



# Treatment of knee osteoarthritis with acupuncture combined with Chinese herbal medicine: a systematic review and meta-analysis

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**Background:** Many studies have demonstrated that acupuncture combined with Chinese herbal medicine (CHM) effectively treats knee osteoarthritis (KOA), with few side effects. However, few systematic reviews have offered evidence-based support. Here we conducted a meta-analysis on the combination of acupuncture with CHM in treating KOA.

**Methods:** Databases including CNKI, Wanfang, VIP, PubMed, EMBASE, and Cochrane library were systematically searched for articles on the treatment of KOA by acupuncture combined with CHM from the establishment of the database to May 2021. Three researchers independently searched, screened, extracted, and included articles that met the inclusion standards. The primary outcome measure was overall response rate (ORR), and the secondary outcome measures included Visual Analogue Scale (VAS) score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and Lysholm score. ORR was a binary variable, while other indicators were continuous variables. The quality of literature was assessed with a modified Jadad scale. The RevMan 5.3 software provided by the Cochrane Collaboration was used for statistical analysis.

**Results:** Thirty-three randomized controlled trials involving 3,954 patients were included. Meta-analysis showed that ORR [odds ratio (OR) =5.41; 95% confidence interval (CI): (4.38, 6.68);  $P < 0.00001$ ], VAS score [mean difference (MD) =-1.86; 95% CI: (-2.44, -1.29);  $P < 0.00001$ ], WOMAC score [MD =-13.05; 95% CI: (-21.70, -4.41);  $P = 0.003$ ], and Lysholm score [MD =10.47; 95% CI: (5.21, 15.72);  $P < 0.0001$ ] in the combination group were significantly superior to those in the control group.

**Discussion:** Compared with acupuncture alone or CHM/Western drug alone, acupuncture combined with CHM can effectively alleviate knee pain, improve knee function, and increase the quality of life. Thus, this combination can be used as a conservative treatment for KOA. However, due to the small number of high-quality articles and possible biases in our analysis, our conclusions need to be further verified in more and higher-quality studies.

**Keywords:** Knee osteoarthritis (KOA); acupuncture; traditional Chinese medicine; randomized controlled trial; meta-analysis

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## Introduction

Osteoarthritis (OA) is a chronic degenerative disease that affects approximately 10% of men and 18% of women worldwide. The incidence of OA is increasing annually, along with increased aging. About 60–65% of people over 60 years of age suffer from symptomatic OA, of which 80% of patients present with symptoms including joint stiffness and limited range of motion, which seriously affects the quality of life of the victims (1,2). Even worse, an increasing proportion of young adults have also suffered from OA. OA is a heterogeneous disease caused by multiple factors and characterized by progressive decomposition of articular cartilage. It is commonly believed that knee osteoarthritis (KOA) results from a result of multiple pathogenic factors, such as age, sex, body quality, trauma and genetics, abnormal mechanical load, insufficient nutrition supply and genetic inducement, as well as metabolic factors and infrapatellar fat pad. and is characterized by joint pain and dysfunction with progressive intraarticular and subchondral bone injury, synovitis, osteophyte formation and reduced joint cava. As the prevalence of OA is rising, the treatment requirements on this disease also increase (3).

The current treatments of KOA mainly include non-steroidal anti-inflammatory drugs (NSAIDs), chondroitin, hyaluronic acid, surgical therapy, traditional Chinese medicine, acupuncture/massage, and exercise therapy. Weight reduction and muscle strength training around the knee joint may also help. Among them, the combination of acupuncture with Chinese herbal medicine (CHM) is highly effective, with few side effects. Also, it is simple and affordable (4,5).

A previous meta-analysis had investigated the efficacy and safety of this strategy, but with low literature quality, small sample size, and a limited number of response assessment indicators (6). As more relevant articles have been published in recent years, an updated meta-analysis with high-quality articles is warranted to provide accurate, reliable, and multifaceted evidence to evaluate the clinical efficacy of the combination in treating KOA. We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/apm-21-2565>).

## Methods

### Literature search strategy

#### Computer-based search

A computer-based search was performed by three researchers.

### Databases

The Chinese databases included CNKI, Wanfang, VIP, and China Biomedical Literature (CBM) database; and English databases included PubMed, EMBASE, and Cochrane Library.

### Search words

The search words included, “acupuncture”, “electroacupuncture”, “traditional Chinese medicine treatment”, “knee osteoarthritis”, “osteoarthritis of the knee”, “knee joint osteoarthritis”, and “KOA”, in Chinese and English, respectively.

### Time period

The period between searches was from the month the databases were created to May 2021.

### Search strategy

The search method of combining subject terms with free-text synonyms was used. An example of searching in PubMed is shown in *Table 1*.

