



# Treatment of rheumatoid arthritis with combination of methotrexate and *Tripterygium wilfordii*: A meta-analysis



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## ABSTRACT

**Aims:** Extracts of *Tripterygium wilfordii* Hook F (TwHF), a traditional Chinese herbal medicine, have been widely used for treating rheumatoid arthritis (RA) in combination with methotrexate (MTX) in China for several decades. However, the efficacy and safety of MTX plus TwHF treatment remain unclear.

**Main methods:** A comprehensive search of databases in both Chinese and English was performed. Data from the selected studies were extracted and analyzed independently by two authors.

**Key findings:** Six randomized controlled trials were included in the final analysis with a total of 643 patients. All trials added TwHF (in the form of *Tripterygium* glycosides) to the MTX-based therapy. For efficacy, the addition of TwHF increased 50% responder rates (RR) (RR 1.337, 95% confidence interval [CI]: 1.188–1.505,  $P < 0.001$ ), and it reduced swollen and tender joint counts, shortened the duration of morning stiffness, decreased the erythrocyte sedimentation rate, and decreased the level of C-reactive protein and rheumatoid factor. For safety, the addition of TwHF did not increase the rate of adverse events (RR 0.824, 95% CI: 0.635–1.068,  $P = 0.143$ ).

**Significance:** MTX plus TwHF therapy may be a more effective and similar safe strategy for treating RA compared to MTX monotherapy. Further large clinical trials to investigate the TwHF add-on therapy are warranted.

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## 1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disorder that affects about 0.5–1.0% of the population, especially women and the elderly [1]. RA is characterized by systemic and synovial inflammation, and it leads to permanent joint damage and disability if uncontrolled. At present, synthetic disease-modifying anti-rheumatoid drugs (DMARDs), particularly methotrexate (MTX), are the first-line drugs to alleviate synovitis and systemic inflammation for treating RA [2]. Second-line immune-selective biologic agents (drugs) may be slightly more tolerable than synthetic DMARDs [3,4]. However, the current pharmacologic therapies cannot produce an adequate response in

many patients [5], and the new pharmacologic strategies for RA treatment are still warranted.

*Tripterygium wilfordii* Hook F (TwHF) is a traditional Chinese medicine herb, and its root has been used to treat RA in traditional Chinese medicine [6]. TwHF extracts have been widely used and have even become a standard therapy in China for treating RA for several decades [7]. Increasing evidence has shown that TwHF extracts are efficacious for treating active RA, such as *Tripterygium* glycosides and triptolide [8–10]. Previous meta-analysis studies support that TwHF extracts are effective and safe for treating RA [11,12]. In two small clinical trials, TwHF extracts also show good efficacy on RA on U.S. patients [13,14]. Recently, several randomized control trials further indicated that the addition of TwHF may be able to achieve better effectiveness than DMARDs monotherapy (such as MTX) in patients with RA [15,16]. Actually, MTX plus TwHF has been empirically used for treating RA in China for decades [17,18]. However, the evidence for the MTX plus TwHF therapy for RA remains inadequate, and it is necessary to have a quantitative meta-analysis of the efficacy and safety of TwHF add-on therapy in patients with RA. Therefore, we performed a quantitative meta-analysis of the efficacy and safety of the combined use of TwHF with MTX for RA.

**Abbreviations:** ACR, American College of Rheumatology; AEs, adverse effects; ALT, alanine transaminase; CI, confidence interval; CRP, C-reactive protein; DMARDs, disease-modifying anti-rheumatoid drugs; DMS, duration of morning stiffness; ESR, erythrocyte sedimentation rate; MTX, methotrexate; RA, rheumatoid arthritis; RRs, risk ratios; SJC, swollen joint counts; TJC, tender joint counts; TwHF, *Tripterygium wilfordii* Hook F.

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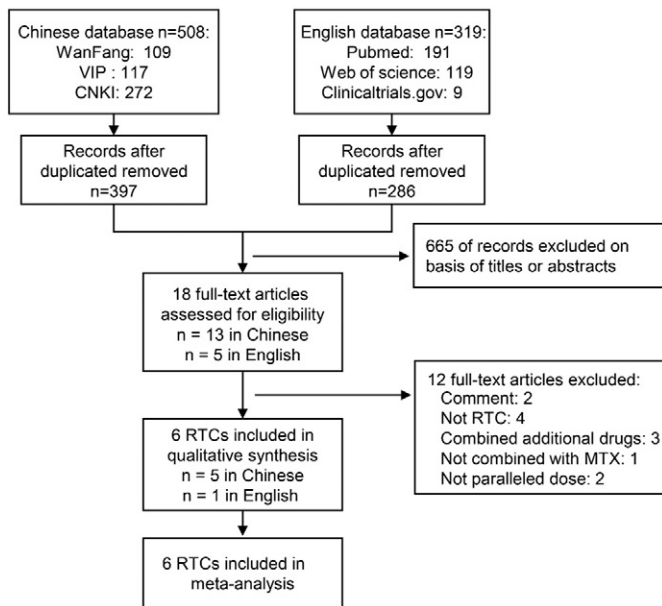


Fig. 1. Flow diagram of the study selection process.

