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Chinese Medicine External Therapy Combined with Conventional Drug Treatment for Rheumatoid Arthritis: A Systematic Review and Meta-analysis

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Introduction: Chinese medicine (CM) external therapy is commonly used to treat rheumatoid arthritis (RA) in combination with conventional drug. This study aims to provide a comprehensive synthesis on the efficacy of CM external therapy combined with conventional drug treatment in RA.

Methods: Randomised controlled trials (RCTs) experimenting the efficacy of CM external therapy (acupuncture, moxibustion and CM fumigation) combined with conventional drug in comparison with conventional drug only in RA patients were collected from PubMed, Medline, Cochrane Central of Controlled Trials (CENTRAL), ClinicalTrials.gov, China National Knowledge Infrastructure (CNKI), and Wanfang databases. Quality was assessed using the Cochrane Risk of Bias Tool. The outcome measures which include Disease Activity Score-28 (DAS28), Visual Analogue Scale (VAS), Swollen Joint Count (SJC), Tumour Necrosis Factor (TNF-α), serum levels of C-reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) were analysed using Review Manager 5.4.1 and GRADEpro GDT online software.

Results: Fifty RCTs fulfilling the criteria were included. Although some level of efficacy was statistically noted on the use of CM external therapies, their certainty levels are mixed, ranging only in between moderate and low.

Conclusions: Mixed levels of certainty has hindered the drawing of conclusion. The addition of CM external therapies to conventional drug treatment may provide some benefits in RA. Further clinical trials with considerations in minimising the risk of bias are recommended to provide more high-quality evidence in the effect of CM external therapies as a complementary treatment in RA.

Keywords: *Chinese medicine, fumigation, meta-analysis, moxibustion, rheumatoid arthritis, systematic review*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease which involves pain, swelling, tenderness, and deformity of joints, leading to significant morbidity and impaired quality of life for millions of individuals worldwide. It is also referred to as a systemic illness as it causes inflammation in multiple tissues, organs, and systems such as the heart, lungs, eyes, blood vessels and skin.[1-3] Between 1980 and 2018, the global prevalence of RA was 460 per 100,000 population, with a 95 percent prediction interval of 0.06–1.27%.[4] In more than 60% of RA patients, a combination of disease-modifying anti-rheumatic drugs (DMARDs) is given as primary treatment to slow down the progression of joint deterioration, with methotrexate (MTX) (55.6%) and hydroxychloroquine (HCQ) (79.7%) being the most prescribed.[5] DMARDs, on the other hand, can cause serious adverse effects, leading to the cessation of treatment. Side effect was revealed as the most significant predictor for treatment discontinuation of MTX (75%) and sulfasalazine (SSZ) (88.9%), with hepatotoxicity and bone marrow suppression as the most reported side effects.[5] Hence, Chinese medicine (CM) was proposed to complement the treatment of RA to reduce the adverse effects of conventional drugs and improve the quality of life.

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In Inner Canon of Huangdi (*Huangdi Neijing*), RA was classified as bi syndrome (impediment syndrome) or *li jie feng*, and was caused by the obstruction of *qi*, phlegm, and blood stasis, as well as the obstructions of meridians and collaterals.[6] Through a holistic approach, CM can be applied in conjunction with conventional treatment of RA to achieve favourable effects, lowered risks of adverse pharmacodynamic interactions and improved drug stability.[7] Besides orally administered Chinese herbal medicine, the external therapies of this traditional modality are often incorporated as a complementary treatment of RA due to its relatively low risk and expense. These therapies, such as acupuncture and moxibustion are known to have anti-inflammatory effects which decrease IL-1, IL-6, and TNF production, regulate the central neurotransmitter level and improve the body's immune function, as well as regulating the production of endorphins, serum cortisol levels, plasma adrenocorticotropic hormone, and synovial nuclear factor kappa B (NF-κB).[8]

While conventional drug therapies have made substantial progress in managing RA, many patients experience incomplete symptom relief and adverse effects. Chinese medicine external therapy, which encompasses a variety of modalities has been increasingly utilised as an adjunct treatment for RA. Hence, this study aims to determine the efficacy of combined CM external therapy and conventional drug in comparison to conventional drug therapy alone to fill the existing knowledge gap and generate evidence-based recommendations for the implementation of this integrative approach. This study had been approved by the IMU Joint Committee on Research and Ethics (IMU-JC).

METHODS

This study was based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Appendix 1).

Study selection

Electronic-based literature search was conducted in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, China National Knowledge Infrastructure (CNKI) and Wanfang databases to collect studies of interest, published in English and Chinese, since the establishment of these databases until year 2021 through search keywords and MeSH terms such as rheumatoid arthritis, Chinese herbal medicine, traditional CM, acupuncture, needling, moxibustion, conventional drug, western medicine, and randomised controlled trials. The Chinese translation of the above keywords was used for Chinese databases (Appendix 2). The eligible research reference lists were also manually searched for additional studies. The title, abstract and full text of these studies were screened by two researchers independently using RefWorks. Studies which met the inclusion criteria were included.

Inclusion criteria

(i) Type of studies

All RCTs that are aimed at evaluating the efficacy of CM external therapy used in conjunction with conventional drugs in the treatment of RA conducted at least for one week for VAS and two weeks for other outcome measures were assessed in this study.

(ii) Type of participants

Patients involved fulfilled the criteria for RA diagnosis (1987 or 2010 ACR/EULAR criteria). No restrictions were placed on patient gender, patient age, patient ethnicity, RA disease course, RA disease severity, or RA disease duration.

(iii) Types of interventions and comparison

For the experimental group, CM external therapy (acupuncture, moxibustion and fumigation) was used in conjunction with conventional drug. For the control group, only conventional drug treatment was implemented. Any dosage, mode and frequency of administration were included.

(iv) Types of outcome measures

The outcomes from both intervention and control groups were assessed using measures such as a 1-10 score on the disease activity score-28 (DAS), visual analogue scale (VAS), swollen joint count (SJC), joint functional activity score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), et cetera. The studies had two time points for the measurement (pre- and post-treatment). The duration of treatment ranged from 2 to 24 weeks.

Exclusion criteria

All matter of studies in relation to animal experiments, review articles, editorials, case reports, comments and letters were excluded. Studies that did not fit to inclusion criteria were also ruled out. Studies involving a combination of CM external therapies, or in conjunction with orally administered Chinese herbal medicine were also excluded.

Data extraction

Data including the first author, year of publication, number of participants, intervention method of control and treatment group, participants' characteristics (sex, age, type of RA, if provided), outcome measures and adverse events were extracted into a spreadsheet. The authors were contacted for any uncertain data. This process was conducted by two researchers independently. Any discrepancy was resolved through discussion with another co-investigator.

Assessment of risk of bias

The qualities of potential eligible studies were evaluated independently by two researchers utilising the Cochrane Risk of Bias Tool.[9] This assessment comprised of random sequence generation, blinding of participants and personnel, blinding of outcome reporting, allocation concealment, selective reporting, incomplete outcome data and other bias. Studies were categorised as having low, high, or unclear risk of bias accordingly. Any inconsistencies among researchers were resolved through discussion.

Statistical analysis

From the extracted data, the outcomes were analysed and expressed through mean difference (MD) with 95% confidence interval (CI). Chi-squared test and I^2 test were applied to reflect statistical heterogeneity of the studies. Fixed effect model was used for $I^2 < 50\%$ and random effect model was used for $I^2 > 50\%$. Funnel plots were utilised to assess publication bias. RevMan 5.4.1[10] was used to perform meta-analysis. Subgroup analysis was not carried out because the acupoint, herb (for fumigation) and drug selection for each study were too diverse. Thus, the sample size for

each subgroup will be too small to draw convincing conclusion (low statistical power). Whereas sensitivity analysis was not carried out because there was no study with decision that was arbitrary or unclear.

