinese medicinal herbs for ED published in the medical literature and most of them reported positive effects. Regarding the mechanisms of Chinese medicinal herb action, it has been reported that Shu gan yi yang capsule (mechanism of soothing liver and replenishing yang) can significantly improve the expression of endothelial nitric oxide synthase and cyclic guanosine monophosphate and inhibit the expression of 5'-phosphodiesterase (PDE5) in the tissue of cavernous body of penis in ED rats (Wang *et al.*, 2011); Moreover, this herb formula can also remarkably improve erectile activity, sexual desire and ejaculatory activity, as well as the reduction in penile venous outflow (Wang *et al.*, 2005). It has a similar effect with sildenafil on PDE5, which may be the important mechanism of it in the treatment of ED.

Nowadays, TCM is practiced side by side with Western medicine in many Chinese hospitals and clinics, and it is

Table 6 Analyses of side effects of included studies

Trials	ADR	Intervention (*n*/*N*)	Control (*n*/*N*)	RR (95% CI)	*P*-value
Tonifying kidney and soothing liver pill versus golden cabinet's kidney qi pill (Jie, 2004)	Dry mouth	18/40	24/40	0.75 (0.49, 1.15)	0.19
Tonifying kidney and soothing liver pill versus golden cabinet's kidney qi pill (Jie, 2004)	Anepithymia	4/40	12/40	0.33 (0.12, 0.95)	0.04
Tonifying kidney and soothing liver pill versus golden cabinet's kidney qi pill (Jie, 2004)	Constipation	6/40	14/40	0.43 (0.18, 1.00)	0.05
Soothing liver and replenishing yang capsule versus placebo or compact yang and tonifying kidney capsule (Wang *et al.*, 2004)	ADR	0/300	0/200	Not estimable	
Tonifying kidney and replenishing heart formula plus BT versus BT (Xue, 2005)	ADR	0/21	Unclear/11	Not estimable	
Tonifying kidney and supplementing essence decoction versus securing kidney decoction (Wu *et al.*, 2005)	ADR	0/30	0/30	Not estimable	
Tonifying kidney and soothing liver pill versus Xian le xiong capsule (Wang, 2006)	ADR	0/40	0/40	Not estimable	
Regenerating essence and assisting yang formula versus Shen-bao oral liquid (Liu, 2006)	ADR	0/168	0/84	Not estimable	
Resolving phlegm and dredging collaterals decoction plus Simvastatin versus Simvastatin (Chen *et al.*, 2009)	ADR	0/96	0/32	Not estimable	
Soothing liver, tonifying kidney and activating blood formula versus Bromocriptine (Lu *et al.*, 2009)	Diarrhoea	Unclear/16	0/16	Not estimable	

BT, basic treatment; CI, confidence interval.

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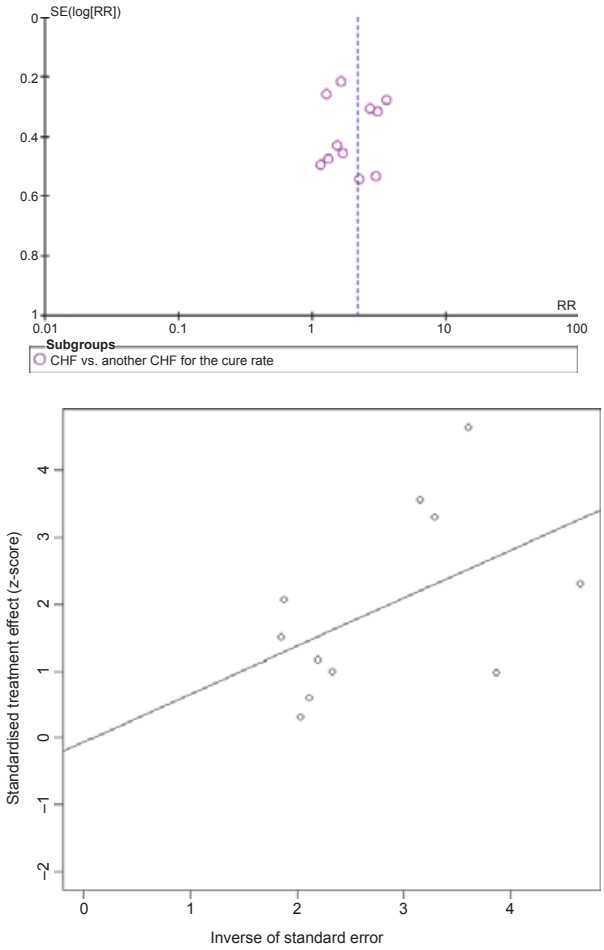

Fig. 2 Egger's test.

