Review Article

Efficacy and Safety of Chinese Medicinal Herbs for the Treatment of Hyperuricemia: A Systematic Review and Meta-Analysis

Jianping Lin,[1] Shaoqing Chen,[2] Shuzhen Li,[2] Meili Lu,[2] Yanan Li,[2] and Youxin Su[3]

[1]*Subsidiary Rehabilitation Hospital, Fujian University of Traditional Chinese Medicine, Fuzhou, China*
[2]*College of Rehabilitation Medicine, Fujian University of Traditional Chinese Medicine, Fuzhou, China*
[3]*Orthopaedics and Traumatology College, Fujian University of Traditional Chinese Medicine, Fuzhou, China*

Correspondence should be addressed to Youxin Su; suyouxin1969@126.com

Background. Chinese medicinal herbs may be useful for the treatment of hyperuricemia, but there has been no systematic assessment of their efficacy and safety. *Objectives*. To systematically assess the efficacy and safety of Chinese medicinal herbs for the treatment of hyperuricemia. *Methods*. Six electronic databases were searched from their inception to December 2015. Randomized controlled clinical trials (RCTs) were included. Cochrane criteria were applied to assess the risk of bias. Data analysis was performed using RevMan software version 5.2. *Results*. Eleven RCTs with 838 patients were included. There was no significant difference in serum uric acid between Chinese medicinal herbs and traditional Western medicine (SME: 0.19, 95% CI: −0.04 to 0.43; $p = 0.10$). In terms of overall efficacy, the Chinese medicinal herbs were significantly superior to Western medicine (RR: 1.11; 95% CI: 1.04 to 1.17; $p = 0.0007$). The Chinese medicinal herbs were better than Western medicine in reducing the adverse reactions (RR: 0.30; 95% CI: 0.15 to 0.62; $p = 0.001$). And all these funnel plots showed unlikelihood of publishing bias. *Conclusions*. The results indicate that Chinese medicinal herbs may have greater overall efficacy with fewer adverse drug reactions, although the evidence is weak owing to the low methodological quality and the small number of the included trials.

1. Introduction

Hyperuricemia (HUE) is a metabolic disease caused by a purine metabolic disturbance that leads to excessive production of uric acid, which is the pathogenic basis for gout. It has been reported that 18.8% of patients with HUE developed gout during a 5-year follow-up period [1]. Studies also show that, in addition to its association with gout, HUE is a strong risk factor for atherosclerosis [2], hypertension [3], and metabolic syndrome [4], which may include obesity, hyperlipidemia, and diabetes mellitus [5].

Rapid economic development in China has led to changes in the daily diet, specifically, an increased rate of high-purine diets, thereby increasing the prevalence of HUE. According to a meta-analysis conducted in 2011, the prevalence of HUE in China was 21.6% among men and 8.6% among women [6], while, in 2010, in the United States, it was 12.7% overall [7]. The many potential complications of HUE may lead to greatly increased healthcare costs. Therefore, it is extremely important to understand HUE not only in China but also around the world.

Because both excess production and decreased excretion of uric acid contribute to HUE, two types of hypouricemic drugs are commonly used for the treatment. Uricosuric drugs (i.e., probenecid and benzbromarone) that reduce the serum uric acid concentration (SUA) by increasing the renal excretion of uric acid and xanthine oxidase inhibitors (i.e., allopurinol) that decrease serum uric acid by inhibiting uric acid synthesis have been the mainstays of conventional HUE treatment [8]. Although these treatments have very good results as hypouricemic agents, they may be associated with gastrointestinal reactions, liver and kidney damage, and other adverse effects [9, 10], and, in rare cases, allopurinol has been associated with reactive hepatitis and fulminant

hepatic failure [11]. Therefore, long-term treatment may not be advisable.

In traditional Chinese medicine (TCM), HUE belongs to the arthromyodynia disease category. Chinese medicinal herbs are administered orally as a liquid formulation prepared by chopping or crushing herbs into a thick powder, immersing the powder in water, boiling, and filtering [12], which has long been used for the treatment of HUE in China and has been associated with positive and unique clinical effects.

In the past decade, many studies have compared Chinese medicinal herbs with traditional Western medicine in the treatment of HUE. However, the treatment protocols and evaluation methodologies of these studies are different [24], which greatly limit their clinical applicability [25]. Therefore, a systematic review to evaluate the efficacy and safety of Chinese medicinal herbs in the treatment of HUE would be of great importance, and, to our knowledge, no such systematic review has been undertaken. We therefore designed this systematic review to investigate the efficacy and safety of Chinese medicinal herbs in the treatment of HUE.

2. Methods

2.1. Eligibility Criteria. Randomized controlled clinical trials (RCTs) in humans were included in this review. According to our study design, the included studies should focus on the effect of the Chinese medicinal herbs (single or compound) in comparison with Western medicine only. Outcome measures should include at least one essential outcome, such as SUA and overall efficacy.

2.2. Patients. In accordance with published diagnostic criteria, HUE [26] is diagnosed on the basis of SUA levels of up to $416\,\mu$mol/L in men or $357\,\mu$mol/L in women, with all other serum and uric influencing factors excluded. All patients included in the study had confirmed diagnoses of HUE. Pregnant women and patients with cancer or blood diseases were excluded.

2.3. Databases and Search Strategy. Original research articles were searched from 6 electronic databases from their inception to December 2015: PubMed, EMBASE, the Cochrane Library, the Chinese Scientific Journal Database (VIP), the China National Knowledge Information Database (CNKI), and Wanfang. The journal languages were restricted to Chinese and English.

We used the following search strategy: ("hyperuricemia") AND ("traditional Chinese medicine" OR "Chinese medicine", "traditional" OR "zhong yi xue" OR "Chinese Traditional Medicine" OR "Traditional Medicine", "Chinese" OR "Drugs", "Chinese Herbal" OR "herbal medicine" OR "Chinese medicine practice") AND ("control" OR "comparison" OR "controlled trial") in the English databases and ("hyperuricemia" AND "Chinese Herbal" AND "comparison") in the Chinese databases.

2.4. Endpoint Indicators. Enumeration data of the efficacy were graded into 4 categories according to the standards of the Guiding Principles for the Clinical Research of New TCM [27]: cure, SUA decreased to normal level; markedly effective, the rate of decrease of SUA was equal to or more than 30%; effective, the rate of decrease of SUA was 5% to 30%; and ineffective, the rate of decrease of SUA was less than 5%. The rate of decrease of SUA is equal to (SUA before intervention minus SUA after intervention) divided by SUA before intervention · 100%. Enumeration data for effective treatment were counted in each group based on the categories of cured, markedly effective, and effective. Measurement data included SUA as a primary indicator.

2.5. Study Identification. Three investigators participated in the data extraction from all publications included in the study. Data including the first author, publication year, total number of cases included in the experimental and control groups, intervention methods, and endpoint evaluation indicators were recorded. Two reviewers (LJP and CSQ) independently screened the title and abstract of the searched studies. Full text of the studies that potentially met the eligibility criteria were obtained, and the potentially relevant references were retrieved according to predefined eligibility criteria. One investigator (LJP) performed the initial data extraction, and a second investigator (CSQ) subsequently reexamined each article and verified the results. Differences were resolved by discussion with the third investigator (SYX) in order to reach consensus. And the original author was contacted if the results could not come to an agreement.

