Original Article

Comparative efficacy and safety of four classical prescriptions for clearing damp-heat recommended by clinical guidelines in treating rheumatoid arthritis: a network meta-analysis

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Background: In China, along with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), some herbal formulae for clearing damp-heat are widely applied in treating rheumatoid arthritis (RA). We aimed to summarize and compare the clinical effects of 4 guideline-recommended formulae, including Baihuguizhi decoction, Dangguiniantong decoction, Simiao pill, and Xuanbi decoction.

Methods: PubMed, Cochrane Library, EMBASE, Chinese National Knowledge Infrastructure (CNKI), Chinese Science and Technique Journals (CQVIP), WanFang, and SinoMed (CBM) databases were searched for randomized controlled trials from inception to July 2020 evaluating the efficacy and safety of these recommended herbal formulae combined with 1 csDMARD versus csDMARD alone in RA patients. A pairwise meta-analysis was conducted in RevMan 5.3 software, and a Bayesian network meta-analysis (NMA) was performed with Stata 14.0, R 4.0.2, GeMTC 0.14.3, and JAGS 4.3.0 software. Cochrane Handbook 5.1.0 was used to assess the risk of bias. Publication bias was evaluated using Egger's test, the trim-fill adjustment, and funnel plots. Trial sequential analysis (TSA) was performed to validate the overall results. The rank probability of interventions was calculated and clustered by the surface under the cumulative ranking curve (SUCRA). Pharmacologic actions of formulae were explored through the network pharmacology approach.

Results: A total of 15 studies, including 1,079 individuals, were identified. Simiao pill + csDMARD [SMPPD, odds ratio (OR) =6.62, 95% confidence interval (CI): 2.88 to 16.84] was superior to csDMARDs alone in clinical efficiency, and was more able to reduce C-reactive protein and erythrocyte sedimentation rate levels [mean difference (MD) =−7.91, 95% CI: −17.41 to −1.25; MD =−9.31, 95% CI: −14.48 to −5.56 respectively]. Although publication bias was observed (P=0.033), the trim-fill method indicated that the pooled values kept stable. Fewer adverse events (AEs) were shown with SMPPD (6.45%). TSA confirmed the results of efficacy rate at SMPPD. Network pharmacology included 5 common components and 66 common targets among 4 formulae in treating RA, involving regulating immunity and relieving inflammation.

Discussion: SMPPD might be a preferable complementary therapy for RA. However, considering the limitations of this study, recommendations for clinical practice should be validated by the results of further well-designed studies.

Keywords: Chinese herbal formula; rheumatoid arthritis (RA); network meta-analysis (NMA); network pharmacology

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Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease (1,2) characterized by chronic, symmetrical, erosive polyarthritis, which affects about 1% of people worldwide. The most apparent symptoms of RA include joint swelling, pain, tenderness, and morning stiffness. The pathological manifestations (3) are persistent synovitis of joints, systemic inflammation, and autoantibody-positivity. The main principle of treating RA (4) is to reduce inflammation and pain in the short-term and delay joint deformity and damage in the long-term. At present, first-line drugs include non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs), and second-line drugs include disease-modifying anti-rheumatic drugs (DMARDs). Among them, DMARDs are divided into 3 types, namely conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). Although the drugs mentioned above have been widely used to deal with RA, the vast economic costs and incurable nature of the condition have seriously increased the risk of psychological burden. Additionally, intolerance of toxic side effects, such as gastrointestinal reactions, liver and kidney damage, bone marrow suppression, osteoporosis, and so on, undermine patients' compliance with medications, making the treatment of RA a serious global challenge (2,5-7). Therefore, some experts and academics have begun to investigate complementary and alternative therapies. Like the overall concept of treating RA under systemic biology (8), based on the theory of syndrome differentiation with multiple components in Chinese herbal formulae (CHF), Chinese herbal medicine anticipated to have considerable clinical efficacy in treating RA potentially.

In traditional Chinese medicine (TCM), RA is called Bi syndrome, and its clinical theory has been relatively mature for a long time. Chinese herbal medicine has been used extensively to improve the quality of life of RA patients. Based on the principle of syndrome differentiation and treatment, some systematic reviews of the evidence (9-11) have manifested that CHF combined with csDMARDs for RA patients have certain synergistic effects in reducing ARs and improving efficacy, and so on. Particularly in recent years, considering the high correlation between clinically active RA and damp-heat arthralgia in the field of TCM (8), many studies have started to explore the clinical effects of various classical prescriptions for clearing heat and dampness. Some studies (12-15) have shown that if the TCM syndrome differentiation is damp-heat arthralgia syndrome, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are significantly higher in other syndrome types, and RA disease activity is the highest. For example, recent randomized controlled trials (RCTs) (16-18) have also demonstrated that the CHF for clearing dampness and heat, such as Simiao pill (SMP), Baihuguizhi decoction (BHGZD), Xuanbi decoction (XBD), combined with the csDMARD, can effectively improve RA symptoms, including reducing inflammatory reaction substances, and relieving joint pain and swelling. Concurrently, the safety of TCM has also been an issue of concern in China and internationally. Some anti-rheumatic monomers of herbs, such as tripterygium wilfordii, total glucosides of peony, and sinomenine (19-21) have been reported to damage despite having shown certain curative effects on the liver and kidney, reproductive system, and digestive tract. However, encouragingly, according to the data of the 2016–2020 National Adverse Drug Reaction Monitoring Center, among drugs with clinical ARs, the probability of ARs of herbs that clear heat and dampness have been low in all categories of TCM, with the incidence of adverse events (AEs) of 4–6% (Figure S1). We suppose that CHF of clearing damp-heat is normally safe and commonly used, which shows a certain clinical value.

In RA treatment, there are many kinds of prescriptions for clearing damp-heat. By searching the clinical guidelines and books related to RA or Bi syndrome of the damp-heat type syndrome, we found that some formulae are more frequently recommended, including BHGZD, Dangguiniantong decoction (DGNTD), SMP, XBD, Daqinjiao decotion (DQJD), Ermiao san (EMS) and Sanmiao san (SMS). The retrieval process, detailed information of included guidelines and books, and recommended frequency of CHF can be seen in Table S1 and *Figure 1*. Nevertheless, the differences in efficacy and safety between different prescriptions are not clear. It is difficult for clinicians to choose the appropriate

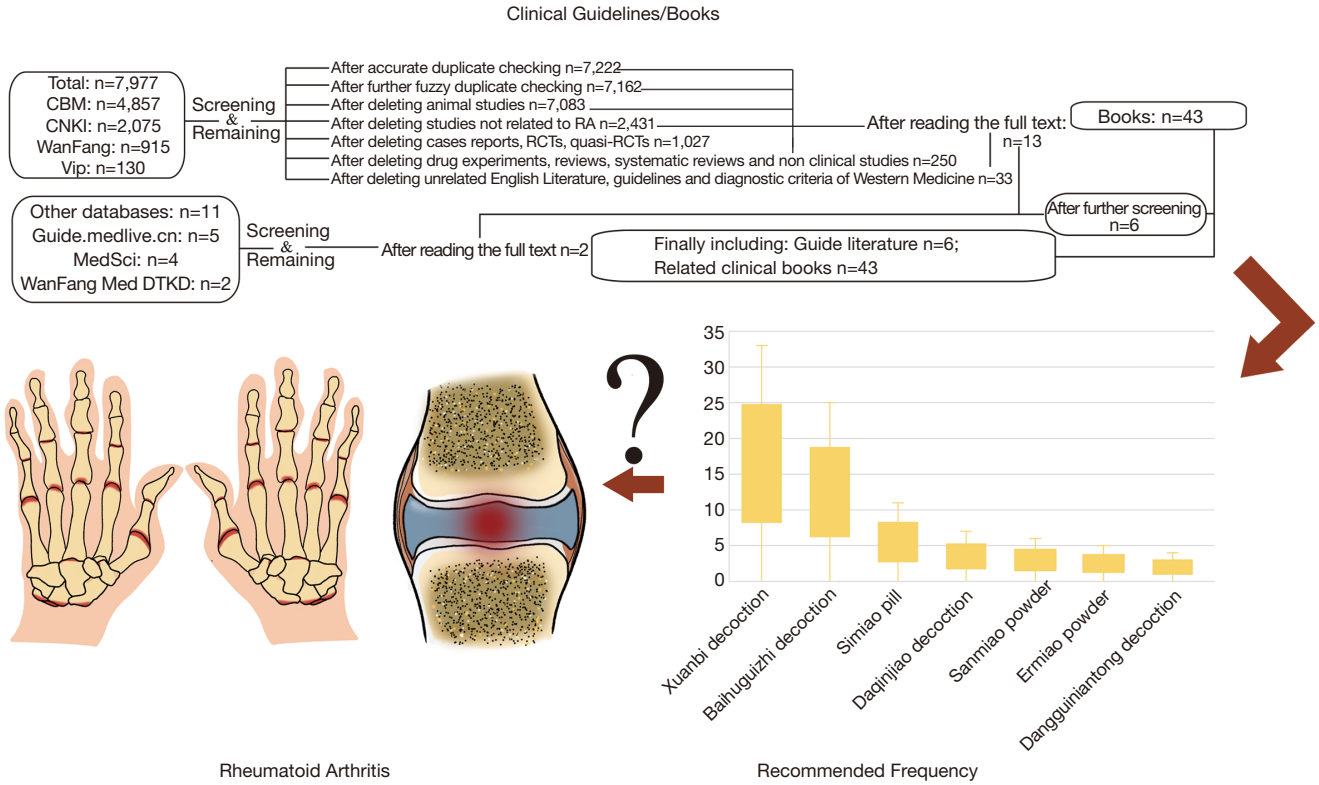


Figure 1 The retrieval process of the guidelines, and the frequency of recommended CHF for treating RA. CHF, Chinese herbal formulae; RA, rheumatoid arthritis.

prescription for RA quickly. Therefore, we used a network meta-analysis (NMA) (22) method that can estimate direct and indirect comparison results to calculate the curative effect ranking and evaluate the differences in efficacy and safety of the above classical prescriptions combined with 1 kind of csDMARD in the treatment of RA. Simultaneously, to reduce the false-positive results caused by clinical differences between the CHF, we included RCTs in the study. Interventions need to be a certain CHF recommended by the guidelines/professional books to be eligible for inclusion. Additionally, the included population had to have damp-heat syndrome RA, and the composition of the decoction used did not involve the toxic herbs listed in Table S2 wherever possible. Moreover, to balance the confounding clinical heterogeneity factors between different treatment groups, we added trial sequential analysis (TSA) in this study to expand the sample statistics to verify the results. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-445). The protocol of this NMA was also registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020200116).

Methods

Search strategies

First, the relevant subject literature should be consulted, and the corresponding search words were initially formulated. By consulting experts in rheumatism and evidence-based medicine, the corresponding theme words and free words were supplemented, and the pre-retrieval protocol was submitted on the PROSPERO platform. After the expert group evaluated the retrieval results, the final retrieval strategy was further improved to reduce differences in study retrieval. A total of 7 electronic databases for systematic review searches were used, as follows: PubMed (https://www.ncbi.nlm.nih.gov/pubmed/); Cochrane Library (http://www.cochranelibrary.com/); EMBASE (http://www.embase.com/); SinoMed (CBM, http://www.sinomed.ac.cn/); China National Knowledge Infrastructure (CNKI,

http://www.cnki.net/), China Science and Technology Journal Database (CQVIP, http://www.cqvip.com/), and Wanfang Data Knowledge Service Platform (http://www.wanfangdata.com.cn/index.html). There was no language restriction in the search strategy. Full-text retrieval was from the establishment of the databases to July 2020. Search strategies included the subject terms and free-text terms, which are displayed in Table S3. Two researchers independently searched, and any differences were resolved after discussion with a third researcher.

Inclusion criteria

Types of studies

All included studies were RCTs, and each trial evaluated the efficacy of CHF recommended by the guidelines combined with 1 csDMARD in the treatment of RA.

Participants

Participants were diagnosed with RA according to the accepted diagnostic criterion or clinical symptoms and signs. We used the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria as an inclusion criterion for diagnosis.

Interventions and comparators

The treatment group used the recommended CHF combined with 1 csDMARD (such as methotrexate or leflunomide). According to the guidelines and clinical books, the very frequently recommended CHF for clearing damp-heat with BHGZD, DGNTD, SMP, XBD, and DQJD. Based on the original prescription, modified decoctions were also included. The formulas EMS and SMS were not searched separately because SMP is a modified decoction of them. There were no restrictions on the quantity, dose, and dosage form of ingredients included in the prescription. The medication must have been consumed orally. The treatment cycle was at least 2 weeks or 3 courses. In the same study, basic drugs were the same among groups and considered as blank interventions. These drugs included low-dose hormones, NSAIDs, stomach medicine, folic acid, and so on.

Main and additional outcomes

Studies that reported 1 or more of the following pre-specified main or additional outcomes were included in this NMA. The primary outcomes included effective rate (ER), ACR 20/50/70, disease activity score-28 (DAS-28), AEs, adverse reactions (ARs), and serological examination, such as ESR, CRP, rheumatoid factors (RF), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1). The secondary outcomes were signs and symptoms assessment, including swollen joint count (SJC), tender joint count (TJC), and morning stiffness time (MST).

Data extraction and quality assessment

First, we used Endnote X9 software (Clarivate Analytics, Philadelphia, PA, USA) to classify and sort the initially retrieved studies to exclude duplicate articles; second, according to the inclusion and exclusion criteria, the 2 researchers eliminated unqualified studies through the titles, keywords, and abstracts, filed the excluded literature, and recorded the reasons and quantity of the exclusion. For incomplete information reports, the original author was contacted to supplement relevant materials, and if that were not possible, it would be removed. Third, the 2 researchers used Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA) tables to extract data from the corresponding studies, including qualitative and quantitative data. All relevant information was independently and carefully screened by 2 reviewers, with any disputes between the 2 parties being, resolved by the third assessor. The datum extracted were as shown below: (I) baseline of variables including first author, year of publication, trial design method, a sample size of participants, age range, course of the disease, diagnostic criteria, intervention measures, duration of treatment, outcomes, and follow-up; (II) dichotomous data or continuous data of the pre-specified outcomes.

The 2 reviewers used the Cochrane risk bias assessment tool to evaluate the quality of the included studies, and the third reviewer cooperated to reach an agreement through discussion. The related items of bias risk tool recommended by the Cochrane Collaboration (23) provided the following 6 evaluation criteria, which were expressed in 3 states: high risk, low risk, and unclear. The 6 items included: (I) whether randomization was mentioned and its random methods were reasonable; (II) whether allocation concealment was mentioned and whether the method was effective; (III) whether the blind method was mentioned and whether it was correct; (IV) whether the outcome data were complete; (V) whether there was a suspicion of selective reporting; (VI) other sources of bias.

Strategy for data synthesis

We conducted a pairwise meta-analysis in a random-effects

model by RevMan 5.3 software (Copenhagen: the Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and performed a Bayesian NMA using the Markov Chain Monte Carlo (MCMC) methods by Stata 14.0, R 4.0.2 (College Station, TX, USA), GeMTC 0.14.3 (http://drugis.org/software/addis1/getmc), and JAGS 4.3.0 software (http://mcmc-jags.sourceforge.net/). We calculated the binary data, such as the ER, ACR20/50/70, and so on, as the odds ratio (OR) with its 95% confidence interval (CI). For the continuous data, such as changes in physical function or inflammation markers, values were presented by mean differences (MD) with 95% CI. When the measurement standard was different, or the result variables were highly inconsistent between studies, standardized mean difference (SMD) was used (24,25).

Each direct comparison of the interventions was drawn in Stata 14.0 software with a network plot command. Different lines had corresponding colors. Green, yellow, and red represented the risk of bias of the random method as low, unclear, and high, respectively. The node size was on behalf of the total sample size under 1 kind of intervention. If there had been a closed loop in the included interventions, an inconsistency test would have been performed; however, we found no direct evidence to form a closed loop, so the consistency test in direct and indirect comparison was unnecessary (26). Nevertheless, the research should also be in accord with the hypothesis of heterogeneity and consistency. There were many outcomes included in this article. To control the conclusions' reliability, we only conducted the NMA for the outcomes, including more than 10 studies. A total of 20,000 iterations were set in the whole calculation process. To eliminate the influence of the original iteration, we set up the first burn-in of 5,000 iterations. The effects of each intervention in RA treatment were estimated, ranked, and clustered by the surface under the cumulative ranking curve (SUCRA) (22,27). These results might ultimately provide clinicians with treatment options via single or multiple factors.

Homogeneity hypothesis and publication bias

The homogeneity test of the NMA came from the direct comparison of the heterogeneity of the pairwise meta-analysis. The Q test was used to test the heterogeneity among the results of the included studies, and the test level was α=0.10. If the heterogeneity test result showed P>0.1, $I^2 \leq 50\%$, it meant that the heterogeneity was low, and the fixed effects model was used for the combined analysis of the meta-analysis (28). Otherwise, the random effects model was used for the combined analysis of efficacy, and the source of the heterogeneity was analyzed. If there was significant heterogeneity in different studies, we performed subgroup analysis to address the source of heterogeneity. Considering the different CHF in the treatment of RA in this study, we thought that the prescription rule of the decoction and the different durations of disease were the 2 major factors of heterogeneity. Using these 2 factors, taking the ER, CRP, and ESR as examples, we compared the combined effect of different formulas in RA patients with that of sub-combination, observed an overlapping effect between groups, and then judged the significance of grouping. Sensitivity analysis by excluding 1 study after another in RevMan 5.3 software was performed to observe the impact of a study on the overall results. If outcomes involved more than 10 studies, a funnel plot was drawn to observe publication bias. Besides, the Egger's regression (29) at significance P<0.05 quantitatively identified potential publication bias. Trim and fill method (30) was used to correct the estimates. Brooks Gelman Rubin's diagnostic method was used to judge the goodness of fit in the stability of the results (31).

TSA

TSA was used for sample size estimation in meta-analysis. In a study, the required sample size was evaluated to the greatest extent. This could avoid the possibility of false positives in meta-analysis and avoid the waste of the resources brought about by multiple repeated tests. Required information size (RIS) was the sample size required for the estimation test. By observing whether the cumulative Z curve crossed the traditional boundary value, TSA boundary value, and RIS line, we judged whether the analysis result was statistically significant, whether there was a definite conclusion, and whether the sample size was up to the expected value.

Network pharmacology analysis

Concerning the ninth edition of the TCM internal medicine standard, we collected the composition of this 4 CHF. Through the TCM systems pharmacology (TCMSP) database (http://tcmspw.com/tcmsp.php), we searched for the related components of CHF following oral absorbability (OB) ≥30% and drug-likeness (DL) ≥0.18. The compositions of Talc, Gypsum, and Oryza sativa were

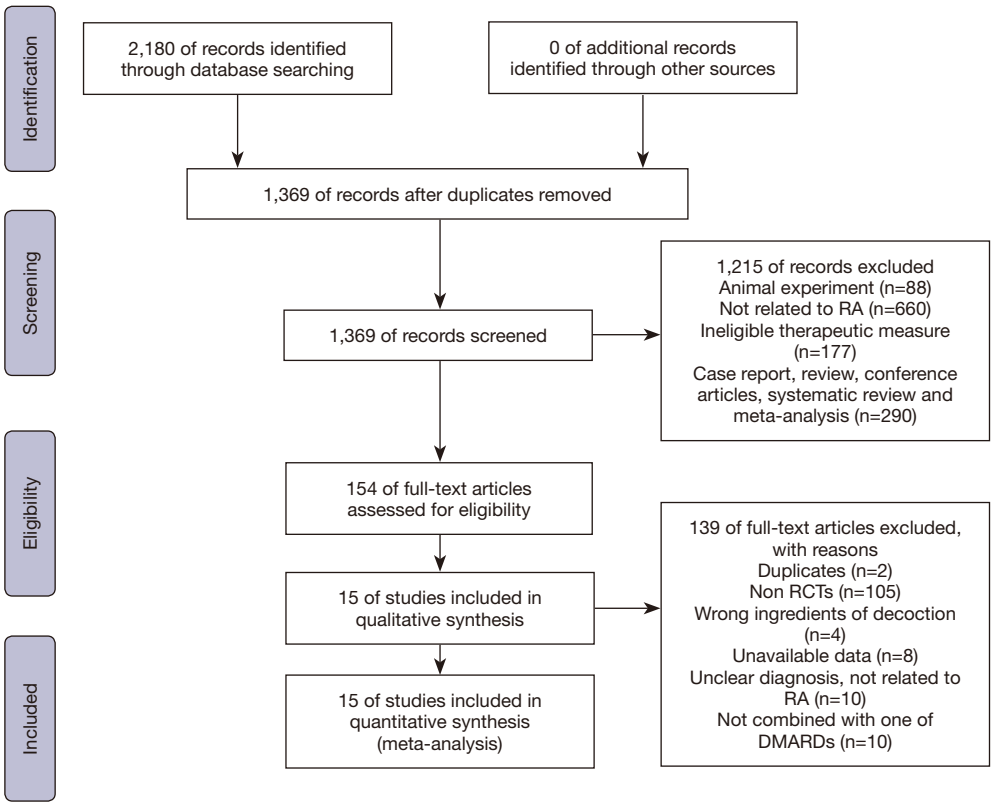


Figure 2 The flow diagram of qualified RCTs screening. RCTs, randomized controlled trials.

determined using the TCM integrated database (TCMID, http://www.megabionet.org/tcmid/) and PharmMapper platform (http://www.lilab-ecust.cn/pharmmapper/) as supplements.

