Journal of Traditional and Complementary Medicine 12 (2022) 437–446

Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

Conventional disease-modifying anti-rheumatic drugs combined with Chinese Herbal Medicines for rheumatoid arthritis: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 5 September 2021
Received in revised form
4 January 2022
Accepted 22 January 2022
Available online 26 January 2022

Keywords:
Chinese herbal medicine
Rheumatoid arthritis
Conventional disease-modifying anti-rheumatic drugs
Adverse event
Efficacy

ABSTRACT

Rheumatoid Arthritis (RA) remains a major global public health challenge. Disease-modifying anti-rheumatic drugs (DMARDs) are standard therapeutic drugs for RA. Conventional DMARDs (c-DMARDs) are a subgroup of approved synthetic DMARDs. The c-DMARDs experienced lesser response with longer disease duration or drug exposure, and unwanted adverse events (AEs). The combination treatments (CTs) of c-DMARDs and Chinese Herbal Medicines (CHMs) were often used in RA clinical trials for increasing the therapeutic effectiveness and reducing the AEs. This systematic review aimed to evaluate the efficacy and safety of the CTs for RA. Databases were searched from inception to October 2020 for identification of randomized controlled trials (RCTs) that investigated the CTs in the management of RA. Twenty-three RCTs with 2,441 participants were included. The assessments and analyses found CTs improved American College of Rheumatology (ACR) 20 (RR: 1.33, 95% CI [1.21, 1.45], 10 studies, n=1,075) and alleviated AEs (RR: -0.40, 95% CI [-0.30, -0.53], 19 studies, n=2,011) in comparison with c-DMARDs. The CTs also significantly improved RA symptoms and patient-reported outcomes; reduced disease activity score (DAS) 28, serum acute-phase reactants and RA biomarkers. The five most commonly used herbs in included studies were *Angelicae Sinensis* Radix, *Paeoniae* Radix Alba, *Cinnamomi* Ramulus, *Glycyrrhizae* Radix et Rhizoma, and *Clematidis* Radix et Rhizoma. Pharmacological studies indicated these CHMs could contribute to the outcomes. The integrated CHMs potentially increased the overall effectiveness of c-DMARDs and alleviated AEs in management of RA. Large sample and rigorously designed RCTs are required for future studies.

Section

Chinese herbal medicine.

Taxonomy

ICD: FA20.Z Rheumatoid arthritis, serology unspecified.
ICD: International Statistical Classification of Diseases and Related Health Problems.

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Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

https://doi.org/10.1016/j.jtcme.2022.01.005

Abbreviations

AA	Adjuvant arthritis
ACPAs	Anti-citrullinated proteins/peptides antibodies
ACR	American College of Rheumatology
AEs	Adverse events
ALT	Alanine aminotransferase
ASR	Angelica sinensi radix
AST	Aspartate aminotransferase
CAM	Complementary and alternative medicine
CHMs	Chinese Herbal Medicines
c-DMARDs	Conventional disease-modifying anti-rheumatic drugs
CI	Confidence interval
COX-2	Cyclooxygenase-2
CR	Cinnamomi ramulus
CRP	C-reactive protein
CRR	Clematidis Radix et Rhizoma
CT	Combination treatment
DALYs	Disability adjusted life years
DAS28	Disease activity score in 28 joints
DGA	Doctor's global assessment
DMS	Duration of morning stiffness
EP-GPCRs-cAMP	E-prostanoid receptors-G protein-coupled rececptors-cyclic adenosine monophosphate
ERE1/2	Extracellular signal-regulated kinase 1/2
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GR	Glycyrrhizae Radix et Rhizoma
GS	Grip strength
HAQ	Health assessment questionnaire
IFN-ϒ:	Interferon-ϒ
IL-6	Interleukin-6
ILG	Isoliquiritigenin
iNOS	Inducible nitric oxide synthase
ITT	Intention-to-treat
IV	Inverse variance
JNK1/2	c-Jun N-terminal kinase 1/2
LEF	Leflunomide
LG	Liquiritigenin
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
MD	Mean difference
MIP-2	Macrophage inflammatory protein-2
MTX	Methotrexate
NF-κB	Nuclear factor kappa B
NO	Nitric oxide
NSAIDs	Nonsteroidal anti-inflammatory drugs
PGA	Patient's global assessment
PGE2	Prostaglandin E2
PRA	Paeoniae Radix Alba
PROs	Patient-reported outcomes
RA	Rheumatoid arthritis
RCTs	Randomized controlled trials
RE	Random effect
RF	Rheumatoid factor
RR	Risk ratio
SJC	Swollen joint count
SMD	Standard mean difference
SSZ	Sulfasalazine
TGP	Total glucosides of paeony
TJC	Tender joint count
TLR	Toll-like receptor
TNF-α:	Tumor necrosis factor-α
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease which occurs in multiple small joints resulting in pain, swelling, functional limitation, and causing disability, death, and socioeconomic burdens.[1] Globally, it was estimated nearly 20 million prevalent cases of RA, and 1.2 million incidences of RA with global disease burden of 3.4 million disability adjusted life years (DALYs) lost in 2017. The prevalence rate and incidence rate are higher in women than those in men. The rates peak at ages 70–74 for women and 75–79 for men worldwide. RA remains a major challenge in global public health.[2]

American College of Rheumatology (ACR) developed a 'core set' of outcome measurements including swollen joint count (SJC), tender joint count (TJC), doctor's global assessment (DGA), patient's global assessment (PGA), pain and physical function, C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF) or antibodies against citrullinated proteins/peptides (ACPAs), which is proposed to identify RA patients for clinical trials and aid in diagnosis.[3,4] The revised ACR classification criteria 1987 and 2010 versions are used in RA trials worldwide.[4,5]

The ACR20 is defined as at least 20% improvement in both of TJC and SJC, plus in three out of other above outcomes at any end-point in time. The ACR20 has become a standardized primary outcome measure in RA trials internationally and used by the US Food and Drug Administration (FDA) to evaluate new therapies for RA. The ACR50 and ACR70 are developed to incorporate different levels of improvements in RA trials.[6]

The disease-modifying anti-rheumatic drugs (DMARDs) aim to attenuate signs and symptoms of RA, improve physical function, and prevent progression of joint damage. The drugs are classified into synthetic and biologic subgroups, and have been used as the standard treatment for RA. Conventional DMARDs (c-DMARDs) are one of the divisions of synthetic DMARDs identified for the treatment of RA based on empiric testing, and their target is unknown. It mainly includes methotrexate (MTX), Leflunomide (LEF), and Sulfasalazine (SSZ). The combination of MTX (25 mg/week) and glucocorticoids as first-line treatment is recommended by ACR and European League Against Rheumatism (EULAR) for the newly diagnosed RA, and has achieved efficacy of up to 40–50% at low disease activity or remission.[7] Despite advanced DMARDs and optimized therapeutic strategies, about 20–25% of RA patients are not able to achieve low disease activity in developed countries and even more so in undeveloped countries.[8] All DMARDs have experienced lesser response with longer disease duration or drug exposure, and unwanted adverse events (AEs) especially in combinational drug treatments.[7]