Assessment of evidence certainty

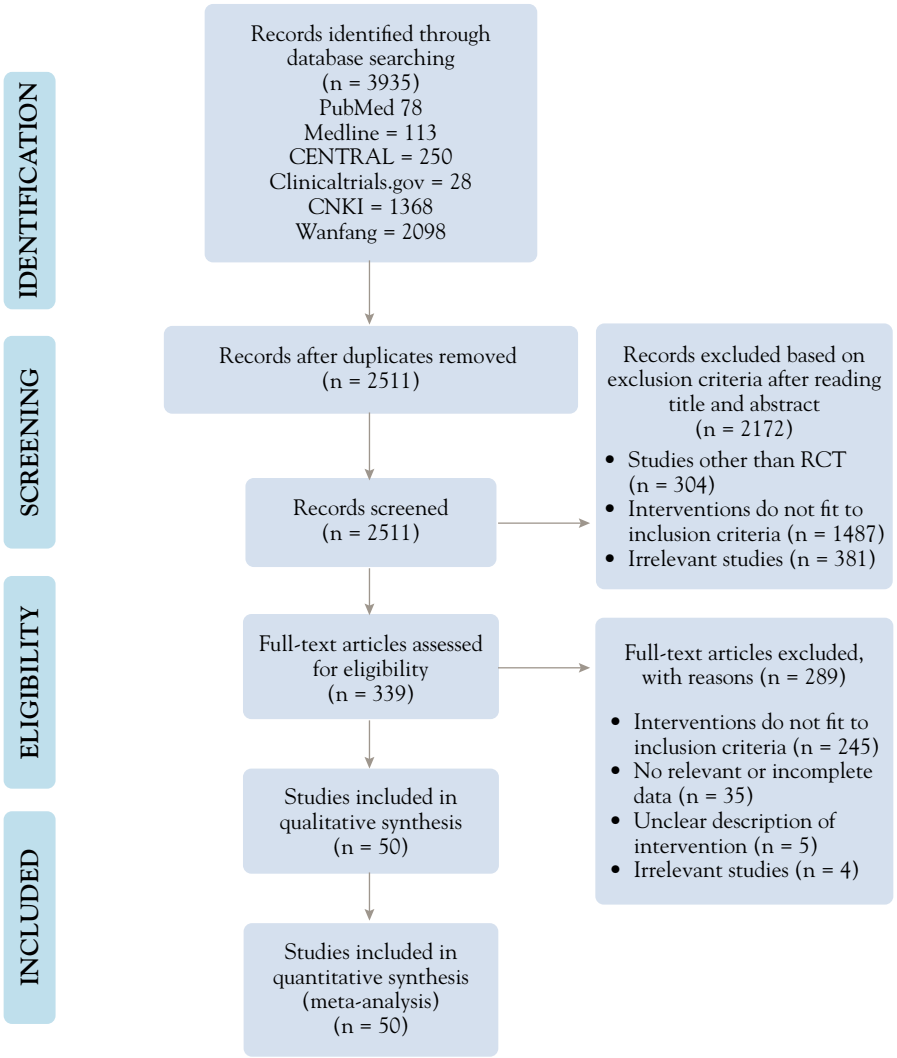
The certainty of the evidence for the most relevant and available metrics pertaining to all critical and important outcomes was evaluated using the GRADE methodology. The certainty of evidence was categorised into four levels: high, moderate, low, and very low. Each outcome's certainty assessment based on GRADE was documented in GRADE evidence profiles. GRADEpro GDT online software[11] was employed to compile these evidence profiles.

RESULTS

Study Selection

In the initial search, 3935 possibly relevant studies have been identified, according to the search strategy. After screening, 50 RCTs[12-61] that fulfilled the criteria were included in the systematic review and meta-analysis. A comprehensive flowchart demonstrating the selection process was shown in a PRISMA flowchart (Figure I).

Figure I: PRISMA flow diagram.



Study Characteristics

The included studies involved a total of 4984 participants. The mean age of the participants ranged from 27.5 to 60.5 years old. The male to female ratio of the studies cannot be determined as some studies failed to mention them. In all the studies, none of the subjects were reported to have other disease complications besides RA; all of them were either healthy or otherwise not reported. Within the studies, the participants were given a wide variety of conventional drugs for RA treatment, such as diclofenac, methotrexate, meloxicam, and leflunomide, et cetera. The CM external therapy includes acupuncture, moxibustion and fumigation. The duration of experiment varied from 2 to 13 weeks. The outcome measures that were utilised within the studies to assess the effectiveness of treatment were DAS28, VAS, SJC, CRP, ESR, IL-1, IL-2, and TNF-α. The characteristics and study design of the included RCTs are presented in Table I.

Table I: Characteristics and study design of included studies.

STUDY ID	DETAILS OF GROUP INTERVENTION		SAMPLE SIZE (EG/CG)	STUDY DURATION (WEEK)	ADVERSE EVENT	OUTCOME MEASURE
	EXPERIMENTAL GROUP (EG)	CONTROL GROUP (CG)				
1. LEE 2006[12]	Moxibustion + MTX, NSAIDs, Loxicam	MTX, NSAIDs, Loxicam	60 (30/30)	13	No adverse event	CRP, ESR
2. CJX 2007[13]	CM fumigation + Diclofenac, MTX	Diclofenac, MTX	118 (78/40)	4	Not reported	VAS, SJC
3. LXD 2008[14]	CM fumigation + Meloxicam, methotrexate	Meloxicam, MTX	22 (12/10)	3	Not reported	CRP, ESR, TNF-α
4. YSL 2008[15]	CM fumigation + Meloxicam, MTX	Meloxicam, MTX	62 (31/31)	3	Not reported	CRP, ESR
5. YY 2009[16]	CM fumigation + DMARDs, NSAIDs, glucocorticosteroids, photomedicine	DMARDs, NSAIDs, glucocorticosteroids, photomedicine	96 (49/47)	2	Not reported	CRP, ESR
6. LY 2010[17]	Acupuncture + LEF	LEF	80 (40/40)	12	Not reported	CRP, ESR
7. LYY 2011[18]	Acupuncture + Meloxicam, MTX, LEF	Meloxicam, MTX, LEF	80 (40/40)	12	Not reported	SJC, CRP, ESR
8. HJL 2011[19]	Acupuncture + Diclofenac, MTX, SSZ	Diclofenac, MTX, SSZ	54 (28/26)	4	Not reported	VAS, SJC, CRP, ESR
9. SF 2011[20]	Moxibustion + MTX, Recoxib	MTX, Recoxib	37 (19/18)	12	No adverse event	DAS28
10. YJ 2012[21]	Moxibustion + MTX	MTX	60 (30/30)	12	Not reported	DAS28, VAS, SJC, CRP, ESR
11. ZLQ 2012[22]	CM fumigation + Meloxicam, MTX	Meloxicam, MTX	42 (21/21)	3	Not reported	SJC, CRP, ESR, IL-2, TNF-α
12. SW 2013[23]	Moxibustion + LEF	LEF	240 (120/120)	12	Not reported	DAS28, VAS, SJC, CRP

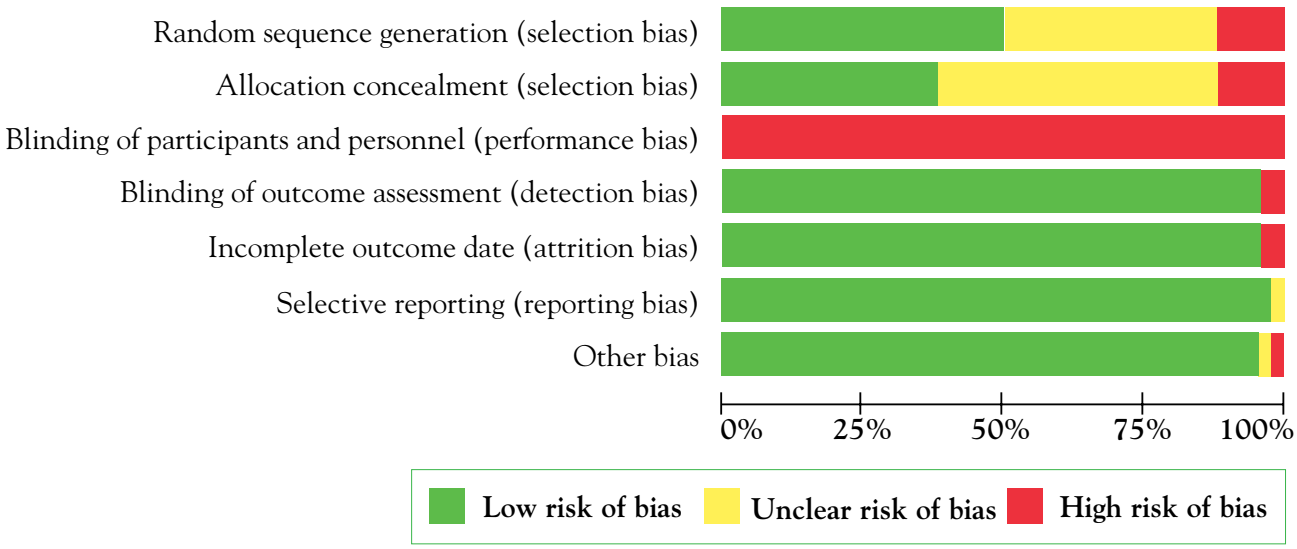
13. CYZ 2013[24]	Moxibustion + MTX, Loxoprofen sodium	MTX, Loxoprofen sodium	40 (20/20)	12	Increased AST, decreased WBC and proteinuria in EG (n=2) and CG (n=4)	DAS28, CRP, ESR
14. WJM 2013[25]	CM fumigation + Meloxicam, MTX	Meloxicam, MTX	52 (28/24)	13	Not reported	DAS28, SJC, CRP, ESR
15. WXL 2014[26]	CM fumigation + Meloxicam, MTX	Meloxicam, MTX	74 (37/37)	8	No adverse event	ESR
16. CXF 2015[27]	CM fumigation + DMARDs, MTX	DMARDs, MTX	35 (18/17)	1	Not reported	VAS
17. SYX 2015[28]	Acupuncture + MTX, Celecoxib	MTX, Celecoxib	76 (38/38)	12	No adverse event	DAS28, CRP, ESR
18. TY 2015[29]	Moxibustion + LEF, SSZ, Meloxicam	LEF, SSZ, Meloxicam	68 (34/34)	12	Not reported	CRP, ESR
19. LIU 2015[30]	Moxibustion + Esomeprazole magnesium, Celecoxib, MTX	Esomeprazole magnesium, Celecoxib, MTX	120 (60/60)	8	Not reported	DAS28, VAS, SJC, CRP, ESR
20. YJY 2015[31]	Moxibustion + LEF	LEF	50 (25/25)	12	Not reported	DAS28, VAS, SJC, CRP, ESR
21. ZK 2015[32]	CM fumigation + Meloxicam, MTX	Meloxicam, MTX	60 (30/30)	2	Not reported	VAS
22. LK 2016[33]	Acupuncture + Ibuprofen, MTX	Ibuprofen, MTX	60 (30/30)	8	Not reported	SJC, CRP, ESR
23. PXM 2016[34]	Acupuncture + Prednisone, MTX	Prednisone, MTX	60 (30/30)	12	Not reported	CRP, ESR
24. HLZ 2016[35]	Moxibustion + MTX, Celecoxib	MTX, Celecoxib	62 (30/32)	2	No adverse event	DAS28, VAS, CRP, ESR
25. YCH 2016[36]	Moxibustion + MTX	MTX	32 (16/16)	12	Not reported	DAS28, VAS, SJC, CRP, ESR
26. GBQ 2017[37]	CM fumigation + MTX	MTX	60 (30/30)	24	Not reported	VAS
27. LCS 2017[38]	Acupuncture + MTX, Diclofenac	MTX, Diclofenac	60 (30/30)	8	Not reported	VAS, SJC, CRP, ESR
28. TH 2017[39]	Moxibustion + MTX, LEF	MTX, LEF	40 (20/20)	12	Not reported	DAS28, VAS, CRP, ESR
29. WH 2017[40]	CM fumigation + MTX, DMARDs	MTX, DMARDs	68 (34/34)	1	Not reported	VAS
30. BY 2018[41]	Moxibustion + MTX or LEF	MTX or LEF	46 (23/23)	8	Not reported	DAS28, VAS, CRP, ESR
31. GYY 2018[42]	Moxibustion + MTX or LEF	MTX or LEF	37 (20/17)	8	Not reported	DAS28, VAS, CRP, ESR
32. LSR 2018[43]	Acupuncture + MTX, folic acid, Diclofenac	MTX, folic acid, Diclofenac	60 (30/30)	6	Nausea, acid reflux, heartburn, gastrointestinal discomfort in CG (n=6)	DAS28, VAS, SJC, CRP, ESR

