Effects and safety of Sinomenine in treatment of rheumatoid arthritis contrast to methotrexate: a systematic review and Meta-analysis

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Abstract

OBJECTIVE: To systematically evaluate the curative clinical efficacy and safety of sinomenine (SIN) in treatment of rheumatoid arthritis (RA) in comparison to methotrexate (MTX).

METHODS: We searched the China National Knowledge Infrastructure Database, Chinese Biomedical Literature Database, China Science and Technology Journal Database, Wanfang Database, Pubmed and Cochrane Library electronically up to August 31, 2015, without language limitation. Only randomized controlled trials (RCTs) were included. Software Review Manager 5.3 was used for Meta-analysis.

RESULTS: A total of 16 eligible studies within 1500 RA patients were included. The meta-analysis indicated that on basis of MTX, SIN was more effective in total effective rate ($P < 0.0001$). Besides, SIN alone versus MTX also showed advantages in RA therapy ($P = 0.04$) Taken together, adverse events occurred less frequently in combination of SIN and MTX than MTX alone ($P < 0.0001$), especially in digestive system ($P < 0.0001$), while occurred more in dermato mucosal system with SIN treatment versus MTX ($P = 0.02$), and were similar for both remedies in nervous system ($P = 0.12$) and hematological system ($P = 0.25$).

CONCLUSION: Compared to MTX, SIN had better clinical efficacy and relatively fewer adverse events in treatment of RA, especially when it was used together with MTX. Due to the poor methodological quality, well-designed, multiple-center RCTs are still required to further confirm the findings.

Keywords: Sinomenine; Randomized controlled trials; Arthritis, rheumatoid; Methotrexate; Meta-analysis

INTRODUCTION

Rheumatoid arthritis (RA) is a progressive, destructive inflammatory disease affecting around 0.5%-2% of the human population, especially females. The domestic prevalence of RA is about 0.2% -0.4%. RA is characterized by synovial inflammation leading to cartilage and bone damage that is largely irreversible. It usually starts as an insidious symmetrical polyarthritis, often with non-specific symptoms such as malaise and fatigue. 50%-90% patients with erosive disease first
develop their erosions > 2 years from disease onset. Although the exact cause of RA remains unknown, the "Bermuda triangle" of genetics, environment and autoimmunity is involved in the pathogenesis of RA. Methotrexate (MTX) is a disease modifying anti-rheumatic drug (DMARD) used as a first line agent for treating RA for its proven efficacy, relative safety, and cost-effectiveness. However, MTX is known to cause bone loss and promote osteoclast formation, which is far from ideal to prevent bone destruction in RA patients.

Sinomenine (SIN) is a pure alkaloid extracted from Chinese medicinal plant Qingfengteng (Caulis Sinomenii). Qingfengteng (Caulis Sinomenii) is recorded initially in Ben Cao Tu Jing of the Song Dynasty, has functions such as dispelling the pathogen of wind and dampness, dredging the channels and collaterals and relieving pain. Studies have demonstrated that SIN possesses potent anti-inflammatory, analgesic, and immunoinhibitory pharmacological effects, which provide the basis for RA treatment.

Natural plant products offer a promising resource for potential anti-arthritis agents, comprising one of the most popular complementary and alternative medicine (CAM) for inflammatory and immune disorders. Over the years, increasing proportion of patients with RA are resorting to CAM for their health needs. The prevalence of CAM usage by RA patients is anywhere between 28% to 90%. In parallel, increasingly studies have shown that SIN used alone or as adjuvant agent combined with MTX had synergistic effects in inhibiting RA response.

In this study, in comparison to MTX, we aimed to evaluate the clinical efficacy and safety of SIN in RA treatment.

METHODS

**Literature retrieval and search strategies**

Two reviewers searched the randomized controlled trials (RCTs) conducted for SIN in treating RA from database of China National Knowledge Infrastructure Database (CNKI), Chinese Biomedical Literature Database (CBM), China Science and Technology Journal Database (VIP), Wanfang Database, Pubmed and Cochrane Library. The search included articles published and updated up to August 31, 2015. Meanwhile, manual searches for gray literatures of conference compilations supplemented electronic searches were performed, while no documents were provided. Full details on the search terms were described as follows:

For Pubmed and Cochrane Library:
- #1 Sinomenine [mh] OR Sinomenium [mh] OR Zheng Qing Feng Tong Ning [mh] OR Zhengqing Fengtongning tablets [mh]
- #2 rheumatoid arthritis [mh] OR RA [mh]
- #3 randomized controlled trials [pt] OR controlled clinical trial [pt] OR randomized [tiab]

For CNKI and other Chinese databases:
- #1 Qing Teng Jian [mh] OR Zheng Qing Feng Tong Ning [mh]
- #2 Lei Feng Shi Guan Jie Yan [mh] OR Joint Pain [mh]
- #1 AND #2

**Inclusion criteria**

(a) Types of studies. Trials must be a randomized, controlled design, regardless of blinding or allocation concealment. Quasi-RCTs were also taken into consideration. Restrictions on language, status or publication date were not set.