Complementary and alternative medicine (CAM) as adjuvant treatment is popular among people who suffer chronic diseases including RA.[9] Chinese Herbal Medicines (CHMs) are one of the preferences in CAM. Great majority of the CHMs are plant origin, traditional usage in China, and well documented. Chinese Herbal Medicines have been used for treating arthritis including

conditions consistent with RA as early as AD 206 in China and other Asian countries. In last two decades, CHMs have been used in combination with c-DMARDs in RA clinical trials in order to enhance the therapeutic effects and attenuate the AEs of c-DMARDs.[10] However, these clinical studies were conducted across different populations, settings, and treatment regimens. There are lacking current literatures on systematic review of specifically the clinically important c-DMARDs combined with CHMs in the treatment of RA.

This systematic review included randomized controlled trials (RTCs) that employed the combinational treatments (CTs) of c-DMARDs and CHMs in the management of RA. It aimed to determine the efficacy and safety of CTs in the management of RA, and to identify which group of CHMs could have potential therapeutic effects in RA. The findings of this study would provide up-to-date information of evidence-based CTs in the treatment of RA for clinicians and patients on the therapeutic decision making.

2. Methods

The procedures of this systematic review and meta-analyses were following the PRISMA statement recommends preferred reporting items for systematic reviews and meta-analyses.[11]

2.1. Study inclusion and exclusion criteria

Included studies were RCTs that employed c-DMARDs combined with CHMs in experimental arms in comparison with the c-DMARDs as control arms, regardless of blinding and reported at least one or more listed primary or secondary outcomes below. Participants were age $\geq$18 years old and were diagnosed with RA in accordance with ACR/EULAR classification criteria. There were no restrictions on gender and race. Oral administration of CHMs in the forms of decoctions, granules, capsules, and pills, or injections of manufactured CHM extracts were included. The CHMs could be used as single herb or in multi-ingredients formulae. Controlled medicines were c-DMARDs monotherapy or combination of c-DMARDs. Studies used additional glucocorticoids or nonsteroidal anti-inflammatory drugs (NSAIDs) as adjuvants to c-DMARDs were included.

The primary outcomes in this review were the ACR 20/50/70 and AEs. The secondary outcomes included disease activity score (DAS) 28, TJC, SJC, duration of morning stiffness (DMS), grip strength (GS), PGA, DGA, health assessment questionnaire (HAQ), pain visual analogue scale (VAS), acute-phase reactants (ERS and CRP) and RA biomarkers (RF and ACPAs).

Participants were age <18 years old, or not diagnosed with RA in accordance with ACR/EULAR classification criteria; or CHMs that were used in fumigation or combined with other traditional therapies including acupuncture, moxibustion, cupping, pricking, and blood-letting; or c-DMARDs were not in the controlled medicines were excluded. Non-RCT clinical studies, animal studies, duplicative studies, reviews, conference abstracts, and incomplete or invalid data were excluded.

2.2. Electronic search methods for study identification and selection

Google Scholar, PubMed, CNKI, Cochrane CENTRE, and WanFang databases were searched from its inception to October 2020. Three groups of search terms including disease, interventions and study design were used to form a search strategy by using the Boolean Operators 'or' and 'and' for searching each database (see supplementary 1). The reference lists from retrieved articles were also screened for potential eligible studies.

Three reviewers (RH, HCR, and STZ) independently searched databases and screened titles and abstracts to identify papers that were eligible for further assessment with full-text articles. Full-text articles were retrieved for assessment of eligibility of inclusion.

2.3. Data extraction process

Two reviewers (RH and HCR) independently extracted data from the included studies by using a pre-designed data extraction form. The data extraction form mainly included the following aspects: general information of author and publication, study design and methods, participants, duration of trial, interventions, outcomes, the ingredients of the CHM formulae, and AEs.

2.4. Risk of bias assessment

The included studies were independently assessed by two reviewers (RH and HCR) based on the guidelines of Cochrane Handbook for Systematic Reviews Version 5.1.0 [12] to determine risk of bias in domains of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. The outcome of assessment for each category was labeled low (L) risk of bias with proper methods, or high (H) risk of bias with improper methods, or unclear (U) which indicates insufficient information to judge the potential risk of bias.

During the processes of identifications and selections of studies, data extractions, and risk of bias assessments, disagreements between the reviewers were resolved through discussions or mediating by DS and MC.

2.5. Statistical analysis

Revman V.5.4 software was used for meta-analysis if two or more studies reported the same outcome. Inverse variance (IV) was used in analysis method. Risk ratio (RR) was calculated for dichotomous data while mean difference (MD) or standardized mean difference (SMD) was used for continuous data with 95% confidence interval (CI). Random effects (RE) model was applied. The Z-test was used for assessing overall effects with a significance level of $p < 0.05$. The I^2 represented the proportion of heterogeneity. It indicated substantial heterogeneity if I^2 was more than 50%.[13] Missing data from the original studies was analyzed with the intention-to-treat (ITT) principle. When the same outcome was reported by greater than 10 or equal studies, funnel plot was used to assess publication bias.

3. Results

The results were reported in narrative and quantitative as below.

3.1. Study selection

A total of 2044 records through electronic searches were identified. Forty-six duplicates were excluded. A total of 1647 out of 1998 studies were excluded by screening the titles and abstracts, and 332 studies were excluded after assessing 355 full-texts. A total of 23 RCTs met the inclusion criteria.[13–35] A flow diagram of the study selection was in Fig. 1.