Secondly, the target proteins of compounds obtained from the TCMSP database were passed through the UniProt database (https://uniprot.org/) to be standardized. The Genecards database (https://www.genecards.org/) and the Online Mendelian Inheritance in Man (OMIM) database (https://omim.org/) were used to search the corresponding disease targets. Then, we selected humans as the search species on the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) platform (http://string-db.org/cgi/input.pl) and summed up the Venn results of the above targets. With 0.9 as the highest reliability, the core targets were selected. Finally, the results were imported into the software of Cytoscape 3.7.1 (https://cytoscape.org) to build a protein interaction network. The software R 4.0.2 software (https://www.R-project.org/) was used to analyze the Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment.

Results

Retrieval results and baseline

We identified 2,180 articles in 7 databases. After deleting duplicate articles, 15 qualified studies were finally screened out according to the inclusion and exclusion criteria. The screening process is shown in *Figure 2*. A total of 15 RCTs investigated the efficacy of different decoctions combined with 1 csDMARD. The groups included BHGZD + csDMARD (BHGZDPD, 2 RCTs), DGNTD + csDMARD (DGNTDPD, 5 RCTs), SMP + csDMARD (SMPPD, 5 RCTs) and XBD + csDMARD (XBDPD, 3 RCTs). The related research of DQJD failed to meet the screening criteria, so it was not discussed in this NMA. The primary details are shown in *Table 1*.

The included studies were all published in Chinese from 2008 to 2020, and the patients' course of disease ranged from 2 months to 35 years. The components of CHF are

Table 1 Characteristics of included studies

Author/ year	Sample size (male/female)		Age (years, T/C)		Disease course		Diagnosis standard	Intervention		Duration	Outcomes	Follow-up report
	T	C	T	C	T	C		T	C			
Zhang, 2019 (32)	39 (8/31)	39 (10/29)	47.59±10.18	47.95±11.94	41.85±20.28 ms	37.00±19.24 ms	ACR/ EULAR 2010; Guidelines for diagnosis and treatment of rheumatoid arthritis in 2017	Modified Simiao Powder (400 mL, 2 times/day) + MTX + NSAIDs	MTX, 7.5–15 mg, 1 times/day; NSAIDs (Diclofenac sodium), 75 mg, 1 time/day	12 wks	ER, AE, ESR, CRP, RF, SJC, TJC, DAS-28	YES
Yuan *et al*., 2019 (33)	15 (2/13)	15 (4/11)	30–50	25–50	6–12 ms	4–12 ms	ACR 1987; Textbook of Chinese Internal Medicine: Bi syndrome	Modified BHGZD (200 mL, 2 times/day) + MTX + NSAIDs	MTX, 15 mg, 1 time/week; NSAIDs (Meloxicam), 7.5 mg, 1 times/day	3 courses of treatment	ER, ESR, CRP, RF, DAS-28	NR
Zhu *et al*., 2014 (34)	56 (29/27)	50 (24/26)	36.4±10.7	35.4±11.7	5.4±1.1 ys	7±1.2 ys	ACR/EULAR 2009; Textbook of Chinese Internal Medicine: Bi syndrome	Modified XBD (1 dose, 2 times/day) + MTX + NSAIDs	MTX, 10 mg/week, 1 time/2.5 mg; NSAIDs (Meloxicam)	3 ms	ER, AE, MST	NR
Pang and Xu, 2010 (35)	50 (18/32)	50 (16/34)	36.2±10.5	37.5±10.2	2.8±1.3 ys	2.9±1.1 ys	ACR 1987; Chinese traditional medicine new drug clinical research guiding principle	Modified XBD (1 dose, 2 times/day) + MTX	MTX, 10 mg/week	3 ms	ER, ESR, CRP, RF, SJC, TJC, MST, DAS-28	NR
Ma, 2016 (36)	55 (25/30)	55 (23/32)	45.5±14.2	46.3±12.9	2.9±1.8 ms	2.8±1.7 ms	Guidelines for diagnosis and treatment of rheumatoid arthritis in 2018; Chinese traditional medicine new drug clinical research guiding principle	Modified BHGZD (300 mL, 1 dose, 2times/ day) + LEF + NSAIDs	LEF, 20 mg, 1 time/day; NSAIDs (Celecoxib), 200 mg, 1 time/day	4 ms	ER, AE, ESR, CRP, RF, TNF-α, IL-1, TJC, MST, ACR20/50/70	NR

Table 1 (*continued*)

Table 1 (*continued*)

Author/ year	Sample size (male/female)		Age (years, T/C)		Disease course		Diagnosis standard	Intervention		Duration	Outcomes	Follow-up report
	T	C	T	C	T	C		T	C			
Jiang and Zhang, 2020 (37)	33 (13/20)	33 (14/19)	56.79±1.42	56.83±1.29	–	–	Chinese traditional medicine new drug clinical research guiding principle	Modified DGNTD (200 mL, 2 times/day) + MTX	MTX, 15 mg, 1 time/week	3 ms	ER, AE, TNF-α, IL-1	NR
Ding *et al*., 2017 (38)	40	40	45.3±3.1	44.9±2.7	5.23±0.74 ys	5.17±0.69 ys	ACR 1987 or ACR/EULAR 2010; Criteria for the diagnosis and treatment of diseases and syndromes in TCM	Modified DGNTD (100–200 mL, 1 dose, 2 times/day) + MTX + NSAIDs	MTX, 10 mg, 1 time/week; NSAIDs (Meloxicam), 15 mg, 1 times/day	2 ms	ER	NR
Ge and Shi, 2017 (39)	40 (17/23)	40 (15/25)	46.48±11.07	48.57±9.98	58.20±5.08ms	59.15±4.17ms	ACR 1987; Chinese traditional medicine new drug clinical research guiding principle	Modified DGNTD (200 mL, 1 dose, 2 times/day) + MTX	MTX, 15 mg, 1 time/week	3 ms	ER, AE, TNF-α, IL-1, ACR 20/50/70	NR
Zheng *et al*., 2015 (40)	30 (7/23)	30 (9/21)	48.33±6.21		1.73±0.82 ys		ACR/EULAR 2009; Chinese traditional medicine new drug clinical research guiding principle	Modified DGNTD (200 mL, 1 dose, 3 times/day) + MTX + NSAIDs	MTX, 10 mg, 1 time/week; NSAIDs (Celecoxib), 200 mg, 1 times/day	3 ms	ER, AE, ESR, CRP, RF, MST	NR
Sheng, 2013 (41)	30 (11/19)	30 (9/21)	20–70		2–12 ms		ACR 1987; Chinese traditional medicine new drug clinical research guiding principle	Modified DGNTD (200 mL, 1 dose, 3 times/day) + LEF + NSAIDs	LEF, 20 mg, 1 time/day; NSAIDs (Celebrex), 200 mg, 1 times/day	4 wks	ER, AE, ESR, CRP, RF	NR

Table 1 (*continued*)

Table 1 (*continued*)

Author/ year	Sample size (male/female)		Age (years, T/C)		Disease course		Diagnosis standard	Intervention		Duration	Outcomes	Follow-up report
	T	C	T	C	T	C		T	C			
Li, 2017 (42)	36 (12/24)	36 (15/21)	47.00±2.35	48.00±2.19	1.00±0.32 ys	1.00±0.39 ys	ACR 1987; Chinese traditional medicine new drug clinical research guiding principle	Modified Simiao Powder (300 mL, 2 times/day) + MTX + NSAIDs	MTX, 10 mg, 1 time/week; NSAIDs (Loxoprofen Sodium), 60 mg, 3 times/day	12 wks	ER, AE, ESR, CRP, RF, SJC, TJC, MST	NR
Yang *et al*., 2011 (43)	20 (7/13)	20 (6/14)	23–50	20–48	0.83–15 ys	0.67–10 ys	ACR 1987; Chinese traditional medicine new drug clinical research guiding principle	Simiao Powder (400 mL, 2 times/day) + MTX + NSAIDs	MTX, 7.5 mg, 1 time/week; NSAIDs (Diclofenac Sodium), 75 mg, 1 times/day	3 ms	ER, AE, ESR, CRP, RF, SJC, TJC, MST	NR
Li and Gao, 2014 (44)	30 (10/20)	30 (8/22)	56.16±10.24	54.02±14.76	10.83±0.57 ys	9.96±1.05 ys	ACR 1987	Modified Simiao Powder (300 mL, 2 times/day) + MTX + NSAIDs	MTX, 10 mg, 1 time/week; NSAIDs (Diclofenac Sodium), 75 mg, 1 times/day	1 ms	ER, ESR, CRP, RF	NR
Wang and Ma, 2008 (45)	42 (15/27)	38 (12/26)	40	46.5	0.5–35 ys	1–35 ys	ACR 1987	Modified XBD (1 dose, 2 times/day) + DMARD + NSAIDs	DMARD + NSAIDs	15 ds	ER	NR
Li, 2016 (46)	29 (6/23)	28 (7/21)	48.79±9.58	49.69±9.16	58.24±29.34 ms	62.07±26.51 ms	ACR 1987; Criteria for the diagnosis and treatment of diseases and syndromes in traditional Chinese Medicine: Wangbi	Modified Simiao Powder (1 dose, 200 mL, 2 times/day) + MTX + NSAIDs	MTX, 7.5–15 mg, 1 time/week; NSAIDs (Diclofenac Sodium), 75 mg, 2 time/week	12 wks	ER, AE, ESR, CRP, TNF-α, IL-1, DAS-28	Yes

T, treatment group; C, control group; BHGZD, Baihuguizhi decoction; DGNTD, Dangguiniantong decoction; XBD, Xuanbi decoction; SMP, Simiao pill; MTX, methotrexate; LEF, leflunomide; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARD, disease-modifying anti-rheumatic drug; wks, weeks; ms, months; NR, not reported; ER, effective rate; AE, adverse events; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; TNF-α, tumor necrosis factor-α; IL-1, interleukin-1; SJC, swollen joint count; TJC, tender joint count; MST, morning stiffness time; DAS-28, disease activity score in 28 joints; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.

shown in *Table 2*.

Quality assessment of included research

All included studies mentioned randomization, but only 7 trials (32,33,36,39,41,43,46) reported appropriate randomization methods; no studies explicitly reported allocation blinding; 1 study (41) mentioned blinding and related methods, and the rest did not report in detail; 5 RCTs (33,35,38,44,45) did not report any ARs or AEs, which might show the risk of selective reporting. The risk of bias plot is displayed in the *Figure 3*.

Evaluation of therapeutic efficacy

A pairwise meta-analysis and network meta-analysis

The results of ER

Including 1,079 participants, 15 studies reported the clinical efficiency of 4 CHF, each combined with 1 csDMARD, and compared it to the efficiency of csDMARD used alone. With a random-effects model set, the pairwise meta-analysis indicated that all 4 CHF + csDMARD had better treatment effects compared to the csDMARD used alone (BHGZD: OR =3.33, 95% CI: 1.29 to 8.57, I^2=0%; DGNTD: OR =3.57, 95% CI: 1.81 to 7.02, I^2=0%; SMP: OR =6.05, 95% CI: 2.71 to 13.51, I^2=0% and XBD: OR =2.73, 95% CI: 1.38 to 5.41, I^2=0%) (*Figure 4*, Table S4). A direct comparison of all interventions formed a network diagram (*Figure 5*). The results of NMA also showed that the 4 treatment groups had statistically significant differences concerning ER in CHF + csDMARD *vs*. csDMARD (BHGZD: OR =3.70, 95% CI: 1.23 to 11.96; DGNTD: OR =4.09, 95% CI: 2.06 to 9.02; SMP: OR =6.62, 95% CI: 2.88 to 16.84; XBD: OR =2.84, 95% CI: 1.27 to 6.82) (*Figure 6*, *Table 3*). Heterogeneity analysis in the pairwise meta-analysis showed that the homogeneity among the studies was acceptable. Comparing the indirect comparison and direct comparison results, the statistics of the models were stable (*Figure 7*).

The results of serological tests (CRP, ESR, RF, TNF-α and IL-1)

Regarding serological examination, by conducting the pairwise meta-analyses, CRP, ESR, and RF changes were observed in the 4 decoctions, and TNF-α and IL-1 were estimated in the BHGZD, DGNTD, and SMP treatment groups. There were statistically significant changes in CRP, ESR, and RF for the treatments of the 4 CHF (P<0.05). Compared with the csDMARD alone, BHGZDPD, DGNTDPD, and SMPPD could also reduce the levels of TNF-α and IL-1 inflammation (P<0.05) (*Figure 4*, Table S4). However, heterogeneity analysis showed that the SMP group had high heterogeneity in the CRP and ESR results (I^2=90%, I^2=80%). We performed subgroup analysis and found that the combined value between the groups had an interaction effect, and the P value was greater than 0.05, which showed that the different prescriptions and the patients' course of disease had no obvious clinical heterogeneity in the study (*Figure 8*). We ran NMA with a random effects model. In terms of NMA, because some studies failed to report enough outcomes, we only carried it out for studies that involved all 4 interventions and contained more than 10 studies, to reduce the bias report due to the small sample size. Regarding changes in CRP and ESR levels, a total of 10 studies involving 667 patients were evaluated in NMA. Compared with the csDMARD alone, the results showed that SMPPD had a significant difference in efficacy. It showed a better effect on reducing CRP levels (MD =−7.91, 95% CI: −17.41 to −1.25). Moreover, significant differences were observed in ESR for XBDPD and SMPPD (MD =−12.39, 95% CI: −22.01 to −2.77; MD =−9.31, 95% CI: −14.48 to −5.56, respectively) (*Figure 6*, *Table 3*). The results of the pairwise meta-analysis and NMA were comparatively accordant, and the model was more reliable (*Figure 7*).

The results of signs and symptoms (TJC, SJC and MST)

Because the sample size was small, and there were only 3 interventions for some of the outcomes, we performed a pairwise meta-analysis instead of NMA. Therefore, the random-effects model was used for direct comparison. Compared with a csDMARD alone, 6 trials evaluated the efficacy of CHF combined with the csDMARD separately in the remission of morning stiffness for RA. With the exception of DGNTD, 3 herbal formulas showed a certain effect on alleviating morning stiffness (BHGZD: MD =−15.60, 95% CI: −18.96 to −12.24; SMPPD: MD =−19.90, 95% CI: −20.99 to −18.81; XBDPD: MD =−11.96, 95% CI: −14.81 to −9.11, P<0.05). A total of 5 studies integrated the effects of BHGZDPD, SMPPD, and XBDPD in treating joint tenderness of RA. Compared with one csDMARD, the combined group showed a certain therapeutic advantage in relieving aching joints (P<0.05). In terms of SJC, SMPPD and XBDPD appeared to be more effective than the csDMARD for relieving joint swelling (P<0.05) (*Figure 4*, Table S4).

The results of disease activity (DAS-28 and ACR 20 50 70)

In evaluating disease activity, the scores of ACR 20, ACR 50, ACR 70, and DAS-28 were more internationally

Table 2 Composition of CHF in each study

Study	Formula		Latin name (pinyin name, scientific name)
Zhang, 2019 (32)	Modified SMP	Components	Phellodendri Chinensis Cortex (Huang Bai, Phellodendron chinense Schneid.); Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.); Achyranthis Bidentatae Radix (Huai Niu Xi, Achyranthes bidentata Blume.); Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf); Persicae Semen (Tao Ren, Prunus persica (L.) Batsch./Prunus davidiana (Carr.) Franch.); Pinelliae Rhizoma (Ban Xia, Pinellia ternata (Thunb.) Breit.); Paeoniae Radix Rubra (Chi Shao, Paeonia lactiflora Pall./Paeonia veitchii Lynch); Angelicae Sinensis Radix (Dang Gui, Angelica sinensis (Oliv.) Diels); Bombyx Batryticatus (Jiang Can, Bombyx mori Linnaeus/Beauveria bassiana (Bals.) Vuillant); Citri Reticulatae Pericarpium (Chen Pi, Citrus × aurantium L. (Citrus reticulata Blanco)); Paeoniae Radix Alba (Bai Shao, Paeonia lactiflora Pall.); Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.)
Yuan *et al*., 2019 (33)	Modified BHGZD	Components	Gypsum Fibrosum (Shi Gao, $CaSO_4 \cdot 2H_2O$) 30 g; Anemarrhenae Rhizoma (Zhi Mu, Anemarrhena asphodeloides Bge.) 20 g; Oryzae Fructus Germinatus (Jing Mi, Oryza sativa L. subsp. japonica Kato) 20 g; Cinnamomi Ramulus (Gui Zhi, Cinnamomum cassia Presl) 6 g; Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 6 g; Angelicae Sinensis Radix (Dang Gui, Angelica sinensis (Oliv.) Diels) 10 g; Rehmanniae Radix (Sheng Di, Rehmannia glutinosa Libosch.) 50 g; Armeniacae Semen Amarum (Xing Ren, Prunus armeniaca L. var. ansu Maxim./Prrunus sibirica L./ Prunus mandshurica (Maxim.) Koehne/Prunus armeniaca L.) 12 g; Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf) 12 g; Clematidis Radix et Rhizoma (Wei Ling Xian, Clematis chinensis Osbeck/Clematis manshurica Rupr.) 12 g; Arnebiae Radix (Zi Cao, Arnebia euchroma (Royle) Johnst./Arnebia guttata Bunge) 30 g; Paeoniae Radix Rubra (Chi Shao, Paeonia lactiflora Pall./Paeonia veitchii Lynch) 30 g
Zhu *et al*., 2014 (34)	Modified XBD	Components	Stephaniae Tetrandrae Radix (Fang ji, Stephania tetrandra S. Moore) 15 g; Talcum (Hua Shi, $[CMg_3(Si_4O_{10})(OH)_2]$) 15 g; Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen(Roman.) Stapf) 30 g; Gardeniae Fructus (Zhi Zi, Gardenia jasminoides Ellis) 10 g; Forsythiae Fructus (Lian Qiao, Forsythia suspensa (Thunb.) Vahl) 15 g; Vignae Semen (Chi Xiao Dou, Vigna umbeuata Ohwi et Ohashi/Vigna angularis Ohwi et Ohashi) 10 g; Lycopodii Herba (Shen Jin Cao, Lycopodium japonicum Thunb.) 15 g; Cynanchi Paniculati Radix et Rhizoma (Xu Chang Qin, Cynanchum paniculatum (Bge.) Kitag.) 15 g
		Formula variation in accordance with signs	a) Obvious morning stiffness: Bombyx Batryticatus (Jiang Can, Bombyx mori Linnaeus/ Beauveria bassiana (Bals.) Vuillant) 12 g; Scorpio (Quan Xie, Buthus martensii Karsch) 10 g b) Arthrophyma, joint deformit, joint stiffness, tongue changes with dark purple color and taut and uneven pulse: Rehmanniae Radix Praeparata (Shu Di Huang, Rehmannia glutinosa Libosch.); Chuanxiong Rhizoma (Chuan Xiong, Ligusticum chuanxiong Hort.); Angelicae Sinensis Radix (Dang Gui, Angelica sinensis (Oliv.) Diels); Paeoniae Radix Alba (Bai Shao, Paeonia lactiflora Pall.); Manis Squama (Chuan Shan Jia, Manis pentadactyla Linnaeus); Eupolyphaga Steleophaga (Tu Bie Chong, Eupolyphaga sinensis Walker./Steleophaga plancyi (Boleny)); Zaocys (Wu Shao She, Zaocys dhumnades (Cantor)); Hirudo (Shui Zhi, Whitmania pigra Whitman/Whitmania acranulata Whitman/Hirudo ni p ponica Whitman)
Pang and Xu, 2010 (35)	Modified XBD	Components	Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf) 30 g; Stephaniae Tetrandrae Radix (Fang ji, Stephania tetrandra S. Moore) 10 g; Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.) 10 g; Bombycis Feculae (Can Sha, Bombyx mori L.) 10 g; Forsythiae Fructus (Lian Qiao, Forsythia suspensa (Thunb.) Vahl) 10 g; Gardeniae Fructus (Zhi Zi, Gardenia jasminoides Ellis) 15 g; Talcum (Hua Shi, $[CMg_3(Si_4O_{10})(OH)_2]$) 20 g; Pheretima (Di Long, Pheretima aspergillum (E. Perrier)/Pheretima vulgaris Chen/Pheretima guillelmi (Michaelsen)/Pheretima pectinifera Michaelsen) 10 g; Lonicerae Japonicae Caulis (Ren Dong Teng, Lonicera japonica Thunb.) 15 g; Spatholob Caulis (Ji Xue Teng, Spatholobus suberectus Dunn) 15 g; Curcumae Longae Rhizoma (Jiang Huang, Curcuma longa. L.) 6 g; Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 5 g

Table 2 (*continued*)

Table 2 (*continued*)