(b) Types of participants. According with specific clinical diagnosis of RA, any participants of selected cases were included whether mentioned patients were in active phase or not. The diagnostic criteria for RA in the trials accorded with the American Rheumatism Association 1987 revised criteria for the classification of RA.

(c) Types of interventions. Only trials of SIN preparations using alone or plus MTX versus MTX were considered Basic treatment may include non-steroidal anti-inflammatory drug (NSAIDs) such as meloxicam, but shouldn’t include any other DMARDs or glucocorticoids.

(d) Types of outcome measures. The primary outcome was the clinical efficacy, the secondary outcomes included morning stiffness time, total clinical effective rate in 4 weeks treatment, swollen joint count (SJC), C-reactive protein (CRP), blood platelet (PLT), disease activity score for rheumatoid arthritis in 28 joints (DAS28), health assessment questionnaire(HAQ) score, and other outcome (anti-CCP).

**Exclusion criteria**

Studies were not considered if they met any of the following criteria. (a) Unpublished or repeated literature; (b) non-RCTs, and clinical trials including experience summary, case report, traditional reviews and animal experiments; (c) studies not using SIN as the main means of intervention; diagnosis complicated with pregnancy, stroke, or other serious organic diseases such as heart, liver, kidney and hematopoietic dysfunction; (d) cases with patients of severe drug allergic medical history; (e) patients with other rheumatic diseases at the same time.

**Data extraction and quality assessment**

The titles and abstracts of potentially relevant references were identified through the literature search and reviewed independently by 2 reviewers (Liu Weimei and Wei Gang) according to predefined criteria and the Cochrane risk of bias tool. Any inconsistencies were resolved by discussion (95% level of agreement) or further evaluated by consensus with another investigator (Wang Yue). We assessed the methodological quality of the included trials strictly according to the Cochrane risk of bias tool. For each item, the judgment was given as "high risk", "unclear risk", or "low risk".

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**Statistical analyses**

Revman (version 5.3, the Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen)\(^{22}\) and Stata 12.0 was used for data analysis. Outcomes were pooled using mean differences (MDs) for continuous variables, and pooled risk ratio (RR) was used for dichotomous variables, both with a 95% confidence interval (95% CI). Heterogeneity was tested using Chi-square (\(\chi^2\)) test and \(I^2\) statistic. When heterogeneity was defined as \(P < 0.05\), \(I^2 > 50\%\) among primary studies, it revealed significant heterogeneity, random effects model was to be used. Otherwise, if \(P > 0.05\), \(I^2 < 50\%\) fixed effects model was to be applied. To maximize the similarities among trials that would be combined, data was further stratified possibly into subgroups based on consideration of clinical factors, such as different types of interventions. Funnel plot analysis and Harbord’s modified test\(^{23}\) was done to determine publication bias. \(P < 0.05\) was considered statistically significant.

**RESULTS**

**Characteristics of included studies**

In this review, the initial search yielded 775 articles.

<table>
<thead>
<tr>
<th>Database</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNKI</td>
<td>357</td>
</tr>
<tr>
<td>CBM</td>
<td>44</td>
</tr>
<tr>
<td>VIP</td>
<td>106</td>
</tr>
<tr>
<td>Wanfang</td>
<td>227</td>
</tr>
<tr>
<td>Pubmed</td>
<td>39</td>
</tr>
<tr>
<td>Cochrane</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>775</td>
</tr>
</tbody>
</table>

Excluded (\(n = 431\))

Duplicated (\(n = 186\)) Irrelevant, animal study, reviews (\(n = 245\))

Full-test articles assessed for eligibility (\(n = 344\))

Excluded (\(n = 328\))

Non-RCTs (\(n = 14\)) Combining SIN injection, other Chinese medicine, acupuncture and massage therapy in test group (\(n = 314\))

Articles included in quantitative synthesis (Meta-analysis) (\(n = 16\))

**Figure 1 Flow chart of literature search**

CNKI: China National Knowledge Infrastructure Database; CBM: Chinese Biomedical Literature Database; VIP: Chinese Scientific Journals Database; RCTs: randomized controlled trials.