3.2. Study description

All 23 included studies were performed in hospitals, China. Twelve out of 23 studies were supported by state or national fundings of China.[13,15,19,21–26,31,33,35] Only two studies were conducted in the setting of multi-centers.[20,23] Twenty studies were

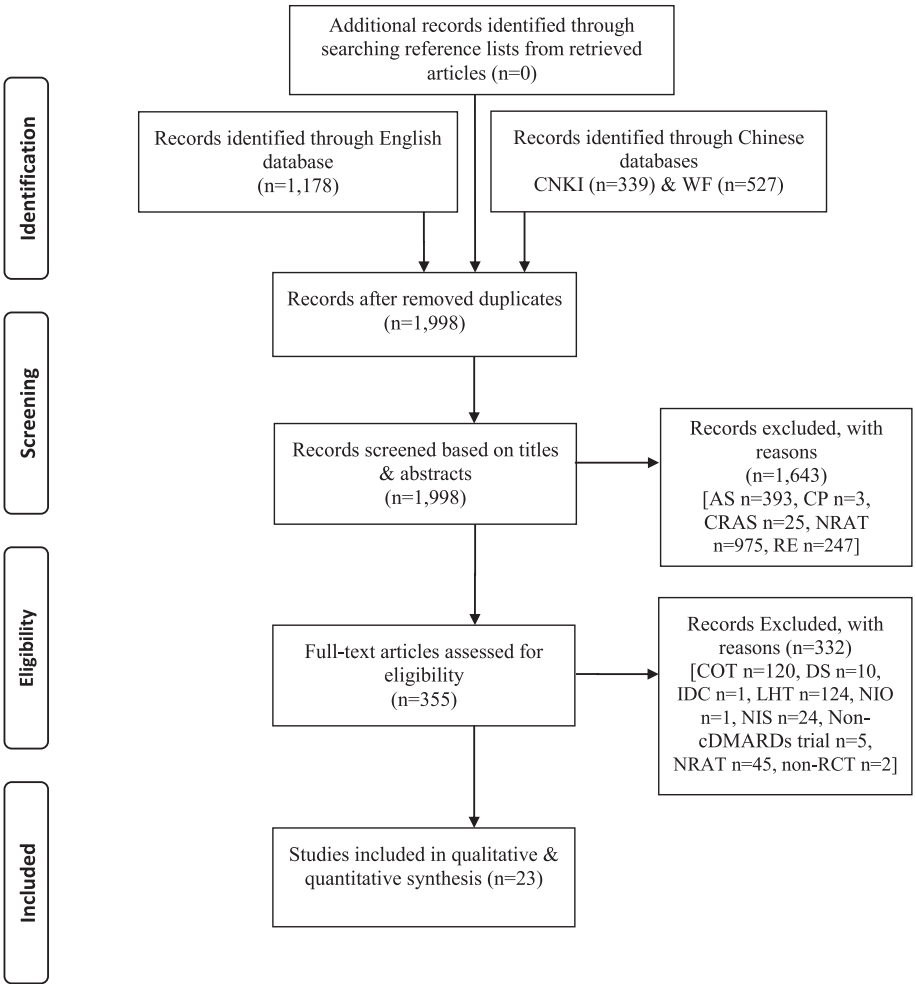

Fig. 1. Flow diagram of the search and selection process of RCTs of c-DMARDs combined with Chinese Herbal Medicines for rheumatoid arthritis AS: animal study; c-DMARDs: conventional DMARDs; COT: combined with other treatments (acupuncture, moxibustion, cupping, pricking, and blood-letting); CP: conference paper; CRAS: Children RA study; DS: duplicative study; IDC: invalid diagnosis criteria; LHT: local herbal therapy (such as fumigation or bath); NIO: non-interest outcome; NIS: non-interest study (HM versus. c-DMARDs, or HM versus. Placebo); NRAT: non-rheumatoid arthritis trial; RE: review.

published in Chinese, and three studies were published in English. All included studies investigated CTs compared to c-DMARDs alone in the treatments of RA. Four included studies[13,20,23,32] also had a second test arm using the CHMs alone. The data were not included in this study. Intervention duration was from 4 weeks to 48 weeks. The characteristics of the included studies were listed in Table 1.

3.3. Study participants

A total of 2441 participants with 650 men and 1791 women were enrolled. The ratio of man and woman was 1:2.8. Five out of the 23 studies reported the mean age of participants was between 50 and 66 years old,[18,20,21,23,25] while others were range of 30–49 years old (mean age). All participants were diagnosed with RA in accordance with 1987–2010 versions of ACR/EULAR classification criteria. The mean disease duration ranged from four months to 7 years (Table 1).

3.4. Study interventions

The CTs versus c-DMARDs alone were conducted in the 23 included studies.

Chinese herbal decoctions which consisted of mixed herbs were used in 15 studies.[13,14,16,19,21,22,24–28,30,33] Herbal extract granules were used in one study.[31] Manufactured herbal tablets/capsules were used in seven studies (Table 1).[15,20,23,29,32,34,35] A total of 99 individual CHMs including six insect products and two minerals were used in included studies. The five most commonly used CHMs in the included studies (n) were *Angelicae Sinensis* Radix (n = 10), *Paeoniae* Radix Alba (n = 10), *Cinnamomi* Ramulus (n = 9), *Glycyrrhizae* Radix et Rhizoma (n = 8), and *Clematidis* Radix et Rhizoma (n = 7). The name of herbal formulae and the pharmacognostic name of 99 individual CHMs appeared in this review were listed in Table 1 and supplementary 2 respectively.

Conventional DMARDs of MTX, LEF, and SSZ were used in the included studies. Monotherapy of MTX regime was used in 13 studies,[13,15,17,19–21,23,24,26–29,33,35] while three studies used LEF.[16,18,34] Combination of c-DMARDs was employed in seven studies.[14,22,25,27,28,31,32] Additional NSAIDs included Celecoxib, Diclofenac Sodium as adjuvants to c-DMARDs were used in six studies,[19,25,29–31,33] and Prednisone was used in two studies[17,31] (Table 1).

3.5. Study outcome measures

Outcomes and number of studies (n) were: ACR20 (n = 10), in

Table 1
The characteristics of 23 included studies.