Study	Formula		Latin name (pinyin name, scientific name)
Ma, 2016 (36)	Modified BHGZD	Components	Anemarrhenae Rhizoma (Zhi Mu, Anemarrhena asphodeloides Bge.) 20 g; Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 10 g; Gypsum Fibrosum (Shi Gao, $CaSO_4 \cdot 2H_2O$) 30 g; Oryzae Fructus Germinatus (Jing Mi, Oryza sativa L. subsp. japonica Kato) 50 g; Cinnamomi Ramulus (Gui Zhi, Cinnamomum cassia Presl) 12 g; Clematidis Radix et Rhizoma (Wei Ling Xian, Clematis chinensis Osbeck/ Clematis manshurica Rupr.) 15 g; Lonicerae Japonicae Caulis (Ren Dong Teng, Lonicera japonica Thunb.) 30 g; Tripterygh Wilfordii Radix (Lei Gong Teng, Tripterygium wilfordii Hook. f.) 30 g; Sinomenii Caulis (Qing Feng Teng, Sinomenium acutum (Thunb) Rehd. et Wils./Sinomenium acutum (Thunb.) Rehd. et Wils. var. cinereum Rehd. et Wils.) 20 g; Mori Ramulus (Sang Zhi, Morus alba L.) 30 g; Smilacis Glabrae Rhizoma (Tu Fu Ling, Smilax glabra Roxb.) 60 g; Trachelospermi Caulis et Folium (Luo Shi Teng, Trachelospermum jasminoides (Lindl.) Lem.) 30 g
Jiang and Zhang, 2020 (37)	Modified DGNTD	Components	Artemisiae Scopariae Herba (Yin Chen, Artemisia scoparia Waldst. et Kit./Artemisia capillaris Thunb.) 20 g; Puerariae Lobatae Radix (Ge Gen, Pueraria lobata (Willd.) Ohwi) 20 g; Notopterygii Rhizoma et Radix (Qiang Huo, Notopterygium incisum Ting ex H. T. Chang/Notopterygium franchetii H. de Boiss) 15 g; Saposhnikoviae Radix (Fang Feng, Saposhnikovia divaricata (Turcz.) Schischk.) 10 g; Alismatis Rhizoma (Ze Xie, Alisma orientalis (Sam.) Juzep.) 10 g; Cimicifugae Rhizoma (Sheng Ma, Cimicifuga heracleifolia Kom./Cimicifuga dahurica (Turcz.) Maxim./Cimicifuga foetida L.) 10 g; Polyporus (Zhu Ling, Polyporus umbellaru (Pers.) Fr.) 10 g; Atractylodis Macrocephalae Rhizoma (Bai Zhu, Atractylodes macrocephala Koidz.) 10 g; Ginseng Radix et Rhizoma (Ren Shen, Panax ginseng C. A. Mey.) 10 g; Sophorae Flavescentis Radix (Ku Shen, Sophora flavescens Alt.) 10 g; Angelicae Sinensis Radix (Dang Gui, Angelica sinensis (Oliv.) Diels) 10 g; Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.) 10 g; Scutellariae Radix (Huang Qin, Scutellaria baicalensis Georgi) 10 g; Anemarrhenae Rhizoma (Zhi Mu, Anemarrhena asphodeloides Bge.) 10 g; Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 5 g
		Formula variation in accordance with signs	(I) Joint swelling and pain: Scrophulariae Radix (Xuan Shen, Scrophularia ningpoensis Hemsl.) 20 g; Moutan Cortex (Dan Pi, Paeonia suf fruticosa Andr.) 10 g; Rehmanniae Radix (Sheng Di, Rehmannia glutinosa Libosch.) 10 g
			(II) Lower limbs swelling and pain: Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf) 20 g; Chaenomelis Fructus (Mu Gua, Chaenomeles speciosa (Sweet) Nakai) 10 g; Cyathulae Radix (Chuan Niu Xi, Cyathula of ficinalis Kuan) 10 g
			(III) Fever: Lonicerae Japonicae Caulis (Ren Dong Teng, Lonicera japonica Thunb.) 20 g; Gypsum Fibrosum (Shi Gao, $CaSO_4 \cdot 2H_2O$) 20 g

Table 2 (*continued*)

Table 2 (*continued*)

Study	Formula		Latin name (pinyin name, scientific name)
Ding *et al*., 2017 (38)	Modified DGNTD	Components	Notopterygii Rhizoma et Radix (Qiang Huo, Notopterygium incisum Ting ex H. T. Chang/ Notopterygium franchetii H. de Boiss) 15 g; Artemisiae Scopariae Herba (Yin Chen, Artemisia scoparia Waldst. et Kit./Artemisia capillaris Thunb.) 15g; Polyporus (Zhu Ling, Polyporus umbellaru (Pers.) Fr.) 9 g; Alismatis Rhizoma (Ze Xie, Alisma orientalis (Sam.) Juzep.) 9 g; Sophorae Flavescentis Radix (Ku Shen, Sophora flavescens Alt.) 6 g; Angelicae Sinensis Radix (Dang Gui, Angelica sinensis (Oliv.) Diels) 9 g; Saposhnikoviae Radix (Fang Feng, Saposhnikovia divaricata (Turcz.) Schischk.) 9 g; Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.) 9 g; Anemarrhenae Rhizoma (Zhi Mu, Anemarrhena asphodeloides Bge.) 9 g; Cimicifugae Rhizoma (Sheng Ma, Cimicifuga heracleifolia Kom./Cimicifuga dahurica (Turcz.) Maxim./Cimicifuga foetida L.) 6 g; Atractylodis Macrocephalae Rhizoma (Bai Zhu, Atractylodes macrocephala Koidz.) 6 g; Puerariae Lobatae Radix (Ge Gen, Pueraria lobata (Willd.) Ohwi) 6 g; Ginseng Radix et Rhizoma (Ren Shen, Panax ginseng C. A. Mey.) 6 g; Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 6 g
		Formula variation in accordance with signs	(I) Significant joint swelling: Chaenomelis Fructus (Mu Gua, Chaenomeles speciosa (Sweet) Nakai); Cocculi Trilobi Radix (Mu Fang Ji, Cocculus orbiculatus (L.) DC.) (II) Significant joint tender: Curcumae Longae Rhizoma (Jiang Huang, Curcuma longa. L.); Corydalis Rhizoma (Yan Hu Suo, Corydalis yanhusuo W.T.Wang)
Ge and Shi, 2017 (39)	Modified DGNTD	Components	Notopterygii Rhizoma et Radix (Qiang Huo, Notopterygium incisum Ting ex H. T. Chang/ Notopterygium franchetii H. de Boiss) 10 g; Artemisiae Scopariae Herba (Yin Chen, Artemisia scoparia Waldst. et Kit./Artemisia capillaris Thunb.) 10g; Polyporus (Zhu Ling, Polyporus umbellaru (Pers.) Fr.) 12 g; Alismatis Rhizoma (Ze Xie, Alisma orientalis (Sam.) Juzep.) 10 g; Sophorae Flavescentis Radix (Ku Shen, Sophora flavescens Alt.) 10 g; Angelicae Sinensis Radix (Dang Gui, Angelica sinensis (Oliv.) Diels) 15 g; Saposhnikoviae Radix (Fang Feng, Saposhnikovia divaricata (Turcz.) Schischk.) 10 g; Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.) 15 g; Anemarrhenae Rhizoma (Zhi Mu, Anemarrhena asphodeloides Bge.) 10 g; Cimicifugae Rhizoma (Sheng Ma, Cimicifuga heracleifolia Kom./Cimicifuga dahurica (Turcz.) Maxim./Cimicifuga foetida L.) 5 g; Atractylodis Macrocephalae Rhizoma (Bai Zhu, Atractylodes macrocephala Koidz.) 15 g; Puerariae Lobatae Radix (Ge Gen, Pueraria lobata (Willd.) Ohwi) 15 g; Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 5 g; Citri Reticulatae Pericarpium [Chen Pi, Citrus × aurantium L. (Citrus reticulata Blanco)] 10 g; Scutellariae Radix (Huang Qin, Scutellaria baicalensis Georgi) 10 g; Scorpio (Quan Xie, Buthus martensii Karsch) 5 g; Pheretima (Di Long, Pheretima aspergillum (E. Perrier)/ Pheretima vulgaris Chen/Pheretima guillelmi (Michaelsen)/Pheretima pectinifera Michaelsen) 15 g; Sojae Semen Nigrum (Hei Dou, Glycine max C (L.) Merr.) 15 g

Table 2 (*continued*)

Table 2 (*continued*)

Study	Formula		Latin name (pinyin name, scientific name)
Zheng *et al*., 2015 (40)	Modified DGNTD	Components	Notopterygii Rhizoma et Radix (Qiang Huo, Notopterygium incisum Ting ex H. T. Chang/ Notopterygium franchetii H. de Boiss) 15 g; Artemisiae Scopariae Herba (Yin Chen, Artemisia scoparia Waldst. et Kit./Artemisia capillaris Thunb.) 20 g; Puerariae Lobatae Radix (Ge Gen, Pueraria lobata (Willd.) Ohwi) 20 g; Cimicifugae Rhizoma (Sheng Ma, Cimicifuga heracleifolia Kom./Cimicifuga dahurica (Turcz.) Maxim./Cimicifuga foetida L.) 10 g; Saposhnikoviae Radix (Fang Feng, Saposhnikovia divaricata (Turcz.) Schischk.) 10 g; Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./ Atractylodes chinenisis (DC.) Koidz.) 10 g; Atractylodis Macrocephalae Rhizoma (Bai Zhu, Atractylodes macrocephala Koidz.) 10 g; Sophorae Flavescentis Radix (Ku Shen, Sophora flavescens Alt.) 10 g; Scutellariae Radix (Huang Qin, Scutellaria baicalensis Georgi) (10 g fired); Anemarrhenae Rhizoma (Zhi Mu, Anemarrhena asphodeloides Bge.) 10 g; Angelicae Sinensis Radix (Dang Gui, Angelica sinensis (Oliv.) Diels) 10 g; Polyporus (Zhu Ling, Polyporus umbellaru (Pers.) Fr.) 10 g; Alismatis Rhizoma (Ze Xie, Alisma orientalis (Sam.) Juzep.) 10 g; Ginseng Radix et Rhizoma (Ren Shen, Panax ginseng C. A. Mey.); Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 5 g
		Formula variation in accordance with signs	(I) Fever: Gypsum Fibrosum (Shi Gao, $CaSO_4 \cdot 2H_2O$) 20 g; Lonicerae Japonicae Caulis (Ren Dong Teng, Lonicera japonica Thunb.) 20 g
			(II) Joint swelling, pain and faint maculopapular eruptions: Rehmanniae Radix (Sheng Di, Rehmannia glutinosa Libosch.) 20 g; Moutan Cortex (Dan Pi, Paeonia suf fruticosa Andr.) 20 g; Scrophulariae Radix (Xuan Shen, Scrophularia ningpoensis Hemsl.) 20 g
			(III) Joint obvious swelling: Hedyotidis Diffusae Herba (Bai Hua She She Cao, Hedyotis dif fusa Willd.) 20 g; Dioscoreae Septmlobae Rhizoma (Bi Xie, Dioscorea septemloba Thunb./D. futschauensis Uline ex R. Knuth/D. hypoglauca Palibin/ Dioscorea spongiosa J. Q. Xi,M. Mizuno et W. L. Zhao) 10 g
			(IV) Lower limbs obvious swelling and pain: Cyathulae Radix (Chuan Niu Xi, Cyathula of ficinalis Kuan)10 g; Chaenomelis Fructus (Mu Gua, Chaenomeles speciosa (Sweet) Nakai) 10 g; Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf) 20 g
Sheng, 2013 (41)	Modified DGNTD	Components	Notopterygii Rhizoma et Radix (Qiang Huo, Notopterygium incisum Ting ex H. T. Chang/ Notopterygium franchetii H. de Boiss) 15 g; Artemisiae Scopariae Herba (Yin Chen, Artemisia scoparia Waldst. et Kit./Artemisia capillaris Thunb.) 15 g; Saposhnikoviae Radix (Fang Feng, Saposhnikovia divaricata (Turcz.) Schischk.) 9 g; Cimicifugae Rhizoma (Sheng Ma, Cimicifuga heracleifolia Kom./Cimicifuga dahurica (Turcz.) Maxim./Cimicifuga foetida L.) 3 g; Puerariae Lobatae Radix (Ge Gen, Pueraria lobata (Willd.) Ohwi) 6 g; Atractylodis Macrocephalae Rhizoma (Bai Zhu, Atractylodes macrocephala Koidz.) 3 g; Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.) 9 g; Polyporus (Zhu Ling, Polyporus umbellaru (Pers.) Fr.) 9 g; Alismatis Rhizoma (Ze Xie, Alisma orientalis (Sam.) Juzep.) 9 g; Sophorae Flavescentis Radix (Ku Shen, Sophora flavescens Alt.) 6 g; Scutellariae Radix (Huang Qin, Scutellaria baicalensis Georgi) (3 g fired); Anemarrhenae Rhizoma (Zhi Mu, Anemarrhena asphodeloides Bge.) 9 g; Angelicae Sinensis Radix (Dang Gui, Angelica sinensis (Oliv.) Diels) 9 g; Ginseng Radix et Rhizoma (Ren Shen, Panax ginseng C. A. Mey.) 6 g; Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 15 g

Table 2 (*continued*)

Table 2 (*continued*)

Study	Formula		Latin name (pinyin name, scientific name)
Li, 2017 (42)	Modified SMP	Components	Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.) 12 g; Phellodendri Chinensis Cortex (Huang Bai, Phellodendron chinense Schneid.) 15 g; Cyathulae Radix (Chuan Niu Xi, Cyathula of ficinalis Kuan) 30 g; Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf) (40 g raw); Lonicerae Japonicae Caulis (Ren Dong Teng, Lonicera japonica Thunb.) 20 g; Smilacis Glabrae Rhizoma (Tu Fu Ling, Smilax glabra Roxb.) 30 g; Angelicae Sinensis Radix (Dang Gui, Angelica sinensis (Oliv.) Diels) 30 g; Paeoniae Radix Rubra (Chi Shao, Paeonia lactiflora Pall./Paeonia veitchii Lynch) 15 g; Salviae Miltiorrhizae Radix et Rhizoma (Dan Shen, Salvia miltiorrhiza Bge.) 30 g; Plantaginis Semen (Che Qian Zi,Plantago asiatica L./Plantago depressa Willd.) 15 g; Alismatis Rhizoma (Ze Xie, Alisma orientalis (Sam.) Juzep.) 30 g; Saposhnikoviae Radix (Fang Feng, Saposhnikovia divaricata (Turcz.) Schischk.) 12 g; Sparganii Rhizoma (San Leng, Sparganium stoloni ferum Buch.-Ham.) 12 g; Curcumae Rhizoma (E Zhu, Curcuma kwangsiensis S. G. Lee et C. F. Liang/Curcuma phaeocaulis Val./Curcuma wenyujin Y. H. Chen et C. Ling) 12 g; Gleditsiae Spina (Zao Jiao Ci, Gleditsia sinensis Lam.) 12 g; Astragali Radix (Huang Qi, Astragalus membranaceus (Fisch.) Bge. Var. mongholicus (Bge) Hsiao/Astragalus membranaceus (Fisch)Bge.) 12 g; Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 6 g
Yang *et al*., 2011 (43)	Modified SMP	Components	Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.) 12 g; Phellodendri Chinensis Cortex (Huang Bai, Phellodendron chinense Schneid.) 12 g; Cyathulae Radix (Chuan Niu Xi, Cyathula of ficinalis Kuan) 12 g; Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf) 12 g
Li and Gao, 2014 (44)	Modified SMP	Components	Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.) 12 g; Phellodendri Chinensis Cortex (Huang Bai, Phellodendron chinense Schneid.) 12 g; Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf) (30 g raw); Cyathulae Radix (Chuan Niu Xi, Cyathula of ficinalis Kuan) 15 g; Piperis Kadsurae Caulis (Hai Feng Teng, Piper kadsura (Choisy) Ohwi) 30 g; Sinomenii Caulis (Qing Feng Teng, Sinomenium acutum (Thunb.) Rehd. et Wils./Sinomenium acutum (Thunb.) Rehd. et Wils. var. cinereum Rehd. et Wils.) 30 g; Smilacis Glabrae Rhizoma (Tu Fu Ling, Smilax glabra Roxb.) 15 g; Atractylodis Macrocephalae Rhizoma (Bai Zhu, Atractylodes macrocephala Koidz.) 15 g
Wang and Ma, 2008 (45)	Modified XBD	Components	Stephaniae Tetrandrae Radix (Fang ji, Stephania tetrandra S. Moore) 15 g; Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf) 15 g; Armeniacae Semen Amarum (Xing Ren, Prunus armeniaca L. var. ansu Maxim./Prrunus sibirica L./Prunus mandshurica (Maxim.) Koehne/Prunus armeniaca L.) 15 g; Talcum (Hua Shi, $[CMg_3(Si_4O_{10})(OH)_2]$) 15 g; Pinelliae Rhizoma (Ban Xia, Pinellia ternata (Thunb.) Breit.) 10 g; Bombycis Feculae (Can Sha, Bombyx mori L.) 10 g; Vignae Semen (Chi Xiao Dou, Vigna umbeuata Ohwi et Ohashi/Vigna angularis Ohwi et Ohashi) 10 g; Gardeniae Fructus (Zhi Zi, Gardenia jasminoides Ellis) 10 g; Forsythiae Fructus (Lian Qiao, Forsythia suspensa (Thunb.) Vahl) 10 g; Erythrinae Coptex (Hai Tong Pi, Erythrina variegata L. var. orientalis (L.) Merr.) 10 g; Curcumae Longae Rhizoma (Jiang Huang, Curcuma longa. L.) 6 g
Li, 2016 (46)	Modified SMP	Components	Atractylodis Rhizoma (Cang Zhu, Atractylodes lancea (Thunb.) DC./Atractylodes chinenisis (DC.) Koidz.) 12 g; Coicis Semen (Yi Yi Ren, Coix lacryma-jobi var. ma-yuen (Roman.) Stapf) (40 g raw and 40 g fried); Phellodendri Chinensis Cortex (Huang Bai, Phellodendron chinense Schneid.) 9 g; Cyathulae Radix (Chuan Niu Xi, Cyathula of ficinalis Kuan) 15 g; Smilacis Glabrae Rhizoma (Tu Fu Ling, Smilax glabra Roxb.) 60 g; Atractylodis Macrocephalae Rhizoma (Bai Zhu, Atractylodes macrocephala Koidz.) 20 g; Paeoniae Radix Rubra (Chi Shao, Paeonia lactiflora Pall./Paeonia veitchii Lynch) 12 g; Paeoniae Radix Alba (Bai Shao, Paeonia lactiflora Pall.) 12 g; Notopterygii Rhizoma et Radix (Qiang Huo, Notopterygium incisum Ting ex H. T. Chang/Notopterygium franchetii H. de Boiss) 9 g; Angelicae Pubescentis Radix (Du Huo, Angelica pubescens Maxim. f. biserrata Shan et Yuan) 9 g; Glycyrrhizae Radix et Rhizoma (Gan Cao, Glycyrrhiza uralensis Fisch./G. inflata Bat./G. glabra L.) 6 g

SMP, Simiao pill; BHGZD, Baihuguizhi decoction; XBD, Xuanbi decoction; DGNTD, Dangguiniantong decoction.

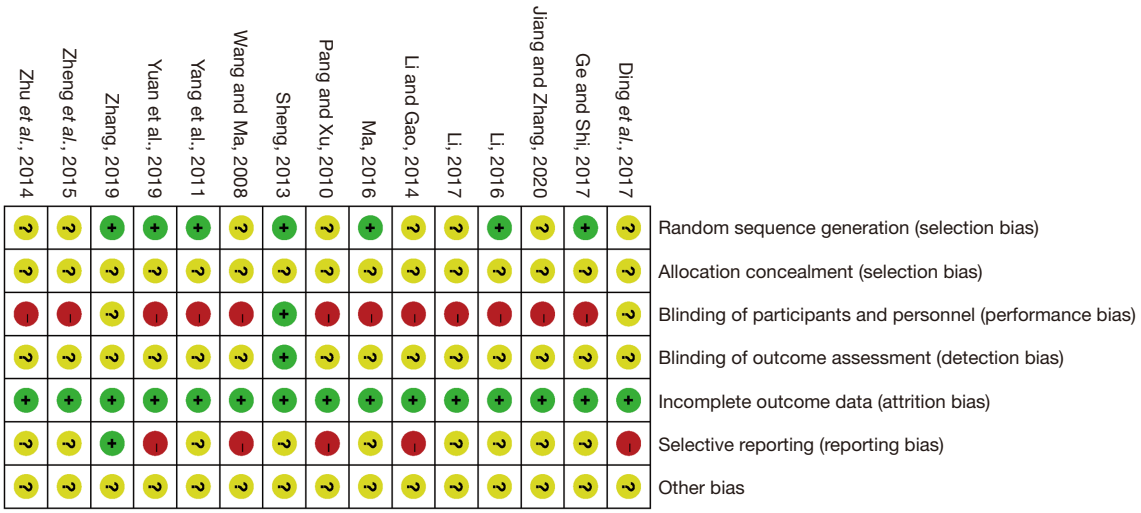


Figure 3 Risk of bias summary.

recognized for use in RA patients. However, some studies did not report these 2 kinds of outcomes or did not specify the scoring criteria. Therefore, we just conducted pairwise meta-analyses with the random-effects model to evaluate these outcomes. The DAS-28 was determined in 5 studies. In DAS-28, there was no significant change in BHGZDPD or SMPPD compared with the csDMARD alone. The pairwise meta-analysis demonstrated that only XBDPD was superior to a csDMARD (SMD =–0.88, 95% CI: –1.29 to –0.47). A total of 2 trials evaluated values on the changes of ACR 20, 50, and 70. The evaluation of ACR 20 and ACR 50, it indicated that BHGZDPD had statistical significance in treating RA (MD =2.63, 95% CI: 1.02 to 6.75, MD =2.25, 95% CI: 1.05 to 4.83). There was no significant difference in other direct comparison results (*Figure 4*, Table S4).

Ranking results and cluster analysis

By different color occupancy areas, the ranking probabilities of different interventions regarding each outcome are presented in (*Figure 9*). From Rank 1 to Rank 4, color occupancy indicated the probability of superiority to inferiority. The larger the area occupied in Rank 1, the better the curative effect. In light of the calculation method shown in the study, the SUCRA value was calculated according to the rank probability. The SUCRA values in each NMA outcome are shown in *Table 4*. Higher values of the SUCRA recommended more advantageous therapies. The comprehensive rank results indicated that SMPPD might be the potential optimizing therapy. However, in clinical practice, when choosing treatment measures, several outcomes usually require comprehensive consideration. Cluster analysis showed that SMPPD, XBDPD, and BHGZDPD could have a certain synergy in terms of improving efficacy and reducing inflammation (*Figure 10*).