CNKI (\(n = 357\)), CBM (\(n = 44\)), VIP (\(n = 106\)), Wanfang Data (\(n = 227\)), Pubmed (\(n = 39\)) and Cochrane Library (\(n = 2\)), of which 431 were excluded owing to duplicated publication (\(n = 186\)) and irrelevant studies (\(n = 245\)). Following the evaluation of the full text, 328 articles not meeting the inclusion criteria were excluded, including non-RCTs (\(n = 14\)), combining other Chinese medicine or traditional Chinese medicine in test group (\(n = 314\)). Finally, a total of 16 RCTs\(^{24-39}\) were available, all published in Chinese Journal Literature Databases from 2005 to 2015. The screening process is summarized in a flow diagram (Figure 1).

**Literature analysis**

The characteristics of the 16 RCTs\(^{24-39}\) are summarized in Table 1, containing a total of 1500 patients, each ranging from 40 to 186 patients. The experimental group consisted of 787 patients, while the control group contained 713 patients. All the studies included more females (67.1%) than males. The average age of the patients was approximately 44.1 years. The disease courses of RA were from 0.16 to 24 years. The dosage of SIN was administered orally from 60 mg qd to
### Table 1 Characteristics of 16 included studies on SIN for RA

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis standard</th>
<th>Number (T/C)</th>
<th>Age (T/C)</th>
<th>Sex (M:F)</th>
<th>Course of disease (years)</th>
<th>Intervention</th>
<th>Trial period (weeks)</th>
<th>Outcome measure</th>
<th>ADEs</th>
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<tr>
<td>Chen YL</td>
<td>CDTES DSTM</td>
<td>80/65</td>
<td>46.0±4.30</td>
<td>61:84</td>
<td>5.62±6.75</td>
<td>ZQFTN 60 mg q.d./p.o.</td>
<td>12</td>
<td>②⑤</td>
<td>Unclear</td>
</tr>
<tr>
<td>Ding H</td>
<td>ACR-1987</td>
<td>31/31</td>
<td>16-63</td>
<td>18:44</td>
<td>0.16-17</td>
<td>ZQFTN 20-40 mg t.i.d. p.o.; MTX 7.5 mg q.w. p.o.</td>
<td>12</td>
<td>①</td>
<td>Yes</td>
</tr>
<tr>
<td>Gu F et al</td>
<td>ACR/EULAR-2010</td>
<td>45/45</td>
<td>40.4±10.11</td>
<td>23:67</td>
<td>7.90±6.03</td>
<td>ZQFTN 40 mg t.i.d. p.o.; MTX 10 mg q.w. p.o.</td>
<td>28</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<td>Huang ZS</td>
<td>ACR-1987</td>
<td>30/30</td>
<td>42.5±7.50</td>
<td>22:38</td>
<td>3.45±3.40</td>
<td>Basic therapy+ZQFTN60 mg b.i.d. p.o.; MTX 7.5 mg q.w. p.o.</td>
<td>12</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<tr>
<td>Ji H et al</td>
<td>ACR-1987</td>
<td>30/30</td>
<td>51.7±9.55</td>
<td>17:43</td>
<td>3.93±3.52</td>
<td>ZQFTN 20-40 mg t.i.d. p.o.; MTX 7.5 mg q.w. p.o.</td>
<td>12</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<tr>
<td>Liu W et al</td>
<td>ACR-1987</td>
<td>60/60</td>
<td>42.7±7.65</td>
<td>19:10</td>
<td>3.15±3.49</td>
<td>ZQFTN 60 mg q.d./b.i.d. p.o.</td>
<td>12</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<tr>
<td>Li Y et al</td>
<td>ACR-1987</td>
<td>48/48</td>
<td>45.2±4.60</td>
<td>21:75</td>
<td>9.75±3.15</td>
<td>Basic therapy+ZQFTN 20-40 mg t.i.d. p.o.; MTX 7.5-15 mg q.w.p.o.</td>
<td>24</td>
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<td>Yes</td>
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<td>Lu Y et al</td>
<td>ACR-1987</td>
<td>40/40</td>
<td>46.7±13.40</td>
<td>19:41</td>
<td>3.50±3.54</td>
<td>Basic therapy+ZQFTN 120 mg b.i.d. p.o.; MTX 10 mg q.w. p.o.</td>
<td>12</td>
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<tr>
<td>Li YN et al</td>
<td>ACR-1987</td>
<td>35/34</td>
<td>40.6±13.50</td>
<td>25:44</td>
<td>4.40±2.90</td>
<td>Basic therapy+ZQFTN 120 mg b.i.d.; MTX 10 mg q.w.</td>
<td>8</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<td>Sun SY</td>
<td>ACR-1987</td>
<td>62/58</td>
<td>25.5-67.5</td>
<td>34:86</td>
<td>0.29-13.5</td>
<td>ZQFTN 120 mg q.d./p.o.; MTX 15 mg q.w. p.o.</td>