2.6. Quality Assessment. The quality of the included studies was assessed independently by two reviewers (LZP and LSZ) using the Cochrane Collaboration tool for assessing the risk of bias [28]. When there were inconsistencies, a third reviewer (CSQ) participated in the assessment and consensus was reached by discussion. The Cochrane-recommended domains that were considered were selection bias, which is a measure of adequate sequence generation and allocation concealment; performance bias, which evaluates blinding of participants and personnel; detection bias, which checks for blinding of outcome assessment; attrition bias, which checks for incomplete outcome data; reporting bias, which indicates selective outcome reporting; and other bias, which covers other sources of bias including baseline imbalance and fraudulent outcomes. Each of these indicators was scored as low risk of bias, high risk of bias, or unclear [29].

2.7. Data Analysis. We calculated the d index and the standard error (SE_d) values of SUA for each RCT before using RevMan. The d index and SE_d values of SUA were continuous, and the standardized mean difference (SMD) and 95% confidence interval (CI) were calculated. Enumeration data (overall efficacy and adverse reactions) were evaluated by relative risk (RR) and 95% CI. Statistical heterogeneity was assessed using a Chi-square test or by calculating Higgins I^2 values [29]. The proper effect models were chosen in accordance with the results: when I^2 is less than 50%, fixed effects models were chosen, and when I^2 is more than 50%, a random effects model was applied [30]. Sensitivity analysis was used to explore the source of heterogeneity. The
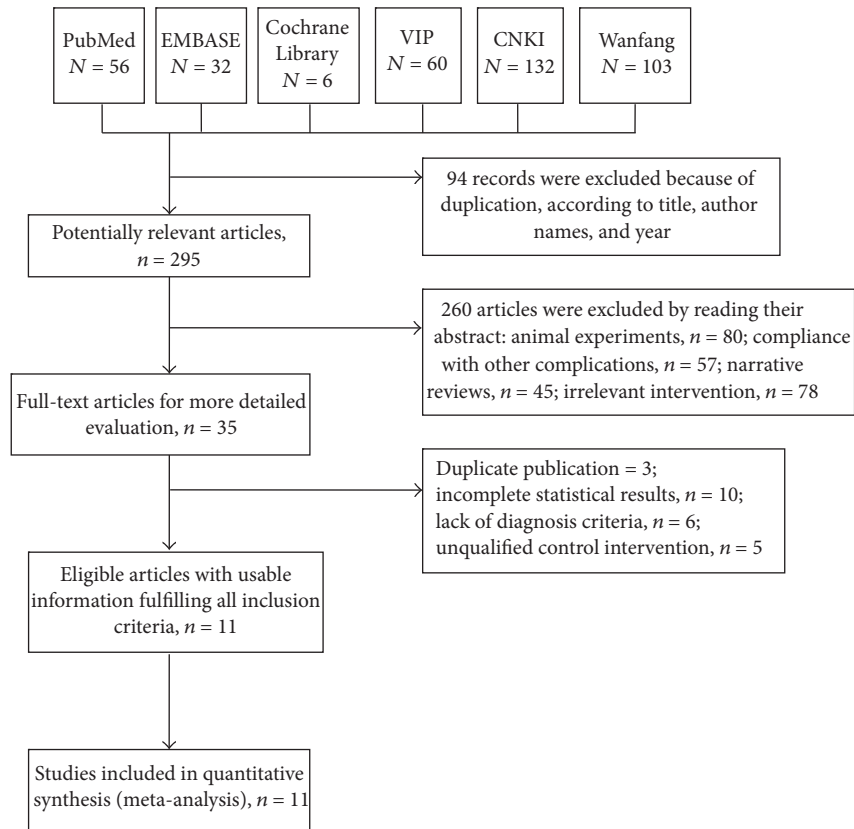
FIGURE 1: Flowchart of the included articles. Abbreviations: VIP: Chinese Scientific Journal Database; CNKI: China National Knowledge Information Database.

Cochrane Collaboration Review Manager Software (RevMan version 5.2.0) was used for all statistical analyses, and all p values were two sided [29].

3. Results

3.1. Description of Studies. The study selection flowchart is presented in Figure 1. A total of 389 records were identified through the database searches. After removing duplicates, 295 studies remained for eligibility screening; 284 of them were ultimately excluded, including 80 that were based on animal experiments, 57 that complied with other complications, 45 that were narrative reviews, 78 that considered irrelevant interventions, 3 that were duplicate publications, 10 that had incomplete statistical results, 6 that did not meet the diagnostic criteria, and 5 that had unqualified control interventions. Thus, 11 articles met the inclusion criteria, and 11 were included in the meta-analysis [13–23].

3.2. Serum Uric Acid Concentration. Ten RCTs provided SUA data in μmol/L. These studies included 766 patients (393 patients in the experimental groups and 373 in the control groups) [14–23]. The subgroup meta-analysis showed that 2 RCTs were statistically significant differences between the TCM Chinese medicinal herbs and allopurinol (SMD 1.14, 95% CI: 0.53 to 1.75 and SMD 0.44, 95% CI: 0.04 to 0.84) because I^2 = 60%, a random effects model was used

for the analysis, and the combined SMD was 0.19 with a 95% CI of −0.04 to 0.43 (p = 0.10). Therefore, there was no significant difference between the Chinese medicinal herbs and the Western pharmaceuticals in terms of SUA reduction (Figure 2(a)). The funnel plot showed symmetrical distribution in 10 experiments, indicating unlikelihood of publishing bias (Figure 2(b)).

3.3. Overall Efficacy of the Chinese Medicinal Herbs. Nine RCTs were analyzed, including 654 patients (340 in the experimental groups and 314 in the control groups) (Table 2) [13, 15–17, 19–23]. On subgroup meta-analysis, 3 RCTs showed statistically significant differences between the TCM Chinese medicinal herbs and allopurinol (SMD 1.17, 95% CI: 1.02 to 1.35; SMD 1.21, 95% CI: 1.02 to 1.44; and SMD 1.71, 95% CI: 1.20 to 2.45). For all studies, the meta-analysis indicated that I^2 = 43%, and a fixed effects model was adopted for the analysis. The combined RR was 1.11, and the 95% CI was 1.04 to 1.17 (p = 0.0007), indicating a significant difference between the overall efficacy of Chinese medicinal herbs and Western pharmaceuticals for the treatment of HUE (Figure 3(a)). The funnel plot showed 9 symmetric distributions of 9 experiments, indicating unlikelihood of publishing bias (Figure 3(b)).