### Inclusion and exclusion criteria

#### Inclusion criteria

The inclusion criteria included: (I) the included patients met the diagnostic criteria of KOA; (II) published randomized controlled trials, with clearly-defined baseline data; (III) whether blinding is used or not; (IV) the combination group included patients who had received the combination of acupuncture with CHM alone, while the control group included patients who had undergone other treatment methods different from the combination of acupuncture and CHM; (V) the outcome measures included any of the following indicators: overall response rate (ORR), Visual Analogue Scale (VAS) score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and Lysholm score. All the outcomes measures were reliable.

#### Exclusion criteria

The exclusion criteria included: (I) articles with poorly-defined diagnostic criteria, efficacy indicators, and/or descriptions; (II) articles with incorrect trial design or statistical methods; (III) reviews, dissertations, conference proceedings, and nursing records; (IV) basic experiments; (V) case reports and anecdotal evidence; (VI) expert experience; (VII) unpublished articles or overlapping publications; (VIII)

**Table 1** The search strategy for PubMed

No.	Search term	Search scope
#1	Acupuncture	[Title/Abstract]
#2	Electroacupuncture	[Title/Abstract]
#3	Traditional Chinese medicine treatment	[Title/Abstract]
#4	#1 OR #2 OR #3	
#5	Knee osteoarthritis	[Title/Abstract]
#6	Osteoarthritis of the knee	[Title/Abstract]
#7	Knee joint osteoarthritis	[Title/Abstract]
#8	KOA	[Title/Abstract]
#9	#5 OR #6 OR #7 OR #8	
#10	#4 AND #9	

articles with obvious errors or incomplete data; (IX) the original full-text is not available; and (X) literature where acupuncture and CHM are used as adjuvant therapy.

### Data extraction

The search, inclusion, and exclusion of the literature were performed by two well-trained and qualified medical practitioners who had clinical experience in rheumatology and acupuncture, and the initial articles were screened after verification. The data extraction of the initial articles was then performed independently by two investigators and checked by a third investigator. In case of disagreement, the third investigator and the principal investigator negotiated to make a final decision. If there were missing data in the literature, the corresponding author was contacted via email or phone call to obtain such data. The extracted data mainly included: (I) basic information about the included articles: first author and year of publication, etc.; (II) information about the included subjects: number and ages of subjects in the combination group and the control groups, etc.; (III) study designs: types of design, interventions, and details, etc.; and (IV) outcome indicators and outcome measures: ORR, WOMAC score, VAS score, and Lysholm knee function score, etc.

### Assessment of literature quality

The bias risk of the included studies was assessed using the Cochrane Bias Risk tool from the Handbook of the

Cochrane Collaboration for Systematic Intervention Reviews, version 5.1.0 (<https://www.cochrane.org/>), which assesses the following seven domains: (I) allocation of the randomization sequence (selection bias); (II) allocation concealment (selection bias); (III) blinding of the participants and the team involved (performance bias); (IV) blinding of outcome evaluators (detection bias); (V) incomplete outcomes (attrition bias); (VI) report of selective outcome (publication bias); and (VII) other sources of bias.

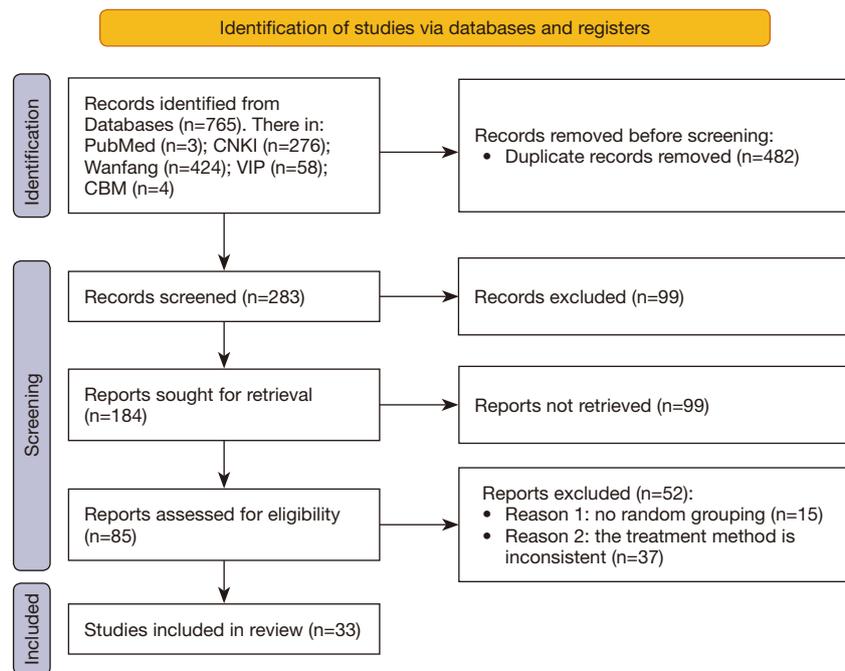
The methodological quality of the literature was evaluated according to the Jadad score by two independent researchers with a valid Good Clinical Practice (GCP) certificate, and checked by a third investigator. In case of disagreement, the third investigator and the principal investigator negotiated to make a final decision. Points were awarded as follows: (I) randomization: 1 point was given if randomization was mentioned; additional 1 point was given if appropriate randomization was used; (II) double blinding: 1 point was given if double blinding was mentioned; additional 1 point was given if the method of double blinding was appropriate; and (III) withdrawals and dropouts: 1 point was given for a clear description of withdrawals and dropouts. Articles were rated as low-quality if scored 0–2 points, and as high-quality if scored 3–5 points.