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<td>②⑤⑥</td>
<td>Yes</td>
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<tr>
<td>Sun SY</td>
<td>ACR-1987</td>
<td>20/20</td>
<td>20.5-57</td>
<td>17:23</td>
<td>unclear</td>
<td>ZQFTN 60 mg q.d./b.i.d.</td>
<td>24</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<td>Wang WQ</td>
<td>ACR-1987</td>
<td>120/66</td>
<td>13.5-71</td>
<td>66:120</td>
<td>0.75-4</td>
<td>Basic therapy+ZQFTN 120 mg b.i.d.; MTX 10 mg q.w.</td>
<td>24</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<td>Xia YK</td>
<td>ACR-1987; GCRNDTCM</td>
<td>52/52</td>
<td>37.5±6.90</td>
<td>21:83</td>
<td>4.60±3.10</td>
<td>ZQFTN 60 mg t.i.d.; MTX 10 mg q.w. p.o.</td>
<td>24</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<td>Zhu FX</td>
<td>RA diagnostic</td>
<td>36/36</td>
<td>&gt; 60</td>
<td>21:51</td>
<td>9.70±1.40</td>
<td>ZQFTN 60 mg b.i.d. p.o.; MTX 10 mg q.w.</td>
<td>24</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<tr>
<td>Zhang J L</td>
<td>RA diagnostic</td>
<td>38/38</td>
<td>47.5±12.40</td>
<td>49:27</td>
<td>2.35±0.45</td>
<td>ZQFTN 120 mg b.i.d.; MTX 10 mg q.w.</td>
<td>24</td>
<td>②⑤⑥</td>
<td>Yes</td>
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<td>Zhang K</td>
<td>ACR-1987; GCRNDTCM</td>
<td>60/60</td>
<td>16-68</td>
<td>60:60</td>
<td>0.33-24</td>
<td>ZQFTN 120 mg b.i.d. p.o.</td>
<td>12</td>
<td>②⑤⑥</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Notes: M: male; F: female; T: test; C: control; RA: rheumatoid arthritis; SIN: sinomeine; ZQFTN: Zhengqingfengtongning tablets; MTX: methotrexate; ADEs: adverse drug events; qd: every day; bid: twice a day; tid: three times a day; qw: once a week; Basic therapy: take NSAIDs and/or folic acid tablets orally; po: take orally; i.m: intramuscular injection; ARA-1987: the American Rheumatism Association 1987 revised criteria; ACR/EULAR-2010: the American College of Rheumatology/European League Against Rheumatoid collaborative initiative 2010 rheumatoid arthritis classification criteria; CDTESDSTCM: criteria of diagnosis and therapeutic effect of surgical diseases and syndromes in Traditional Chinese Medicine; GCRNDTCM: Guidelines of clinical Research of New Drugs of TCM. ① clinical efficacy; ② morning stiffness time; ③ swollen joint count; ④ grip strength; ⑤ erythrocyte sedimentation rate; ⑥ C-reactive protein; ⑦ anti cyclic citrullinated peptide; ⑧ blood platelet; ⑨ disease activity score for RA in 28 joints; ⑩ health assessment questionnaire score.
120 mg bid over 8 weeks. For the experimental group, except 4 studies \cite{24,25,34,39} taking SIN alone, the rest of the studies \cite{25-30,33-35,38-39} were treated plus MTX versus MTX treatment alone, 5 trials \cite{27-30,32,35} adopted basic therapy, one \cite{30} used folic acid to ameliorate side effects, 4 trials \cite{27-30,32} used meloxicam during treatment, including one \cite{30} also added folic acid. The dosages and treatment courses were not limited. 12 trials \cite{25-28,35-39} used the American Rheumatism Association 1987 revised criteria for the classification of RA (ARA-1987), including one \cite{39} added the double criteria of Grading standard. \cite{30} One trial \cite{25} used the American College of Rheumatology/European League Against Rheumatoid collaborative initiative 2010 RA classification criteria (ACR/EULAR-2010). For TCM diagnostic criteria, one trial \cite{29} reported Wang et al. in criteria of diagnosis and therapeutic effect of surgical diseases and syndromes in traditional Chinese medicine (CDTETSCTCM), one trial \cite{25} applied with wind-dampness and blood-stagnant blocking collaterals syndrome according to Guidelines of Clinical Research of New Drugs of TCM (GCRNDTCM), 2 trials \cite{37,38} have not reported clear diagnostic criteria.