Reference No. (Sample size: T/C)	Gender (male) T/C; Age T/C; Course of RA T/C	Test arm (CHM + CM): CHM name; dosage; duration. (CM same as control arm)	Control arm: CM name dosage; duration	Outcomes
13 (56/56)	19/21; 32.73 ± 11.34/ 36.52 ± 14.57; 7.12 ± 3.72/ 6.93 ± 4.13 years	*Sanbitang* decoction; one/day, take 6 days/week; 16 weeks.	MTX 7.5 mg, twice a week; 16 weeks.	DAS28; HAQ; pain-VAS; ESR; CRP; ACPAs.
14 (30/30)	8/9; 49.69 ± 11.84/ 50.16 ± 12.14; 169.38 ± 25.84/ 155.47 ± 24.94 days	*Bizhengning* decoction; one/day; 12 weeks.	MTX 10 mg/weeks, LEF 10 mg/day; 12 weeks.	ACR20; ACR50; ACR70; pain-VAS; TJC; SJC; MS; GS; ESR; CRP; RF; AEs.
15 (40/40)	28/28; 36.8 ± 9.3/36.8 ± 9.3; 3.7 ± 2.3 years	*Xinfeng* capsule; 3 capsules, tid; 12 weeks.	MTX 10 mg/week; 12 weeks.	Efficacy; PGA; TJC; STC; MS; DAS28; ESR; CRP; RF; AEs.
16 (44/44)	20/26; 47.3 ± 11.2/48.2 ± 10.1; 5.5 ± 1.6/5.3 ± 1.4 years	*Bizhengzinifang* decoction; one/ day; 24 weeks.	LEF 20 mg/day; 24 weeks.	ACR20; ACR50; ACR70; MS; DAS28; ESR; CRP; RF.
17 (20/18)	3/2; 42.25 ± 15.24/ 42.00 ± 13.00; 8.00 ± 6.00 months	*Fengshikang* decoction; one/day; 4 weeks.	MTX 10 mg/weeks, Prednisone 4 mg/day; 4 weeks.	ESR; CRP; RF.
18 (30/30)	14/17; 66 ± 3.1/64 ± 2.0; 20 ± 8.5 months	*Duhuojishengjiajian* decoction; one/ day; 12 weeks.	LEF 20 mg/day; 12 weeks.	Efficacy; TJC; SJC; MS; ESR; CRP; RF; AEs.
19 (36/36)	10/8; 37.5 ± 11.9/38.6 ± 12.7; ns	*Zhudanxitongfengfang jiajian* decoction; one/day; 12 weeks.	MTX 10 mg/week; plus NSAIDs; 12 weeks	ACR20; TJC; STC; MS; ESR; CRP; RF; AEs
20 (80/80)	19/13; 51.76 ± 11.67/ 48.62 ± 13.01; 5.46 ± 6.11/ 5.03 ± 4.24 years	*Kunxian* capsule; 0.3g–0.6g each time, tid; 12 weeks.	MTX 10 mg/week; 12 weeks.	ACR20; ACR50; pain-VAS; TJC; SJC; GS; MS; DAS28; ESR; CRP; RF; ACPAs; AEs
21 (45/45)	7/8; 56 ± 8/55 ± 8; 13 ± 13 years	*Sanhuangyilong* decoction; one/ day, 4 weeks.	MTX; 10–15 mg/week; 4 weeks	DAS28; CRP; ESR
22 (40/20)	9/5; 41.5 ± 11.2/40.6 ± 13.2; 2.8 ± 1.3 years	*Fengshi* No.1 liquid; 30 ml each time, bid; 24 weeks.	CHM placebo 30 ml each time, bid; MTX 5–10mg/ week; SSZ 0.5–1.0g, tid; 24weeks.	Efficacy; TJC; STC; MS; GS; ESR; CRP; RF; AEs
23 (69/69)	14/13; 50.6 ± 8.6/51.0 ± 10.3; 76.3 ± 92.3/58.8 ± 88.7 months	*Tripterygium wilfordii* Hook F tablet; 20 mg, tid; 24 weeks.	MTX 7.5 mg increasing to 12.5 mg (within 4 weeks); 24 weeks.	ACR20; ACR50; ACR70; PGA; DGA; TJC; STC; DAS28; ESR; CRP; AEs
24 (84/84)	32/33; mean 43/mean 45; 0.3 –146/0.8–142 months	*Chinese herbal medicine* decoction; one/day; 4 weeks.	MTX 10 mg/week; 4 weeks.	Efficacy, TJC, SJC, AEs
25 (74/74)	9/7; 53.12 ± 13.07, 51.50 ± 12.65; 51.30 ± 27.23/ 52.07 ± 27.05 months	*Traditional Chinese Medicine* decoction; one/day; 12 weeks.	MTX 7.5 increasing to 15mg/week, LEF 10 mg/ day; plus, Diclofenac 75 mg/day; 24 weeks.	TJC; SJC; DAS28; ESR
26 (120/120)	31/33; 31.62 ± 14.28/ 33.93 ± 12.46; 6.56 ± 4.63 years	*Bushenquhantang* decoction; one/ day; 24 weeks.	MTX 10 mg/week; 24 weeks.	ACR20; ACR50; ACR70; DGA; PGA; TJC; SJC; GS; MS; DAS28; ESR; CRP; AEs;
27 (47/41)	8/6; 42.82 ± 12.45/ 44.78 ± 12.38; 3. 8 ± 6. 2 years	*Yangxuetongluofang* decoction; one/day; 12 weeks.	MTX 10 mg/week; LEF 10 mg/day; 12 weeks.	ACR20; TJC; SJC; MS; ESR; CRP; RF; AEs
28 (28/28)	10/9; 35.5 ± 6.6/35.9 ± 6.9; 4.9 ± 2.8/4.7 ± 2.5 years	*Leifengtang jiajian* decoction; one/ day; 12 weeks.	MTX 10 mg/week; LEF 10 mg/day; 12 weeks.	Efficacy; AEs;
29 (35/35)	8/7; 42.5 ± 15.1/52.7 ± 6.8; 42.5 ± 15.1 months	*Tripterygium wilfordii* polyglycosides tablet; 10 mg, tid; 12 weeks. MTX: 7 .5 mg/week. Others the same as control	MTX 15 mg/week; plus Indomethacin 0.1g, tid or Diclofenac 25 mg, tid; 12 weeks	PGA; DGA; TJC; SJC; GS; MS; ESR; RF; AEs
30 (61/61)	22/21; 36.91 ± 4.03/ 37.10 ± 3.64; 4.48 ± 1.31/ 4.76 ± 1.3 years	*Xuanbidajing* decoction; one/day; 12 weeks.	LEF 20 mg/day; plus Clofenac 20 mg/day; 12 weeks.	Efficacy; SJC; MS; ESR; CRP; RF
31 (79/80)	16/18; 47.59 ± 14.43/ 44.70 ± 16.41; 6.46 ± 6.92/ 7.18 ± 8.37 years	Extract of *Artemisia annua* L.) granules; 30g, qd; 48 weeks.	LEF 10 mg/day; MTX 7.5 mg increasing to 15 mg/ week; prednisone and celecoxib on as-needed basis; 48 weeks	ACR20; TJC; SJC; ESR; CRP; RF; ACPAs; AEs
32 (120/60)	38/18; 37.1 ± 11.5/36.5 ± 10.4; 2.9 ± 1.6/2.8 ± 1.2 years	*Xiatianwu* tablet; 0.3g, tid; 12 weeks.	LEF 20 mg/day; SSZ 1g, bid; plus Celecoxib 0.2 g, bid; 12 weeks.	Efficacy; TJC; STC; MS; GS; ESR; CRP; RF
33 (35/33)	4/3; 42.0 ± 9.6/43.1 ± 9.5; 5.6 ± 1.6/5.8 ± 1.9 years	*Hebifang* decoction; one/day; 24 weeks.	MTX 7. 5 mg increasing to 12.5 mg/week; plus Folic acid 10 mg/week; diclofenac 75 mg, qd; 24 weeks.	ACR20; ESR; CRP; RF; AEs
34 (40/40)	18/14; 31.0 ± 8.9/30.0 ± 9.6; 4.0 ± 3.8/5.0 ± 4.9 years	*Total Glucosides of Paeony* tablet; 0.6g, tid; 12 weeks.	LEF 10 mg/day; 12 weeks.	MS; GS; ESR; CRP; RF; ACPAs
35 (64/40)	8/4; 42.4 ± 12.6/40.7 ± 11.1; 2.2 ± 0.6/2.0 ± 0.5 years	*Xiatianwu* tablet; 0.6 g, tid; 12 weeks.	MTX 10 mg/week; 12 weeks.	ACR20; ACR50; ACR70; ESR; CRP; RF; ACPAs; AEs