Safety

Of the 15 RCTs included, 5 trials (33.33%) did not record AEs/ARs during the treatment period, and the remaining 10 studies (66.67%) reported AEs/ARs. According to the treatment of different interventions, different types of AEs/ARs were reported (*Table 5*). The ARs mainly included abnormal liver function, abnormal renal function, blood test abnormalities, gastrointestinal reactions, cough, skin rash, myelosuppression. We could also draw 3 main findings: first, the incidences of ARs in patients who used a csDMARD alone (27.42%) or XBDPD (26.79%) were higher; second, SMPPD (6.45%) and DGNTDPD (6.77%) had lower incidences of ARs; third, the incidence of gastrointestinal reactions (10.84%) was the highest among all treatments.

Heterogeneity, publication bias and Brooks-Gelman-Rubin diagnosis

The studies shown in the funnel plot were close to the bottom or scattered, indicating small sample size bias and other potential biases (*Figure 11*). Egger's test reported a publication bias in CRP results (P=0.033). Nevertheless, the correction using the trim and fill method for this bias did not alter the overall result, which meant that the pooled value was retained as reliable (*Table 6* and Table S5). In CRP

Outcomes	Intervention/No. of studies OR /MD/SMD, 95% CI/Sample size							
ER	BHGZDPD *vs.* csDMARD	2	DGNTDPD *vs.* csDMARD	5	SMPPD *vs.* csDMARD	5	XBDPD *vs.* csDMARD	3
	3.33 [1.29, 8.57]	70/70	3.57 [1.81, 7.02]	173/173	6.05 [2.71, 13.51]	154/153	2.73 [1.38, 5.41]	148/138
CRP	BHGZDPD *vs.* csDMARD	2	DGNTDPD *vs.* csDMARD	2	SMPPD *vs.* csDMARD	5	XBDPD *vs.* csDMARD	1
	-6.19 [-8.47, -3.91]	70/70	-1.91 [-3.09, -0.72]	60/60	-6.64 [-8.99, -4.30]	154/153	-9.31 [-10.99, -7.63]	50/50
ESR	BHGZDPD *vs.* csDMARD	2	DGNTDPD *vs.* csDMARD	2	SMPPD *vs.* csDMARD	5	XBDPD *vs.* csDMARD	1
	-6.70 [-9.31, -4.08]	70/70	-2.37 [-3.74, -1.00]	60/60	-9.23 [-11.77, -6.70]	154/153	-12.35 [-15.22, -9.48]	50/50
RF	BHGZDPD *vs.* csDMARD	2	DGNTDPD *vs.* csDMARD	2	SMPPD *vs.* csDMARD	4	XBDPD *vs.* csDMARD	1
	-0.93 [-1.27, -0.58]	70/70	-1.21 [-1.86, -0.56]	60/60	-7.72 [-11.38, -4.06]	125/125	-0.54 [-0.94, -0.14]	50/50
DAS-28	BHGZDPD *vs.* csDMARD	1	DGNTDPD *vs.* csDMARD	0	SMPPD *vs.* csDMARD	2	XBDPD *vs.* csDMARD	1
	-0.65 [-1.39, 0.09]	15/15	NA	NA	-0.28 [-0.86, 0.30]	68/67	-0.88 [-1.29, -0.47]	50/50
TNF-α	BHGZDPD *vs.* csDMARD	1	DGNTDPD *vs.* csDMARD	2	SMPPD *vs.* csDMARD	1	XBDPD *vs.* csDMARD	0
	-0.72 [-1.10, -0.33]	55/55	-1.32 [-2.16, -0.48]	73/73	-0.53 [-1.06, -0.00]	29/28	NA	NA
IL-1	BHGZDPD *vs.* csDMARD	1	DGNTDPD *vs.* csDMARD	2	SMPPD *vs.* csDMARD	1	XBDPD *vs.* csDMARD	0
	-1.08 [-1.48, -0.68]	55/55	-1.95 [-2.98, -0.93]	73/73	-1.08 [-1.48, -0.68]	29/28	NA	NA
SJC	BHGZDPD *vs.* csDMARD	0	DGNTDPD *vs.* csDMARD	0	SMPPD *vs.* csDMARD	3	XBDPD *vs.* csDMARD	1
	NA	NA	NA	NA	-1.14 [-1.73, -0.55]	95/95	-1.97 [-2.29, -1.65]	50/50
TJC	BHGZDPD *vs.* csDMARD	1	DGNTDPD *vs.* csDMARD	0	SMPPD *vs.* csDMARD	3	XBDPD *vs.* csDMARD	1
	-2.93 [-3.62, -2.24]	55/55	NA	A	-1.24 [-2.19, -0.30]	95/95	-3.86 [-4.52, -3.20]	50/50
MST	BHGZDPD *vs.* csDMARD	1	DGNTDPD *vs.* csDMARD	1	SMPPD *vs.* csDMARD	2	XBDPD *vs.* csDMARD	2
	-15.60 [-18.96, -12.24]	55/55	-6.76 [-15.65, 2.13]	30/30	-19.90 [-20.99, -18.81]	56/56	-11.96 [-14.81, -9.11]	106/100
ACR 20	BHGZDPD *vs.* csDMARD	1	DGNTDPD *vs.* csDMARD	1	SMPPD *vs.* csDMARD	0	XBDPD *vs.* csDMARD	0
	2.63 [1.02, 6.75]	55/55	0.81 [0.33, 1.99]	40/40	NA	NA	NA	NA
ACR 50	BHGZDPD vs. csDMARD	1	DGNTDPD *vs.* csDMARD	1	SMPPD *vs.* csDMARD	0	XBDPD *vs.* csDMARD	0
	2.25 [1.05, 4.83]	55/55	1.62 [0.61, 4.25]	40/40	NA	NA	NA	NA
ACR 70	BHGZDPD *vs.* csDMARD	1	DGNTDPD *vs.* csDMARD	1	SMPPD *vs.* csDMARD	0	XBDPD *vs.* csDMARD	0
	2.01 [0.82, 4.91]	55/55	8.27 [0.97, 70.73]	40/40	NA	NA	NA	NA

Figure 4 Results of the pairwise random-effects meta-analysis for RA treatment. Underline indicated that the result was statistically significant (Italic meant MD/SMD). RA, rheumatoid arthritis; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug); ER, effective rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; TNF-α, tumor necrosis factor-α; IL-1, interleukin-1; SJC, swollen joint count; TJC, tender joint count; MST, morning stiffness time; DAS-28, disease activity score in 28 joints; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.

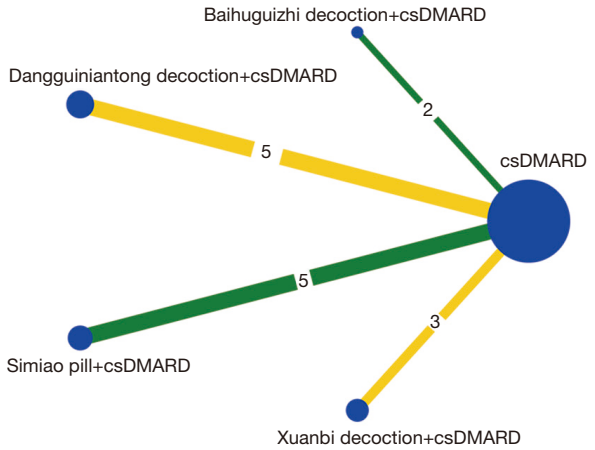


Figure 5 The network diagram for ER. ER, effective rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug.

and ESR results, the SMPPD studies were scattered outside the interval, indicating that it might have been the source of heterogeneity between studies. To observe the source of heterogeneity, we also conducted a sensitivity analysis by removing each trial 1 by 1, and performed a subgroup analysis to find the confounding factors. It showed that the results of the pairwise meta-analysis were credible (Table S4). Heterogeneity may have come from the variation of intrinsic authenticity in the research of detection methods, but this needs to be further verified. After 5,000 iterations, the potential scale reduced factor (PSRF) was calculated. The median value and 97.5% of the reduction factor quickly reached stability, indicating that the model had stable convergence and reliable statistical results (Figure S2). However, due to the small sample size, the results might have exaggerated the therapeutic effect, so we should treat the conclusions with caution.

Sample cumulative results

The TSA results showed that the cumulative Z-value curve of XBDPD and DGNTDPD exceeded the traditional curve and crossed the TSA threshold, indicating that a positive conclusion was obtained before the expected amount of information was reached. The SMPPD results showed that the cumulative Z-value curve exceeded the traditional curve, and crossed the TSA threshold. Simultaneously, the cumulative amount of information reached the expected amount, indicating that a positive conclusion had been obtained, and this conclusion would not change with the increase of sample size. However, in the BHGZDPD group,

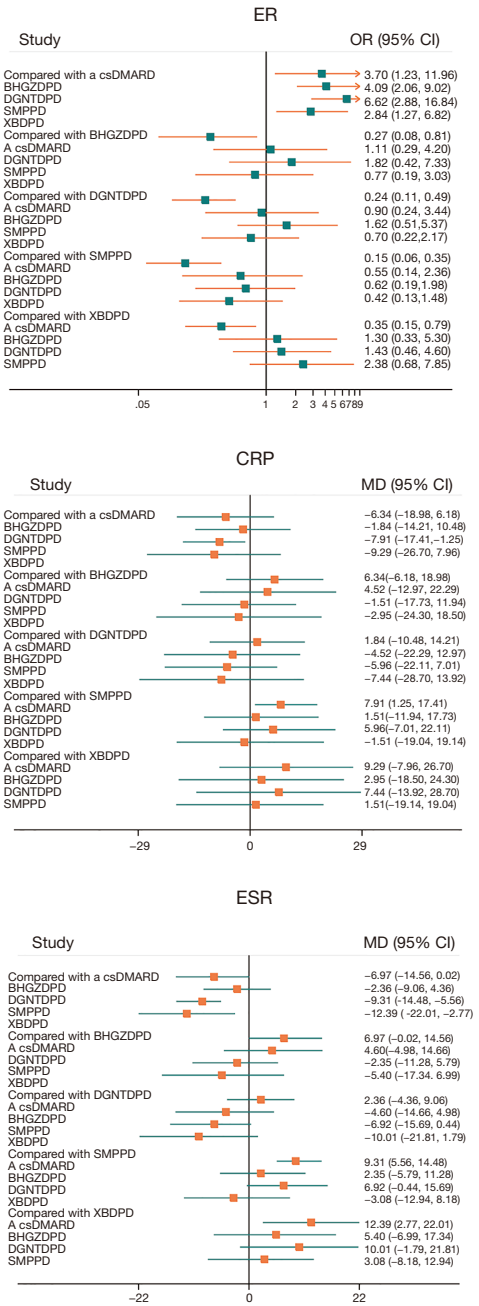


Figure 6 Forest plots for ER, CRP, and ESR. ER, effective rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

Table 3 Results of the NMA with regard to ER, CRP and ESR

Intervention	ER	CRP	ESR
csDMARD *vs.* BHGZDPD	0.27 (0.08, 0.81)	6.34 (–6.18, 18.98)	6.97 (–0.02, 14.56)
DGNTDPD	0.24 (0.11, 0.49)	1.84 (–10.48, 14.21)	2.36 (–4.36, 9.06)
SMPPD	0.15 (0.06, 0.35)	7.91 (1.25, 17.41)	9.31 (5.56, 14.48)
XBDPD	0.35 (0.15, 0.79)	9.29 (–7.96, 26.70)	12.39 (2.77, 22.01)
BHGZDPD *vs.* csDMARD	3.70 (1.23, 11.96)	–6.34 (–18.98, 6.18)	–6.97 (–14.56, 0.02)
DGNTDPD	0.90 (0.24, 3.44)	–4.52 (–22.29, 12.97)	–4.60 (–14.66, 4.98)
SMPPD	0.55 (0.14, 2.36)	1.51 (–11.94, 17.73)	2.35 (–5.79, 11.28)
XBDPD	1.30 (0.33, 5.30)	2.95 (–18.50, 24.30)	5.40 (–6.99, 17.34)
DGNTDPD *vs.* csDMARD	4.09 (2.06, 9.02)	–1.84 (–14.21, 10.48)	–2.36 (–9.06, 4.36)
BHGZDPD	1.11 (0.29, 4.20)	4.52 (–12.97, 22.29)	4.60 (–4.98, 14.66)
SMPPD	0.62 (0.19, 1.98)	5.96 (–7.01, 22.11)	6.92 (–0.44, 15.69)
XBDPD	1.43 (0.46, 4.60)	7.44 (–13.92, 28.70)	10.01 (–1.79, 21.81)
SMPPD *vs.* csDMARD	6.62 (2.88, 16.84)	–7.91 (–17.41, –1.25)	–9.31 (–14.48, –5.56)
BHGZDPD	1.82 (0.42, 7.33)	–1.51 (–17.73, 11.94)	–2.35 (–11.28, 5.79)
DGNTDPD	1.62 (0.51, 5.37)	–5.96 (–22.11, 7.01)	–6.92 (–15.69, 0.44)
mXBDPD	2.38 (0.68, 7.85)	1.51 (–19.14, 19.04)	3.08 (–8.18, 12.94)
XBDPD *vs.* csDMARD	2.84 (1.27, 6.82)	–9.29 (–26.70, 7.96)	–12.39 (–22.01, –2.77)
BHGZDPD	0.77 (0.19, 3.03)	–2.95 (–24.30, 18.50)	–5.40 (–17.34, 6.99)
DGNTDPD	0.70 (0.22, 2.17)	–7.44 (–28.70, 13.92)	–10.01 (–21.81, 1.79)
SMPPD	0.42 (0.13, 1.48)	–1.51 (–19.04, 19.14)	–3.08 (–12.94, 8.18)

csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ER, effective rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NMA, network meta-analysis; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

the cumulative Z-value curve exceeded the traditional curve. However, it did not cross the TSA threshold, and the cumulative amount of information did not reach the expected amount, indicating that the meta-analysis might have had a false-positive conclusion, and more trials are needed to be included to confirm the efficacy (*Figure 12*).

Results of network pharmacology analysis

Composition information of 4 CHF

The TCMSP database was used to retrieve 30 TCM ingredients, and other platforms were used to retrieve 3 TCM ingredients. After screening out the repeated components, finally, BHGZD included 101 components, DGNTD included 197 components, SMP included 35 components, and XBD included 46 components. The 4 CHF had 5 common components, as shown in *Figure 13A* and *Table 7*.

Protein interaction network and key target information

After screening the targets obtained on the TCMSP and PharmMapper databases, we sorted out the related targets of the 4 CHF and let these targets intersect with RA related targets. The 4 CHF had 66 common targets for RA treatment, as shown in *Figure 13B*,*C*,*D*,*E*,*F*. A network of "active ingredients-targets-disease" is shown in *Figure 13G*. The protein interaction network and 58 key targets are

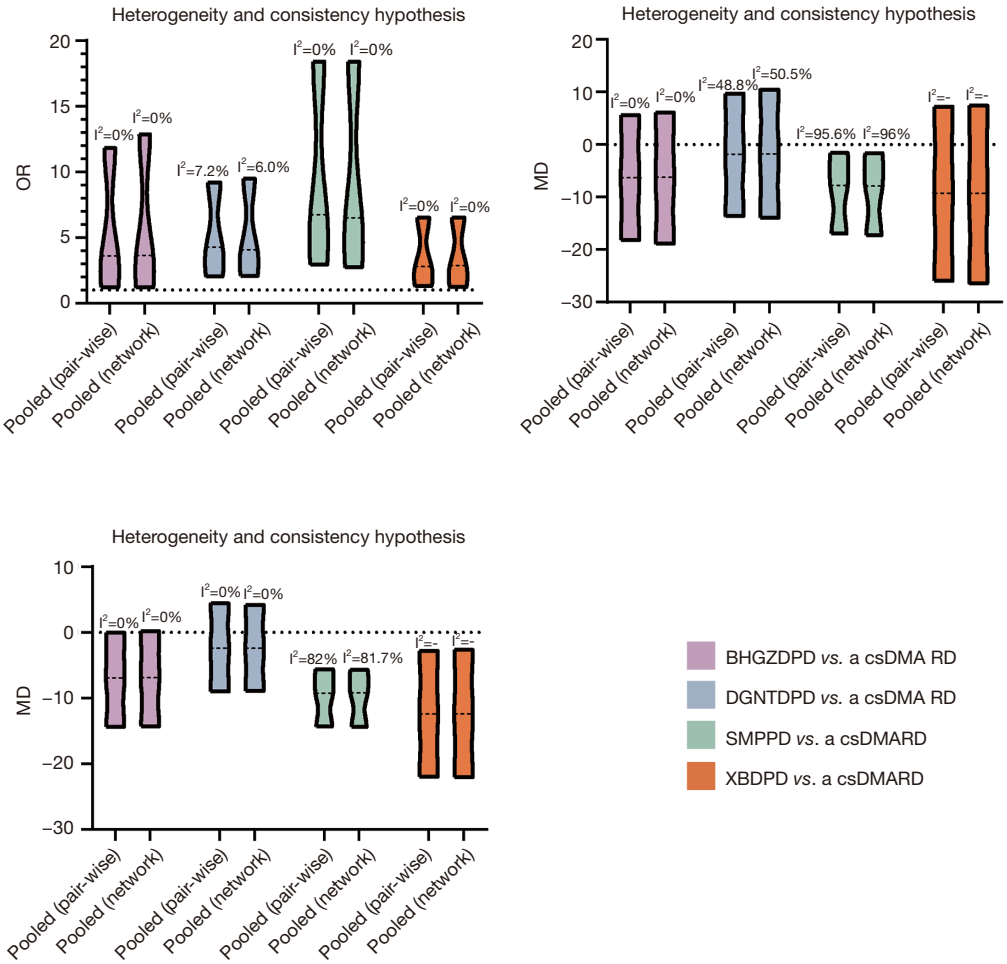


Figure 7 Violin plots in Heterogeneity and Consistency Hypothesis for ER, CRP, and ESR. ER, effective rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

shown in *Figure 13H* and Table S6. Node proteins were closely related to inflammatory factors, neovascularization, tumor cells, and so on.

KEGG enrichment analysis of key targets

We used R 4.0.2 software to perform KEGG enrichment analysis on the common targets of the 4 CHF for the treatment of RA. The KEGG results showed that the signaling pathways involved in RA treatment were mainly inflammation-related pathways, such as the TNF signaling pathway, and PI3k-Akt signaling pathway, and so on (*Figure 13I*).

Discussion

Description of research findings

By collating clinical guidelines and books related to RA or damp-heat type Bi syndrome, we conducted a pairwise meta-analysis and NMA to summarize the efficacy and safety of 4 highly recommended CHF combined with 1 csDMARD in treating RA. The evaluation and ranking were carried out according to the comparison results. In this study, after comprehensively assessing all the outcomes, SMPPD seemed to have a double guarantee of safety

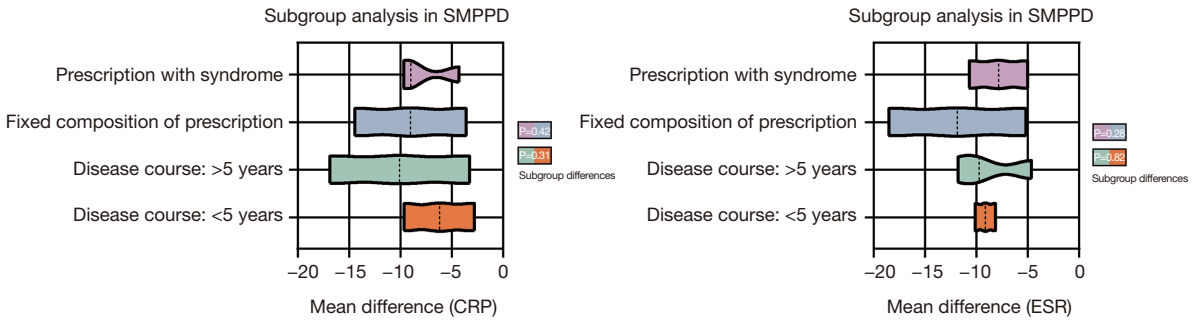


Figure 8 Subgroup analysis for CRP and ESR in SMPPD. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug).