Methodological quality assessment
Study quality was evaluated by Cochrane risk of bias tool. All the eligible trials were RCTs, including one quasi-RCT \cite{29}. None of the studies reported whether blinding was used, or described allocation concealment. Only 2 studies \cite{25,26} described specific methods of generating the random sequence, one \cite{26} described as random digits table, and the other \cite{25} represented as sequence of medical order, while the rest lacked a description. One study \cite{24} reported 1 drop-out during the duration of treatment. Interestingly, one study \cite{25} described some clear secondary outcomes, while lacking data of clinical efficacy, we considered it may had selective reporting (Figures 2, 3). In addition, none of the trials reported a follow-up.

Clinical efficacy
Only 15 trials \cite{25,27-39} including 1410 patients took clinical efficacy as outcome measure. Meta-analysis showed little significant heterogeneity among the studies \((I^2 = 0\% < 50\%\), \(RR = 1.13, 95\% [1.08, 1.19]\). Fixed effects model was taken into consideration. The overall effect tests \((P = 0.0001)\) suggested that test group combined with SIN had a more significant effective rate in treating RA than that of MTX (Figure 4).

Publication bias
The publication bias in 15 included articles \cite{24-39} was identified by funnel shape and Harbord’s modified test. The reversed funnel-shape plot showed generally symmetrical (Figure 5), and the result of Harbord’s modified test was not significant \((t = 1.07, P = 0.302\), Figure 6), indicating there might be no publication biases in those studies.

Subgroup analysis
Subgroup analysis was made on the clinical efficacy according to SIN alone and SIN plus MTX therapy both contrast to MTX group in RA therapy. 11 studies \cite{25-28,30-33,35-38} used SIN plus MTX as experimental group, while 4 studies \cite{24,25,34,39} took only SIN as test group. The heterogeneity \((P = 0.45 > 0.05, I^2 = 0\% < 50\%\) indicated that fixed effect model should be applied. The result revealed that groups with SIN alone also had higher effective rate than that of MTX \((P = 0.04\), Figure 7).

Sensitivity analysis
We removed the most \cite{29} and the least \cite{39} weighted of every subgroup and replaced fixed effects model to random effects model to confirm the stability of the 15 included studies \cite{24-39} on clinical efficacy. After removing the most weighted, the result was RR = 1.10, 95\% CI \((1.06, 1.15)\) (Figure 8), and the result of removing the least weighted was \([RR = 1.11, 95\% CI \(1.07, 1.16\)\), Figure 9]. Compared with the former results RR = 1.13, \([95\% CI \(1.08, 1.19\)\), Figure 4], there was no clear difference of RR values, which indicated low sensitivity and sound stability of the study.

Improvement of total clinical effective rate in 4 weeks treatment
Two trials \cite{33,36} were mentioned onset time in 4 weeks during trial period. There was significant heterogeneity \((P < 0.00001, I^2 = 95\% > 50\%\), random effect model was taken. The Meta-analysis showed that there weren’t significant difference between groups of SIN plus MTX and MTX alone \((P = 0.12\), Figure 10).

Morning stiffness time
Among 12 studies \cite{24,26,30,32,34,39} there were 1162 patents
with the description of morning stiffness time (min). High obvious heterogeneity was found ($P < 0.0001$, $I^2 = 91\% > 25\%$), random effect model was applied. The result showed the test group with SIN could decrease morning stiffness time better than that of MTX ($P < 0.0001$). Moreover, the subgroup analysis indicated that SIN alone also had better efficacy in decreasing morning stiffness time versus MTX ($P = 0.008$, Figure 11).