3.4. Adverse Reactions. Six RCTs including 476 patients (247 in the experimental groups and 229 in the control

Study or subgroup	Std. mean difference	SE	Weight	Std. mean difference IV, random, 95% CI	Std. mean difference IV, random, 95% CI
1.5.1 Allopurinol					
Li 2007	−0.017	0.2243	10.5%	−0.02 [−0.46, 0.42]	
Zhou et al. 2010	0.502	0.2637	9.1%	0.50 [−0.01, 1.02]	
Chen 2008	−0.21	0.2341	10.1%	−0.21 [−0.67, 0.25]	
Tan et al. 2013	−0.126	0.2596	9.3%	−0.13 [−0.63, 0.38]	
Hong and Shen 2011	1.143	0.312	7.7%	1.14 [0.53, 1.75]	
Yu 2012	0.438	0.203	11.2%	0.44 [0.04, 0.84]	
Cai et al. 2014	0.374	0.2023	11.3%	0.37 [−0.02, 0.77]	
Xiang et al. 2014	−0.045	0.1986	11.4%	−0.04 [−0.43, 0.34]	
Subtotal (95% CI)			80.6%	0.23 [−0.04, 0.50]	

Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 19.65$, df = 7 ($p = 0.006$); $I^2 = 64\%$
Test for overall effect: $Z = 1.69$ ($p = 0.09$)

1.5.2 Probenecid					
Hu 2006	0.298	0.2256	10.4%	0.30 [−0.14, 0.74]	
Subtotal (95% CI)			10.4%	0.30 [−0.14, 0.74]	

Heterogeneity: not applicable
Test for overall effect: $Z = 1.32$ ($p = 0.19$)

1.5.3 Benzbromarone					
Zhang et al. 2011	−0.252	0.2697	9.0%	−0.25 [−0.78, 0.28]	
Subtotal (95% CI)			9.0%	−0.25 [−0.78, 0.28]	

Heterogeneity: not applicable
Test for overall effect: $Z = 0.93$ ($p = 0.35$)

Total (95% CI)			100.0%	0.19 [−0.04, 0.43]	

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 22.61$, df = 9 ($p = 0.007$); $I^2 = 60\%$
Test for overall effect: $Z = 1.65$ ($p = 0.10$)
Test for subgroup differences: $\chi^2 = 2.97$, df = 2 ($p = 0.23$), $I^2 = 32.8\%$
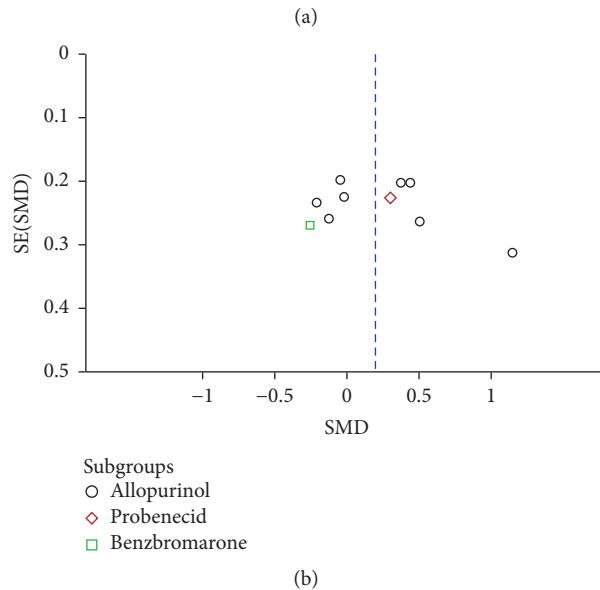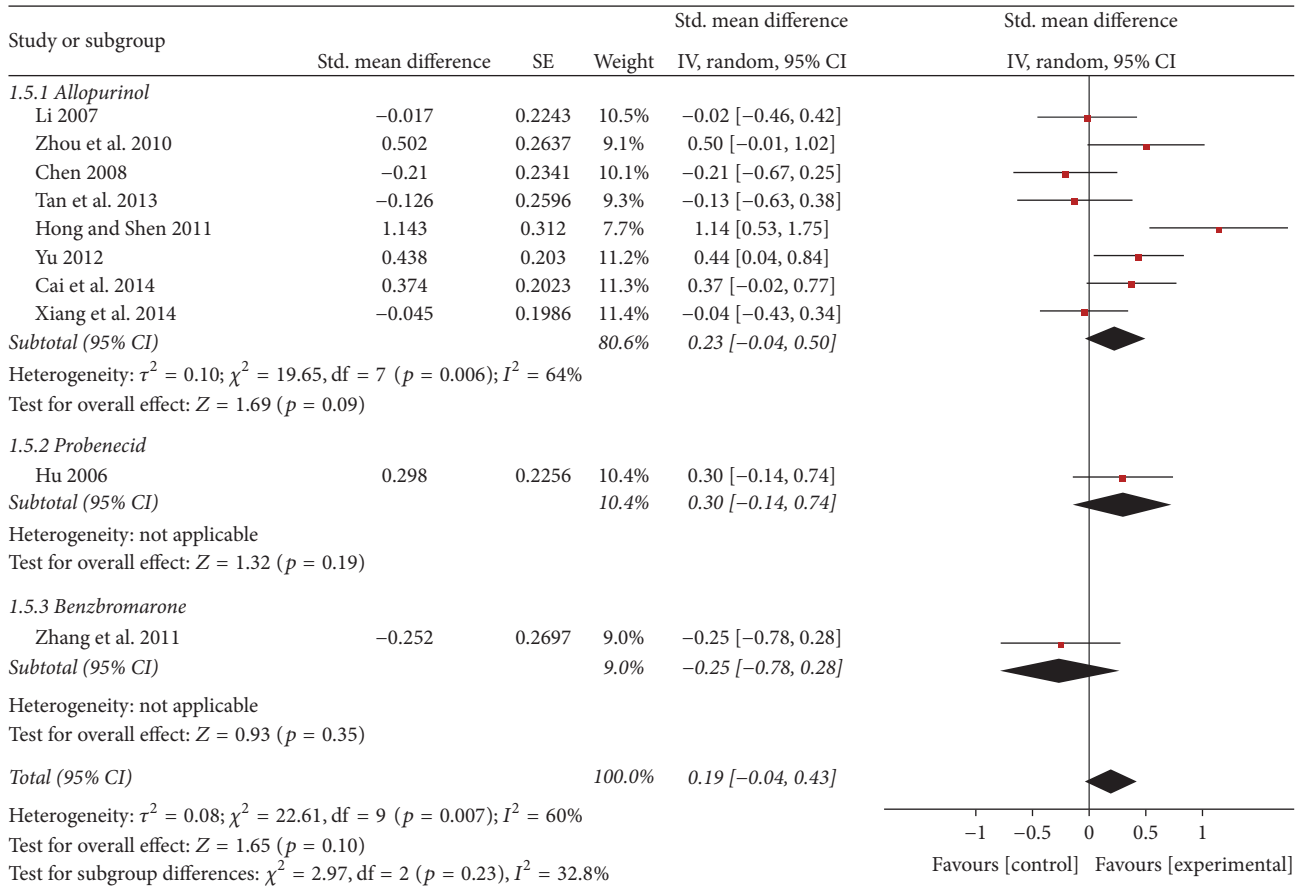
Favours [control] Favours [experimental]