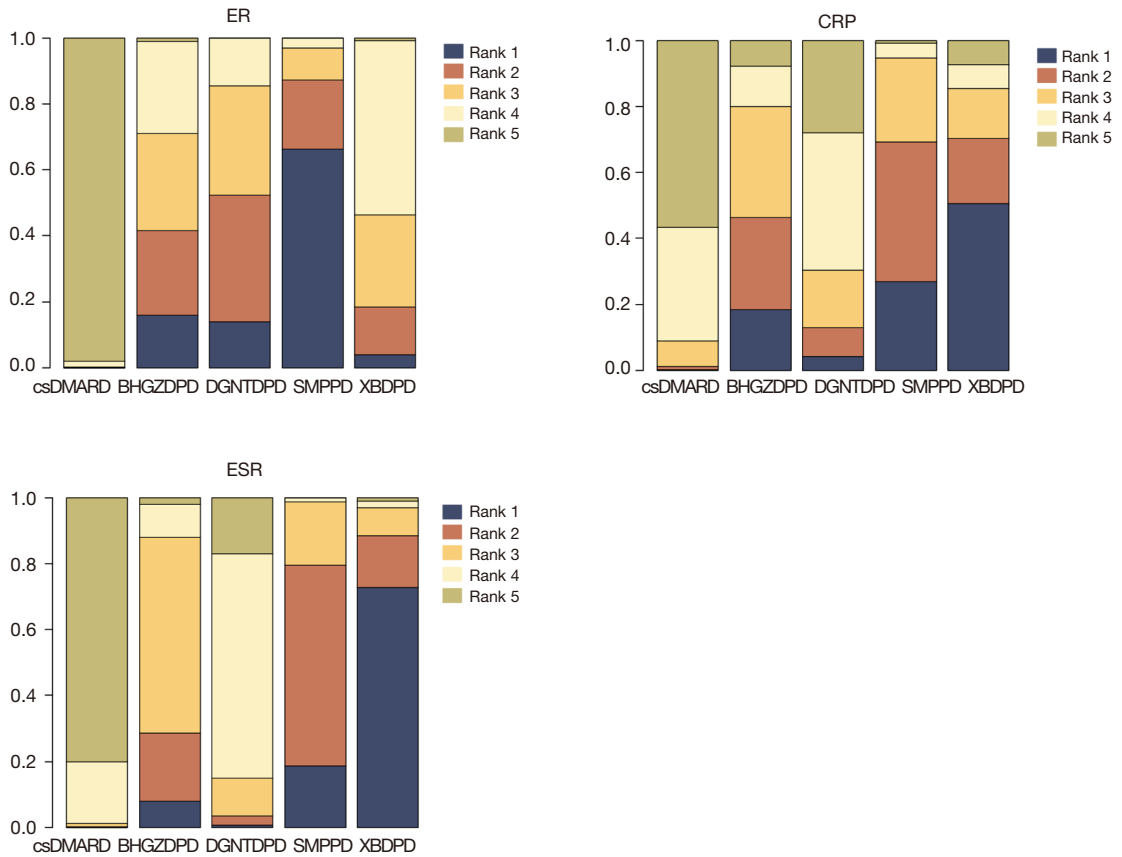


Figure 9 Ranking plots for ER, CRP, and ESR. ER, effective rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

Table 4 Results of SUCRA in the NMA

Intervention	ER		CRP		ESR	
	SUCRA (%)	Rank	SUCRA (%)	Rank	SUCRA (%)	Rank
csDMARD	0.005	5	0.13	5	0.05	5
BHGZDPD	0.57	3	0.59	3	0.56	3
DGNTDPD	0.63	2	0.30	4	0.25	4
SMPPD	0.88	1	0.73	2	0.74	2
XBDPD	0.42	4	0.75	1	0.89	1

ER, effective rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SUCRA, surface under the cumulative ranking curve; NMA, network meta-analysis; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

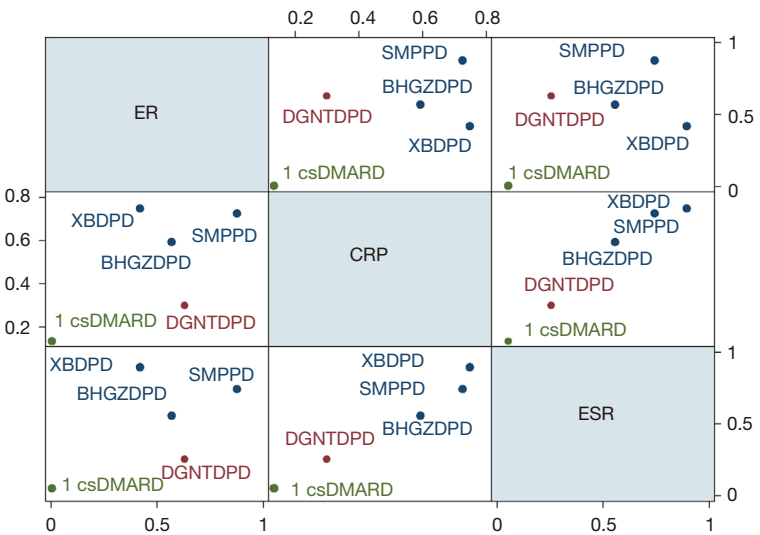


Figure 10 Cluster plots for ER, CRP, and ESR. ER, effective rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

and efficacy. Besides, in the selection of Chinese patent medicines, an expert consensus (47) had also shown that more than 50% of experts recommended SMP (accounting for 53.6%) for the treatment of active RA, and another systematic review had reported that in the treatment of RA, SMP combined with western medicine could effectively reduce the inflammatory reaction, improve drug tolerance, and relieve joint symptoms (16).

In terms of TCM clinical effective rate, the statistical results of NMA showed that compared with the csDMARD alone, 4 CHF combined with 1 csDMARD could partly improve the ER, which was consistent with the results of direct comparisons. The changes of ESR and CRP were also important serological indicators to help diagnose the curative effect or evaluate the disease activity. In this study, the pairwise meta-analysis indicated that CHF + csDMARD

Table 5 The incidence of different types of adverse drug reactions in different interventions

Adverse reactions	csDMARD	BHGZDPD	DGNTDPD	SMPPD	XBDPD	Total
Hepatic dysfunction	5.26% (19/361)	12.73% (7/55)	0.75% (1/133)	0.81% (1/133)	1.79% (1/56)	3.92% (29/738)
Renal dysfunction	1.39% (5/361)	–	0.75% (1/133)	–	–	1.21% (6/494)
Blood text abnormalities	0.56% (2/361)	–	–	–	–	0.55% (2/361)
Gastrointestinal reactions	14.96% (54/361)	10.91% (6/55)	3.76% (5/133)	5.64% (7/133)	14.29% (8/56)	10.84% (80/738)
Cough	1.11% (4/361)	–	0.75% (1/133)	–	–	1.01% (5/494)
Both hepatic dysfunction and renal dysfunction	0.55% (2/361)	–	–	–	–	0.55% (2/361)
Skin rash	1.11% (4/361)	–	–	–	3.57% (2/56)	1.43% (6/417)
Myelosuppression	19.39% (7/361)	–	–	–	7.14% (4/56)	2.63% (11/417)
Other	0.55% (2/361)	–	0.75% (1/133)	–	–	0.61% (3/494)
Total	27.42% (99/361)	23.64% (13/55)	6.77% (9/133)	6.45% (8/124)	26.79% (15/56)	–

csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

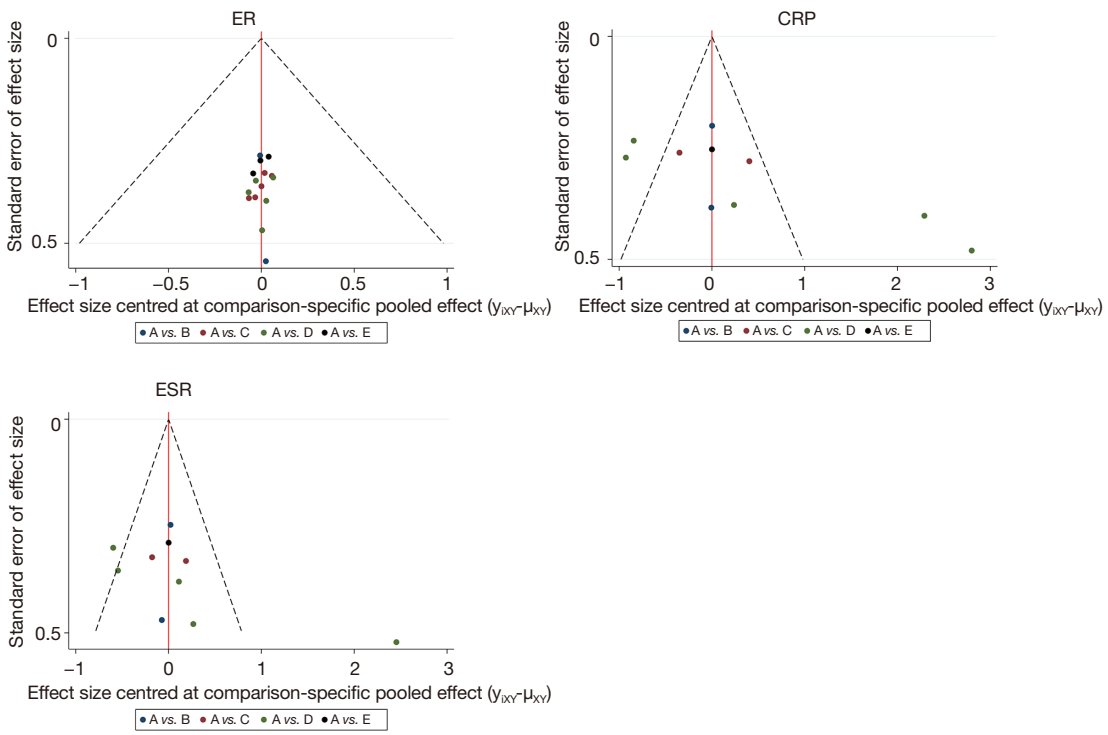
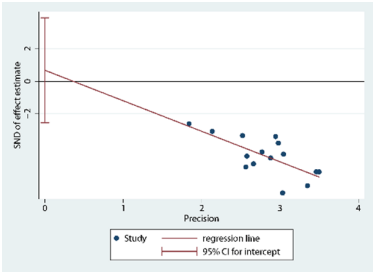
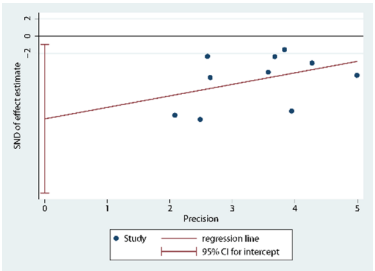
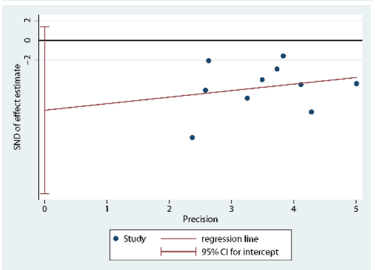


Figure 11 The funnel plot of ER, CRP, and ESR. (A) 1 csDMARD, (B) BHGZDPD; (C) DGNTDPD; (D) SMPPD; (E) XBDPD; ER, effective rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

Table 6 Egger's test of publication bias between selected studies

		STD EFF	Coef	Std err	*t*	P>|t|	95% Conf. Interval
ER		SLOPE	−1.879	0.525	−3.58	0.003	−3.014 to −0.744
		BIAS	0.678	1.498	0.45	0.659*	−2.559 to 3.915
CRP		BIAS	1.321	1.051	1.260	0.244	−1.103 to 3.746
		SLOPE	−9.511	3.703	−2.570	0.033	−18.051 to −0.971
ESR		BIAS	0.659	1.011	0.65	0.532	−1.671 to 2.990
		SLOPE	−7.049	3.658	−1.93	0.09*	−15.484 to 1.387

*indicated that there was no publication bias. ER, effective rate; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Std eff, standard efficiency; Coef, coefficient; Std err, standard error; *t*, *t*-test; P>|t|, 2-tailed P value.

could reduce inflammatory markers, but the NMA results demonstrated that only SMPPD and XBDPD could reduce the inflammatory levels of ESR and CRP. The differences between the 2 results also alerted us to the bias results caused by a small sample size or other factors. Meanwhile, due to the insufficient sample of other outcomes, we could not carry out NMA to evaluate and rank the other outcomes. Also, because the results of TSA suggested that our studies had too low samples, the results of meta-analysis might have had false-positive results among the 4 treatment groups. Therefore, whether CHF could reduce the levels of RF, IL-1, and TNF-α, and improve limb symptoms, such as TJC, SJC and MST, still needs to be further supported by the inclusion of more high-quality studies. Moreover, due to the differences in trial designs and small sample sizes, the results with high clinical heterogeneity should be treated cautiously. Based on the ER, ESR, and CRP measurement, the ranking results of this study indicated that XBDPD and SMPPD had potential advantages in anti-inflammatory and analgesic effects. In the results of cluster analysis, XBDPD, BHGZDPD, and SMPPD clearly stated a synergistic effect. This result was consistent with the many recommendations of the guidelines. Also, the NMA results showed that there was no statistical difference in the efficacy of the 4 CHF, which might be related to the presence of the same active ingredients among the 4 decoctions. For example, common ingredients included quercetin, stigmasterol, sitosterol, kaempferol, β-sitosterol, and so on, which have shown similar effects on regulating immunity and relieving joint symptoms in other studies (48).

However, the safety of drug administration was still an essential criterion for evaluating the treatment of RA. A lower incidence of ARs was associated with DGNTDPD and SMPPD, showing that they seemed to reduce toxic side effects or enhance the synergy of combination with 1 csDMARD. Moreover, the evidence of 9 retrieved systematic reviews (16,17,49-55) (Table S7) showed that ARs of each of the above CHF in treating rheumatic

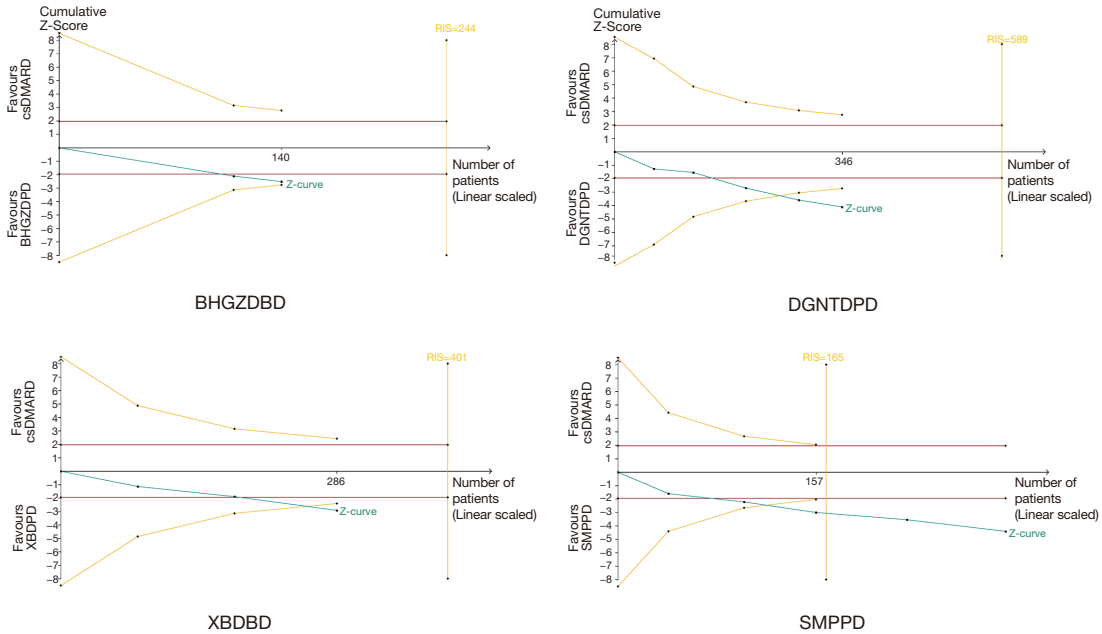


Figure 12 TSA results of ER. TSA, trial sequential analysis; ER, effective rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

immune disease decreased. Nevertheless, both XBDPD and csDMARD had a high incidence of ARs, and the specific ARs were not recorded. Future studies need to report related ARs while demonstrating the efficacy. In addition, it is worth noting that Chinese medicines often cause ARs because of their abuse, but they are generally safe if used correctly (56). Therefore, we also need to pay great attention to the clinical application standard of TCM.

Common pharmacological actions

In this study, the 4 recommended CHF all reflected some evidence of efficacy. To explore the active ingredients and pharmacological effects of these classic prescriptions in the treatment of RA, we analyzed the 4 CHF under the perspective of systems biology and network pharmacology, especially exploring the common components, targets and signalling pathways. The results showed that the common ingredients in the 4 CHF were: quercetin, stigmasterol, sitosterol, kaempferol, and β-sitosterol. These 5 critical compounds might act on 66 vital targets such as ESR-1, RELA, EGFR, FOS, CCND-1, MAPK-8, NR3C-1, AR, IL-6, CASP-8, and so on, and are mainly enriched in the PI3k-Akt signaling pathway, TNF signaling pathway, prolactin signaling pathway, and so on. These targets and signalling pathways have been understood to play an important role in reducing inflammation, controlling hormones, regulating immunity, and slowing down joint destruction for a long time.

Previous experimental results have pointed out that sex hormones could affect the development of immune cells and have immunomodulatory effects (57). For example, estrogen receptor alpha (ESR1) has been related to the risk of inducing erosive arthritis (58), which was reflected in the fact that women were more likely to develop RA; and other studies (59) have shown that reduced androgen also meant an increased risk of RA. The synovial inflammatory response of RA was similar to the growth of tumors, showing aggressive hyperplasia and expressing epidermal growth factor receptor (EGFR) and its ligands (60). Studies (61) have also specified that EGFR plays a vital role in the process of osteoclast formation and synovial inflammation. Its activation (62) was shown to relate to the proliferation of RA synovial fibroblasts, and it participated in most of the process of RA development. Also, MAPK-8, as the target protein found in the Wnt signaling pathway, which is

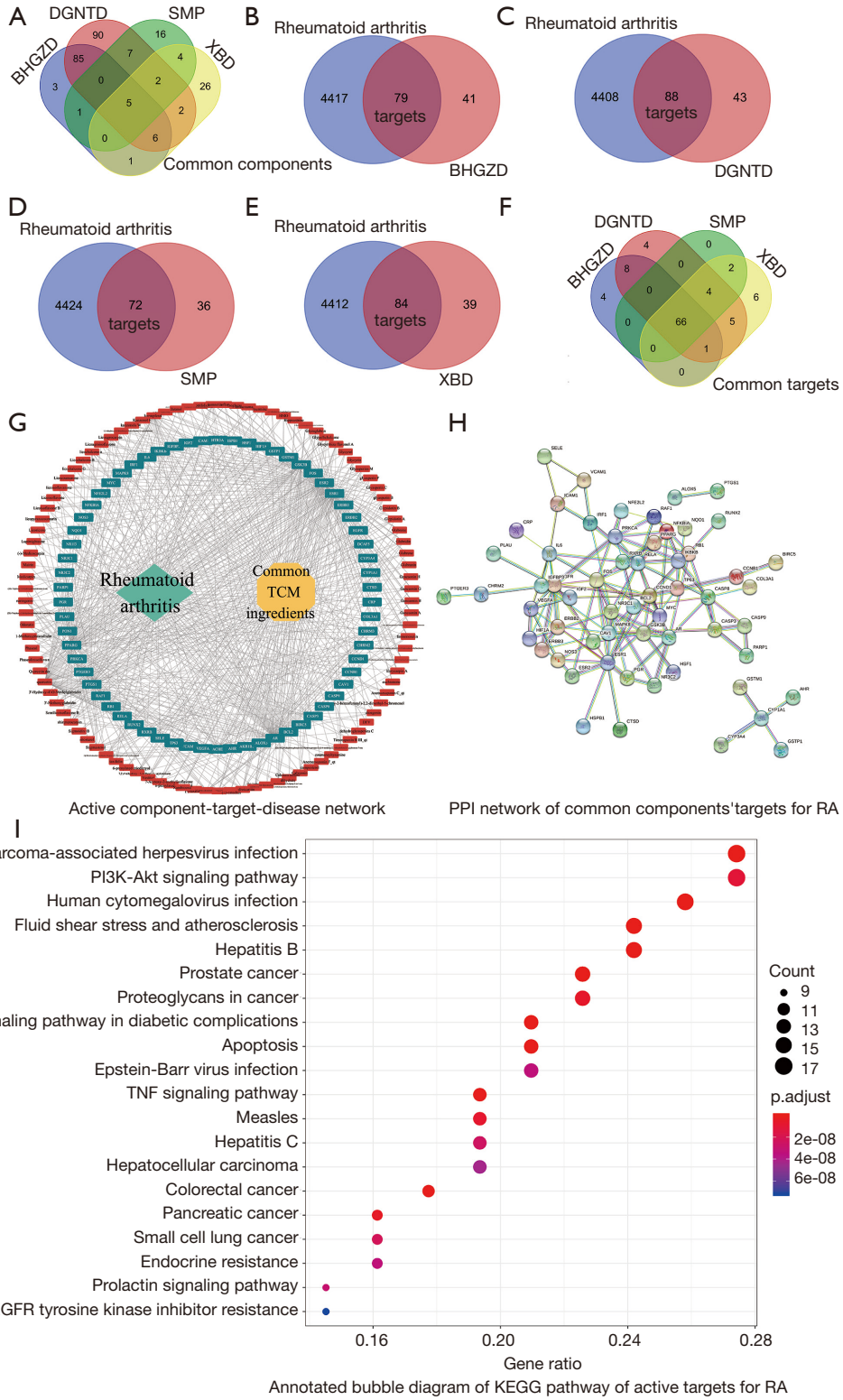
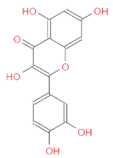
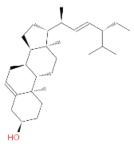
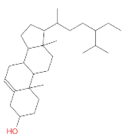
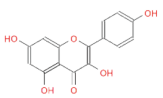
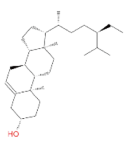


Figure 13 The results of network pharmacology analysis. BHGZDPD, BHGZD + csDMARD (Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug); DGNTDPD, DGNTD + csDMARD (Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug); SMPPD, SMP + csDMARD (Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug); XBDPD, XBD + csDMARD (Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug).

Table 7 Characteristics of 5 important components

MOL ID	Compound name	First category	PubChem CID	CAS ID	Compound structure
MOL000098	Quercetin	Flavonoids	5280343	117-39-5	
MOL000449	Stigmasterol	Terpenoids/Phytosterol	5280794	83-48-7	
MOL000359	Sitosterol	Terpenoids/Phytosterol	12303645	5779-62-4	
MOL000422	Kaempferol	Flavonoids	5280863	520-18-3	
MOL000358	β-sitosterol	Terpenoids/Phytosterol	222284	83-46-5	

closely related to the pathogenesis of RA, was shown to be a vital signal transduction target that participates in various cell biological processes (63). At the same time, studies (64) have also shown that RELA and MAPK-8 might be mainly involved in immune cell transport and intercellular inflammatory signal transmission in RA treatment. Nowadays, cytokine-targeted therapy has gradually changed the results of many chronic inflammatory diseases. The cytokine IL-6 (65,66) affects the differentiation of T cells and B cells, as a critical driver of the acute phase response of RA, and has become a good target for RA treatment. Significantly, on the one hand, IL-6 might regulate joint inflammation and injury by influencing chondrocytes and osteoclasts; on the other hand, it might also mediate systemic inflammation caused by RA.