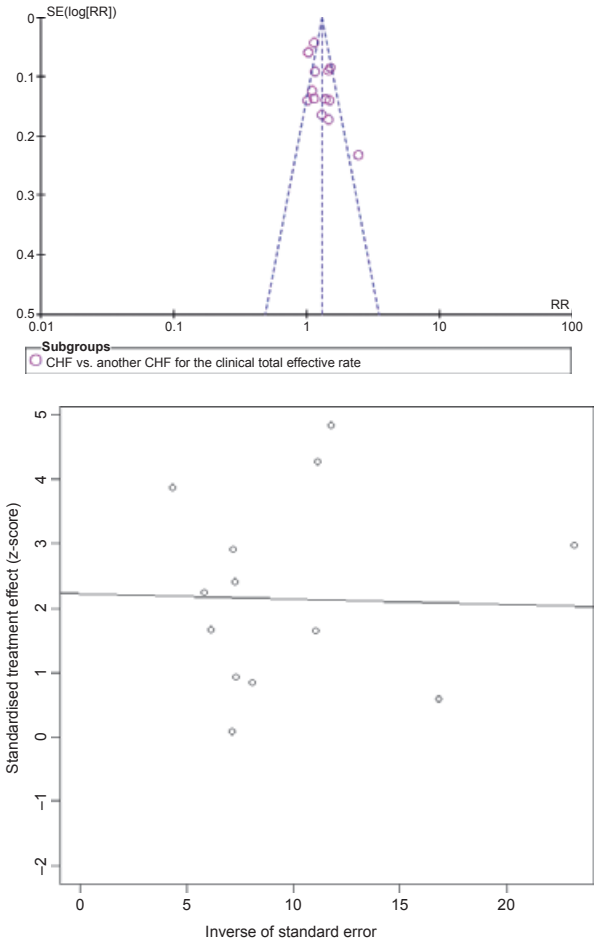

Fig. 3 Egger's test.

also widely used in other countries such as the United States. According to the 2007 National Health Interview Survey, which included questions on the use of various CAM therapies, approximately 17 per cent of adults take natural products, including herbs, making it the most commonly used therapy, and more than one-third of the patients at six large acupuncture clinics said they also received Chinese herbal treatments (NCCAM, 2012). Chinese medicinal herbs have been used for treating ED for more than 2000 years and are still widely used in China. Every year, an increasing number of new Chinese herbal drugs have been officially registered and approved for use in the treatment of ED by the State Food and Drug Administration of P.R. China (SFDA, 2012b).

The present systematic review suggests that some CHF therapies based on the guidance of TCM theory using alone or combined with WMT or BT compared with the controls may have beneficial effects on the outcome on clinical comprehensive effects (CR and TCER), improvements of various scales for erectile functions (IIEF-5 score, erectile quality score, TCM-SC score), erection angle of penis and time of erection recovery for adult patients with ED, and these herb prescriptions have fewer side effects. Moreover, the 'worst-case scenario' analysis of three trials stated missing data for patients in two groups, the effect sizes and directions did not change significantly compared with the controls by counting those lost in the treatment group as treatment failures and those in the control group as responders.

In short, this review suggests: (i) soothing liver and replenishing yang capsule, resolving phlegm and dredging collaterals decoction, resolving phlegm and dredging collaterals decoction plus Simvastatin, tonifying kidney and soothing liver formula, regenerating essence and assisting yang formula and tonifying kidney and supporting body pill showed improvement of the CRs; (ii) soothing liver and replenishing yang capsule, relieving depression and treating flaccidity decoction, soothing liver, tonifying kidney and activating blood formula, activating blood, resolving depression and treating flaccidity decoction plus

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hypoglycaemic treatment, Revised Right-Restoring Pill plus hypoglycaemic treatment, resolving phlegm and dredging collaterals decoction plus Simvastatin, tonifying kidney and activating blood formula, life-saving kidney qi decoction, kidney-supplementing and liver-soothing pill, kidney-boosting and liver-soothing pill and regenerating essence and assisting yang formula showed improvement of the TCER; (iii) resolving phlegm and dredging collaterals decoction and soothing liver, tonifying kidney and activating blood formula, tonifying kidney and replenishing heart formula plus antihypertension treatment, replenishing qi and nourishing yin formula plus hypoglycaemic treatment, resolving phlegm and dredging collaterals decoction plus Simvastatin and two rehmannia-turtle shell decocted pill showed significant improvement of the IIEF-5 score; (iv) resolving phlegm and dredging collaterals decoction or plus Simvastatin showed significant improvement of erectile quality score and erection angle of penis; (v) soothing liver and replenishing yang capsule showed shorter recovery time of erection; (vi) eight trials reported the outcomes of adverse effects, mostly involving gastrointestinal symptoms. Tonifying kidney and soothing liver pill showed less cases of anepithymia compared with golden cabinet's kidney qi pill.