33. ZY 2018[44]	Acupuncture + MTX, folic acid, ibuprofen	MTX, folic acid, ibuprofen	56 (28/28)	12	Not reported	DAS28, CRP, ESR
34. PJ 2018[45]	Acupuncture + Diclofenax, MTX	Diclofenax, MTX	60 (30/30)	8	No adverse event	CRP, ESR
35. XSG 2018[46]	CM fumigation + LEF	LEF	70 (35/35)	8	Not reported	ESR
36. DJY 2019[47]	Moxibustion + MTX, folic acid, LEF	MTX, folic acid, LEF	66 (34/32)	8	Blister caused by moxibustion in EG (n=2)	DAS28, VAS, SJC, CRP, ESR
37. HY 2019[48]	Moxibustion + LEF, ketoprofen	LEF, ketoprofen	60 (30/30)	12	Not reported	VAS
38. LW 2019[49]	Moxibustion + Fluorometer special tablets, Celecoxib	Fluorometer special tablets, Celecoxib	500 (250/250)	12	Not reported	SJC, CRP, ESR
39. TXW 2019[50]	Moxibustion + LEF, Celecoxib	LEF, Celecoxib	176 (88/88)	12	Not reported	DAS28, CRP, ESR
40. WCF 2019[51]	CM fumigation + MTX, LEF	MTX, LEF	60 (30/30)	12	Nausea, head discomfort in EG (n=2) GI discomfort, headache, 1 case raised ALT in CG (n=9)	SJC, CRP, ESR, TNF-α
41. WJL 2019[52]	Moxibustion + MTX, LEF	MTX, LEF	60 (30/30)	8	2 cases of blister caused by moxibustion	VAS, CRP
42. ZLY 2019[53]	CM fumigation + MTX, LEF	MTX, LEF	36 (18/18)	4	GI discomfort in EG (n=2)	DAS28, SJC, CRP, ESR
43. ZY 2019[54]	Moxibustion + MTX, folic acid	MTX, folic acid	46 (23/23)	4	Not reported	DAS28, CRP, ESR
44. CYY 2020[55]	CM fumigation + LEF, Celecoxib	LEF, Celecoxib	61 (31/30)	4	Not reported	DAS28, SJC, CRP, ESR, IL-1
45. LYL 2020[56]	Acupuncture + MTX	MTX	96 (48/48)	2	Not reported	SJC, ESR
46. JL 2020[57]	Acupuncture + MTX, folic acid, Diclofenac	MTX, folic acid, Diclofenac	40 (20/20)	12	Mouth ulcer, nausea, gastric discomfort in CG (n=2)	VAS, SJC, CRP, ESR
47. WXG 2020[58]	CM fumigation + MTX, LEF	MTX, LEF	83 (42/41)	6	Not reported	SJC
48. WYY 2020[59]	Moxibustion + MTX, folic acid, LEF	MTX, folic acid, LEF	64 (31/33)	8	Blister caused by moxibustion in EG (n=2)	DAS28, VAS, CRP, ESR
49. YAH 2020[60]	CM fumigation + MTX	MTX	124 (62/62)	13	Not reported	DAS28, VAS
50. YZY 2020[61]	Moxibustion + MTX, folate, LEF	MTX, folate, LEF	66 (34/32)	8	Not reported	DAS28, VAS, CRP, ESR

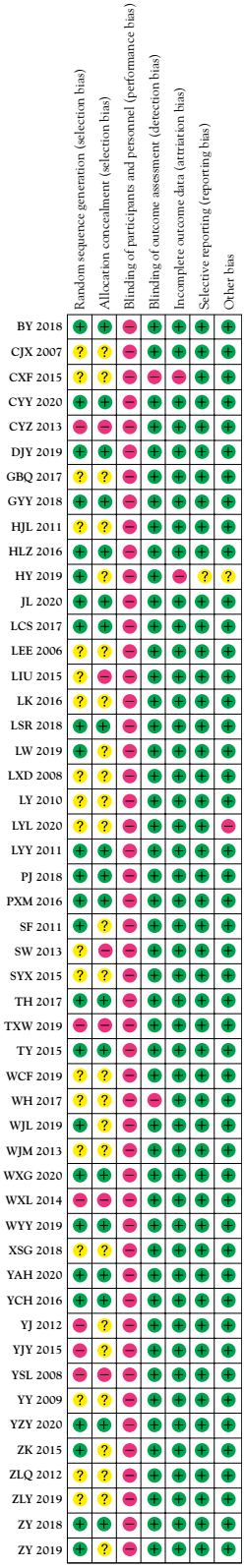
MTX = Methotrexate, LEF = Leflunomide, DAS28 = Disease activity score-28, VAS = Visual analogue scale, SJC = Swollen joint count, CRP = C-reactive protein, ESR = Erythrocyte sedimentation rate, IL-1= Interleukin-1, IL-2= Interleukin-2, TNF-α= Tumour Necrosis Factor-α, EG= Experiment group, CG= Control group, GI= Gastrointestinal.

Assessment of Risk of Bias

Most of the studies showed low risk of bias in blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. More than 35% of the studies have an unclear risk of bias in random sequence generation and allocation concealment as they were not reported in the studies. As for the blinding of participants and personnel, all studies showed high risk of bias. One study[56] reflected high risk of bias in other bias as the treatment duration only lasted for two weeks, which was insufficient to evaluate the treatment outcome for a chronic disease like RA. The results are shown in the risk of bias graph (Figure II). The justifications of risk of bias for each study are listed in Appendix 3.



a) Risk of bias graph



b) Risk of bias summary

Figure II. Risk of bias findings.

Data Analysis

1. DAS28

DAS-28 is a composite score that combines the assessment of tender and swollen joint counts, the patient's global assessment of disease activity (PGA), and either ESR or C-reactive protein (CRP) levels. It provides a quantitative measure of disease activity, with higher scores indicating more severe disease.

a) Drug + acupuncture

Three included RCTs involving 192 participants compared the DAS28 score after the treatment. Fixed effect model was adopted as no significant heterogeneity was detected (P = 0.50, I^2 = 0%). A significant difference (MD = 0.56, 95% CI [0.26, 0.87], P = 0.0003) between both groups (Figure IIIa) and moderate certainty of evidence (Appendix 5: Table 1) were observed.