**Swollen joint count (SJC)**

Nine studies\(^{24,27-29,32,34,36,37,39}\) reported improvement in numbers of SJC. Heterogeneity test showed that studies had a considerable degree of heterogeneity ($P = 0.0009 < 0.05$, $I^2 = 70\% > 50\%$), so random model was chosen, there were significantly difference ($P = 0.008$). In parallel, subgroup analysis showed that SIN alone had better efficacy in improving SJC ($P = 0.02$), while SIN plus MTX had no advantages ($P = 0.23$), both taken MTX as the contrast standard (Figure 12).

**Grip strength**

6 trials\(^{27-30,32,36,39}\) took grip strength (kpa) as the outcome measure. There was significant heterogeneity ($P < 0.0001$, $I^2 = 86\% > 50\%$), random effect model was taken. The Meta-analysis showed that test group combined with SIN was better than MTX alone in promoting grip strength ($P = 0.03$). The subgroup analysis indicated that there was significant difference in the group of SIN plus MTX ($P = 0.04$), while no difference in SIN alone ($P = 0.71$), both with the comparison of MTX therapy (Figure 13).

**Erythrocyte sedimentation rate (ESR)**

12 trials\(^{25-33,35-37,43}\) reported improvement in ESR. Heterogeneity test showed that the including studies had a considerable degree of heterogeneity ($P = 0.0001$, $I^2 = 76\% > 50\%$), so random model was chosen, the result showed that there were significantly difference ($P < 0.0001$). The subgroup analysis showed that SIN alone had no advantages in decreasing ESR ($P = 0.41$), while SIN plus MTX had better efficacy ($P < 0.0001$, Figure 14).

**C-reactive protein (CRP)**

Exact 11 studies\(^{26,28,30,33,35-37,43}\) referred to the improvement in decreasing CRP. Due to the heterogeneity ($P < 0.0001$, $I^2 = 88\% > 50\%$), we chose a random model. The result revealed that SIN combined with MTX had better efficacy in decreasing CRP than MTX alone ($P < 0.0001$, Figure 15).

**Anti cyclic citrullinated peptide (anti-CCP)**

Anti-CCP testing presents early in RA process and has proved to predict severe disease and irreversible damage.\(^{44}\) Unfortunately only was one trial\(^{36}\) mentioned anti-CCP, we didn’t take it in meta-analysis. The result in trial showed SIN plus MTX had better efficacy than MTX alone in decreasing anti-CCP ($P < 0.05$).

**Blood platelet (PLT)**

Two trials\(^{32,35}\) took PLT as outcome measure. Due to the heterogeneity ($P = 0.26 > 0.05$, $I^2 = 21\% < 50\%$), we choose a fixed model. The overall effect test ($P < 0.0001$) indicated that the test group combined with SIN had a significantly effective rate in decreasing PLT than MTX alone (Figure 16).

**Disease activity score for rheumatoid arthritis in 28 joints (DAS28)**

There were 4 studies\(^{31,35,37,39}\) reported improvement in the DAS28. Heterogeneity test showed that the including studies had little heterogeneity ($P = 0.85 > 0.05$, $I^2 = 0\% < 25\%$), so fixed effects model was chosen, the re-
The result showed that SIN with MTX had better efficacy in decreasing DAS28 than MTX alone ($P < 0.0001$).

The health assessment questionnaire (HAQ) score among 3 studies was shown to be 0.32, 0.35, and 0.36, respectively. Heterogeneity was shown in the study ($P < 0.0001$).

The meta-analysis of the total clinical effective rate of sinomenine vs methotrexate in rheumatoid arthritis treatment was performed.

The funnel plot of the clinical effective rate was shown.

The Harbord's modified test of clinical effective rate was performed.

The meta-analysis for subgroups of sinomenine alone versus Sinomenine plus methotrexate in clinical efficacy was performed.
The random effect model was used. The result showed that there was no obvious difference between the two remedies in improvement of HAQ score ($P = 0.08$, Figure 18).