(a)

(b)

FIGURE 2: (a) Effects of Chinese medicinal herbs on serum uric acid in hyperuricemic patients. (b) A funnel plot: effects of Chinese medicinal herbs on serum uric acid in hyperuricemic patients.

groups) provided safety evaluation data [15–18, 21, 22]. Subgroup meta-analysis showed statistical significance in the allopurinol subgroups (RR: 0.31 and 95% CI: 0.15 to 0.65; $p = 0.002$). The meta-analysis showed that I^2 for all

6 studies was 29%, and the analysis was performed using a fixed effects model. The combined RR value was 0.30 and the 95% CI was 0.15 to 0.62 ($p = 0.001$), indicating that, among the studies included, there were fewer adverse

Study or subgroup	Experimental		Control		Weight	Risk ratio	Risk ratio
	Events	Total	Events	Total		IV, fixed, 95% CI	IV, fixed, 95% CI
1.2.1 Allopurinol							
Li 2007	35	40	32	40	9.1%	1.09 [0.90, 1.33]	
Zhou et al. 2010	26	30	20	30	4.1%	1.30 [0.97, 1.74]	
Tan et al. 2013	29	30	28	30	25.4%	1.04 [0.92, 1.16]	
Hong and Shen 2011	35	36	15	18	7.5%	1.17 [0.94, 1.44]	
Yu 2012	48	50	41	50	17.2%	1.17 [1.02, 1.35]	
Cai et al. 2014	46	50	38	50	11.1%	1.21 [1.02, 1.44]	
Zhou 2007	33	36	15	28	2.7%	1.71 [1.20, 2.45]	
Subtotal (95% CI)		272		246	77.2%	1.14 [1.07, 1.22]	
Total events	252		189				
Heterogeneity: $\chi^2 = 9.13$, df = 6 ($p = 0.17$); $I^2 = 34\%$							
Test for overall effect: $Z = 3.89$ ($p = 0.0001$)							
1.2.2 Probenecid							
Hu 2006	36	40	34	40	12.5%	1.06 [0.90, 1.25]	
Subtotal (95% CI)		40		40	12.5%	1.06 [0.90, 1.25]	
Total events	36		34				
Heterogeneity: not applicable							
Test for overall effect: $Z = 0.67$ ($p = 0.50$)							
1.2.3 Benzbromarone							
Zhang et al. 2011	24	28	26	28	10.3%	0.92 [0.77, 1.11]	
Subtotal (95% CI)		28		28	10.3%	0.92 [0.77, 1.11]	
Total events	24		26				
Heterogeneity: not applicable							
Test for overall effect: $Z = 0.86$ ($p = 0.39$)							
Total (95% CI)		340		314	100.0%	1.11 [1.04, 1.17]	
Total events	312		249				
Heterogeneity: $\chi^2 = 14.01$, df = 8 ($p = 0.08$); $I^2 = 43\%$							
Test for overall effect: $Z = 3.38$ ($p = 0.0007$)							
Test for subgroup differences: $\chi^2 = 4.89$, df = 2 ($p = 0.09$), $I^2 = 59.1\%$							

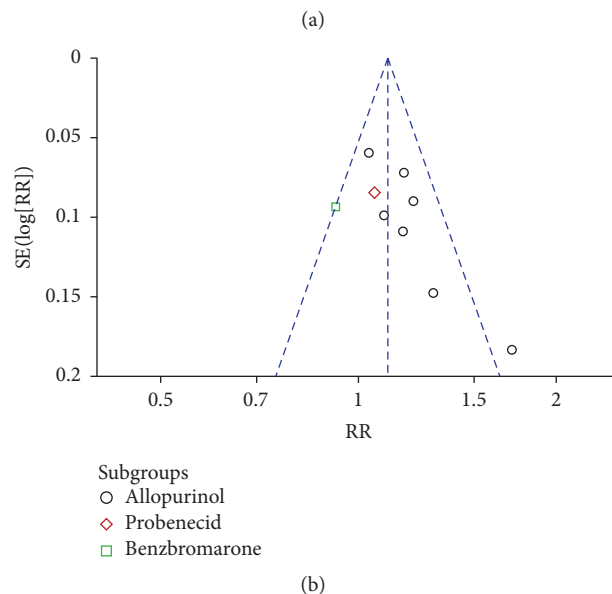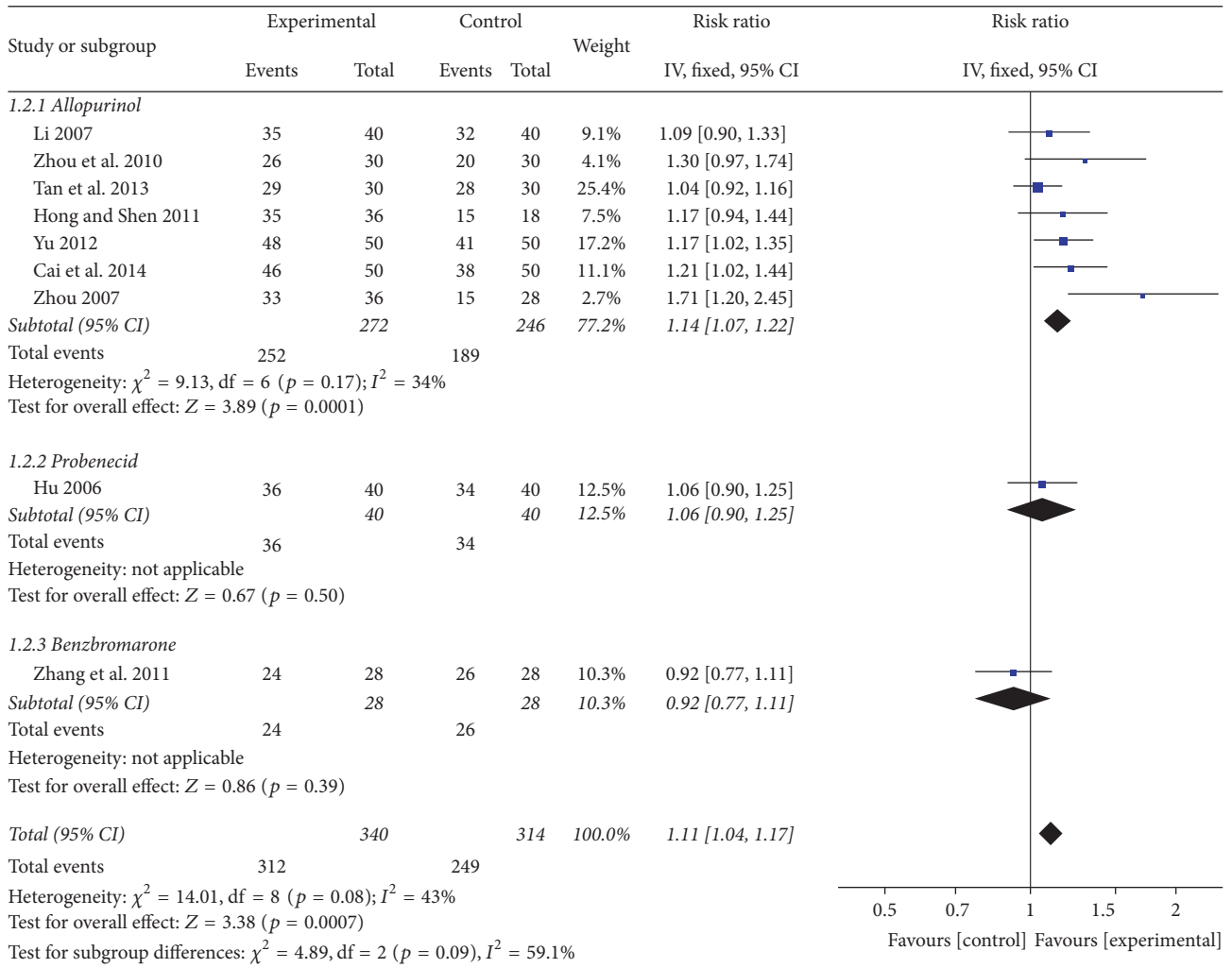Favours [control]   Favours [experimental]