As a classical pathway for understanding and treating RA, the PI3K-Akt signaling pathway is considered to be involved in synovitis, cartilage destruction, bone erosion, and pannus (67,68). The TNF signaling pathway is also a classic pathway for the treatment of RA. For example, TNF-α inhibitors have been used clinically for many years and could antagonize the activity of pathogenic inflammatory factors or signal transduction pathway activators (69,70). Besides, in the research of the prolactin signaling pathway, we have observed that prolactin extensively acts on the proliferation and differentiation of various cells in the immune system, and is closely related to rheumatic immune diseases (71). Prolactin (72,73) could

prevent chondrocyte apoptosis, increase trabecular bone area, prevent bone destruction and bone loss, and reduce the expression of proinflammatory cytokines in the synovium. However, the shared mechanism of these 4 prescriptions for clearing dampness and heat in RA treatment has not been thoroughly studied. Therefore, in future research, we could further study their common components, targets, and pathways through pharmacological and clinical experiments.

Limitations and prospects

This NMA had some limitations and prospects:

(I) The RCTs included were all Chinese studies, and the sample size was small, which could easily have led to publication bias, and exaggerated the publication of positive results (as shown by the TSA, Egger's test, and Trim-Fill analysis results). Meanwhile, there were some defects in the experimental design, such as randomization method, allocation process, measurement standard and so on. Therefore, the results need to be further confirmed by a large sample and high-quality research.

(II) In the clinical setting, csDMARDs would also be used in combination. However, our study lacked relevant RCTs for comparison. The NMA should include some multi-arm studies for analysis and exploration in the future.

(III) Most studies did not report the internationally recognized criteria for disease activity, such as the ACR20/50/70 and DAS-28 scores. Other serological outcomes and radiological examinations should also be observed in addition to the subjective measurement of symptoms and signs.

(IV) The lack of standardization between TCM prescriptions, such as differences in drug composition, dosage form, and dose, will cause the existence of clinical heterogeneity, and maybe lead to biased results of publication. Therefore, in future research, we should incorporate the distinction between granules, pills, and decoctions, and strictly follow the dosage standard of pharmacopoeia.

(V) The safety reports of CHF were insufficient, and the ARs were not described in detail. The relationship between the side effects and drug combination should be explored in the future. Moreover, the feasible and cost-effective safety detection methods of TCM should be further developed in the future. The public media should report the efficacy of TCM correctly and report the safety comprehensively to reduce misleading. Meanwhile, we should improve the rules and regulations of important quality control and use.

(VI) The common pharmacological mechanisms of recommended CHF in the treatment of RA had not been confirmed, especially the compounds included in the database were not comprehensive, and the related targets were not updated in time. Therefore, the potential mechanism needs to be further confirmed through pharmacological and clinical trials.

Conclusions

Considering all the outcomes, this systematic review and NMA showed that SMP + csDMARD might be a more productive choice in relieving inflammation, reducing AEs, and improving efficacy for RA patients. Compared with the csDMARD alone, the combination of the recommended CHF and 1 csDMARD had a particularly better curative effect. However, due to the limitations of this study, further extensive, rigorous, standardized, and high-quality research is required for confirmation. For the study of the potential mechanisms, we found that in the treatment of RA, the 4 CHF had common components, targets, and pathways to regulate immune and inflammatory responses. Nevertheless, we still need more corresponding basic research to verify and explain these findings.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-445). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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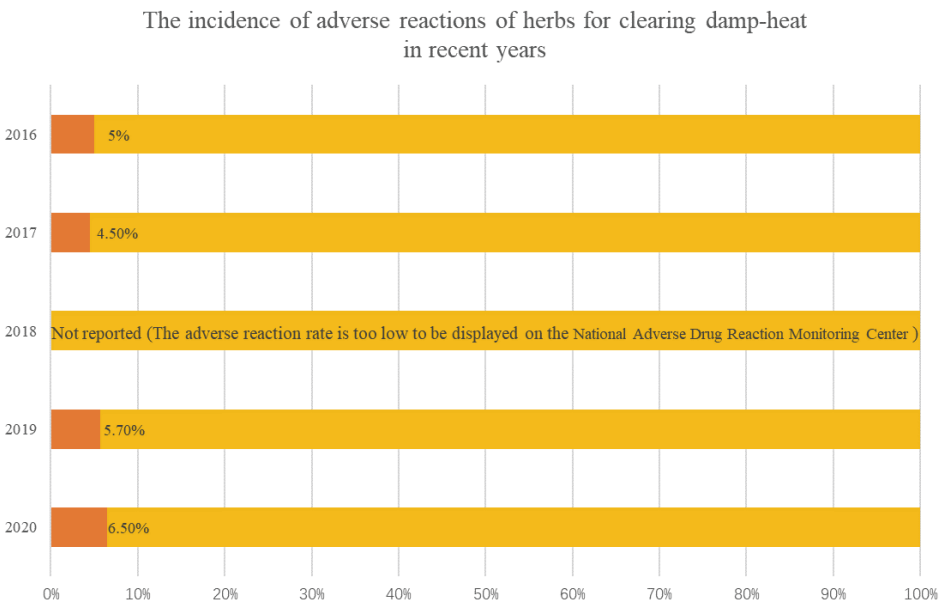

Figure S1 The probability of adverse reactions of herbs that clearing heat and dampness.

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Table S1 The detailed information of included guidelines.

Guides / Books	Year	Publishing unit / Chief editor	Publisher	ISBN/DOI	Recommended prescription	Type of syndrome
Textbook of TCM[13th]	2018	Jinshui Chen	People's Medical Publishing House	ISBN: 978-7-1172-6688-8	Xuan Bi Decoction	wind-damp-heat syndrome
Guidelines for diagnosis and treatment of rheumatoid arthritis	2018	Rheumatism branch of Chinese Medicine Association	Journal of traditional Chinese Medicine	DOI: 10.13288/j.11-2166/r.2018.20.018	Xuan Bi Decoction, Dang Gui Nian Tong Decoction, Er Miao Powder, Qing Re Huo Xue Decoction,Si Miao Xiao Bi Decoctio, Qing Luo Yin, Si Miao Pill	dampness-heat blockage type
Evidence-based clinical practice guidelines of TCM: internal medicine of TCM	2011	China Academy of Chinese Medical Sciences	China Press of TCM	ISBN: 978-7-5132-0270-1	Si Miao Pill、Xuan Bi Decoction、Qing Bi Decoction、Bi Xiao Zhong Decoction	dampness-heat blockage type
Guidelines for diagnosis and treatment of arthralgia syndrome	2011	China Association of Chinese Medicine	Chinese Medicine Modern Distance Education of China	DOI: 10.3969/j.issn.1672-2779.2011.11.100	Bai Hu Gui Zhi Decoction、Xuan Bi Decoction	wind-damp-heat syndrome
Guidelines for diagnosis and treatment of rheumatoid arthritis	2011	China Association of Chinese Medicine	Chinese Medicine Modern Distance Education of China	DOI: 10.3969/j.issn.1672-2779.2011.11.101	Da Qin Jiao Decoction	dampness-heat blockage type
Clinical practice guide of traditional Chinese medicine rehabilitation · rheumatoid arthritis	2020	Clinical practice guide of traditional Chinese medicine rehabilitation ·Working group on rheumatoid arthritis	Journal of rehabilitation	Doi: CNKI:SUN:FYXB.0.2020-01-006	Xuan Bi Decoction、Dang Gui Nian Tong Decoction、Er Miao Powder	dampness-heat blockage type
Guidelines for clinical diagnosis and treatment of TCM	2013	Zongsheng Zhang	Jilin Science and Technology Press	ISBN: 978-7-5384-7159-5	Bai Hu Gui Zhi Decoction	wind-damp-heat syndrome
TCM Guidelines for diagnosis and treatment of common clinical diseases	2013	Yingming Pan et al	Tianjin Science and Technology Press	ISBN: 7-5308-5019-9	Si Miao Pill、Bai Hu Gui Zhi Decoction	wind-damp-heat syndrome
Guidelines for syndrome differentiation and treatment of common diseases in TCM	2014	Yuhong Gao	Xi'an Jiaotong University Press	ISBN: 978-7-5605-6489-0	Si Miao Pill、Bai Hu Gui Zhi Decoction	wind-damp-heat syndrome
Guidelines for diagnosis and treatment of common diseases in internal medicine of TCM	2008	China Association of Chinese Medicine	China traditional Chinese Medicine Press	ISBN: 978-7-80231-437-5	Bai Hu Gui Zhi Decoction- Xuan Bi Decoction	wind-damp-heat syndrome
New series of clinical disciplines of TCM rheumatology	2018	Jianyun Pan et al	Science Press	ISBN: 978-7-03-055374-4	Zhu Ye Shi Gao Decoction	wind-damp-heat syndrome
Practical rheumatology of traditional Chinese Medicine	2009	Chengde Wang et al	People's Medical Publishing House	ISBN: 978-7-117-11537-7	Da Qin Jiao Decoction	wind-damp-heat syndrome
Rheumatology of TCM	2003	Deji Chen	The Medicine Science and Technology Press of China	ISBN: 7-5067-2667-X	Xuan Bi Decoction、Si Miao Pill- Xuan Bi Decoction	dampness-heat blockage type
					Yi Yi Ren Decoction	dampness-heat blockage type
Rheumatology of TCM	2010	Yulin Lou	People's Medical Publishing House	ISBN: 978-7-117-12198-9	Xuan Bi Decoction、Li Jie Qing Yin、Si Miao Pill、Cang Bai Er Miao Pill、Mu Fang Ji Decoction	dampness-heat blockage type
					Cang Zhu Bai Hu Decoction-San Miao Pill、Qing Bi Decoction、Nian Tong Decoction、Da Qin Jiao Decoction、Yin Qiao Powder、Bai Hu Gui Zhi Decoction -Xuan Bi Decoction、Qing Zao Jiu Fei Decoction- Yi Guan Jian、Bai Hu Gui Zhi Decoction	wind-damp-heat syndrome
					Dang Gui Nian Tong Decoction	wind-damp-heat syndrome / dampness-heat blockage type
					Modified Er Miao Pill	wind-damp-heat syndrome / dampness-heat blockage type
Practical internal medicine of integrated traditional Chinese and Western Medicine	1998	Keyi Chen	Beijing Medical University / Peking Union Medical University Press	ISBN: 7-81034-738-1	Xuan Bi Decoction- Er Miao Pill	damp-heat syndrome
					Si Miao Yong An Decoction	damp-heat syndrome (heat syndrome is obvious)
Interpretation of clinical diagnosis and treatment guidelines of TCM ·Rheumatism Division	2015	Chinese medicine standardization branch of China Association for Standardization	China Press of TCM	ISBN: 978-7-5132-2667-7	Da Qin Jiao Decoction	dampness-heat blockage type
Internal medicine of integrated traditional Chinese and Western Medicine	2014	Jun Zhao et al	Science and Technology Literature Press	ISBN: 978-7-5023-9534-6	Xuan Bi Decoction- San Miao Pill	dampness-heat blockage type
Rheumatoid arthritis	2011	Guangxian Cai et al	Hunan Journal of TCM	Doi: CNKI:SUN:HNZO.0.2011-03-074	Da Qin Jiao Decoction、Si Miao Pill、Xuan Bi Decoction	wind-damp-heat syndrome
Diagnosis and treatment of common rheumatism and related orthopedic diseases with integrated traditional Chinese and Western Medicine	2015	Xiaoping Yan et al	People's Medical Publishing House	ISBN: 978-7-117-21524-4	Xuan Bi Decoction- Sanr Miao Pill	dampness-heat blockage type
Internal medicine of TCM[5th] (new century textbook)	1985	Boyu Zhang	Shanghai Science and Technology Press	ISBN: 978-7-5323-0226-0	Bai Hu Gui Zhi Decoction、Xuan Bi Decoction	wind-damp-heat syndrome
Internal medicine of TCM[6-8th] (new century textbook)	1997	Yongyan Wang	Shanghai Science and Technology Press	ISBN: 7-5323-4105-4	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	Obvious damp-heat syndrome
	2003	Zhongying Zhou	China Press of TCM	ISBN: 7-80156-313-1	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	wind-damp-heat syndrome
	2007	Zhongying Zhou	China Press of TCM	ISBN: 7-80156-313-1	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	wind-damp-heat syndrome
	2012	Mianhua Wu et al	China Press of TCM	ISBN: 978-7-5132-0846-8	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	wind-damp-heat syndrome
Internal medicine of TCM[10th] (new century textbook)	2017	Boli Zhang et al	China Press of TCM	ISBN: 978-7-5132-3482-5	Bai Hu Gui Zhi Decoction	wind-damp-heat syndrome
Integrated traditional Chinese and Western medicine internal medicine[1th]	2003	Shaoyuan Yu	Science Press	ISBN: 978-7-03-012119-8	Da Qin Jiao Decoction	dampness-heat blockage type
Integrated traditional Chinese and Western medicine internal medicine[2th]	2008	Shaoyuan Yu et al	Science Press	ISBN: 978-7-03-020539-1	Si Miao Pill	dampness-heat blockage type
Integrated traditional Chinese and Western medicine internal medicine[3th]	2018	Huanlin Wu et al	Science Press	ISBN: 978-7-03-033236-3	Si Miao Pill、Dang Gui Nian Tong Decoction、Xuan Bi Decoction-San Miao Pill	dampness-heat blockage type
Internal medicine of TCM[1-2th] (Chinese medicine textbooks for general higher education in China)	2006	Delu Tian et al	Shanghai Science and Technology Press	ISBN: 7-5323-8447-0	Bai Hu Gui Zhi Decoction	wind-damp-heat syndrome
	2013	Delu Tian et al	Shanghai Science and Technology Press	ISBN: 978-7-5478-1577-9	Bai Hu Gui Zhi Decoction	wind-damp-heat syndrome
Internal medicine of TCM[3th] (Chinese medicine textbooks for general higher education in China)	2018	Xiaoping Yu et al	Shanghai Science and Technology Press	ISBN: 978-7-5478-3944-7	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	wind-damp-heat syndrome
Internal medicine of TCM[1th] (Teaching materials for national higher education of TCM	2002	Delu Tian	People's Medical Publishing House	ISBN: 7-117-04465-9	Bai Hu Gui Zhi Decoction	heat syndrome
Internal medicine of TCM[2-3th] (Teaching materials for national higher education of TCM	2012	Boli Zhang	People's Medical Publishing House	ISBN: 978-7-117-16059-9	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	wind-damp-heat syndrome
	2016	Boyu Xue et al	People's Medical Publishing House	ISBN: 978-7-117-22571-7	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	wind-damp-heat syndrome
Internal medicine of TCM[1th] (Reference series of colleges and universities of traditional Chinese Medicine)	2008	Zhongying Zhou et al	People's Medical Publishing House	ISBN: 978-7-117-09412-2	Bai Hu Gui Zhi Decoction	wind-damp-heat syndrome
Internal medicine of TCM[1th] (Teaching materials for national higher vocational education of TCM)	2018	Jianzhang Chen	People's Medical Publishing House	ISBN: 978-7-117-26380-1	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction、Da Qin Jiao Decoction	wind-damp-heat syndrome
Internal medicine of integrated traditional Chinese and Western Medicine (the national 11-12th-five planning textbooks)	2005	Guangxian Cai et al	China Press of TCM	ISBN: 7-80156-668-8	Si Miao Pill	dampness-heat blockage type
	2012	Zhiqiang Chen	China Press of TCM	ISBN: 978-7-5132-1007-2	Si Miao Pill	dampness-heat blockage type
Internal medicine of integrated traditional Chinese and Western Medicine (the national 13th-five planning textbooks)	2016	Zhiqiang Chen et al	China Press of TCM	ISBN: 978-7-5132-3477-1	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	wind-damp-heat syndrome
					Xuan Bi Decoction- San Miao Pill	dampness-heat blockage type
Internal medicine of traditional Chinese Medicine[2th] (Teaching materials for higher vocational education of Chinese medicine industry in China)	2018	Yingxin Zhou et al	China Press of TCM	ISBN: 978-7-5132-4961-4	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	wind-damp-heat syndrome
Internal medicine of traditional Chinese Medicine[2th] (Series teaching materials of TCM for national medical colleges and Universities)	2016	Ren luo et al	Science Press	ISBN: 978-7-03-047276-2	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	wind-damp-heat syndrome
Internal medicine of traditional Chinese Medicine (Textbook planning for National Medical Colleges)	2017	Yan shi	Science Press	ISBN: 978-7-03-053683-9	Bai Hu Gui Zhi Decoction	wind-damp-heat syndrome
					Xuan Bi Decoction	Obvious damp-heat syndrome
Practical internal medicine of traditional Chinese Medicine[1-2th]	1986	Yaozhong Fang et al	Shanghai Science and Technology Press	ISBN: 14119-1665	Xuan Bi Decoction- San Miao Pill	dampness-heat blockage type
	2009	Yongyan Wang et al	Shanghai Science and Technology Press	ISBN: 978-7-5323-9303-9	Xuan Bi Decoction- San Miao Pill	dampness-heat blockage type
Internal medicine of integrated traditional Chinese and Western Medicine	2006	Boyu Xue	China Press of TCM	ISBN: 7-80231-017-2	Bai Hu Gui Zhi Decoction-Xuan Bi Decoction	dampness-heat blockage type

Table S2 Common toxic herbs.