**Adverse events (ADEs)**

12 studies including 1177 cases reported adverse events (ADEs) during RA treatment, mainly included digestive system including gastrointestinal upset (T/C: 23/46) and Serum alanine transaminase (ALT) raising (T/C: 6/26), hematological system including white blood cell (WBC) declining (T/C: 8/16), dermato mucosal system including skin rash (T/C: 26/8), and nervous system including dizziness (T/C: 2/6) (Table 2). The heterogeneity was no significant ($P = 0.5 > 0.05, I^2 = 0% < 25%$), so the fixed model was applied. Taken together, ADEs occurred less frequently with the combination use of SIN than using MTX alone ($P < 0.0001$, Figure 19). Additionally, we made detailed analysis for ADEs of different systems, the results indicated that events occurred less frequently in the digestive system ($P < 0.0001$, Figure 20) during the combination use of SIN treatment than during MTX therapy, but occurred more in the dermato mucosal system ($P = 0.02$, Figure 21) with SIN treatment than MTX therapy, while adverse events of the nervous system and hematological system were similar for both treatments.
DISCUSSION

This review aimed to ascertain whether SIN therapy is efficacious for RA, especially when combined with MTX treatment. It must be acknowledged, however, that the methodological quality of the studies was gen-

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### Figure 14: Meta-analysis of erythrocyte sedimentation rate in subgroups of sinomenine alone and sinomenine plus methotrexate vs methotrexate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu W 2006</td>
<td>30.2 (14.74)</td>
<td>60 (32.14)</td>
<td>60 (15.33)</td>
<td>9.2%</td>
</tr>
<tr>
<td>Zhang K 2005</td>
<td>41.26 (15.11)</td>
<td>60 (42.52)</td>
<td>14.95 (60)</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

Subtotal (95% CI): 120 (18.5%), Heterogeneity: $\chi^2 = 0.00$, df = 1 ($P = 0.86$), $I^2 = 0$

Test for overall effect: $Z = 0.82$ ($P = 0.41$)

### Figure 15: Meta-analysis of C-reactive protein in sinomenine plus methotrexate vs methotrexate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gu F 2014</td>
<td>29.39 (12.89)</td>
<td>45 (42.3)</td>
<td>24.59 (45)</td>
<td>2.9%</td>
</tr>
<tr>
<td>Huang ZS 2010</td>
<td>6.5 (2.3)</td>
<td>30 (7.1)</td>
<td>2.6 (30)</td>
<td>33.3%</td>
</tr>
<tr>
<td>Ji H 2006</td>
<td>15.11 (7.74)</td>
<td>30 (15.57)</td>
<td>5.44 (30)</td>
<td>85.5%</td>
</tr>
<tr>
<td>Li YN 2008</td>
<td>31.9 (23.8)</td>
<td>35 (46.5)</td>
<td>20.3 (34)</td>
<td>1.9%</td>
</tr>
<tr>
<td>Ling 2014</td>
<td>3.64 (0.98)</td>
<td>48 (4.97)</td>
<td>1.41 (48)</td>
<td>44.3%</td>
</tr>
<tr>
<td>Lu Y 2011</td>
<td>7.12 (8.24)</td>
<td>40 (9.65)</td>
<td>8.96 (40)</td>
<td>7.8%</td>
</tr>
<tr>
<td>Sun SY 2006</td>
<td>8.9 (5.6)</td>
<td>62 (18.1)</td>
<td>10.2 (62)</td>
<td>9.4%</td>
</tr>
<tr>
<td>Wang Q 2010</td>
<td>6.33 (3.22)</td>
<td>120 (10.12)</td>
<td>3.36 (120)</td>
<td>13.8%</td>
</tr>
<tr>
<td>Xia YK 2012</td>
<td>10.3 (9.1)</td>
<td>52 (18.1)</td>
<td>8.1 (52)</td>
<td>5.2%</td>
</tr>
<tr>
<td>Zhang K 2005</td>
<td>17.38 (13.56)</td>
<td>60 (19.52)</td>
<td>14.31 (60)</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

Total (95% CI): 558 (499), Heterogeneity: $\chi^2 = 4.22$, df = 10 ($P = 0.0001$), $I^2 = 88$

Test for overall effect: $Z = 4.30$ ($P = 0.0001$)

### Figure 16: Meta-analysis of blood platelet in sinomenine plus methotrexate vs methotrexate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li YN 2008</td>
<td>349.9 (72.6)</td>
<td>35 (394.8)</td>
<td>52.9 (34)</td>
<td>71.3%</td>
</tr>
<tr>
<td>ZHU FX 2013</td>
<td>215.25 (63.23)</td>
<td>13 (292.18)</td>
<td>56.49 (12)</td>
<td>22.9%</td>
</tr>
</tbody>
</table>

Total (95% CI): 48 (100%), Heterogeneity: $\chi^2 = 1.27$, df = 1 ($P = 0.26$), $I^2 = 21$

Test for overall effect: $Z = 4.21$ ($P = 0.0001$)