(a)

(b)

FIGURE 3: (a) An analysis of the overall efficacy of Chinese medicinal herbs and Western medicine in hyperuricemic patients. (b) A funnel plot: an analysis of the overall efficacy of Chinese medicinal herbs and Western medicine in hyperuricemic patients.
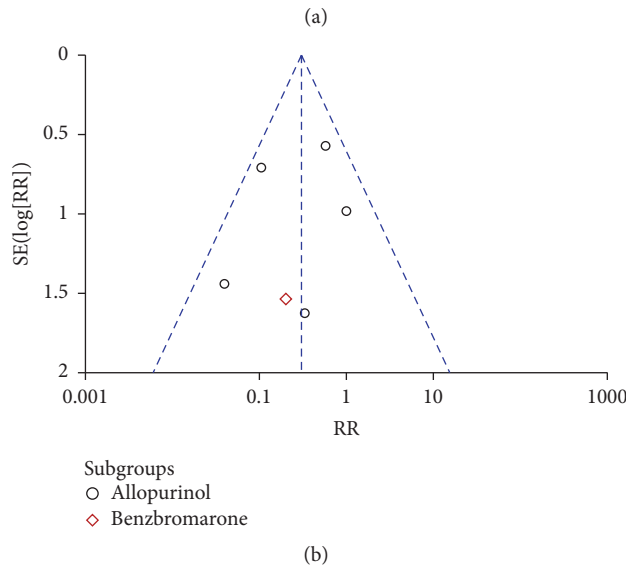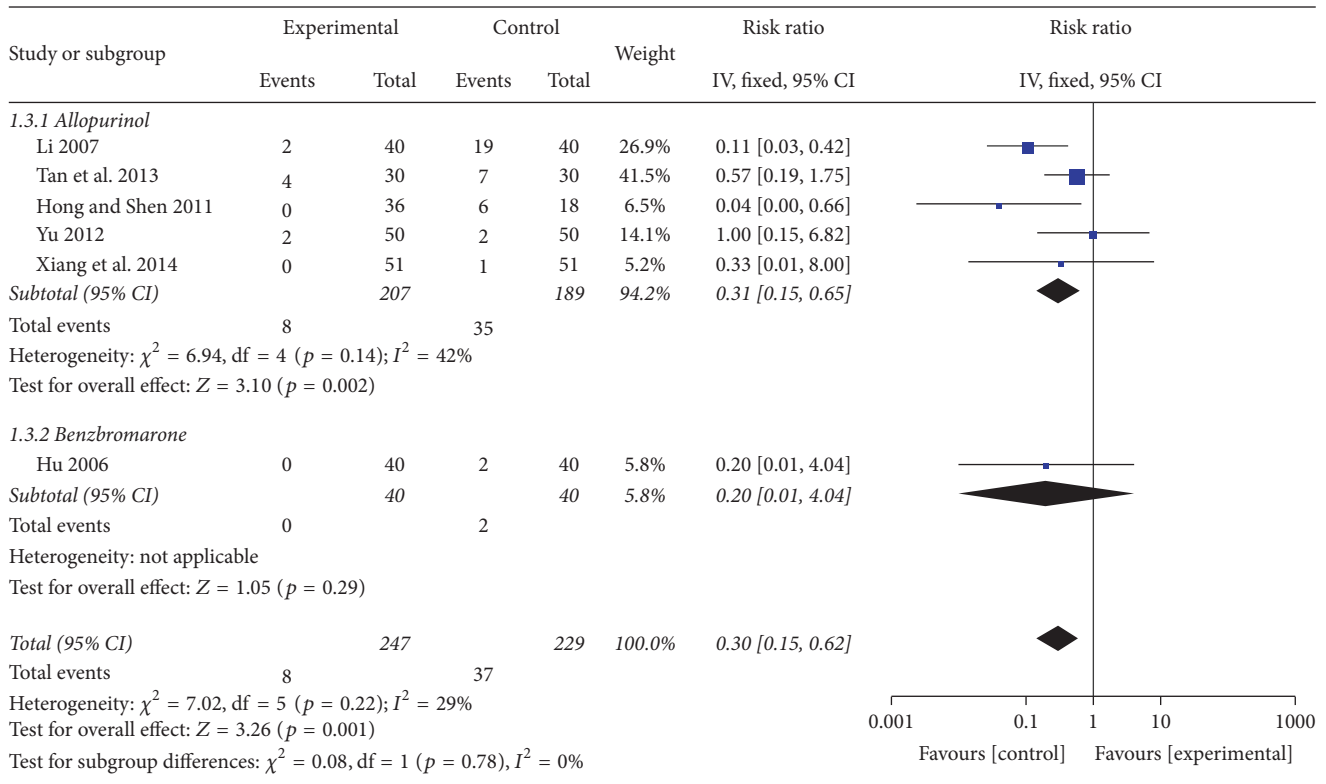
Study or subgroup	Experimental		Control		Weight	Risk ratio	Risk ratio
	Events	Total	Events	Total		IV, fixed, 95% CI	IV, fixed, 95% CI
1.3.1 Allopurinol							
Li 2007	2	40	19	40	26.9%	0.11 [0.03, 0.42]	
Tan et al. 2013	4	30	7	30	41.5%	0.57 [0.19, 1.75]	
Hong and Shen 2011	0	36	6	18	6.5%	0.04 [0.00, 0.66]	
Yu 2012	2	50	2	50	14.1%	1.00 [0.15, 6.82]	
Xiang et al. 2014	0	51	1	51	5.2%	0.33 [0.01, 8.00]	
Subtotal (95% CI)		207		189	94.2%	0.31 [0.15, 0.65]	
Total events	8		35				
Heterogeneity: $\chi^2 = 6.94$, df = 4 ($p = 0.14$); $I^2 = 42\%$							
Test for overall effect: $Z = 3.10$ ($p = 0.002$)							
1.3.2 Benzbromarone							
Hu 2006	0	40	2	40	5.8%	0.20 [0.01, 4.04]	
Subtotal (95% CI)		40		40	5.8%	0.20 [0.01, 4.04]	
Total events	0		2				
Heterogeneity: not applicable							
Test for overall effect: $Z = 1.05$ ($p = 0.29$)							
Total (95% CI)		247		229	100.0%	0.30 [0.15, 0.62]	
Total events	8		37				
Heterogeneity: $\chi^2 = 7.02$, df = 5 ($p = 0.22$); $I^2 = 29\%$							
Test for overall effect: $Z = 3.26$ ($p = 0.001$)							
Test for subgroup differences: $\chi^2 = 0.08$, df = 1 ($p = 0.78$), $I^2 = 0\%$							