28 kinds of toxic Chinese medicine management varieties	Aconitum carmichaeli Debeaux (Chuan Wu, Aconiti Radix); Strychnos nux-vomica L. (Ma Qian Zi, Strychni Semen); Hyoscyamus niger L. (Tian Xian Zi, Hyoscyami Semen); Croton tiglium L. (Ba Dou, Crotonis Fructus); Rhododendron molle (Blume) G.Don (Nao Yang Hua, Rhododendri Mollis Flos); Aconitum kusnezoffii Rchb. (Cao Wu, Aconiti Kusnezoffii Radix); Mylabris phalerata Pallas (Ban Mao, Mylabris); Sauromatum giganteum (Engl.) Cusimano & Hett. (Bai Fu Zi, Typhonii Rhizoma); Pinellia ternata (Thunb.) Makino (Ban Xia, Pinelliae Rhizoma); Bufo bufo gargarizans Cantor (Chan Su, Bufonis Venenum); Aconitum carmichaelii Debx. (Fu Zi, Aconiti Lateralis Radix Praeparaia); Euphorbia kansui S.L.Liou ex S.B.Ho (Gan Sui, Kansui Radix); Euphorbia fischeriana Steud. (Lang Du, Euphorbiae Ebracteolatae Radix); Euphorbia lathyris L. (Qian Jin Zi, Euphorbiae Semen) and so on.
83 kinds of Chinese medicine specified in the 2015 Pharmacopoeia	Aconitum carmichaeli Debeaux (Chuan Wu, Aconiti Radix); Strychnos nux-vomica L. (Ma Qian Zi, Strychni Semen); Strychnos nux-vomica L. (Ma Qian Zi Fen, Strychni Semen Pulveratum); Hyoscyamus niger L. (Tian Xian Zi, Hyoscyami Semen); Croton tiglium L. (Ba Dou, Crotonis Fructus); Croton tiglium L. (Ba Dou Shuang, Crotonis Semen Pulveratum); Rhododendron molle (Blume) G.Don (Nao Yang Hua, Rhododendri Mollis Flos); Aconitum kusnezoffii Rchb. (Cao Wu, Aconiti Kusnezoffii Radix); Mylabris phalerata Pallas (Ban Mao, Mylabris); Hydrargyri Oxydum Rubrum (Hong Fen). Sauromatum giganteum (Engl.) Cusimano & Hett. (Bai Fu Zi, Typhonii Rhizoma); Ginkgo biloba L. (Bai Guo, Ginkgo Semen); Chelidonium majus L. (Bai Qu Cai, Chelidonii Herba); Pinellia ternata (Thunb.) Makino (Ban Xia, Pinelliae Rhizoma); Ricinus communis L. (Bi Ma Zi, Ricini Semen); Xanthium strumarium subsp. Strumarium (Cang Er Zi, Xanthii Fructus); Bufo bufo gargarizans Cantor (Chan Su, Bufonis Venenum); Hydrangea febrifuga (Lour.) Y.De Smet & Granados (Chang Shan , Dichroae Radix); Laggera crispata (Vahl) Hepper & J.R.I.Wood (Chou Ling Dan Cao, Laggerae Herba); Aconitum carmichaelii Debx. (Fu Zi, Aconiti Lateralis Radix Praeparaia); Toxicodendron vernicifluum (Stokes) F.A.Barkley (Gan Qi, Toxicodendri Resina); Euphorbia kansui S.L.Liou ex S.B.Ho (Gan Sui, Kansui Radix); Physochlaina infundibularis Kuang (Hua Shan Shen, Physochlainae Radix); (Jin Qian Bai Hua She , Bungarusparvus); Euphorbia pekinensis Rupr. (Jing Da Ji, Euphorbiae Pekinensis Radix); Melia azedarach L. (Ku Lina Pi, Meliae Cortex); Euphorbiafischeriana Steud. (Lang Du, Euphorbiae Ebracteolatae Radix); Anemonoides raddeana (Regel) Holub (Liang Tou Jian, Anemones Raddeanae Rhizoma); (Liu Huang, Sulfur); Momordica cochinchinensis (Lour.) Spreng. (Mu Bie Zi, Momordicae Semen); (Qi She, Agkistrodon); Euphorbia lathyris L. (Qian Jin Zi, Euphorbiae Semen); Euphorbia lathyris L. (Qian Jin Zi Shuang, Euphorbiae Semen Pulveratum); Ipomoea nil (L.) Roth (Qian Niu Zi, Pharbitidis Semen); (Qing Fen, Calomelas); Buthus martensii Karsch (Quan Xie, Scorpio); Berberis vulgaris L. (San Ke Zhen, Berberidis Radix); Sophora tonkinensis Gagnep. (Shan Dou Gen, Sophorae Tonkinensis Radix Et Rhizoma); Phytolacca americana L. (Shang Lu, Phytolaccae Radix); Arisaema erubescens (Wall.) Schott (Tian Nan Xing, Arisaematis Rhizoma); Pseudolarix amabilis (J.Nelson) Rehder (Tu Jing Pi, Pseudolaricis Cortex); Scolopendra subspinipes mutilans L.Koch (Wu Gong, Scolopendra); Curculigo orchioides Gaertn. (Xian Mao, Curculiginis Rhizoma); Periploca sepium Bunge (Xinag Jia Pi, Periplocae Cortex); (Xiong Huang, Realgar); Daphne genkwa Siebold & Zucc. (Yuan Hua, Genkwa Flos); Datura metel L. (Yang Jin Hua, Daturae Flos); Papaver somniferum L. (Ying Su Qiao, Papaveris Pericarpium); Aconitum kusnezoffii Rchb. (Zhi Cao Wu, Aconiti Kusnezoffii Radix Cocta); Aconitum carmichaeli Debeaux (Zhi Chuan Wu, Aconiti Radix Cocta); Arisaema erubescens (Wall.) Schott (Zhi Dan Nan Xing, Arisaematis Rhizoma Preparatum); (Zhu Sha, Cinnabaris). Artemisia argyi H.Lév. & Vaniot (Ai Ye, Artemisiae Argyi Folium); Menispermum dauricum DC. (Bei Dou Gen, Menispermi Rhizoma); Aconitum kusnezoffii Rchb. (Cao Wu Ye, Aconiti Kusnezoffii Folium); Melia azedarach L. (Chuan Lian Zi, Toosendan Fructus); Gleditsia sinensis Lam. (Da Zao Jiao, Gleditsiae Sinensis Fructus); Illicium difengpi B.N.Chang (Di Feng Pi, Illicii Cortex); Erycibe obtusifolia Benth. (Ding Gong Teng, Erycibes Caulis); Euphorbia hirta L. (Fei Yang Cao, Euphorbiae Hirtae Herba); Carpesium abrotanoides L. (He Shi, Carpesii Fructus); Knoxia roxburghii subsp. brunonis (Wall. ex G.Don) R.Bhattacharjee & Deb (Hong Da Ji, Knoxiae Radix); Impatiens balsamina L. (Ji Xing Zi, Impatientis Semen); Tribulus terrestris L. (Ji Li, Tribuli Fructus); Psammosilene tunicoides W.C.Wu & C.Y.Wu (Jin Tie Suo, Psammosilenes Radix); Murraya paniculata (L.) Jack (Jiu Li Xiang, Murrayae Folium Et Cacumen); Entada phaseoloides (L.) Merr. (Ke Teng Zi, Entadae Semen); Picrasma quassioides (D.Don) Benn. (Ku Mu, Picrasmae Ramulus Et Folium); Prunus armeniaca L. (Ku Xing Ren, Armeniacae Semen Amarum); Zanthoxylum nitidum (Roxb.) DC. (Liang Mian Zhen, Zanthoxyli Radix); Dryopteris crassirhizoma Nakai (Mian Ma Guan Zhong, Dryopteridis Crassirhizomatis Rhizoma); “Dryopteris crassirhizoma Nakai (Mian Ma Guan Zhong Tan, Dryopteridis Crassirhizomatis Rhizoma Carbonisatum); “Osmunda japonica Thunb. (Zi Qi Guan Zhong, Osmundae Rhizoma); Daucus carota L. (Nan He Shi, Carotae Fructus); Cnidium monnieri (L.) Cusson (She Chuang Zi, Cnidii Fructus); (Shui Zhi, Hirudo); (Tu Bie Chong, Eupolyphaga Steleophaga); Podophyllum hexandrum Royle (Xiao Ye Lian, Sinopodophylli Fructus); Brucea javanica (L.) Merr. (Ye Dan Zi, Bruceae Fructus); Bassecoia hookeri (C.B.Clarke) V.Mayer & Ehrend. (Yi Shou Cao, Pterocephali Herba); Paris polyphylla var. yunnanensis (Franch.) Hand-Mazz. (Chong Lou, Paridis Rhizoma); Gleditsia sinensis Lam. (Zhu Zao Ya, Gleditsiae Fructus Abnormalis).

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Table S3 Search strategy.

Search Strategies in PubMed (Number of Articles Retrieved: 11)		
Search block	Number	Search terms
Participants	#1	arthritis, rheumatoid[Mesh]
	#2	arthritis, rheumatoid[Title/Abstract]
	#3	rheumatoid arthritis[Title/Abstract]
	#4	bi syndrome[Title/Abstract]
	#5	RA[Title/Abstract]
	#6	rheumatism arthritis[Title/Abstract]
	#7	rheumatic arthritis[Title/Abstract]
	#8	rheumarthritis[Title/Abstract]
	#9	rheumarthrosis[Title/Abstract]
	#10	rheumatoid disease[Title/Abstract]
	#11	arthritis deformans[Title/Abstract]
	#12	arthritis deformans[Title/Abstract]
	#13	arthrinosos deformans[Title/Abstract]
	#14	arthorheumatism[Title/Abstract]
	#15	articular rheumatism[Title/Abstract]
	#16	chronic articular rheumatism[Title/Abstract]
	#17	chronic rheumatoid arthritis[Title/Abstract]
	#18	chronic rheumatic arthritis[Title/Abstract]
	#19	chronic progressive polyarthritis[Title/Abstract]
	#20	chronic polyarthritis[Title/Abstract]
	#21	chronic infectious arthritis[Title/Abstract]
	#22	chronic inflammatory arthritis[Title/Abstract]
	#23	chronic rheumatism[Title/Abstract]
	#24	atrophic arthritis[Title/Abstract]
	#25	infectious nonspecific polyarthritis[Title/Abstract]
	#26	proliferative arthritis[Title/Abstract]
	#27	primary chronic polyarthritis[Title/Abstract]
	#28	rheumatic polyarthritis[Title/Abstract]
	#29	beauvais disease[Title/Abstract]
	#30	polyarthritis chronique evolutive[Title/Abstract]
Combination 1	#31	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
Intervention	#32	baihuguizhi[Mesh]
	#33	baihuguizhi[Title/Abstract]
	#34	xuanbi[Mesh]
	#35	xuanbi[Title/Abstract]
	#36	simiao[Mesh]
	#39	simiao[Title/Abstract]
	#40	daojiriqiu[Mesh]
	#41	daojiriqiu[Title/Abstract]
	#42	ermiao[Mesh]
	#43	ermiao[Title/Abstract]
	#44	dangguiniantong[Mesh]
	#45	dangguiniantong[Title/Abstract]
	#46	sanmiao[Mesh]
	#47	sanmiao[Title/Abstract]
Combination 2	#48	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
Combination 3	#49	#31 AND #48

Search Strategies in CNKI (Number of Articles Retrieved: 453)		
Search block	Number	Search terms
Participants	#1	主题检索' 或', " 类风湿"
	#2	主题检索' 或', " 类风关"
	#3	主题检索' 或', " 类风湿关节炎"
	#4	主题检索' 或', " 类风湿性关节炎"
	#5	主题检索' 或', " 类风湿病"
	#6	主题检索' 或', " 风"
	#7	主题检索' 或', " 痹证"
	#8	主题检索' 或', " 痹证"
	#9	主题检索' 或', " 痹痛"
	#10	主题检索' 或', " 痹病"
	#11	主题检索' 或', " 热痹"
	#12	主题检索' 或', " 风湿热痹"
	#13	主题检索' 或', " 湿热痹"
	#14	主题检索' 或', " 顽痹"
	#15	主题检索' 或', " 历节"
Combination 1	#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
Intervention	#17	主题检索' 或', " 白虎桂枝汤"
	#18	主题检索' 或', " 桂枝白虎汤"
	#19	主题检索' 或', " 白虎加桂枝汤"
	#20	主题检索' 或', " 宣痹汤"
	#21	主题检索' 或', " 四妙丸"
	#22	主题检索' 或', " 四妙散"
	#23	主题检索' 或', " 二妙丸"
	#24	主题检索' 或', " 二妙散"
	#25	主题检索' 或', " 三妙丸"
	#26	主题检索' 或', " 三妙散"
	#27	主题检索' 或', " 大秦艽汤"
	#28	主题检索' 或', " 当归拈痛丸"
	#29	主题检索' 或', " 当归拈痛汤"
Combination 2	#30	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
Combination 3	#31	#16 AND #30

Search Strategies in CQVIP (Number of Articles Retrieved: 238)		
Search block	Number	Search terms
Participants	#1	题名或关键词' 和 ' (类风湿)
	#2	题名或关键词' 和 ' (类风关)
	#3	题名或关键词' 和 ' (类风湿关节炎)
	#4	题名或关键词' 和 ' (类风湿性关节炎)
	#5	题名或关键词' 和 ' (类风湿病)
	#6	题名或关键词' 和 ' (风)
	#7	题名或关键词' 和 ' (痹证)
	#8	题名或关键词' 和 ' (痹证)
	#9	题名或关键词' 和 ' (痹痛)
	#10	题名或关键词' 和 ' (痹病)
	#11	题名或关键词' 和 ' (热痹)
	#12	题名或关键词' 和 ' (风湿热痹)
	#13	题名或关键词' 和 ' (湿热痹)
	#14	题名或关键词' 和 ' (顽痹)
	#15	题名或关键词' 和 ' (历节)
Combination 1	#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
Intervention	#17	题名或关键词' 和 ' (白虎桂枝汤)
	#18	题名或关键词' 和 ' (桂枝白虎汤)
	#19	题名或关键词' 和 ' (白虎加桂枝汤)
	#20	题名或关键词' 和 ' (宣痹汤)
	#21	题名或关键词' 和 ' (四妙丸)
	#22	题名或关键词' 和 ' (四妙散)
	#23	题名或关键词' 和 ' (二妙丸)
	#24	题名或关键词' 和 ' (二妙散)
	#25	题名或关键词' 和 ' (三妙丸)
	#26	题名或关键词' 和 ' (三妙散)
	#27	题名或关键词' 和 ' (大秦艽汤)
	#28	题名或关键词' 和 ' (当归拈痛丸)
	#29	题名或关键词' 和 ' (当归拈痛汤)
Combination 2	#30	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
Combination 3	#31	#16 AND #30

Search Strategies in EMBASE (Number of Articles Retrieved: 16)		
Search block	Number	Search terms
Participants	#1	'arthritis, rheumatoid'/exp OR 'arthritis, rheumatoid': ti, ab, kw OR 'rheumatoid arthritis': ti, ab, kw OR 'bi syndrome': ti, ab, kw OR RA: ti, ab, kw OR 'rheumatism arthritis': ti, ab, kw OR 'rheumatic arthritis': ti, ab, kw OR rheumarthritis: ti, ab, kw OR 'rheumatoid disease': ti, ab, kw OR 'arthritis deformans': ti, ab, kw OR 'arthritis deformans': ti, ab, kw OR 'arthrinosos deformans': ti, ab, kw OR arthorheumatism: ti, ab, kw OR 'articular rheumatism': ti, ab, kw OR 'chronic articular rheumatism': ti, ab, kw OR 'chronic rheumatoid arthritis': ti, ab, kw OR 'chronic rheumatic arthritis': ti, ab, kw OR 'chronic progressive polyarthritis': ti, ab, kw OR 'chronic polyarthritis': ti, ab, kw OR 'chronic infectious arthritis': ti, ab, kw OR 'chronic inflammatory arthritis': ti, ab, kw OR 'chronic rheumatism': ti, ab, kw OR 'atrophic arthritis': ti, ab, kw OR 'infectious nonspecific polyarthritis': ti, ab, kw OR 'proliferative arthritis': ti, ab, kw OR 'primary chronic polyarthritis': ti, ab, kw OR 'rheumatic polyarthritis': ti, ab, kw OR 'beauvais disease': ti, ab, kw OR 'polyarthritis chronique evolutive': ti, ab, kw
Intervention	#2	'baihuguizhi'/exp OR 'baihuguizhi': ti, ab, kw OR 'xuanbi'/exp OR 'xuanbi': ti, ab, kw OR 'simiao'/exp OR 'simiao': ti, ab, kw OR 'daojiriqiu'/exp OR 'daojiriqiu': ti, ab, kw OR 'ermiao'/exp OR 'ermiao': ti, ab, kw OR 'dangguiniantong'/exp OR 'dangguiniantong': ti, ab, kw OR 'sanmiao'/exp OR 'sanmiao': ti, ab, kw
Combination 1	#3	#1 AND #2

Search Strategies in Cochrane Library (Number of Articles Retrieved: 7)		
Search block	Number	Search terms
Participants	#1	MeSH descriptor: [arthritis, rheumatoid] explode all trees
	#2	(arthritis, rheumatoid): ti, ab, kw
	#3	(bi syndrome): ti, ab, kw
	#4	(RA): ti, ab, kw
	#5	(rheumatism arthritis): ti, ab, kw
	#6	(rheumatic arthritis): ti, ab, kw
	#7	(rheumarthritis): ti, ab, kw
	#8	(rheumatoid): ti, ab, kw
	#9	(rheumatoid disease): ti, ab, kw
	#10	(arthritis deformans): ti, ab, kw
	#11	(arthrosis deformans): ti, ab, kw
	#12	(arthrinosos deformans): ti, ab, kw
	#13	(arthorheumatism): ti, ab, kw
	#14	(articular rheumatism): ti, ab, kw
	#15	(chronic articular rheumatism): ti, ab, kw
	#16	(chronic rheumatoid arthritis): ti, ab, kw
	#17	(chronic rheumatic arthritis): ti, ab, kw
	#18	(chronic progressive polyarthritis): ti, ab, kw
	#19	(chronic polyarthritis): ti, ab, kw
	#20	(chronic infectious arthritis): ti, ab, kw
	#21	(rheumatoid arthritis): ti, ab, kw
	#22	(chronic infectious arthritis): ti, ab, kw
	#23	(chronic inflammatory arthritis): ti, ab, kw
	#24	(chronic inflammatory arthritis): ti, ab, kw
	#25	(chronic rheumatism): ti, ab, kw
	#26	(infectious nonspecific polyarthritis): ti, ab, kw
	#27	(proliferative arthritis): ti, ab, kw
	#28	(primary chronic polyarthritis): ti, ab, kw
	#29	(primary chronic polyarthritis): ti, ab, kw
	#30	(rheumatic polyarthritis): ti, ab, kw
	#31	(polyarthritis chronique evolutive): ti, ab, kw
Combination 1	#32	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
Intervention	#33	MeSH descriptor: [baihuguizhi] explode all trees
	#34	(baihuguizhi): ti, ab, kw
	#35	MeSH descriptor: [xuanbi] explode all trees
	#36	(xuanbi): ti, ab, kw
	#37	MeSH descriptor: [simiao] explode all trees
	#38	(simiao): ti, ab, kw
	#39	MeSH descriptor: [daojiriqiu] explode all trees
	#40	(daojiriqiu): ti, ab, kw
	#41	MeSH descriptor: [ermiao] explode all trees
	#42	(ermiao): ti, ab, kw
	#43	MeSH descriptor: [dangguiniantong] explode all trees
	#44	(dangguiniantong): ti, ab, kw
	#45	MeSH descriptor: [sanmiao] explode all trees
	#46	(sanmiao): ti, ab, kw
Combination 2	#47	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
Combination 3	#48	#32 AND #47

Search Strategies in Wanfang (Number of Articles Retrieved: 1056)		
Search block	Number	Search terms
Participants	#1	主题检索：" 类风湿"
	#2	主题检索：" 类风关 "
	#3	主题检索：" 类风湿关节炎 "
	#4	主题检索：" 类风湿性关节炎 "
	#5	主题检索：" 类风湿病 "
	#6	主题检索：" 风 "
	#7	主题检索：" 痹证 "
	#8	主题检索：" 痹证 "
	#9	主题检索：" 痹痛 "
	#10	主题检索：" 痹病 "
	#11	主题检索：" 热痹 "
	#12	主题检索：" 风湿热痹 "
	#13	主题检索：" 湿热痹 "
	#14	主题检索：" 顽痹 "
	#15	主题检索：" 历节 "
Combination 1	#16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
Intervention	#17	主题检索：" 白虎桂枝汤 "
	#18	主题检索：" 桂枝白虎汤 "
	#19	主题检索：" 白虎加桂枝汤 "
	#20	主题检索：" 宣痹汤 "
	#21	主题检索：" 四妙丸 "
	#22	主题检索：" 四妙散 "
	#23	主题检索：" 二妙丸 "
	#24	主题检索：" 二妙散 "
	#25	主题检索：" 三妙丸 "
	#26	主题检索：" 三妙散 "
	#27	主题检索：" 大秦艽汤 "
	#28	主题检索：" 当归拈痛丸 "
	#29	主题检索：" 当归拈痛汤 "
Combination 2	#30	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
Combination 3	#31	#16 AND #30

Search Strategies in CBM (Number of Articles Retrieved: 399)		
Search block	Number	Search terms
Participants	#1	" 类风湿 "[常用字段：智能] OR " 类风关 "[常用字段：智能] OR " 类风湿关节炎 "[常用字段：智能] OR " 类风湿性关节炎 "[常用字段：智能] OR " 类风湿病 "[常用字段：智能] OR "风"[常用字段：智能] OR " 痹证 "[常用字段：智能] OR " 痹证 "[常用字段：智能] OR " 痹痛 "[常用字段：智能] OR " 痹病 "[常用字段：智能] OR " 热痹 "[常用字段：智能] OR " 风湿热痹 "[常用字段：智能] OR " 湿热痹 "[常用字段：智能] OR " 顽痹 "[常用字段：智能] OR " 历节 "[常用字段：智能]
Intervention	#2	" 白虎桂枝汤 "[常用字段：智能] OR " 桂枝白虎汤 "[常用字段：智能] OR " 白虎加桂枝汤 "[常用字段：智能] OR " 宣痹汤 "[常用字段：智能] OR " 四妙丸 "[常用字段：智能] OR " 四妙散 "[常用字段：智能] OR " 二妙丸 "[常用字段：智能] OR " 二妙散 "[常用字段：智能] OR " 三妙丸 "[常用字段：智能] OR " 三妙散 "[常用字段：智能] OR " 大秦艽汤 "[常用字段：智能] OR " 当归拈痛丸 "[常用字段：智能] OR " 当归拈痛汤 "[常用字段：智能]
Combination 1	#3	#1 AND #2

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Table S4 Sensitivity analysis of the included studies.

ER:

Excluded studies	OR 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Ma 2016	5.09 [0.50, 52.29]	0.17	0.00	-
Omitting Yuan *et al.* 2019	3.06 [1.09, 8.62]	0.03	0.00	-
Pooled estimate	3.33 [1.29, 8.57]	0.01	0.00	0.00
DGNTDPD vs. csDMARD				
Omitting Jiang *et al* 2020	3.24 [1.59, 6.61]	0.001	0.00	0.00
Omitting Ge *et al* 2017	3.21 [1.41, 7.32]	0.006	0.06	0.08
Omitting Ding *et al* 2017	3.13 [1.53, 6.39]	0.002	0.00	0.00
Omitting Zheng *et al* 2015	4.70 [2.10, 10.50]	0.0002	0.00	0.00
Omitting Sheng, 2013	4.17 [1.85, 9.39]	0.0006	0.03	0.05
Pooled estimate	3.57 [1.81, 7.02]	0.0002	0.00	0.00
SMPPD vs. csDMARD				
Omitting Zhang 2019	5.43 [2.13, 13.83]	0.0004	0.00	0.00
Omitting Li 2017	6.49 [2.57, 16.37]	< 0.0001	0.00	0.00
Omitting Yang 2011	6.01 [2.54, 14.21]	< 0.0001	0.00	0.00
Omitting Li *et al* 2014	6.09 [2.57, 14.43]	< 0.0001	0.00	0.00
Omitting Li 2016	6.26 [2.50, 15.72]	< 0.0001	0.00	0.00
Pooled estimate	6.05 [2.71, 13.51]	< 0.0001	0.00	0.00
XBDPD vs. csDMARD				
Omitting Pang 2010	3.05 [1.25, 7.43]	0.01	0.00	0.00
Omitting Zhu 2014	2.25 [0.98, 5.16]	0.06	0.00	0.00
Omitting Wang *et al* 2008	2.98 [1.34, 6.64]	0.008	0.00	0.00
Pooled estimate	2.73 [1.36, 5.41]	0.004	0.00	0.00

OR, odds ratio; CI, confidence interval; ER, effective rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHQZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; DGNTDPD, DGNTD + csDMARD [Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug]; XBDPD, XBD + csDMARD [Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug].