However, because the literature search had limitations in this study, the Cochrane Central Register of Controlled Trials and other grey literature such as meeting abstract databases were not included; the bias in provision of data cannot be ruled out. At present, there is lack of sufficient evidence to recommend or deny any of these medicinal herb compounds for treatment of ED due to a variety of risks of bias of the included trials. These above encouraging findings have to be interpreted conservatively because of the following reasons:

Risk of bias

The majority of the RCCTs included in this review are unclear or have high risks of bias. Twenty trials were reported in Chinese and the qualities of journals and 17 articles cannot be evaluated due to insufficient information. Seven studies (33.33%) stated that table of random number assignments was used, most trials stated only random assignment, but did not give sufficient information to allow a judgement of whether or not it was conducted properly. Only one study applied the opaque envelope to conceal allocation. Five trials (23.81%) employed a blinding procedure, but they provided only limited descriptions of blinding methods. Only one trial stated application of the double-dummy method (same appearance, shape, colour, size and odour for placebo and herb formula capsules) for blinding. Eight trials (38.10%) stated the outcome of ADR, and the others selectively reported outcomes. Only three trials reported withdrawals, and only three trials mentioned the follow-up of incomplete cases. Obviously, as for the risks of bias, these less rigorous included trials show larger differences between experimental and control groups than do those conducted with better rigour. One multi-centre, large scale RCT was identified, but the blinding method was incomplete, and double blinding was only used in three centres.

Due to inadequate reporting of the allocation sequence, allocation concealment, blinding, intention-to-treat analysis and drop outs account in the majority of trials, it was possible that there was performance bias and detection bias due to patients and researchers being aware of the therapeutic interventions for the subjective outcome measures. Therefore, it is concluded that the majority of included studies with unclear risks of bias may be high risks of bias in fact from a more conservative point of view. We caution that the differences between Chinese herbal formulae and control groups may be associated with the less rigorous trials which had high or unclear risks of bias.

Funnel plot asymmetry

Even if the funnel plot showed symmetry of nine trials comparing CHF to other CHF on the CRs, publication bias analysis of 12 studies included on the clinical total effective rates was obvious asymmetrical on both visual inspection and quantitative Egger's test. The main explanation for the funnel plot asymmetry is the existence of publication bias and risks of bias. Vickers *et al.* (1998) found that some countries, including China, publish unusually high proportions of positive trial results, for which publication bias is a possible explanation. All trials included in this review were conducted in China, and 20 of 21 were published in Chinese. The presence of publication bias suggests that trials with negative findings remain unpublished. Moreover, the heterogeneity of Chinese medicinal herbs and control interventions may contribute to the asymmetry.

Nonstandard controls

Except for six trials that investigated CHF versus WMT, the controls were another Chinese herb formula in 12 trials and non-specific therapies in three trials. The standard medical therapies were used as controls only in two studies, namely PDE5 inhibitor and Andriol. Only one trial used placebo as control intervention. Obviously, the positive results from internal comparison between one Chinese herb formula and another one were lack of robust reasoning and conviction.

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On the other hand, we are not able to exclude the possibility that these non-specific drugs may have had a negative effect on ED. This could lead to an inflated positive effect of Chinese medicinal herbs. However, in one multicentre, randomised controlled trials random trial, soothing liver and replenishing yang capsule versus placebo showed similar effects as Chinese medicinal herbs versus non-specific interventions.

Inconsistent evaluation criteria of outcome

The primary goal in the management strategy of a patient with ED is to determine the aetiology of the disease and treat it when possible, and not to treat the symptom alone (Burnett AL, 2010). However, ED can be treated successfully with current treatment options, but cannot be cured. Because most men with ED are not cause-specific, the advantage of Chinese herb formula for clinical practice of ED is alleviation of adverse symptoms and improvement of erectile function (Burnett AL, 2010). So the assessments of clinically relevant outcomes from long-term follow-up, such as IIEF score, sexual health inventory for men, erectile function domain of the IIEF, erection hardness grading scale, erection dysfunction inventory of treatment satisfaction, sexual experience questionnaire, the rate of partner's satisfaction and tolerance and safety of CHF, are especially important.

Nevertheless, available outcomes from the included trials mainly used the IIEF-5 scale system, the evaluation criteria of therapeutic effect in nine studies were drawn up by the researchers, the precision and accuracy had not been verified, and the use of composite outcome measures in 21 trials to evaluate overall improvement of symptoms limits the generalisation of the findings. Furthermore, the inconsistence of different standards was not in favour of the comparison between different experimental results. Therefore, we are not able to draw unequivocal conclusions about these important outcomes.

The classification of cure, significantly effective, effective, or ineffective, and the total effective rate is not internationally recognised, and these outcome measurements are vague to interpret the effect. We propose future trials to comply with international standards, especially recommended by the AUA, ISSM and EAU, in the evaluation of treatment and safety effects.