(a)

(b)

FIGURE 4: (a) An analysis of the adverse reactions of Chinese medicinal herbs and Western medicine in hyperuricemic patients. (b) A funnel plot: an analysis of the adverse reactions of Chinese medicinal herbs and Western medicine in hyperuricemic patients.

reactions in patients using Chinese medicinal herbs (Figure 4(a)). The funnel plot showed 6 symmetric distributions of 6 experiments, indicating unlikelihood of publishing bias (Figure 4(b)).

3.5. Methodological Quality. Among 11 included RCTs, 8 reported no significant differences at baseline between patients in the Chinese medicinal herbs groups and those in the Western medicine groups. Only 3 trials described a randomization technique (random sequence generation

using a random number table), while 8 did not describe the randomization technique and 10 failed to describe concealed random allocation. Although only 1 trial had a double-blind design, the outcome measurements of other 9 trials relied on objective indicators that were not expected to be influenced by lack of blinding (Figure 5).

3.6. Sensitivity Analysis. The results of sensitivity analysis were relatively stable through performance from a fixed effects model to a random effects model (Figures 2–4).
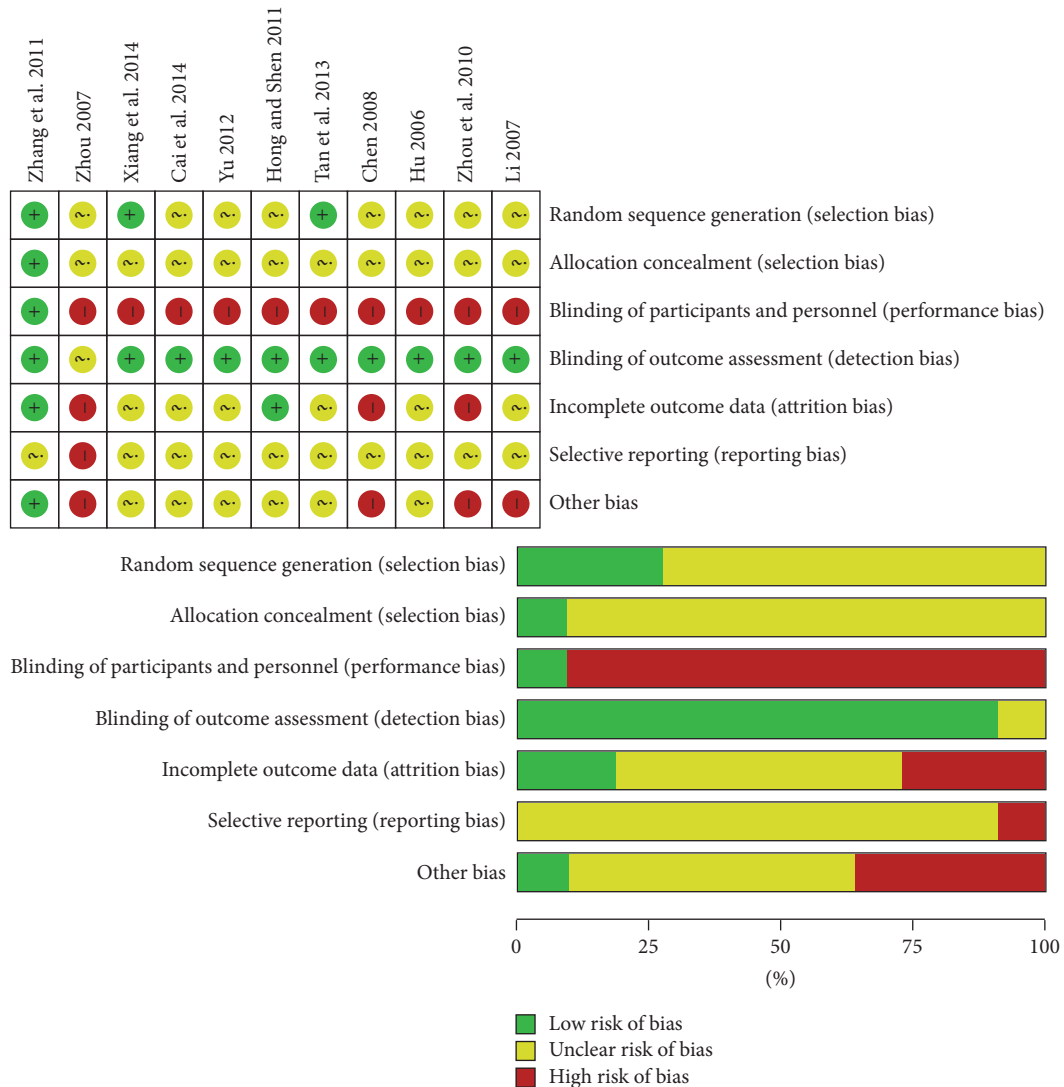
FIGURE 5: Risk of bias summary and graph.

4. Discussion

This systematic review included 11 RCTs with 838 total patients comparing Chinese medicinal herbs with Western medicine for the treatment of HUE. The outcome measures included change in SUA values, overall efficacy, and adverse reactions. Our analysis showed that Chinese medicinal herbs and traditional Western medicine had a similar effect for reducing SUA values, but, in terms of overall treatment efficacy and adverse reactions, there were significant advantages for the Chinese medicinal herbs.

The above results showed that it could not just observe SUA values, but overall treatment efficacy should be considered in order to systematically assess the efficacy and safety of Chinese medicinal herbs for the treatment of hyperuricemia. The enumeration data of the efficacy were graded into 4 categories according to the standards of the Guiding Principles for the Clinical Research of New TCM, which were advantageous to the standardization of TCM

research. However, it needs more argumentation and research to get internationally recognized [31]. Therefore, no definitive conclusion can be drawn that Chinese medicinal herbs have greater overall efficacy than Western medicine. And additional studies will be needed in the future.

The results indicate that Chinese medicinal herbs have a positive therapeutic effect with fewer adverse drug reactions. We believe that the main reason for the efficacy of Chinese medicinal herbs in the treatment of HUE relates to the active ingredients of these extracts [32]. The bulbs of *pseudobulb cremastra seu pleiones*, which is an ingredient of decoctions used by Li [17], Zhang et al. [23], and others, contain colchicine [33]. In addition, the Chinese medicinal herbs used by Zhou [13], Yu [15], Tan et al. [16], and Li [17] contain *glabrous greenbrier rhizome* (Table 1), which has astilbin as an active ingredient. Astilbin has been associated with increased renal blood flow and has shown anti-inflammatory and analgesic actions. *Plantago* contains the active ingredient aucubin [34], which Chen [14], Tan et al. [16], Li [17], and

TABLE 1: Characteristics of the included studies.