CRP:

Excluded studies	MD 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-6.60 [-11.89, -1.31]	0.01	-	-
Omitting Yuan *et al*, 2019	-6.10 [-8.63, -3.57]	< 0.00001	-	-
Pooled estimate	-6.19 [-8.47, -3.91]	< 0.00001	0.00	0.00
DGNTDPD vs. csDMARD				
Omitting Zheng *et al* 2015	-1.18 [-2.64, 0.28]	0.11	-	-
Omitting Sheng, 2013	-2.41 [-3.46, -1.36]	< 0.00001	-	-
Pooled estimate	-1.91 [-3.09, -0.72]	0.002	0.33	0.44
SMPPD vs. csDMARD				
Omitting Zhang 2019	-7.38 [-10.14, -4.63]	< 0.00001	5.44	0.93
Omitting Li 2017	-7.15 [-10.99, -3.30]	0.0003	11.33	0.87
Omitting Yang 2011	-5.68 [-7.46, -3.89]	< 0.00001	2.40	0.86
Omitting Li *et al* 2014	-8.31 [-12.64, -3.98]	0.0002	15.00	0.89
Omitting Li 2016	-7.21 [-9.87, -4.55]	< 0.00001	5.27	0.93
Pooled estimate	-6.64 [-8.99, -4.30]	< 0.00001	4.93	0.90
XBDPD vs. csDMARD				
Omitting Pang 2010	-	-	-	-
Pooled estimate	-9.31 [-10.99, -7.63]	< 0.00001	-	-

MD, mean difference; CI, confidence interval; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHQZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; DGNTDPD, DGNTD + csDMARD [Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug]; XBDPD, XBD + csDMARD [Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug].

ESR:

Excluded studies	MD 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-8.13 [-15.61, -0.65]	0.03	-	-
Omitting Yuan *et al*, 2019	-6.50 [-9.29, -3.71]	< 0.00001	-	-
Pooled estimate	-6.70 [-9.31, -4.08]	< 0.00001	0.00	0.00
DGNTDPD vs. csDMARD				
Omitting Zheng *et al* 2015	-2.38 [-3.93, -0.83]	0.003	-	-
Omitting Sheng, 2013	-2.34 [-5.22, 0.54]	0.11	-	-
Pooled estimate	-2.37 [-3.74, -1.00]	0.0007	0.00	0.00
SMPPD vs. csDMARD				
Omitting Zhang 2019	-8.98 [-11.84, -6.11]	< 0.00001	6.35	0.84
Omitting Li 2017	-9.93 [-14.08, -5.77]	< 0.00001	14.03	0.83
Omitting Yang 2011	-7.97 [-9.78, -6.17]	< 0.00001	1.97	0.64
Omitting Li *et al* 2014	-10.36 [-13.88, -6.84]	< 0.00001	9.42	0.81
Omitting Li 2016	-10.19 [-13.20, -7.18]	< 0.00001	6.57	0.82
Pooled estimate	-9.23 [-11.77, -6.70]	< 0.00001	5.76	0.80
XBDPD vs. csDMARD				
Omitting Pang 2010	-	-	-	-
Pooled estimate	-12.35 [-15.22, -9.48]	< 0.00001	-	-

MD, mean difference; CI, confidence interval; ESR, erythrocyte sedimentation rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHQZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; DGNTDPD, DGNTD + csDMARD [Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug]; XBDPD, XBD + csDMARD [Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug].

RF:

Excluded studies	SMD 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-0.74 [-1.48, 0.00]	0.05	-	-
Omitting Yuan *et al*, 2019	-0.98 [-1.37, -0.58]	< 0.00001	-	-
Pooled estimate	-0.93 [-1.27, -0.58]	< 0.00001	0.00	0.00
DGNTDPD vs. csDMARD				
Omitting Zheng *et al* 2015	-0.89 [-1.42, -0.36]	0.001	-	-
Omitting Sheng, 2013	-1.55 [-2.13, -0.97]	< 0.00001	-	-
Pooled estimate	-1.21 [-1.86, -0.56]	0.0003	0.14	0.63
SMPPD vs. csDMARD				
Omitting Zhang 2019	-13.61 [-21.19, -6.04]	0.0004	40.79	0.99
Omitting Li 2017	-7.09 [-10.64, -3.31]	0.0002	8.71	0.98
Omitting Yang 2011	-13.50 [-21.08, -5.92]	0.0005	40.82	0.99
Omitting Li *et al* 2014	-2.73 [-5.39, -0.07]	0.04	5.35	0.98
Pooled estimate	-7.72 [-11.38, -4.06]	< 0.0001	11.89	0.98
XBDPD vs. csDMARD				
Omitting Pang 2010	-	-	-	-
Pooled estimate	-0.54 [-0.94, -0.14]	0.009	-	-

SMD, standard mean difference; CI, confidence interval; RF, rheumatoid factor; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHQZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; DGNTDPD, DGNTD + csDMARD [Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug]; XBDPD, XBD + csDMARD [Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug].

DAS-28:

Excluded studies	SMD 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Yuan *et al*, 2019	-	-	-	-
Pooled estimate	-0.65 [-1.39, 0.09]	0.08	-	-
SMPPD vs. csDMARD				
Omitting Zhang 2019	0.03 [-0.49, 0.55]	0.91	-	-
Omitting Li 2016	-0.57 [-1.02, -0.11]	0.01	-	-
Pooled estimate	-0.28 [-0.86, 0.30]	0.34	0.11	0.65
XBDPD vs. csDMARD				
Omitting Pang 2010	-	-	-	-
Pooled estimate	-0.88 [-1.29, -0.47]	< 0.0001	-	-

SMD, standard mean difference; CI, confidence interval; DAS-28, disease activity score in 28 joints; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHQZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug]; XBDPD, XBD + csDMARD [Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug].

TNF-α:

Excluded studies	SMD 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-	-	-	-
Pooled estimate	-0.72 [-1.10, -0.33]	0.0003	-	-
DGNTDPD vs. csDMARD				
Omitting Jiang *et al* 2020	-0.91 [-1.37, -0.45]	0.0001	-	-
Omitting Ge *et al* 2017	-1.77 [-2.34, -1.19]	< 0.00001	-	-
Pooled estimate	-1.32 [-2.16, -0.48]	0.002	0.00	0.81
SMPPD vs. csDMARD				
Omitting Li 2016	-	-	-	-
Pooled estimate	-0.53 [-1.06, -0.00]	0.05	-	-

SMD, standard mean difference; CI, confidence interval; TNF-α, tumor necrosis factor-α; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHQZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; DGNTDPD, DGNTD + csDMARD [Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug].

IL-1 :

Excluded studies	SMD 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-	-	-	-
Pooled estimate	-1.08 [-1.48, -0.68]	< 0.00001	-	-
DGNTDPD vs. csDMARD				
Omitting Jiang *et al* 2020	-1.45 [-1.95, -0.96]	< 0.00001	-	-
Omitting Ge *et al* 2017	-2.50 [-3.15, -1.85]	< 0.00001	-	-
Pooled estimate	-1.95 [-2.98, -0.93]	< 0.00001	0.46	0.84
SMPPD vs. csDMARD				
Omitting Li 2016	-	-	-	-
Pooled estimate	-0.61 [-1.14, -0.08]	0.02	-	-

SMD, standard mean difference; CI, confidence interval; IL-1, interleukin-1; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHQZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; DGNTDPD, DGNTD + csDMARD [Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug].

SJC:

Excluded studies	MD 95%CI	P-value	tau^2	I^2
SMPPD vs. csDMARD				
Omitting Zhang 2019	-1.71 [-3.89, 0.46]	0.12	1.99	0.77
Omitting Li 2017	-1.88 [-3.63, -0.12]	0.04	1.14	0.64
Omitting Yang 2011	-0.93 [-1.26, -0.61]	< 0.00001	0.03	0.44
Pooled estimate	-1.14 [-1.73, -0.55]	0.0002	0.16	0.67
XBDPD vs. csDMARD				
Omitting Pang 2010	-	-	-	-
Pooled estimate	-1.97 [-2.29, -1.65]	< 0.00001	-	-

MD, standard mean difference; CI, confidence interval; SJC, swollen joint count; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug]; XBDPD, XBD + csDMARD [Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug].

TJC:

Excluded studies	MD 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-	-	-	-
Pooled estimate	-2.93 [-3.62, -2.24]	< 0.00001	-	-
SMPPD vs. csDMARD				
Omitting Zhang 2019	-1.05 [-2.42, 0.31]	0.13	0.65	0.52
Omitting Li 2017	-1.73 [-2.45, -1.02]	< 0.00001	0.00	0.00
Omitting Yang 2011	-1.08 [-2.08, -0.08]	0.03	0.45	0.85
Pooled estimate	-1.24 [-2.19, -0.30]	0.01	0.48	0.78
XBDPD vs. csDMARD				
Omitting Pang 2010	-	-	-	-
Pooled estimate	-3.86 [-4.52, -3.20]	< 0.00001	-	-

MD, mean difference; CI, confidence interval; TJC, tender joint count; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHQZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug]; XBDPD, XBD + csDMARD [Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug].

MST:

Excluded studies	MD 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-	-	-	-
Pooled estimate	-15.60 [-18.96, -12.24]	< 0.00001	-	-
DGNTDPD vs. csDMARD				
Omitting Zheng *et al* 2015	-	-	-	-
Pooled estimate	-6.76 [-15.65, 2.13]	0.14	-	-
SMPPD vs. csDMARD				
Omitting Li 2017	-20.00 [-29.90, -10.10]	< 0.0001	-	-
Omitting Yang 2011	-19.90 [-21.00, -18.80]	< 0.00001	-	-
Pooled estimate	-19.90 [-20.99, -18.81]	< 0.00001	0.00	0.00
XBDPD vs. csDMARD				
Omitting Pang 2010	-11.61 [-14.56, -8.66]	< 0.00001	-	-
Omitting Zhu 2014	-16.80 [-27.77, -5.83]	0.003	-	-
Pooled estimate	-11.96 [-14.81, -9.11]	< 0.00001	0.00	0.00

MD, mean difference; CI, confidence interval; MST, morning stiffness time; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHQZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; DGNTDPD, DGNTD + csDMARD [Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug]; XBDPD, XBD + csDMARD [Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug].

ACR 20 50 70:

Excluded studies	OR 95%CI	P-value	tau^2	I^2
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-	-	-	-
Pooled estimate	2.63 [1.02, 6.75]	0.04	-	-
DGNTDPD vs. csDMARD				
Omitting Ge *et al* 2015	-	-	-	-
Pooled estimate	0.81 [0.33, 1.99]	0.65	-	-
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-	-	-	-
Pooled estimate	2.25 [1.05, 4.83]	0.04	-	-
DGNTDPD vs. csDMARD				
Omitting Ge *et al* 2015	-	-	-	-
Pooled estimate	1.62 [0.61, 4.25]	0.33	-	-
BHQZDPD vs. csDMARD				
Omitting Ma 2016	-	-	-	-
Pooled estimate	2.01 [0.82, 4.91]	0.12	-	-
DGNTDPD vs. csDMARD				
Omitting Ge *et al* 2015	-	-	-	-
Pooled estimate	8.27 [0.97, 70.73]	0.05	-	-

OR, odds ratio; CI, confidence interval; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHQZDPD, BHSZD + csDMARD [Bahuguzhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; DGNTDPD, DGNTD + csDMARD [Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug].

Table S5 Trim and fill analysis of CRP.

Note: default data input format (theta, se_theta) assumed.

Meta-analysis

Method	Pooled Est	95% CI Lower	Upper	Asymptotic z_value	p_value	No. of studies
Fixed	-1.294	-1.470	-1.118	-14.413	0.000	10
Random	-1.644	-2.311	-0.976	-4.826	0.000	

Test for heterogeneity: Q= 123.776 on 9 degrees of freedom (p= 0.000)

Moment-based estimate of between studies variance = 1.056

Trimming estimator: Linear

Meta-analysis type: Random-effects model

iteration	estimate	Tn	# to trim	diff
1	-1.644	32	1	55
2	-1.787	33	1	2
3	-1.787	33	1	0

Filled

Meta-analysis (exponential form)

Method	Pooled Est	95% CI Lower	Upper	Asymptotic z_value	p_value	No. of studies
Fixed	0.225	0.190	0.266	-17.577	0.000	11
Random	0.166	0.083	0.335	-5.033	0.000	

Test for heterogeneity: Q= 169.821 on 10 degrees of freedom (p= 0.000)

Moment-based estimate of between studies variance = 1.295

CRP, C-reactive protein; CI, confidence interval.

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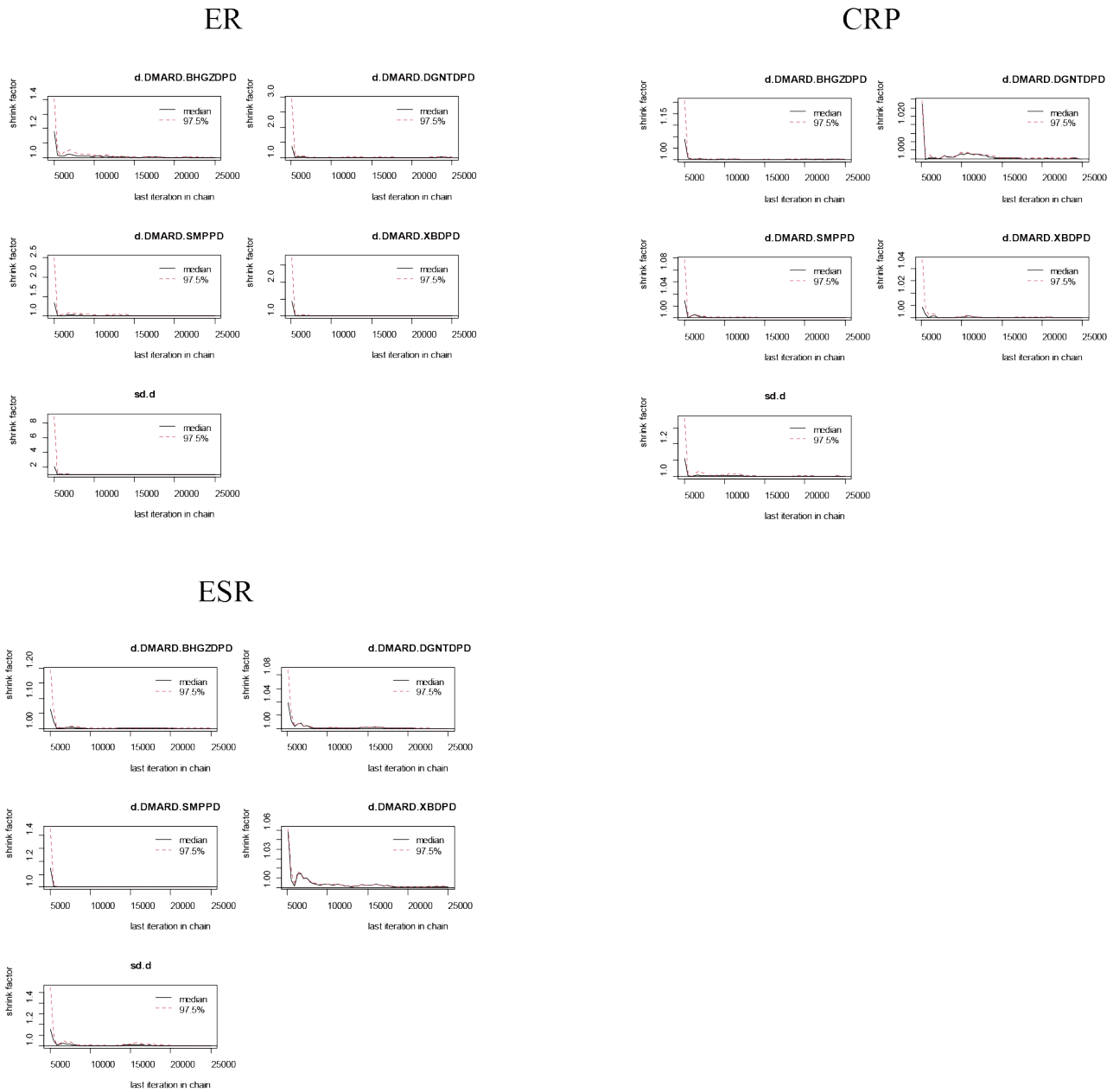

Figure S2 Brooks-Gelman-Rubin Diagnosis. (ER, effective rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; BHGZDPD, BHGZD + csDMARD [Baihuguizhi decoction + conventional synthetic disease-modifying anti-rheumatic drug]; DGNTDPD, DGNTD + csDMARD [Dangguiniantong decoction + conventional synthetic disease-modifying anti-rheumatic drug]; SMPPD, SMP + csDMARD [Simiao pill + conventional synthetic disease-modifying anti-rheumatic drug]; XBDPD, XBD + csDMARD [Xuanbi decoction + conventional synthetic disease-modifying anti-rheumatic drug])

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Table S6

Number	Targets	Times
1	ESR1	13
2	RELA	13
3	EGFR	12
4	FOS	11
5	CCND1	10
6	MAPK8	10
7	NR3C1	10
8	AR	8
9	IL6	8
10	CASP8	7
11	ERBB2	7
12	GSK3B	7
13	MYC	7
14	PRKCA	7
15	RB1	6
16	VEGFA	6
17	BCL2	5
18	CASP3	5
19	IKBKB	5
20	NOS3	5
21	PGR	5
22	CYP1A1	4
23	HIF1A	4
24	ICAM1	4
25	IRF1	4
26	NFKBIA	4
27	PPARG	4
28	CASP9	3
29	CAV1	3
30	ERBB3	3
31	ESR2	3
32	IGF2	3
33	IGFBP3	3
34	NFE2L2	3
35	NR3C2	3
36	RAF1	3
37	RXRB	3
38	TP63	3
39	VCAM1	3
40	CCNB1	2
41	CHRM2	2
42	NQO1	2
43	PARP1	2
44	SELE	2
45	AHR	1
46	ALOX5	1
47	BIRC5	1
48	COL3A1	1
49	CRP	1
50	CTSD	1
51	CYP3A4	1
52	GSTM1	1
53	GSTP1	1
54	HSF1	1
55	HSPB1	1
56	PLAU	1
57	PTGER3	1
58	PTGS1	1
59	RUNX2	1

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Table S7 Common adverse reactions of 4 CHF included in 9 systematic reviews.

Group	Disease	Study	Adverse reactions (n)		Frequency of occurrence (Treatment group/ Control group)	
DGNTD vs. Western medicine	Rheumatoid arthritis	Hu et al, 2021	Digestive system	Gastrointestinal reaction (3), Abnormal liver function (1)	8/280	37/274
			Blood system	-		
			Respiratory system	Dyspnea (2), Cough (1)		
			Nervous system	-		
			Urinary system	Abnormal renal function (1)		
			Cardiovascular system	-		
			Reproductive system	-		
			Skin damage	-		
			Damage of facial features	-		
SMP used alone vs. Western medicine	Gout	Zhou et al, 2016	Digestive system	Gastrointestinal reaction (5)	5 /123	20 /121
			Blood system	-		
			Respiratory system	-		
			Nervous system	-		
			Urinary system	-		
			Cardiovascular system	-		
			Reproductive system	-		
			Skin damage	-		
			Damage of facial features	-		
SMP used alone vs. Colchicine	Gout	Li et al, 2019	Digestive system	Gastrointestinal reaction (11)	14/239	62/234
			Blood system	Myelosuppression (1)		
			Respiratory system	-		
			Nervous system	Peripheral muscular neuropathy (1)		
			Urinary system	-		
			Cardiovascular system	-		
			Reproductive system	-		
			Skin damage	Drug eruption (1)		
			Damage of facial features	-		
SMP used alone vs. Colchicine	Acute gouty arthritis	Du et al, 2015	Digestive system	Gastrointestinal reaction (1)	4/95	22/93
			Blood system	-		
			Respiratory system	-		
			Nervous system	-		
			Urinary system	-		
			Cardiovascular system	-		
			Reproductive system	-		
			Skin damage	-		
			Damage of facial features	-		
			other	Not specified (3)		
SMP vs. Western medicine	Gouty arthritis	Du et al, 2015	Digestive system	Gastrointestinal reaction (7)	10/296	87/301
			Blood system	-		
			Respiratory system	-		
			Nervous system	-		
			Urinary system	-		
			Cardiovascular system	-		
			Reproductive system	-		
			Skin damage	-		
			Damage of facial features	-		
			other	Not specified (3)		
SMP + External application of TCM vs. Western medicine	Gouty arthritis	Yi, 2017	Digestive system	Gastrointestinal reaction (7)	7/407	138/394
			Blood system	-		
			Respiratory system	-		
			Nervous system	-		
			Urinary system	-		
			Cardiovascular system	-		
			Reproductive system	-		
			Skin damage	-		
			Damage of facial features	-		
XBD used alone or combined with Western medicine vs. Western medicine	Gouty arthritis	Ping, 2015	Digestive system	Gastrointestinal reaction (2)	2/102	10/102
			Blood system	-		
			Respiratory system	-		
			Nervous system	-		
			Urinary system	-		
			Cardiovascular system	-		
			Reproductive system	-		
			Skin damage	-		
			Damage of facial features	-		
BHGZD used alone or combined with Western medicine vs. Western medicine	Rheumatoid arthritis	LAM, 2017	Digestive system	Gastrointestinal reaction (3), Abnormal liver function (7), Loss of appetite (2)	12/87	22/85
			Blood system	-		
			Respiratory system	-		
			Nervous system	Dizzy (1)		
			Urinary system	-		
			Cardiovascular system	-		
			Reproductive system	-		
			Skin damage	-		
			Damage of facial features	-		
SMP combined with Western medicine vs. Western medicine	Rheumatoid arthritis	Wang, 2020	Digestive system	Gastrointestinal reaction (10), Abnormal liver function (1)	13/451	333/451
			Blood system	-		
			Respiratory system	-		
			Nervous system	-		
			Urinary system	-		
			Cardiovascular system	-		
			Reproductive system	-		
			Skin damage	Erythema (2)		
			Damage of facial features	-		

DGNTD: Dangguiniantong decoction; SMP: Si miao pill; BHGZD: Baihuguizhi decoction; XBD: Xuanbi decoction; n: Number

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