### Figure 17: Meta-analysis of disease activity score for rheumatoid arthritis in 28 joints in sinomenine plus methotrexate vs methotrexate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Control Mean (SD)</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ling 2014</td>
<td>3.14 (1.42)</td>
<td>48 (5.18)</td>
<td>1.65 (48)</td>
<td>33.3%</td>
</tr>
<tr>
<td>Wang Q 2010</td>
<td>1.1 (0.7)</td>
<td>120 (1.2)</td>
<td>0.5 (120)</td>
<td>76.8%</td>
</tr>
<tr>
<td>Xia YK 2012</td>
<td>9.2 (1.6)</td>
<td>52 (13.8)</td>
<td>1.9 (52)</td>
<td>32.9%</td>
</tr>
</tbody>
</table>

Total (95% CI): 220 (166), Heterogeneity: $\chi^2 = 4.37$, $I^2 = 184.80$, df = 2 ($P = 0.0001$), $I^2 = 99$

Test for overall effect: $Z = 1.78$ ($P = 0.08$)
### Table 2 Characteristics of 16 included studies on adverse events for rheumatoid arthritis

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment group (n)</th>
<th>Control group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DS</td>
<td>RS</td>
</tr>
<tr>
<td>Chen YL 2013</td>
<td>7/45</td>
<td>Unclear</td>
</tr>
<tr>
<td>Ding H 2010</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Gu F et al 2014</td>
<td>4/0</td>
<td>0/3</td>
</tr>
<tr>
<td>Huang ZS et al 2010</td>
<td>3/0</td>
<td>3/0</td>
</tr>
<tr>
<td>Ji H et al 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu W et al 2006</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Ling Y et al 2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu Y et al 2011</td>
<td>0/0</td>
<td>0/1</td>
</tr>
<tr>
<td>Li YN et al 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun SY et al 2006</td>
<td>2/0</td>
<td>0/1</td>
</tr>
<tr>
<td>Sun SY 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang WQ 2010</td>
<td>0/0</td>
<td>9/0</td>
</tr>
<tr>
<td>Xia YK et al 2012</td>
<td>12/0</td>
<td>0/5</td>
</tr>
<tr>
<td>Zhu FX et al 2013</td>
<td>3/0</td>
<td>0/1</td>
</tr>
<tr>
<td>Zhang JL 2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang K et al 2005</td>
<td>2/0</td>
<td>0/2</td>
</tr>
</tbody>
</table>

Notes: DS: digestive system; RS: respiratory system; DMS: dermato mucosal system; HS: hematological system; NS: nervous system; A: number of adverse events; T: case number in treatment group; C: case number in control group.

Figure 19: Meta-analysis of adverse events in the groups combined with sinomenine vs methotrexate.

Figure 20: Meta-analysis of digestive systemic adverse events in the groups combined with sinomenine vs methotrexate.
erally not high. Firstly, the cases in our included articles were from 40 to 186, which meant there were no large-scale RCTs, the current evidence was insufficient to make a routine recommendation of SIN for RA treatment. Besides, we thoroughly searched the English database, while no eligible studies were found.

Secondly, among the 16 eligible trials, only 4 trials applied an A versus B design (totally different make-up between the two groups), rest of the trials used an A + B versus B design where patients are randomized to receive an experimental treatment plus the control treatment (Treatment Group) versus the control treatment (Control Group). This kind of design tend to generate false positive results. Thus, stakeholders should take critical thinking about the positive conclusions.

Thirdly, the duration of therapy in our included trials was indeed too short to achieve conclusive results during the chronic course of RA. Furthermore, none was mentioned a follow-up period. The outcomes were only assessed at the end of the treatment (ranging from 8-24 weeks). Some long-term ADEs such as liver and kidney functional damage would not be properly assessed. Additionally, it is worth noting that all the trials mentioned the number of ADEs, without distinguishing whether its stands for patients’ number of ADEs or the number of ADE phenomenon itself, which may lead to repeated counting and the final heterogeneity in our Meta-analysis.

In conclusion, Meta-analysis can save cost and time disposing the data of multiple independent trials to increase sample size and to sharpen test performance. Besides, it can provide evidence-based medical evidence for clinicians in the areas of clinical practice. This Meta-analysis from 15 aspects mentioned above revealed that SIN therapy, especially combined with MTX for RA had better clinical efficacy with less adverse events than MTX therapy alone.
SIN may be a valuable way to treat RA in clinical practice, and the combination of SIN and MTX should be taken more seriously clinically, although current evidence needs to be further verified by more high-quality trials.

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REFERENCES