Author, year	Sample size (EG▲)	Sample size (CG▲)	Age (EG)	Age (CG)	Disease severity (EG)	Disease severity (CG)	Intervention method (/d) (EG)	Intervention methods (/d) (CG)	Duration treatment (d) (EG)	Duration treatment (d) (CG)
Zhou, 2007 [13]	36	36	55.2 ± 6.1	53.8 ± 6.3	SUA■ (umol/L): 518.2 ± 56.4	SUA (umol/L): 518.6 ± 46.8	Swordlike atractylodes (15 g), largehead atractylodes rhizome (15 g), Indian buead (15 g), plantain seed (10 g), etc.	Allopurinol (0.1 g * 3)	21	21
Chen, 2008 [14]	38	36	22~65	22~65	N/A★	N/A	Glabrous greenbrier rhizome (45 g), seven-lobed yam rhizome (30 g), Carica papaya (15 g), plantain seed (15 g), etc.	Allopurinol 0.2 g	28	28
Yu, 2012 [15]	50	50	48.12 ± 10.2	47.12 ± 11.5	SUA (umol/L) (585.83 ± 93.93)	SUA (umol/L) (584.94 ± 90.29)	Glabrous greenbrier rhizome (50 g), herba lysimachiae (50 g), cortex phellodendri chinensis (15 g), swordlike atractylodes (15 g), etc.	Allopurinol (0.1 g * 2)	30	30
Tan et al., 2013 [16]	30	30	44.17 ± 8.27	45.23 ± 9.35	The course of disease: (8.54 ± 4.07) years	The course of disease: (8.10 ± 3.46) years	Glabrous greenbrier rhizome (15 g), seven-lobed yam rhizome (20 g), jobstears seed (10 g), herba lysimachiae (15 g), etc.	Allopurinol (0.1 g * 3)	56	56
Li, 2007 [17]	40	40	55~81	52~78	N/A	N/A	Jobstears seed (30 g), glabrous greenbrier rhizome (30 g), plantain deed (20 g), seven-lobed yam rhizome (20 g), etc.	Allopurinol (0.1 g * 3)	60	60
Xiang et al., 2014 [18]	51	51	45.62 ± 5.05	44.72 ± 5.58	The course of disease: (1.96 ± 0.45) years	The course of disease: (1.13 ± 0.46) years	Radix clematidis (60 g), rhizoma polygonati odorati (20 g), radix achyranthis bidentatae (15 g), cortex phellodendri chinensis (15 g), etc.	Allopurinol (0.05 g * 3)	90	90
Cai et al., 2014 [19]	50	50	48 ± 10	47 ± 12	SUA (umol/L) (517.2 ± 86.33)	SUA (umol/L) (514.5 ± 90.29)	Cortex phellodendri chinensis (15 g), swordlike atractylodes (15 g), plantain seed (10 g), oriental waterplantain rhizome (10 g), etc.	Allopurinol (0.1 g * 3)	28	28
Zhou et al., 2010 [20]	30	30	35~74	32~75	N/A	N/A	Glabrous greenbrier rhizome (40 g), cortex phellodendri chinensis (15 g), swordlike atractylodes (15 g), jobstears seed (20 g), etc.	Allopurinol (0.1 g * 2)	28	28
Hong and Shen, 2011 [21]	36	18	51.8 ± 6.6	49.7 ± 5.1	SUA (umol/L) (546.0 ± 78.1)	SUA (umol/L): (533.0 ± 62.31)	Glabrous greenbrier rhizome (15 g), cortex phellodendri chinensis (10 g), swordlike atractylodes (10 g), jobstears seed (30 g), etc.	Allopurinol (0.1 g * 3)	60	60
Hu, 2006 [22]	40	40	39.38 ± 10.89	40.88 ± 11.13	The course of disease: (2.64 ± 1.96) years, hypertension: 11, diabetes: 4, and hyperlipidaemia: 17	The course of disease: (2.69 ± 1.86) years, hypertension: 14, diabetes: 1, and hyperlipidaemia: 15	Glabrous greenbrier rhizome (30 g), jobstears seed (15 g), oriental waterplantain rhizome (15 g), herba lysimachiae (20 g), etc.	Probenecid (0.25 * 2)	28	28
Zhang et al., 2011 [23]	28	28	56.07 ± 17.62	53.18 ± 16.40	Hypertension: 9, diabetes: 7, hyperlipidaemia: 6, and coronary heart disease: 5	Hypertension: 11, diabetes: 8, hyperlipidaemia: 7, and coronary heart disease: 5	Glabrous greenbrier rhizome (35 g), seven-lobed yam rhizome (18 g), pseudobulb cremastra seu pleiones (15 g), radix achyranthis bidentatae (10 g), etc.	Benzbromarone (50 mg * 1)	20	20

▲EG: experimental group; ▲CG: control group.
★N/A: not applicable.
■SUA: serum uric acid concentration.

TABLE 2: Outcomes.