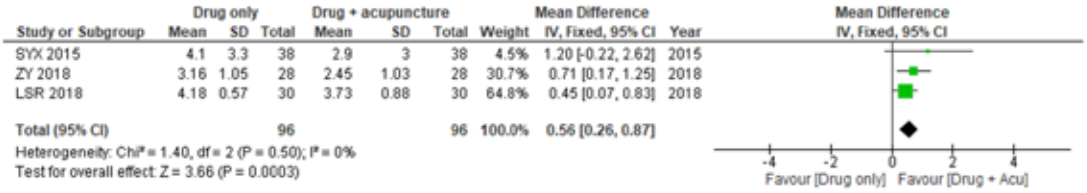


Figure IIIa: Drug + acupuncture [experimental group] VS drug only [control group], outcome: DAS28.

b) Drug + moxibustion

Sixteen RCTs involving 1,120 participants measured DAS28 score. Random effect model was adopted due to significant heterogeneity detected among the trials (P < 0.00001, I^2 = 82%). There is statistically significant difference between both groups (MD = 0.77, 95% CI [0.53, 1.01], P < 0.00001) (Figure IIIb), and low certainty of evidence (Appendix 5: Table 2).

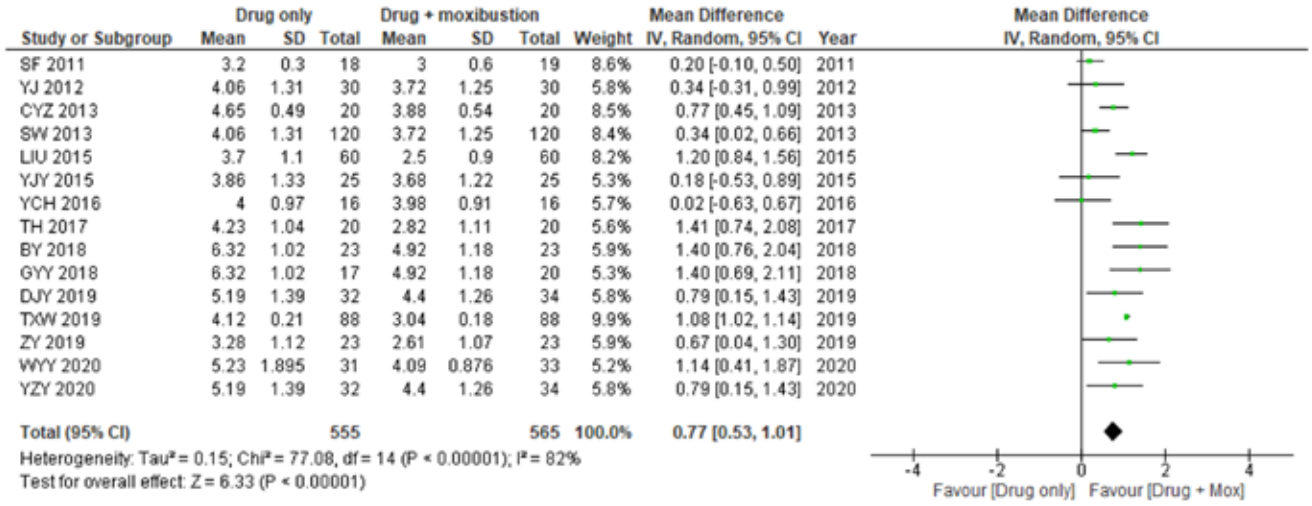


Figure IIIb: Drug + moxibustion [experimental group] VS drug only [control group], outcome: DAS28.

c) Drug + fumigation

Four included RCTs involving 273 participants compared the DAS28 score after treatment. Random effect model was adopted due to the substantial heterogeneity (P = 0.10, I^2 = 52%). A significant difference between both groups (MD = 0.80, 95% CI [0.50, 1.10], P < 0.00001) (Figure IIIc) and low certainty of evidence (Appendix 5: Table 3) were observed.

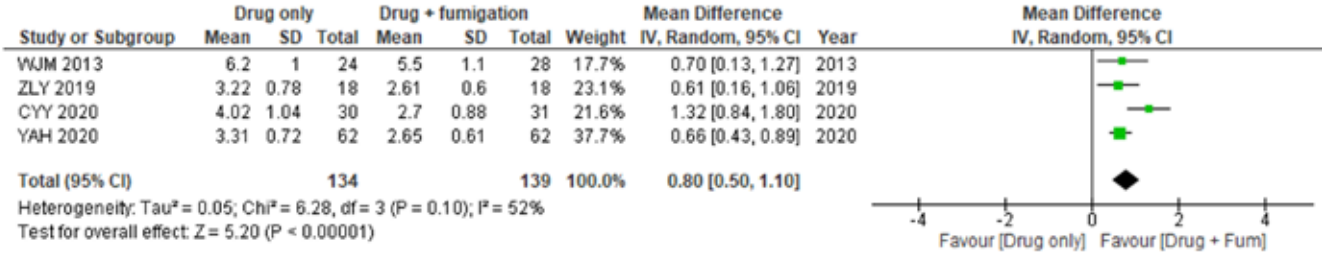


Figure IIIc: Drug + fumigation [experimental group] VS drug only [control group], outcome: DAS28.

2. VAS

The VAS involves patients marking a point on a straight line to indicate the intensity of their pain or overall disease activity. It provides a subjective measure of pain or disease perception. A higher score indicates a higher pain intensity.

a) Drug + acupuncture

Four included RCTs involving 240 participants compared the VAS score after the treatment. For substantial heterogeneity among the studies (P = 0.09, I^2 = 54%), random effect model was utilised. The result revealed significant difference (MD = 1.08, 95% CI [0.70, 1.46], P < 0.00001) between both groups (Figure IVa), and low certainty of evidence (Appendix 5: Table 1).

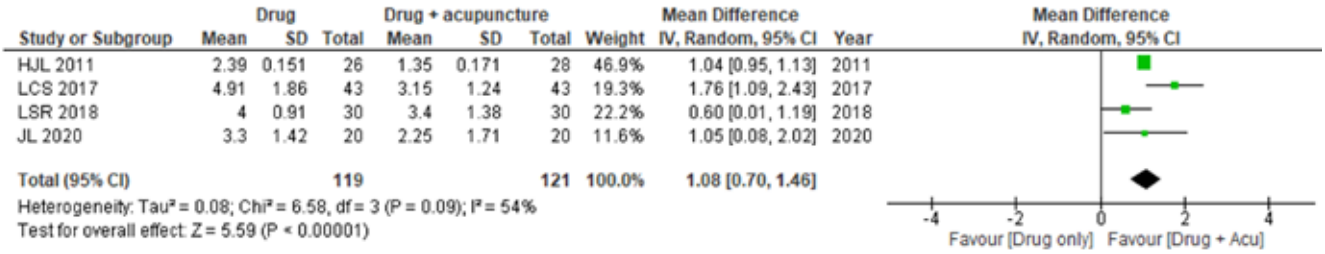


Figure IVa: Drug + acupuncture [experimental group] VS drug only [control group], outcome: VAS.

b) Drug + moxibustion

Fourteen RCTs involving 1,003 participants measured using VAS. The heterogeneity was notable (P < 0.00001. I^2= 81%). Hence, random effect model was adopted. The results showed a significant difference between both groups (MD=1.17. 95% CI [0.82, 1.52], P < 0.00001) (Figure IVb), and low certainty of evidence (Appendix 5: Table 2).

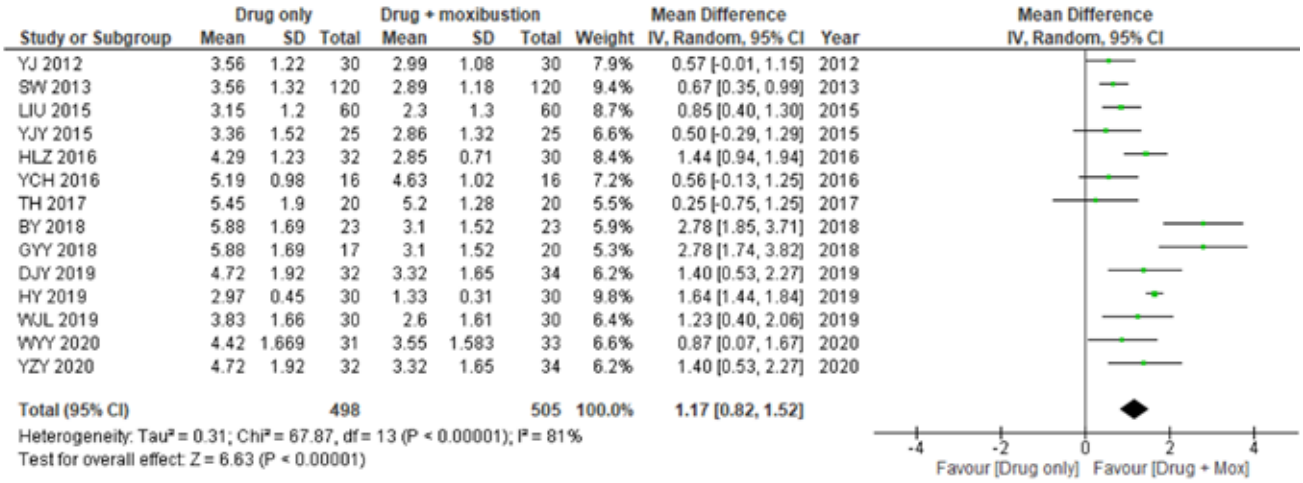


Figure IVb: Drug + moxibustion [experimental group] VS drug only [control group], outcome: VAS.

c) Drug + fumigation

Six included RCTs involving 465 participants compared the VAS score after the treatment. Random effect model was adopted due to high heterogeneity ($P < 0.0001$, $I^2 = 81\%$). There were significant difference (MD = 1.68, 95% CI [1.24, 2.13], $P < 0.00001$) between both groups (Figure IVc) and low certainty of evidence (Appendix 5: Table 3).