ACPAs: Anti-citrullinated peptide antibodies; ACR: American college of Rheumatology; AEs: adverse events; CHM: Chinese Herbal Medicine; CM: conventional medicine (c-DMARDs or combined with NSAIDs/Steroid); CRP: C-reactive protein; DAS28: disease activity scores 28-joint counts; DGA: Doctor's global assessment; Efficacy: other assessment criteria rather than ACR; ESR: erythrocyte sedimentation rate; HAQ: GS: grip strength; Health assessment questionnaire; LEF: Leflunomide; MTX: Methotrexate; No.: number; NS: non-specified; NSAIDs: nonsteroidal anti-inflammatory drugs; PGA: patient's global assessment; RF: rheumatoid factor; SJC: swollen joint count; SSZ: Sulfasalazine; T/C: Test arm/Control arm; TJC: tender joint count; VAS: visual analogue scale; qd: once a day; bid: twice a day; tid: three times a day.

which six of them also reported ACR50/70; DAS28 (n = 8); AEs (n = 19); PGA (n = 4); DGA (n = 3); Pain VAS (n = 3); HAQ (n = 6), TJC (n = 15), SJC (n = 16); DMS (n = 13); GS (n = 7); ESR (n = 21); CRP (n = 19); RF (n = 16); and ACPAs (n = 5) (Table 1). In addition, other assessment criteria for therapeutic efficacy were used by seven studies: the 'Guiding Principles for Clinical Research of New Chinese Medicines' in two studies[30,32]; the 'Revised Standard of Curative Effect Evaluation by the Rheumatism Professional

Committee of the Chinese Integrative Medicine Association' in two studies[18,28]; the 'Efficacy Evaluation Standards of Auranofin Treating and Study Co-operation Group' in one study[22]; and two studies used authors' own criteria.[15,24] These data were not included in the meta-analyses.

3.6. Risk of bias assessment

The results of risk of bias assessments for each of included studies were presented in Fig. 2. Twelve studies were judged 'low' risk of sequence generation,[13,21–28,31,33,35] and others were 'unclear' risk. Three studies[20,23,31] owned 'low' risk of allocation concealment. Others had 'unclear' risk. One study used identical placebo in control arm and the blinding was carried out through the trial.[22] It was 'low' risk of performance bias and detection bias. Placebo control wasn't used in other studies which were marked as 'high' risk of performance bias. Assessors/evaluators in two studies were blinded in the trials.[23,31] These two studies were 'low' risk of detection bias. Other studies were 'high' risk of detection bias on subjective outcomes and 'low' risk on objective outcomes such as serological tests that were performed by laboratory technicians who usually weren't participation in trials. Six studies were judged 'high' risk of attrition bias with breached the principle of 'intent to treat',[13,15,19,25,31,33] other studies were 'low' risk. Non-protocols of the included studies were retrievable. Two studies failed to report all the pre-specified outcomes in the 'Results' section. They were 'high' risk of selection bias,[25,27] and others were 'unclear' risk. The baselines in all included studies were reported balance between groups, the 'other sources of bias' was 'low' risk in all included studies.

3.7. Meta-analyses

Meta-analyses were conducted in the following outcomes, and presented in Table 2. The forest plots for each outcome were in supplementary 3, and funnel plots for relevant outcome were in supplementary 4.

3.7.1. ACR20

Ten studies reported ACR20 with 1075 participants. The CTs significantly improved the response of ACR20 (RR: 1.36, 95% CI [1.24, 1.48], I^2 = 14%) (Table 2). Funnel plot presented graphic symmetry (Supplementary 4A).

3.7.2. ACR50

Six studies reported ACR50 with 790 participants. The pooling result was in favor of the CTs (RR: 1.40, 95% CI [0.99, 1.99], $I^2 = 65\%$) (Table 2).

3.7.3. ACR70

Data of ACR70 were available in six studies with 718 participants. The pooling result showed the CTs significantly increased ACR70 response (RR: 1.83, 95% CI [1.19, 2.83], $I^2 = 44\%$) (Table 2).

3.7.4. DAS28

The DAS28 is commonly used for quantitative assessment of the disease activity and the disease states. One study presented DAS28 with dichotomous data.[20] Seven studies reported DAS 28 with continuous data, and were pooled. The CTs significantly improved outcome of DAS28 (reduction of mean score) (MD: −1.27, 95% CI [−1.84, −0.69], $I^2 = 94\%$) with 896 participants (Table 2).

3.7.5. PGA

In patient-reported outcomes (PROs), PGA is commonly reported in RA trials. It reflects the perception of patient on the