Author, year	The overall efficacy (EG▲) C/M/E/I☆	The overall efficacy (CG▲) C/M/E/I☆	The overall efficacy (RR, 95% CI); p value	SUA● (umol/L) (EG: B/A■)	SUA (umol/L) (CG:B/A)	SUA (SMD, 95% CI); p value	Adverse reactions (EG)	Adverse reactions (CG)	Adverse reactions (RR, 95% CI)
Zhou, 2007 [13]	16/0/17/3☆	5/0/10/13	1.71 (1.20, 2.45); $p < 0.05$	N/A★	N/A	N/A	N/A	N/A	N/A
Liming Chen, 2008	N/A	N/A	N/A	488.91 ± 70.51/316.12 ± 86.25	489.61 ± 69.89/301.93 ± 93.77	0.16 (−0.30, 0.61); $p > 0.05$	N/A	N/A	N/A
Yu, 2012 [15]	0/12/36/2	0/8/33/9	1.17 (1.02, 1.35); $p < 0.01$	585.83 ± 93.93/319.13 ± 87.63	584.94 ± 90.29/358.86 ± 88.53	−0.45 (−0.84, −0.05); $p < 0.05$	Diarrhea: 2	Liver damaged: 2	1.00 (0.15, 6.82)
Tan et al., 2013 [16]	0/15/14/1	0/17/11/2	1.04 (0.92, 1.16); $p = 0.266$	546.69 ± 51.45/354.72 ± 27.29	550.33 ± 45.99/352.14 ± 25.67	0.10 (−0.41, 0.60); $p = 0.000$	Liver damaged: 1, kidney damaged: 1, leucopenia: 0, nausea: 2, and acute arthritis: 0	Liver damaged: 2, kidney damaged: 1, leucopenia: 1, nausea: 1, and acute arthritis: 2	0.57 (0.19, 1.75)
Li, 2007 [17]	0/21/14/5	0/19/13/8	1.09 (0.90, 1.33); p: N/A	524.43 ± 43.14/410.17 ± 60.25	528.50 ± 45.72/413.46 ± 55.84	−0.06 (−0.49, 0.38); $p < 0.05$	Diarrhea: 2	Liver damaged: 10, leucopenia: 8, and itchy skin: 1	0.11 (0.03, 0.42)
Xiang et al., 2014 [18]	N/A	N/A	N/A	451.33 ± 98.55/370.45 ± 91.45	442.64 ± 97.46/357.35 ± 98.57	0.14 (−0.25, 0.53); $p < 0.05$	None	Itchy skin: 1	0.33 (0.15, 0.65)
Cai et al., 2014 [19]	11/0/35/4	6/0/32/12	1.21 (1.02, 1.44); $p < 0.05$	517.2 ± 86.33/328.8 ± 87.56	514.5 ± 90.29/359.4 ± 88.63	−0.34 (−0.74, 0.05); $p < 0.01$	N/A	N/A	N/A
Zhou et al., 2010 [20]	0/14/12/4	0/8/12/10	1.30 (0.97, 1.74); $p < 0.05$	521.84 ± 75.32/290.45 ± 74.76	514.43 ± 83.35/323.44 ± 71.98	−0.44 (−0.96, 0.07); $p < 0.05$	N/A	N/A	N/A
Hong and Shen, 2011 [21]	29/0/6/1	7/0/8/3	1.17 (0.94, 1.44); $p < 0.05$	546.0 ± 78.1/353.0 ± 122.6	533.0 ± 62.3/425.0 ± 169.1	−0.51 (−1.08, 0.07); $p < 0.05$	None	Liver damaged: 3, abnormal changes of blood cells: 2, and acute episode of gout: 1	0.04 (0.00, 0.66)
Hu, 2006 [22]	0/20/16/4	0/22/12/6	1.06 (0.90, 1.25); $p > 0.05$	575.38 ± 52.62/389.30 ± 13.07	568.48 ± 53.10/398.30 ± 610.08	−0.20 (−0.64, 0.24); $p > 0.05$	None	Nausea: 1 and itchy skin: 1	0.2 (0.01, 4.04)
Zhang et al., 2011 [23]	0/14/10/4	0/18/8/2	0.92 (0.77, 1.11); $p > 0.0167$	508.00 ± 89.46/386.57 ± 69.60	493.71 ± 65.45/352.21 ± 66.79	0.5 (−0.04, 1.03); $p > 0.05$	None	N/A	N/A

☆C/M/E/I: cure/markedly effective/effective/ineffective.
▲EG: experimental group; ▲CG: control group.
■B/A: before intervention/after intervention.
★N/A: not applicable.
●SUA: serum uric acid concentration.

Zhang et al. [23] believe has a significant effect toward facilitating urine production and promoting the excretion of urea and chloride [35]. Moreover, other herbs have been used, such as seven-lobed yam rhizome [36], jobstears seed [37], and *radix achyranthis bidentatae* [38], all of which enhancing additional functions including promotion of uric acid excretion, reduction of platelet accumulation resulting in improved microcirculation, and anticoagulant function. The actions of these ingredients contribute to reductions in SUA and amelioration of potential side effects during treatment.

Traditional Western medicines such as allopurinol, probenecid, and benzbromarone have been cornerstones in the treatment of HUE and gout for decades [39]. Allopurinol is an analogue of hypoxanthine, which inhibits xanthine oxidase. In most patients, it is well tolerated. However, about 2% of patients will develop a skin rash, and allopurinol has been associated with rare life-threatening hypersensitivity syndromes at a rate of approximately 4/1000 cases [40–42]. Probenecid and benzbromarone, the uricosuric drugs, may lead to renal tubular aggregation of urate crystals and induce renal damage. Finally, in 2003, benzbromarone was withdrawn from the market because of serious hepatotoxicity. Although it is still marketed in several countries by other drug companies, withdrawal by the French manufacturer Sanofi-Synthélabo has greatly limited its availability around the world [43]. As per physicians practicing TCM, HUE is a condition that is caused by a congenital deficiency and a circulatory blockade. Blood stasis in combination with phlegm and exogenous pathogenic factors blocks the meridians and collaterals or even goes deep to the bone, transforms to heat, and finally causes renal damage [44]. Thus, Chinese herbal prescriptions usually contain several herbal components for dissipating blood stasis and reinforcing the kidneys, and these herbal components work synergistically [45]. For example, Tan et al. [16] and others add *radix achyranthis bidentatae* and *Salvia miltiorrhiza* Bge. to the prescription, which serves to inhibit platelet aggregation, expand small arteries, improve microcirculation, inhibit atherosclerotic lesions, ameliorate renal fibrosis, and protect the kidneys [37, 46]. These benefits may be among the reasons that the active ingredients in Chinese medicinal herbs are able to effectively reduce the potentially adverse effects.

Most evaluations of Chinese medicinal herbs that reduce SUA have focused on the active ingredients of individual herbs. However, Chinese medicinal herbs are usually compounded in a liquid decoction. Because Chinese herbal formulations may contain several herbal components, the active ingredients of each should be considered [47]. Furthermore, many of the available reports concerned animal experiments, and large-scale clinical trials in humans were lacking. Therefore, additional studies in humans should be a goal in the future.

The present systematic review has limitations, mainly because of the low methodological quality and small number of the included trials. Indeed, most of the included RCTs were of poor quality. Of 11 trials, only 3 described a randomization method, only 1 had a double-blind design, and none described the calculation of the sample size. Moreover, no multicenter large-scale RCT met our inclusion criteria. The low quality of the research included in this review may lead to some overestimation of the overall efficacy of Chinese medicinal herbs in comparison to traditional Western medicines (Figure 5). Furthermore, only 6 of the 11 RCTs described adverse reactions. Owing to insufficient descriptions, enumeration data for adverse reactions included only renal and hepatic dysfunction, skin reaction, gastrointestinal reaction, and acute arthritis. Therefore, a more rational approach for the evaluation of adverse drug reactions from Chinese medicinal herbs with the development of large-scale and well-designed RCTs will be needed in the future.

5. Conclusion

The results of this review indicate that Chinese medicinal herbs have a positive therapeutic effect in the treatment of HUE and can safely reduce SUA while ameliorating adverse effects. Because of the low methodological quality and the small number of the included trials, no definitive conclusion can be drawn at this point, and these results should be interpreted cautiously. Additional large-scale, well-designed trials are needed.

Competing Interests

All authors declare they have no competing interests.

Authors' Contributions

Jianping Lin, Youxin Su, and Shaoqing Chen conceived and designed the study. Jianping Lin, Yanan Li, and Meili Lu performed the article search. Jianping Lin, Shuzhen Li, and Youxin Su analyzed the data. Shuzhen Li contributed reagents/materials/analysis tools. Jianping Lin wrote the paper. Jianping Lin, Shaoqing Chen, Shuzhen Li, Meili Lu, Yanan Li, and Youxin Su read and approved the final manuscript.

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