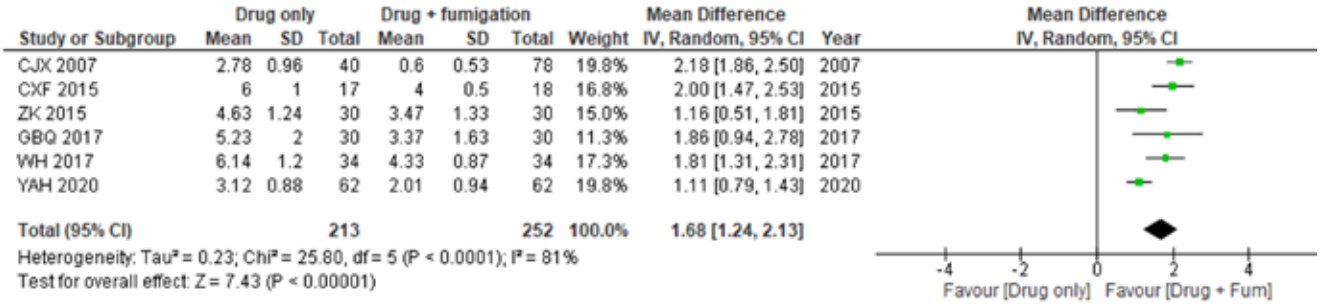


Figure IVc: Drug + fumigation [experimental group] VS drug only [control group], outcome: VAS.

3. SJC

SJC is an assessment utilised to reflect the amount of inflamed synovial tissue of RA patients by physically examining and counting the number of joints with pain and swelling. The higher the score, more joints are involved and thus an increased severity.

a) Drug + acupuncture

In seven included RCTs, SJC after the treatment for 476 participants were observed. Minimal heterogeneity was detected ($P = 0.23$, $I^2 = 26\%$) and a fixed effect model was adopted. The result demonstrated a significant lower SJC in experimental group (MD = 0.81, 95% CI [0.44, 1.17], $P < 0.0001$) (Figure Va), and moderate certainty of evidence (Appendix 5: Table 1).

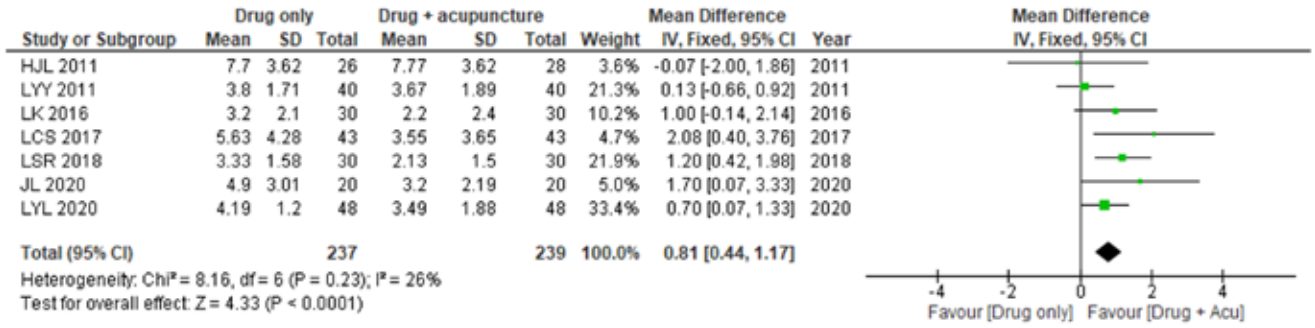


Figure Va: Drug + acupuncture [experimental group] VS drug only [control group], outcome: SJC.

b) Drug + moxibustion

SJC was measured in four studies involving 1036 patients. Random effect model was adopted due to high heterogeneity (P < 0.00001, I^2 = 81%). The results indicated a significant difference between both groups (MD=1.89, 95% CI [1.40, 2.37], P < 0.00001) (Figure Vb), and low certainty of evidence (Appendix 5: Table 2).

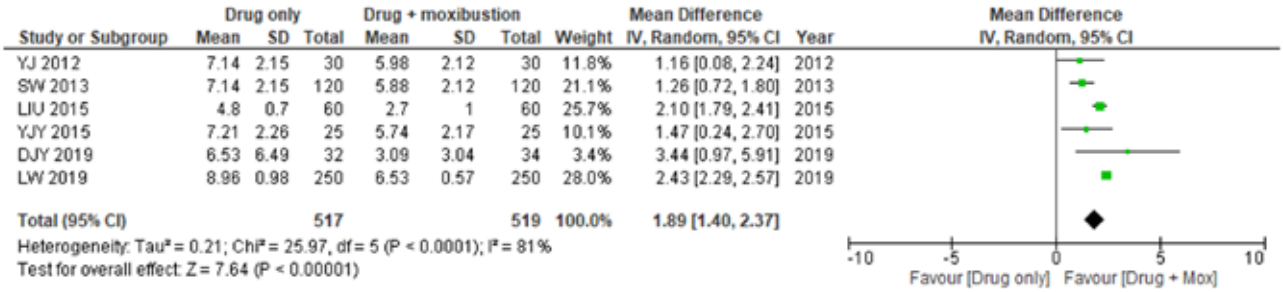


Figure Vb: Drug + moxibustion [experimental group] VS drug only [control group], outcome: SJC.

c) Drug + fumigation

Seven included RCTs involving 452 participants were observed. Substantial heterogeneity was detected (P = 0.10, I^2 = 44%) and a fixed effect model was adopted. SJC in experimental group was observed to be significantly lower when compared to experimental group (MD = 2.39, 95% CI [2.12, 2.67], P < 0.00001) (Figure Vc), with low certainty of evidence (Appendix 5: Table 3).

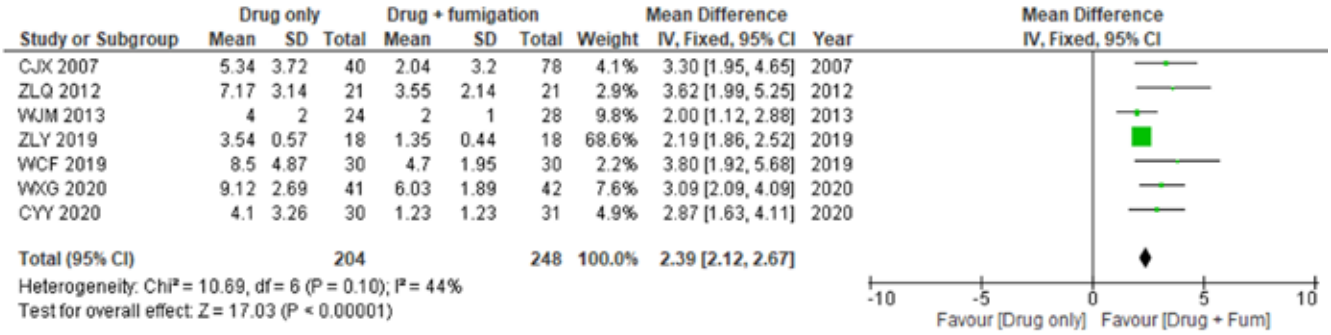


Figure Vc: Drug + fumigation [experimental group] VS drug only [control group], outcome: SJC.

4. CRP

CRP is measured from a blood sample. The level of CRP in the blood indicates the presence and intensity of inflammation. An increase in CRP indicates more inflammation, thus, an increased severity.

a) Drug + acupuncture

Serum level of CRP was measured in 11 included RCTs involving 712 participants. There was high heterogeneity among the studies ($P < 0.00001$, $I^2 = 79\%$) and a random effect model was utilised. The pooled analysis manifested that the serum level of CRP is significantly lower in the experimental group (MD = 4.78, 95% CI [2.73, 6.82], $P < 0.00001$) (Figure VIa). GRADE approach indicated low certainty of evidence (Appendix 5: Table 1).