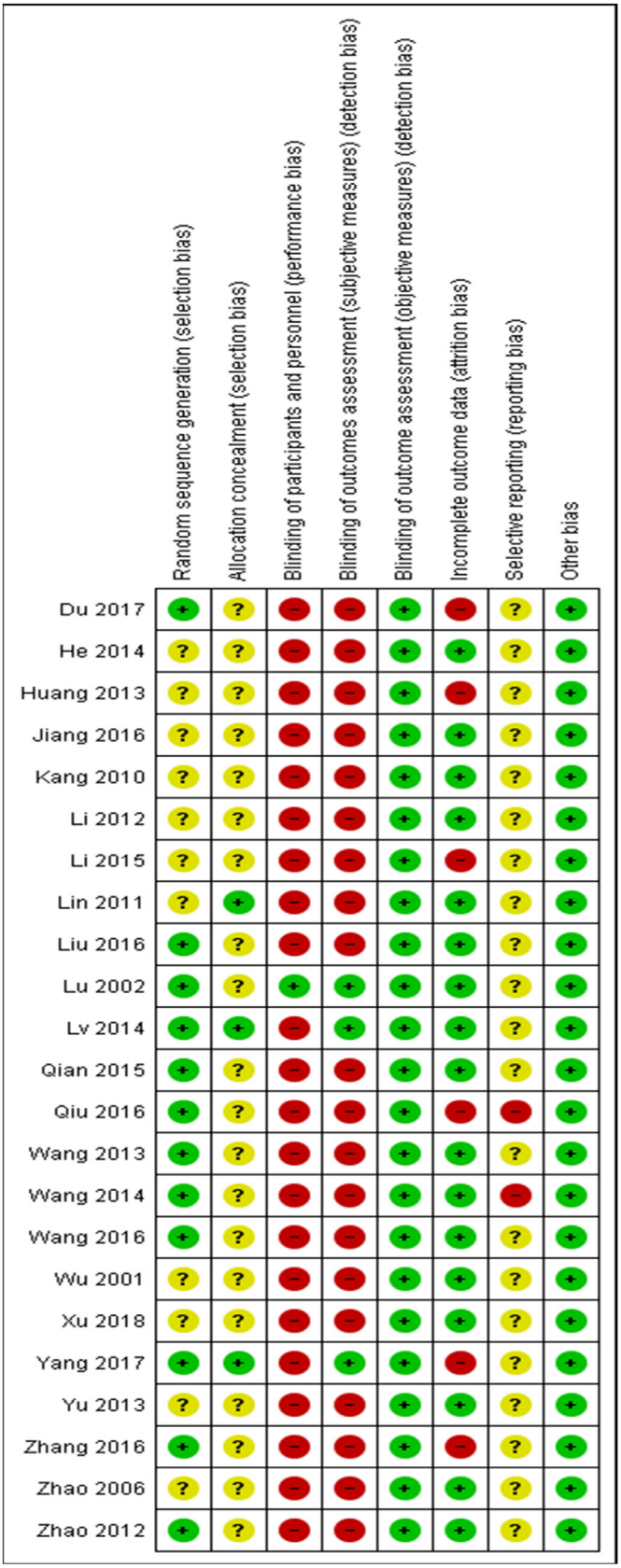

Fig. 2. Risk of bias assessments of 23 included studies Red: high risk; Yellow: unclear: Green: low risk.

Table 2
The results of meta-analyses for each outcome measure (Random effects, 95%CI).

Outcome	No. studies (No. participant)	RR, I^2, p	MD/SMD, I^2, p	Reference No.
ACR20	10 (1075)	RR 1.36 [1.24, 1.48], 14%, $p < 0.00001$	–	14, 16, 19, 20, 23, 26, 27, 31, 33, 35
ACR50	6 (790)	RR 1.40 [0.99, 1.99], 65%, $p = 0.05$	–	14, 16, 20, 23, 26, 35
ACR70	6 (718)	RR 1.83 [1.19, 2.83], 44%, $p < 0.006$	–	14, 16, 23, 26, 27, 35
DAS28	7 (896)	–	MD-1.27 [-1.84, -0.69], 94%, $p < 0.0001$	13, 15, 16, 21, 23, 25, 26
PGA	4 (528)	–	SMD -0.25 [-1.28, 0.78], 96%, $p = 0.64$	15, 23, 26, 29
DGA	3 (448)	–	SMD -0.29 [-0.55, -0.02], 45%, $p = 0.04$	23, 26, 29
HAQ	6 (818)	–	MD -0.43 [-0.60, -0.26], 72%, $p < 0.00001$	13, 15, 16, 20, 23, 26
Pain VAS	3 (332)	–	MD -1.25 [-1.63, -0.86], 43%, $p < 0.00001$	13, 14, 20
TJC	15 (1771)	–	MD -1.71 [-2.41, -1.01], 91%, $p < 0.00001$	14-16, 18–20, 22–27, 29, 31, 32
SJC	16 (1893)	–	MD -1.09 [-2.46, 0.29], 99%, $p = 0.12$	14-16, 18–20, 22–27, 29-32
DMS	13 (1360)	–	SMD -1.07 [-1.51, -0.63], 93%, $p < 0.00001$	14-16, 18–20, 22, 26, 27, 29, 30, 32, 34
GS	6 (690)	–	SMD 0.40 [-0.40, 1.21], 95%, $p = 0.32$	14, 22, 26, 29, 31, 34
ESR	21 (2217)	–	MD -8.34 [-11.70, -4.98], 93%, $p < 0.00001$	13-23, 25–27, 29-35
CRP	19 (1999)	–	SMD -0.89 [-1.17, -0.61], 89%, $p < 0.00001$	13-18, 19, 20–23, 26, 27, 30–32, 33-35
RF	16 (1529)	–	SMD -0.89 [-1.22, -0.55], 89%, $p < 0.00001$	13-15, 17, 18, 20, 22, 27, 29, 30–35
ACPAs	5 (615)	–	SMD -0.30 [-0.51, -0.09], $I^2 = 42\%$, $p = 0.006$	13, 20, 31, 34, 35
AEs	19 (2011)	RR -0.40 [-0.30, -0.53], 47%, $p < 0.00001$	–	13-16, 18–20, 22–29, 31, 33–35

ACR: American College of Rheumatology; ACPAs: Antibodies to citrullinated protein antigens; AEs: adverse events; CI: confidence interval; CRP: C-reactive protein; DAS28: disease activity score in 28 joints; DGA: doctor's global assessment; DMS: duration of morning stiffness; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; I^2: test of heterogeneity in meta-analysis, over 50% represents substantial heterogeneity; MD: mean difference; No.: number; PGA: patient's global assessment; RF: rheumatoid factor; RR: risk ratio; SMD: Standard mean difference; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

matters of global health and disease activity.[36] The VAS was adopted in PGA. The higher scores represent the worsen disease status. Two studies reported PGA with VAS 0–100 (mm)[23,26] while other two with VAS 0–10 (cm).[15,29] Four studies with 528 participants were pooled using SMD effect measure to incorporate in different scales. The PGA was not significantly different between the two treatments (SMD: −0.25, 95% CI [−1.28, 0.78], $I^2 = 96\%$) (Table 2).

3.7.6. DGA

As a well-validated outcome recommended by ACR, DGA is a component of the RA core set. It reflects doctor's assessment of the disease activity.[5] Pooling result of three studies with 448 participants indicated DGA was statistically in favor of CTs without substantial heterogeneity (SMD: −0.29, 95% CI [−0.55, −0.02], $I^2 = 45\%$) (Table 2).

3.7.7. HAQ

Validated HAQ is one of PROs for assessing health-related quality of life, and is commonly used for many chronic diseases including RA. It mainly includes assessments of disability, pain, and patient global health.[37] The pooling result of six studies with 818 participants showed the CTs significantly improved the HAQ (MD: −0.43, 95% CI [−0.60, −0.26], $I^2 = 72\%$) (Table 2).

3.7.8. Pain-VAS

Pain-VAS is a pain-assessment tool which provides numerical rating scale to determine the intensity of pain. Its reliability, feasibility and good compliance have been proven.[38] The CTs significantly reduced the pain intensity compared to c-DMARDs (MD: −1.25, 95% CI [−1.63, −0.86], $I^2 = 43\%$) (Table 2).