## 2. Material and methods

### 2.1. Literature search

Two authors independently performed a systematic search of PubMed, Web of Science, and Clinical Trials.gov for clinical trials up to April 8, 2016. Comprehensive searching was conducted using the terms (“*Tripterygium*”, “lei gong teng”, or “thunder god vine”) and (“rheumatoid arthritis”, “atrophic arthritis,” or “rheumatism”). In addition, we also searched Chinese databases, including Wan Fang Data, VIP, and CNKI, for Chinese-language studies using the terms “lei gong teng” (for *Tripterygium*), “jia an die ling” (for MTX), and “guan jie yan” (for arthritis) in Chinese. Chinese literature was further restricted to RA by reviewing the titles and abstracts. Our study was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [19].

### 2.2. Selection criteria

The following criteria were adopted: (1) clinical randomized control trials (RCTs) aiming to study using MTX plus TwHF for treating RA; (2) a well-defined efficacy rate of 50% or American College of Rheumatology (ACR) 50 index (ACR50); (3) follow-up duration  $\geq 3$  months; (4) patients receiving a diagnosis of RA according to ACR guidelines; and (5) there are no other treatment factors between the combination and control group.

We excluded the following articles: (1) non-RCTs; (2) incomplete or duplicative data; (3) follow-up duration  $< 3$  months; (4) people

enrolled were not given a diagnosis according to ACR guidelines; and (5) there are additional treatment factors (such as drugs or Chinese medicine) in the combination group and/or the control group.

### 2.3. Data extraction and quality assessment

Similar to our previous study [20], two authors (X. W. and Y. Z.) independently browsed the title, abstract, and the full text of the literature meeting the criteria. Any discrepancies were resolved by consensus with the corresponding author (Z. X.). Each study's clinical characteristics were summarized, and each study's main outcomes were extracted or calculated. Adverse events (AEs) were also collected. Study quality was evaluated using a modified Jadad scale [21] to assess reported randomization, blinding, withdrawals, dropouts, inclusion/exclusion criteria, AEs, and the statistical analysis, with a maximum score of 8 points (Supplementary Table 1). Low-quality studies yielded scores of 0 to 3, and high-quality studies achieved scores of 4 to 8. In addition, to assess publication bias, Egger's test or Begg's funnel plot was performed, if possible.

### 2.4. Statistical analysis

Comprehensive meta-analysis was performed to calculate risk ratios (RRs) or mean difference, and their 95% confidence interval (CI) by comprehensive meta-analysis software V2.0. Statistical heterogeneity was assessed by Cochran's Q statistic and the  $I^2$  statistic. The fixed-effect model was used to pool studies when statistical heterogeneity was absent and that substantial heterogeneity was defined as  $I^2 > 50\%$  or chi-squared test  $P < 0.1$ ; otherwise, the random-effects model was employed.

## 3. Results

### 3.1. RCT selection

The study selection process is depicted in Fig. 1. Notably, two RCTs were excluded because they used MTX at 15 mg/kg in the control group but MTX at 7.5 mg/kg and MTX plus TwHF groups [18,22], while another one was excluded because it was not an RCT related to the MTX plus TwHF treatment [10].

Finally, six completed RCTs ( $n = 643$ ) were included in the current meta-analysis [15,16,23–26]. All six RCTs used TwHF in the form of *Tripterygium* glycosides, which is a tablet containing chloroform/methanol extract of TwHF [7,17]. The dose of MTX was similar among the six study (about 10 mg/week), while the dose of TwHF differed among the six studies. One study used TwHF at 10 mg/d [23], two studies used TwHF at 30 mg/d [24,25], and the other three studies used TwHF at 60 mg/d [15,16,26]. Lv et al. also tested the TwHF monotherapy in parallel [15]. The details of the included studies are summarized in Table 1. The details of the modified Jadad scale for each included study are shown in Supplementary Table 2.

Table 1  
The details of included studies.

Study	Number of patients		Dose		Duration (weeks)	Modified JADAD score
	MTX (mg/w)	MTX + TwHF (mg/d)	MTX (mg/w)	MTX + TwHF (mg/d)		
Tan and Xiao [23]	52	52	10	+TG(10)	12	3
Zhang and Tan [16]	42	47	10–15	+TG(60)	12	3
Yang et al. [24]	40	40	10	+TG(30)	24	5
Wang [25]	50	76	15	+TG(30)	12	5
Wang and Luan [26]	53	53	10	+TG(60)	12	4
Lv et al. [15]	69	69	7.5–12.5	+TG(60)	12	5

MTX: methotrexate; TG: *Tripterygium* glycosides; mg/w: mg/week; mg/d: mg/day.

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