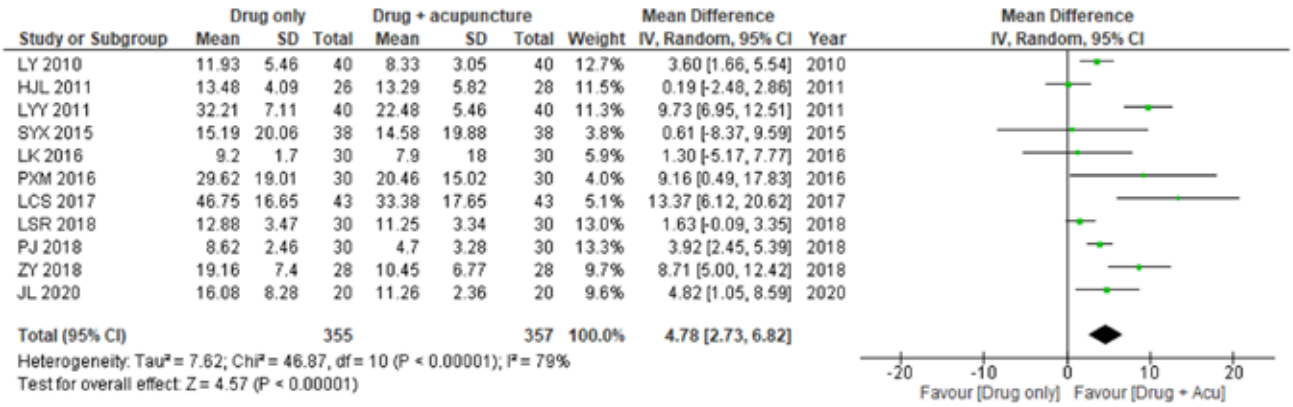


Figure VIa: Drug + acupuncture [experimental group] VS drug only [control group], outcome: CRP.

b) Drug + moxibustion

CRP serum level was measured in 19 RCTs involving 1833 patients. A significantly high heterogeneity was observed ($P < 0.00001$, $I^2 = 95\%$), hence random effect model was adopted. There is significant difference between both groups (MD=2.91, 95% CI [1.21, 4.61], $P = 0.0008$) (Figure VIb) and very low certainty of evidence (Appendix 5: Table 2).

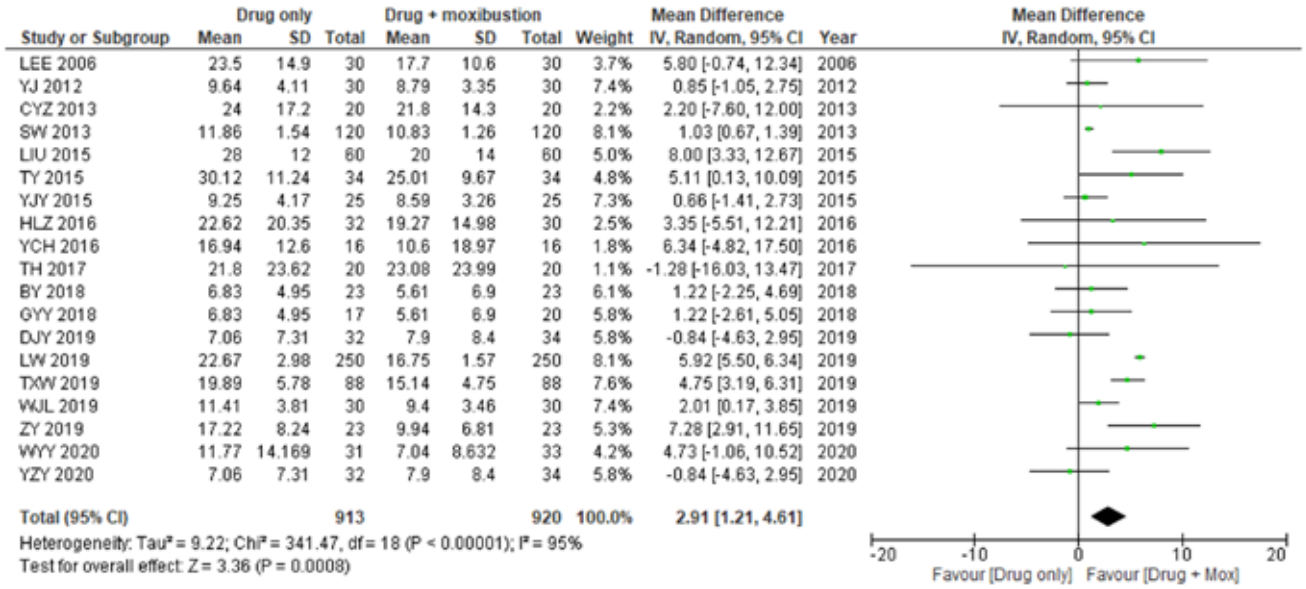


Figure VIb: Drug + moxibustion [experimental group] VS drug only [control group], outcome: CRP.

c) Drug + fumigation

Serum level of CRP was measured in 8 included RCTs involving 712 participants. There was high heterogeneity among the studies ($P < 0.00001$, $I^2 = 83\%$) and random effect model was used. The pooled result showed lower level of CRP in the experimental group (MD = 3.41, 95% CI [0.85, 5.97], $P = 0.009$) (Figure VIc). GRADE assessment indicated very low certainty of evidence (Appendix 5: Table 3).

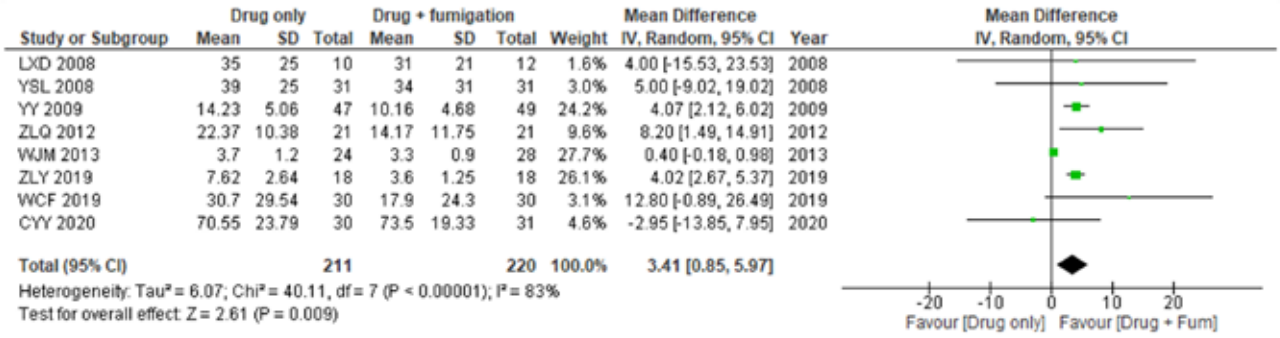


Figure VIc: Drug + fumigation [experimental group] VS drug only [control group], outcome: CRP.

5. ESR

ESR is used to indicate and monitor an increase of inflammatory activity in the body. It is measured by taking a blood sample and placing it in a specialised tube. The rate at which red blood cells settle to the bottom of the tube is measured over a specific time period. An elevated sedimentation rate indicates greater inflammation.

a) Drug + acupuncture

Twelve trials involving 808 participants measured the serum level of ESR after the treatment. Significant heterogeneity was detected among the trials (P < 0.00001, I^2 = 81%) and hence, a random effect model was utilised. The pooled analysis signified that there was a statistically significant difference between both groups (MD = 7.37, 95% CI [4.48, 10.27], P < 0.00001). A lower level of ESR was observed in experimental group (Figure VIIa). There was low certainty of evidence (Appendix 5: Table 1).

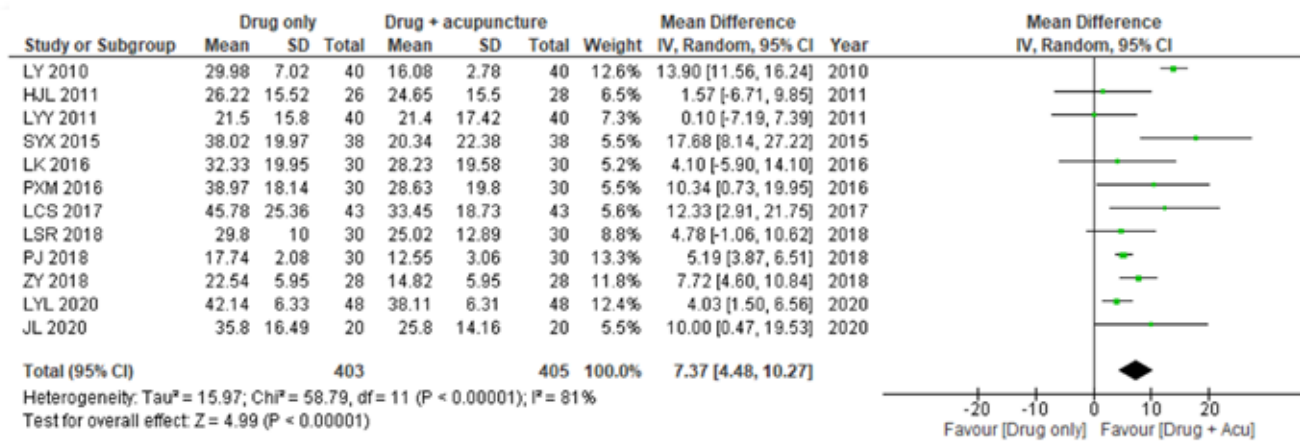


Figure VIIa: Drug + acupuncture [experimental group] VS drug only [control group], outcome: ESR.

b) Drug + moxibustion

ESR was measured in seventeen RCTs involving 1533 patients. Random effect model was adopted due to high heterogeneity ($P < 0.00001$, $I^2 = 95\%$). Significant difference between both groups (MD = 6.44, 95% CI [4.17, 8.71], $P < 0.00001$) was observed, with lower level of ESR in the experimental group (Figure VIIb). GRADE assessment indicated very low certainty of evidence (Appendix 5: Table 2).