Other clinical heterogeneity

Disease diagnostic criteria were not consistent. A total of 10 trials (47.62%) specified definite diagnostic criteria according to the official standard, including The Guiding Principle for Clinical Research on Traditional Chinese Medicine New Drugs issued by the Ministry of Health of P.R.C., The Chinese Guideline for Diagnosis and Treatment of Male ED issued by the Chinese Medical Association, and 13 studies (61.90%) made clear statements of the exclusion criteria. All studies stated syndrome differentiation of TCM, but only 11 trials (52.38%) declared definite diagnosis basis according to the classic TCM theory, these syndromes types of TCM are different, and most included syndromes of Kidney-yang deficiency, Liver-qi depression, deficiency and stagnation of Blood.

The compositions of Chinese medicine compounds were not consistent. According to the principle of 'syndrome differentiation and treatment' of TCM, the compositions of herb formulae markedly varied and were heterogeneous. The treatment duration varied from 4 days to 3 months. Therefore, the overall effects cannot be pooled for analysis. Furthermore, the clinical heterogeneity reduced the external validities and limited the generalisation of the findings.

Scant safety outcomes were studied and reported. No conclusion on adverse events associated with using Chinese medicinal herbs can be drawn from this review because of the limited number of trials identified, and the duration of treatment and follow-up, as well as inadequate recording and reporting of adverse events. Only eight trials (38.10%) stated ADR outcomes, mostly involving gastrointestinal symptoms. Two of eight trials were unclear. Only one trial reported that tonifying kidney and soothing liver pill versus golden cabinet's Kidney qi pill showed less cases of anepithymia. Most of the trials did not mention whether they monitored adverse effects at all. In total, the information on ADR reported was so insufficient that we could not make a judgement of whether these CHF were safe or were less harmful for participants or not compared with the control. The scant safety outcome limited the generalisation of the findings. Nowadays, Chinese medicinal herbs are not considered to have no toxic effect, many adverse events have been reported (SFDA, 2012a). The efficacy and safety should be equally concerned and researched in clinical trials. The safety of Chinese medical herbs needs to be monitored, and occasional and severe adverse events need to be investigated in observational epidemiological studies.

Future research issues and direction

In the present review, some TCM herbs seem to have an effect on relieving the ED patients' syndrome scores, improving the IIEF-5 and erectile quality scores, increasing the success rate of intercourse and erection angle of penis, which should encourage new trials to verify this efficacy for ED. Potentially, Chinese medicinal herbs, possibly combined with conventional therapy or Western medicine, may be revealed to be an attractive option.

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However, because of the generally high or unclear risks of bias, the controls were not standard therapies, the inclusive and exclusive criteria, diagnostic and evaluation criteria of therapeutic effect were obvious heterogeneous, the great variations of the CHF used, as well as the publication bias, CHF therapies are not recommended for ED.

Before the use of CHF therapies can be advocated, further high-quality studies with larger sample size that demonstrates their mechanisms of action and meaningful efficacies must be carried out. The following aspects should be addressed: (i) reducing the bias risks of clinical trials of Chinese medicinal herbs for ED are the key: proper randomisation and allocation concealment techniques need to be clearly described and fully reported; blinding and double dummy should be used and reported clearly although double dummy of the herbal decoction might be very difficult; application of blinding of participants, personnel and outcome assessor to minimise performance and assessment biases; application with placebo or standard Western medicine control; clear description of withdrawal/dropout during the trial and reporting of clinically important outcome measures from long-term follow-up, use of intention-to-treat principle and appropriate method for including drop out into data analyses; informed consent must be gained from the participants; (ii) the definite diagnosis and exclusion criteria should use international standards, especially refer to the guideline made by professional associations such as EAU (Wespes *et al.*, 2012), AUA (Montague *et al.*, 2012) and International Society for Sexual Medicine (Montorsi *et al.*, 2010); and the diagnosis of TCM syndrome complex must be made according to the related criteria issued by official institutions or the Association of Chinese Medicine; (iii) the outcome measures should preferably include the generally acknowledged questionnaire or scale and objective means of laboratory tests such as colour duplex ultrasound of penis blood outflow and nocturnal penile tumescence and rigidity. Standardised monitoring or an effective self-reporting system should be used to identify adverse events. Simultaneously, application of the therapeutic evaluation criteria of TCM should be encouraged; (iv) the prescriptions and different forms of CHF must base on the guidance of TCM theory, and be clear and consistent during the whole treatment; (v) the basic research of the mechanism of Chinese herb drugs action should be strengthened; (vi) the research proposal of TCM clinical trials should be registered (World Health Organization, 2012), and trials should be reported according to the CONSORT Statement (The CONSORT Group, 2012) or CONSORT for TCM (Wu *et al.*, 2007). Look forward to further well-designed randomised trials could conclude explicit evidence to support or refute the positive findings.

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