3.7.9. TJC

Fifteen studies with 1771 participants reported TJC. The CTs were statistically better than the c-DMARDs in the reduction of TJC (MD: −1.71, 95% CI [−2.41, −1.01], $I^2 = 91\%$) (Table 2). Funnel plot appeared asymmetry with missed data in the bottom right corner of graph (Supplementary 4B).

3.7.10. SJC

Sixteen studies with 1893 participants reported SJC. The pooling result showed there wasn't statistically different between the two treatment groups (MD: −1.09, 95% CI [−2.46, 0.29], $I^2 = 99\%$) (Table 2). A symmetry funnel plot with two outliers in the top was presented (Supplementary 4C).

3.7.11. DMS

Thirteen studies reported outcome of DMS. Four out of 13 studies used 'hour' as measure unit,[15,19,32,34] while nine studies used 'minute'.[14,16,18,20,22,26,27,29,30] The pooling results of 13 studies with 1360 participants showed CTs significantly reduced DMS compared to c-DMARDs alone (SMD: −1.07, 95% CI [−1.51, −0.63], $I^2 = 93\%$) (Table 2). Funnel plot presented graphic asymmetry with most of the studies were in the middle region along the vertical axis with tow outliers (Supplementary 4D).

3.7.12. GS

Seven studies reported outcome of GS. Six studies used 'mmHg' as measure unit while one study used 'kg' as measure unit.[34] Lin, (2011)[20] who measured left and right hand separately was excluded. Pooling six studies showed non-difference between the two treatments (SMD: 0.40, 95% CI [−0.40, 1.21], $I^2 = 95\%$) (Table 2).

3.7.13. ESR

Twenty-one studies with 2217 participants investigated the efficacy of CTs on reduction of ESR (mm/hour). The pooling result showed the CTs had reduced the rate of ESR significantly (MD: −8.34, 95% CI [−11.70, −4.98], $I^2 = 93\%$) (Table 2). Funnel plot was cylindrical with one outlier (Supplementary 4E).

3.7.14. CRP

Nineteen studies reported CRP in three different gauges: mg/L, ng/L and μg/L. Of 'ng/L' and 'μg/L' was used in one study respectively.[19,33] The pooling result of the 19 studies with 1999 participants indicated the CTs significantly reduced serum CRP (SMD: −0.89, 95% CI [−1.17, −0.61], $I^2 = 89\%$) (Table 2). Funnel plot was cylindrical with one outlier (Supplementary 4F).

3.7.15. RF

Sixteen studies with 1529 participants presented RF results. Three different measurements were adopted in these studies: IU/mL,[14,15,17,22,29,30,33–35] U/mL,[13,16,27,31,32] and IU/L.[18,20] The CTs significantly reduced serum RF (SMD: −0.89, 95% CI [−1.22, −0.55], $I^2 = 89\%$) (Table 2). Funnel plot presented graphic symmetry with

most of the studies were in the top region along the vertical axis with one outlier (Supplementary 4G).

3.7.16. ACPAs

Five studies reported ACPAs. Four studies used gauge of 'RU/mL'[13,20,34,35] while one study used 'U/mL'.[31] The pooling result showed CTs significantly reduced serum ACPAs (SMD: −0.30, 95% CI [−0.51, −0.09], $I^2 = 42\%$) (Table 2).

3.7.17. AEs

None severe AEs such as death, vital organ serious/permanent damages were reported in the included studies. The AEs mainly included impairment of liver function (elevations of alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), and aspartate aminotransferase (AST)), Myelosuppression (leukocytopenia, anemia and thrombocytopenia), gastrointestinal AEs (nausea/vomiting, diarrhea, regurgitation, loss of appetites, abdominal distention, and abdominal discomfort), skin rashes, alopecia, headache/dizziness, irregular menstruation, mouth ulcer and palpitation. These were consistent with reported AEs of c-DMARDs.[7] The severity of AEs was mild to moderate. The CTs had statistically reduced total incidences of AEs compared to c-DMARDs alone (RR: 0.40, 95% CI [0.30, 0.53], $I^2 = 47\%$) in the pooling 19 studies with moderate heterogeneity (Table 2). Funnel plot presented graphic asymmetry with missed data in the bottom right corner of graph (Supplementary 4H).

4. Discussion

Twenty-three included studies were published from 2001 to 2018. The female participants were 2.8 times more than those in male. It was consistent with the higher incidence rate of RA in the female population globally. The majority of participants were in the mean age of 30–49 years old. It was younger than global RA population that the prevalent cases peak in the 60–64 age group for both men and women.[2] The age is usually not an independent predictor of response to c-DMARDs in RA population.[39] The relative younger participants in this review was not likely to affect the generalizability of the results. Meta-analyses found the CTs significantly improved the clinical response of ACR20 by 33% (RR: 1.33), ACR50 by 40% (RR: 1.40), and ACR70 by 83% (RR: 1.83), and reduced 1.27 mean score of DAS28 (MD: −1.27) compared to the active control of c-DMARDs therapies. The total incidences of AEs in the CT groups were 60% (RR: 0.40) less than c-DMARDs alone. The results were consistent with a recent mete-analysis study that evaluated the efficacy and safety of CHMs combined with Western Medicine for RA.[40]

There is an increasing trend of patient-centered care in RA. The PROs i.e., HAQ, Pain-VAS and PGA are important in assessing RA symptoms which directly (pain) or indirectly (fatigue, emotional and social consequence) link to inflammatory process. The PROs consist of multi-domains including symptoms (pain, fatigue), signs, functional status, health-related quality of life, psychological distress, work and social life. They have played important roles in RA trials and treatment decision.[41] In this review, the CTs had improved the outcomes of HAQ and Pain-VAS. These were consistence with the result of DGA. However, the PGAs had showed no difference between the two treatment groups. The reasons of the inconsistent results between the individual PROs were unknown due to the limitation of data e.g., the property of each PROs in individual study was unknown. The discordance between PGAs and DGAs was evidenced in RA trials. These may reflect the differences between patient's and doctor's perspectives, e.g., pain, quality of life with non-signs of inflammation, co-occurrence of disease, and psychological distress are more concerned by patients whereas doctors valuate objective measurements of joint counts and acute phase reactants.[36]

Joint counts, acute phase reactants and serological tests are relatively objective measurements in RA trials compared to PROs. Swelling joint, TJC and DMS are signs of synovitis. The elevated ESR and CRP were signs of acute inflammation. The RF and ACPAs are specific biomarkers of RA. The sensitivity of ACPAs is generally higher than RF in classification of RA. ACPAs also appear to be better than RF in prediction of prognosis of RA in terms of articular damage and irreversible disability.[42] The meta-analyses showed significant improvements of TJC, DMS, ESR, CRP, ACPAs and RF in CTs compared to c-DMARDs alone. The results implicated the CTs may be more effectiveness than the c-DMARDs alone in controlling the inflammatory activity of RA. Overall, the additional CHMs potentially enhanced the effectiveness of c-DMARDs in the managements of RA.