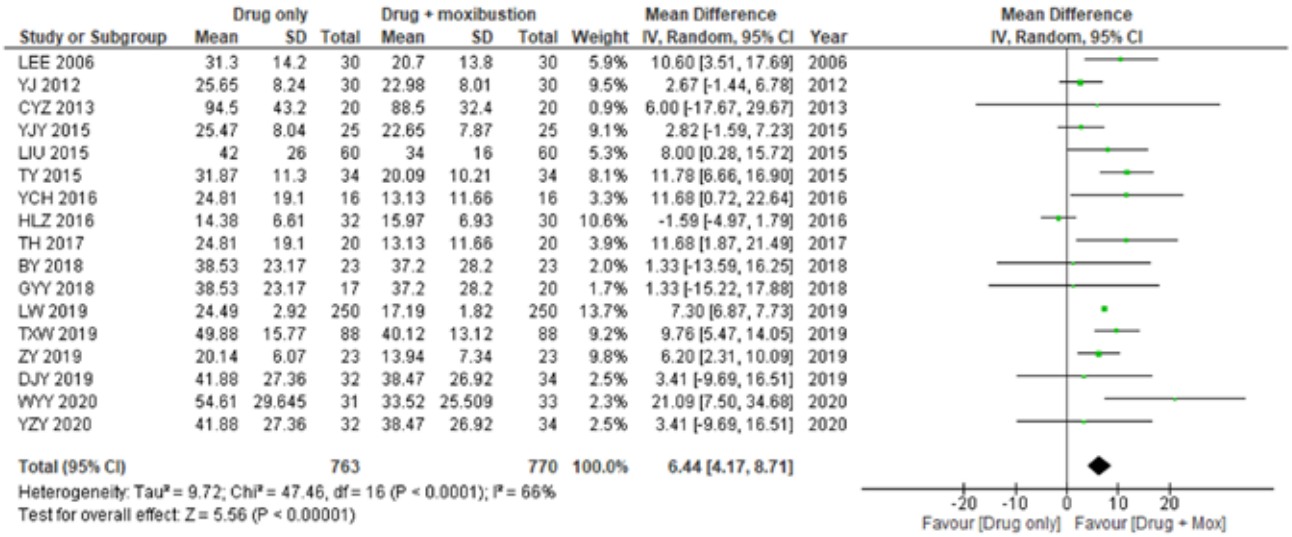


Figure VIIb: Drug + moxibustion [experimental group] VS drug only [control group], outcome: ESR.

c) Drug + fumigation

Ten trials involving 575 participants observed the change in serum level of ESR after treatment. There was significant heterogeneity detected among the trials ($P < 0.00001$, $I^2 = 95\%$), thus random effect model was utilised. The pooled analysis signified that there was a statistically significant difference between both groups (MD = 12.44, 95% CI [8.07, 16.81], $P < 0.00001$) (Figure VIIc). Low certainty of evidence was obtained through GRADE approach (Appendix 5: Table 1).

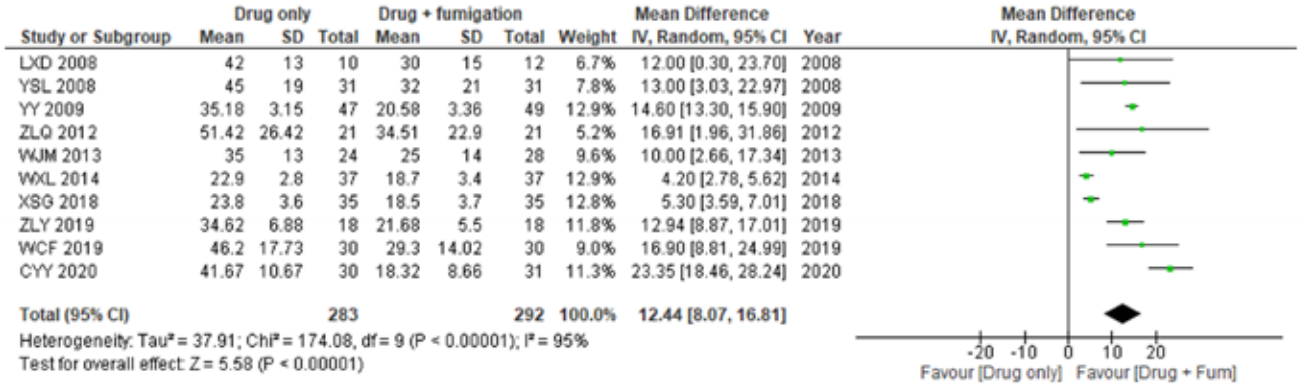


Figure VIIc: Drug + fumigation [experimental group] VS drug only [control group], outcome: ESR.

6. TNF-α

TNF-α is a cytokine involved in the inflammatory process, and its levels can provide insights into the inflammatory state of the patient. The measurement of TNF-α involves collecting a blood sample from the patient. Advanced laboratory techniques, such as enzyme-linked immunosorbent assay (ELISA), are used to quantify the concentration of TNF-α in the blood. Elevated TNF-α indicates higher severity of RA.

There was no acupuncture and moxibustion study assessing TNF-α.

a) Drug + fumigation

Three RCTs involving 124 participants observed the change in serum level of TNF-α post-treatment. No significant heterogeneity was detected ($P < 0.88$, $I^2 = 0\%$), thus, a fixed effect model was adopted. The pooled result signified that there was a significant difference between both groups (MD = 9.61, 95% CI [6.82, 12.40], $P < 0.00001$), showing lower level of TNF-α in experiment group (Figure VIII). There was moderate certainty of evidence (Appendix 5: Table 3).

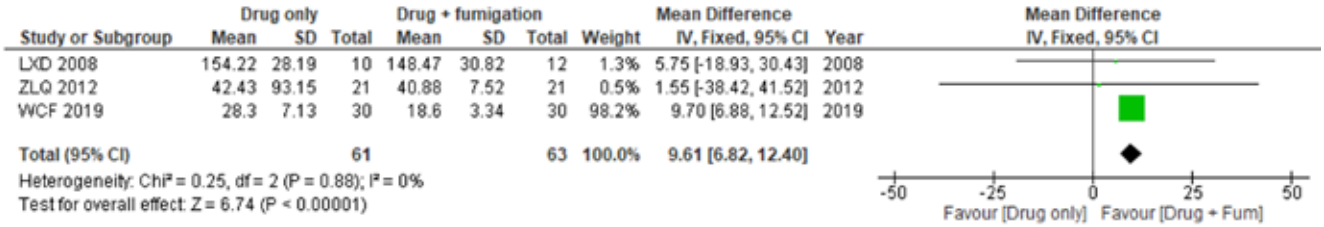


Figure VIII: Comparison of drug + fumigation [experimental group] versus drug only [control group], outcome: TNF-α.

Publication bias

The funnel plots, results of Egger's and Begg's tests showed that there is no significant publication bias (Appendix 4).

Adverse events

Eight studies[24, 43, 47, 51, 52, 53, 57, 59] had reported adverse events, six studies[12, 20, 26, 28, 35, 45] had reported no adverse event, while the rest of the studies had no report on adverse events. The adverse events mostly happened to the control group utilising drug only for treatment, include nausea and gastrointestinal discomfort (n=17)[43, 51, 57], mouth ulcer (n=1)[57] and raised ALT level (n=1)[51]. One study[24] observed increased AST, decreased WBC and proteinuria in the experimental group involving moxibustion combined with drug (n=2) and control group (n=4). Two studies[51, 53] had observed gastrointestinal and head discomfort in the experimental group applying CM fumigation combined with drug treatment (n=3). These adverse events were claimed to be related to the use of anti-rheumatic drugs. Six patients in three of the studies[47, 52, 59] experienced blisters caused by moxibustion, which was a common adverse reaction to moxibustion. There was no severe adverse event causing withdrawal from the study.

DISCUSSION

1. Summary of main findings

There were six outcomes measured in these included studies, which were DAS28, VAS, SJC, CRP, ESR and TNF-α. All outcome measures showed statistically significant difference between both experimental and control groups. The results outcomes were significantly higher in the control group compared to experimental group, suggesting that CM external therapy combined with drug may improve the outcomes in RA patients compared to drug only. However, as GRADE approach were not carried out, these results need to be interpreted with caution. It was observed that the MD in the control group for DAS28, VAS, SJC in fumigation studies were the highest, followed by moxibustion and lastly acupuncture. In studies that used acupuncture, patients in the interventional group experienced greater efficacy in lowering CRP as compared with the control group (MD = 4.78, 95% CI [2.73, 6.82], *P* <0.00001). This is followed by studies using fumigation (MD = 3.41, 95% CI [0.85, 5.97], *P* = 0.009) and moxibustion (MD=2.91, 95% CI [1.21, 4.61], *P* = 0.0008). As for ESR, the intervention group in fumigation studies showed the highest efficacy in reducing it ((MD = 12.44, 95% CI [8.07, 16.81], *P* < 0.00001), followed by acupuncture (MD = 7.37, 95% CI [4.48, 10.27], *P* < 0.00001) and moxibustion (MD = 6.44, 95% CI [4.17, 8.71], *P* < 0.00001). TNF-α was only assessed in three studies using fumigation plus drug for their experimental group. IL-1 and IL-2 were omitted from meta-analysis as there was only one study each with results of the mentioned outcome measures. Most of the results showed substantial or high heterogeneities. This may be due to inconsistency in the selection of acupoints and herbal medicine used in the studies. This is an intrinsic characteristic of Chinese medicine which focuses on individualised treatment based on the condition of each patient. Some of the included studies either inadequately reported or did not clearly report the methodology implemented, hence, the risk of bias in random sequence generation and allocation concealment is classified as unclear. All studies showed a high risk of bias for the blinding of participants and personnel due to unclear methodology and inability to perform blinding of patients and therapists owing to the nature of CM external treatment. One study reflected high risk of bias in other bias due to a short treatment duration for a chronic disease in the experiment. The high heterogeneities and high risk of biases may have a negative impact on the reproducibility of the results of this study.

Overall, this meta-analysis revealed that acupuncture, moxibution and fumigation combined with drug are more effective and had less adverse events compared to drug only in RA. Among these CM external therapies, fumigation was observed to be most effective in improving all the outcomes except for CRP level. Moxibustion also showed overall slightly higher efficacy than acupuncture in most outcome measures. Acupuncture had the greatest effect in CRP.

2. Mechanism of CM acupuncture, moxibustion and fumigation

These CM external therapies involve application of needles, burning mugwort leaves and herbal medicine steam on the acupoints, thus closely related to the meridians and cutaneous regions. CM believes that all parts of the body communicate and interact through the meridian system, which plays an essential role in physiological and pathological processes. The acupoints and cutaneous regions, as parts of the meridians, can receive treatment stimulation and then transfer these effects throughout the body through the meridians.[62]

For RA, these treatments are known to have beneficial effects through mechanisms such as anti-inflammation, autonomic nervous system modulation, and analgesia. Studies showed that acupuncture enhances autonomic tone and acetylcholine production while reducing IL-1 and IL-6, CRP and ESR and induces anti-inflammatory neuropeptide, regulate plasma adrenocorticotropic hormone, serum cortisol levels and synovial NF-κB immune-activity, inhibit synovial mast cell's function, as well as restoring the hypothalamus-pituitary-adrenal axis.[63] By stimulating the nervous system, acupuncture can induce the production of endorphins and neurohumoral substances, and increases local microcirculation, which aids in the dispersal of swelling.[64] Moxibustion was also found to increase the levels of anti-inflammatory cytokines and decrease the levels of proinflammatory cytokines, which in turn can preserve the synovium of joints in animal models of RA.[65]

All these therapies involve the meridian system, however, there is addition of thermal effect in fumigation and moxibustion. This is probably the reason why fumigation and moxibustion showed higher efficacy than acupuncture. Especially for fumigation, most of the studies applied a temperature of 43°C or more in the steam bath using anti-rheumatic and anti-inflammatory herbs for the treatment. Moxibustion, which is involving the application of burning mugwort (or *artemisia vulgaris*) leaves without flame on the skin indirectly can produce temperature as high as 65°C on the skin and 45°C in the subcutaneous layer.[62] It is known that heat can increase the blood flow and activate the human keratinocytes to express thermo-sensitive transient receptor potential types, TRPV1 (activated at 43°C), TRPV3 and TRPV4 (both activated at 28-38 °C).[66-68] The high temperature could also lead to the regional temperature rise of the joints. This increases the rate of vasodilation and blood circulation to the affected joints to allow tissue repair and healing. Improved blood circulation enhances the excretion of body metabolites by acting on the circulatory and lymphatic systems, which can regulate the body's humoral and cellular immunity. Besides, the vasodilation can cause skin pores and the muscle interstices (*cou li*) to be opened and dredged, leading to smoother blood flow and reduced blood viscosity. As a result, the inflammation, joint swelling and pain could be reduced. Thus, this may explain the good effect of fumigation and moxibustion on DAS28, VAS, and SJC, ESR, CRP, and TNF-α. Another strength of fumigation and moxibustion is the integration of Chinese herbal medicine, which enhances the treatment effect. Studies had shown that the active compounds of the herbal medicine could enter the body through fumigation and causes vasodilation,

reduce swelling, absorb blood stasis and improve joint functionality.[69-7]1 Fumigation for RA mostly uses herbal medicines with actions to relieve pain by eliminating wind, cold and dampness pathogens, as well as activating *qi* and blood circulation. From our study, it is found that notopterygium root (*qiang huo*), pubescent angelica root (*du huo*), taxillus (*sang ji sheng*), radix aconiti preparata (*chuan wu*), radix aconiti kusnezoffii preparata (*cao wu*), radix clematidis (*wei ling xian*), herba lycopodii (*shen jin cao*), and rhizoma chuanxiong (*chuan xiong*) are more frequently used. Mugwort used in moxibustion, are known to have the actions to warm the meridians, dispel cold and relieve pain. It consists of bioactive compounds such as flavonoids, sesquiterpenoids, essential oils, tannins, phenols, and saponins which may produce an anti-inflammatory response by inhibiting the activity of prostaglandins synthesising enzyme.[72]

3. Comparison with previous studies

There were a few similar systematic reviews published in the recent years. In 2020 and 2021, two meta-analysis[73,74] on the clinical efficacy of moxibustion in treatment of RA were published. Comparing to our study, these meta-analysis only focused on moxibustion RCTs while our study includes acupuncture and fumigation in addition to moxibustion. For the results, our findings on moxibustion are mostly consistent with these studies, which suggest a higher efficacy in treatment of RA. Secondly, the previous meta-analysis involved different types of intervention compared to this study. The first meta-analysis[73] involved moxibustion only (experimental group) and without moxibustion (control group), and the second meta-analysis[74] involved moxibustion only (experimental group) and conventional drug only (control group). Whereas our study involved moxibustion combined with conventional drug (experimental group) and conventional drug only (control group).

4. Strength and limitations

It has always been a challenge to perform systematic review and meta-analysis on CM external therapies due to its diversity. We noted that there are other systematic reviews published recently on this similar topic, focused on one specific type of modality. However, we would like to summarise and integrate the three most used CM external treatment methods in RA, namely acupuncture needling, moxibustion and fumigation. We had excluded trials which applied a combination of CM treatment methods, so we could observe the evidence of the effect of these modalities individually.

Several limitations were acknowledged in this review. (1) The studies collected were published in English or Chinese only, potential eligible studies in other languages might be missed. All the trials included were conducted in China, this casted doubt on whether our findings could be applied to other geographic locations and ethnicities. (2) Although all included studies claimed that randomisation and blinding were used, most of them did not specify the technique of randomisation implemented, this may give considerable selection bias. Blinding of the personnel was also a big challenge for CM external therapies. (3) Many studies used general efficacy rate as their outcome measure, this was omitted from our meta-analysis as there was no proper standard for this measure. (4) The sample size of most trials was relatively small, leading to smaller weight in the meta-analysis. (5) Most of the clinical trials

were conducted within three months, the outcome assessment was carried out immediately following the intervention period without follow-up on the long-term treatment effect. Therefore, the long-term benefit of this combined treatment was still uncertain and pending for further investigation. (6) There may be other factors that are important but not considered in this study, such as moderator effect, disease staging, gender, and regional variation.

In future trials, larger sample size, transparency in reporting the study design, implementation, and data analysis, are recommended to increase the reliability and accuracy of study results. Multi-centre trials in different regions of the world are also recommended to include a wider range of population groups for comparison and increase generalisability of the study. We also suggest future trials to use standardised outcome measures. More studies with long-term follow-up are necessary to examine the effectiveness of CM external therapy and to assess the sustainability of effect. Further research to investigate the mechanisms of these therapies is suggested to achieve a higher level of evidence for the treatment effects.

Conclusion

In conclusion, fumigation and moxibustion which involves heat and Chinese herbal medicines may be more effective than acupuncture in reducing inflammation, joint swelling and pain. Evidence is mixed with regards to integration of CM external therapies and conventional drugs in treatment of RA patients as there are moderate and low certainty of evidence in the outcome measures, mostly due to high risk of bias in blinding and substantial heterogeneity. Thus, it is recommended to researchers to further investigate these modalities in clinical trials with consideration of minimising the risk of bias, to provide more high-quality evidence in the effect of CM external therapies as a complementary treatment in RA.

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