Experimental data and clinical studies in the herb-drug interactions between CHM and c-DMARDs are limited, and concerned by clinical physicians and researchers. Future research into this field is need. Theoretically, herb and drug administrated simultaneously can induce agonistic or antagonistic responses through pharmacodynamic or pharmacokinetic interactions between herb and drug. Consequently, the interactions result in either increasing or decreasing the pharmacologic effectiveness and toxicity of drug.[43] In this review, neither decreasing effectiveness of c-DMARDs nor increasing toxicity of c-DMARDs were showed in the CTs in comparison with c-DMARDs alone. Therefore, it appeared safe to concurrently use these herbs with c-DMARDs in the context of current settings.

The methodological biases and heterogeneity were existence. Characterized with special color and taste, the CHMs, especially in the form of decoctions are impossible to undergo blinding of participants without an identical placebo setting in control arm. In this review, only one study applied placebo in control arm.[22] Others did not implement blinding of participants. Thus, there was high risk of performance bias. All trials were carried out in China where many people who suffer from chronic diseases including RA believe integration of CHMs and drugs would be beneficial to their conditions. In the interpretation of subjective outcomes, the placebo effect should be considered in such a cultural context. The majority of studies were relatively small with average of 106 participants per study. Small studies tend to overestimate the true effects.[12] The asymmetry graphic funnel plots in some outcomes implied high risk of publication bias.[44] All data were collected from published scientific papers. Existing heterogeneity is inevitable. The high percentages of I^2 indicated substantial heterogeneity of the outcomes. The heterogeneity could derive from various sources, e.g., participant's demographic information, sample size, treatment regimens and duration, outcome measure, duration of follow up, etc. In order to investigate heterogeneity, sensitivity analyses were conducted in fixed effects model and the heterogeneity was constantly existence. Therefore, the random effects model was adopted in the final meta-analysis process to incorporate in the heterogeneity among the studies.

The rational for combining CHMs with c-DARMDs was to enhance effectiveness of the treatment and alleviate AEs of c-DMARDs. Recent review studies on the pharmacological activities of the five most commonly used CHMs in this review indicated the crude extracts and bio-constituents of these CHMs possessed multiple pharmacological activities that may contribute to the reported outcomes.

Total glucosides of paeony (TGP) are extracted from the roots of *Paeonia lactiflora* Pall which is the botanic origin of *Paeoniae* Radix Alba (PRA). TGP and its main effective component Paeoniflorin (Pae) demonstrated anti-inflammatory and immuno-modulatory

against the pathogenesis of RA. In the RA models of adjuvant arthritis (AA) rats and collagen-induced arthritis (CIA) rats, TGP and Pae inhibited over active synoviocytes and the immune cells of T-cell, B-cell, monocytes, and macrophages; decreased the expression of inflammatory factors of prostaglandin E2 (PGE2), interleukin-1(IL-1), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), and restored abnormal signalling of EP-GPCRs-cAMP and MAPK pathways.[45]

Total saponins of *Clematidis* Radix et Rhizoma (CRR) alleviated RA activities via inhibiting JAK2/STAT3 signal pathway in AA rats. Saponin clematichineonside AR from CRR inhibited RA activities in the human RA derived fibroblast-like synoviocyte cell-line MH7A. The crud extracts and saponins from CRR inhibited nitric oxide (NO) production and expression of TNF-α in RAW 264.7 macrophages activated by lipopolysaccharide (LPS). The extract of CRR showed cartilage protection in rabbit articular cartilage via promoting extracellular matrix deposition in chondrocytes. Vascular endothelial growth factor (VEGF) is positively correlated with RA activity. Clemochinenosides from CRR inhibited the angiogenic activity induced by VEGF in human umbilical vein endothelial cell.[46]

Angelica sinensi radix (ASR) ethyl acetate extract inhibited NF-κB luciferase activity and down-regulated TNF-α, IL-6, macrophage inflammatory protein-2 (MIP-2) and NO in LPS plus IFN-γ-stimulated RAW 264.7 cells.[47] The ASR crude extracts and pure compounds also possessed pharmacological activities including antioxidative, hepatoprotective, nephroprotective, neuro protective, and pro-hematopoietic *in vitro*/*in vivo*.[48]

Essential oil from *Cinnamomi* ramulus (CR) exhibited anti-inflammatory activity by inhibiting expression of TNF-α, IL-1β, NO, PGE2, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in mice with paw oedema induced by carrageenan. Cinnamaldehyde derived from the essential oil suppressed the expression of pro-inflammatory cytokines via reducing ROS release and suppressing the activation of JNK1/2 and ERE1/2 signallings in LPS-stimulated J774A.1 macrophages. The essential oil also exhibited analgesic activity in animal models of acid-induced writhing and oxytocin-induced writhing, and significantly suppressed intensity of hyperalgesia in the carrageenan-induced paw inflammation model in mice.[49]

Isoliquiritigenin (ILG) and liquiritigenin (LG) are the main bioconstituents of *Glycyrrhizae* Radix et Rhizoma (GR). The two compounds possessed anti-inflammatory activity by inhibiting expression of NO, iNOS and the activation of NF-κB/IκBa in RAW 264.7 macrophages. The hepatoprotective of LG significantly reduced the elevated serum levels of ALT, GGT, and AST, and suppressed the expression of TNF-α, IL-1β, IL-6 mRNA in mice induced by the *tert*-butyl hydrogen peroxide (t-BHP). The anti-depressant and anti-anxiety activities of LG were associated with its anti-inflammatory and decreasing expression of brain-derived neurotrophic factor/tropomyosin receptor kinase B pathway.[50] Triterpene saponins from GR also showed hepatoprotective activities in liver disease and drug-induced liver injury *in vitro* and *in vivo*.[51]

Overall, these CHMs possessed the pharmacological activities including anti-inflammation, immunomodulation, analgesia activity, antioxidative, cartilage protective, anti-angiogenic, anti-depressant, pro-hematopoietic and hepatoprotective, etc. It appeared that some of these CHMs may directly contribute to the anti-inflammatory effects in RA while others may act to alleviating AEs.

5. Conclusion

The results of this study indicated that integration of CHMs with c-DMARDs significantly increased the overall effectiveness of c-DMARDs and reduced incidences of AEs compared to using c-DMARDs alone. The CHMs possess multiple pharmacological activities that may contribute to the reported outcomes. However, methodological flaws and high heterogeneity in some outcomes across the included studies weakened the strength of the evidences. Therefore, interpretation of these results should be tentative. Large sample and rigorously designed RCTs are required for future studies.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtcme.2022.01.005.

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