### Outcome measures

The primary outcome measure was ORR, and the secondary outcome measures included VAS score, WOMAC score, and Lysholm score.

### Statistical analysis

Meta-analysis was performed using RevMan software (version 5.3; Cochrane Collaboration). Both fixed- and random-effects models were used. Heterogeneity was quantified by  $I^2$  statistics.  $I^2 < 50\%$  suggested no heterogeneity, and the data were pooled using the fixed-effects model;  $I^2 > 50\%$  suggested the presence of heterogeneity among the studies, and the random-effects meta-analysis was employed. If more than 10 studies were included for a specific outcome measure, the presence of morbidity bias was analyzed using inverted funnel plots. The odds ratio (OR) was used as the effect measure for binary variables, and the mean difference (MD) was used for measures with the same unit and measurement method. A 95% confidence interval (CI) was given, and a P value of  $< 0.05$  was considered statistically significant.



**Figure 1** Literature search & screening flowchart.

## Results

### Literature search and screening

A flow chart of the study selection process is shown in *Figure 1*.

### Basic features of the included studies

The basic features of the included 33 studies are summarized in *Table 2*. There is no English literature.

### Quality of the included articles

The included articles' biases were assessed using the relevant tools in the Cochrane Handbook for Systematic Reviews of Interventions. A bar graph showing the assessment results is shown in *Figure 2*, and a pooled graph is shown in *Figure 3*.

### Outcome measures

#### ORR

ORR was calculated in 31 articles (*Figure 4*). The heterogeneity among studies was low ( $P=0.03$ ;  $I^2=36\%$ ), so the fixed-effects model was used [OR =5.41 and its 95%

CI was (4.38, 6.68);  $Z=15.66$ ;  $P<0.00001$ ]. Meta-analysis showed that the combination group had a higher ORR than the control group. In particular, acupuncture combined with orally administered CHM had significantly higher clinical efficacy compared with other treatment methods. The funnel plot is shown in *Figure 5*. The plot shows only slight asymmetry, indicating a possible minor publication bias.

#### VAS score after treatment

VAS score was mentioned in 3 articles (*Figure 6*). The heterogeneity among studies was high ( $P<0.00001$ ;  $I^2=98\%$ ), so the random-effects model was used [MD =-1.86 and its 95% CI was (-2.44, -1.29);  $Z=6.37$ ;  $P<0.00001$ ]. Meta-analysis showed that the combination group had a larger decrease in VAS score after treatment than the control group. In particular, acupuncture combined with orally administered CHM had significantly higher VAS score improvement than other treatment methods. Thus, the combination could dramatically alleviate the pain symptoms.

#### WOMAC score after treatment

WOMAC score was mentioned in 3 articles (*Figure 7*). The heterogeneity among studies was high ( $P<0.00001$ ;

**Table 2** Information of the included studies

Articles	Group	Pooled sample size (n)	Gender (male/female)	Age (years)	Disease course (years)	Interventions	Treatment course	Response evaluation criteria
Mo LL, 2013 (7)	Combination group	320	160 (63/97)	72.40±3.50	4.50±2.52	Acupuncture + CHM	2 months	VAS score, LKSS score, Lysholm score, response rate
	Control group		160 (76/84)	71.50±3.25	4.60±2.60	Acupuncture		
Zhang BY, 2017 (8)	Combination group	80	40 (9/31)	53±7	2.2	Acupuncture + CHM	4 weeks	ORR
	Control group		40 (12/28)	52±9	2.4	CHM		
Guo PF, 2010 (9)	Combination group	93	55 (16/39)	38–65	15 days–11 years	Acupuncture + CHM	25 days	ORR
	Control group		38 (12/26)	40–68	16 days–14 years	Indomethacin		
Chen HL, 2011 (10)	Combination group	92	48 (19/29)	45–71	20 days–15 years	Acupuncture + CHM	25 days	ORR
	Control group		44 (16/28)	41–76	18 days–13 years	Acupuncture		
Li HT, 2020 (11)	Combination group	80	40 (12/28)	55±5	7.24±1.46	Acupuncture + CHM	8 weeks	ORR, WOMAC score, and VAS score
	Control group		40 (15/25)	53±7	7.69±2.01	CHM		
Sun J, 2014 (12)	Combination group	60 (16/44)	30	56.85	23.7 months	Acupuncture + CHM	4 weeks	Recovery of joint function and WOMAC score
	Control group		30			Acupuncture		
Zhang H, 2015 (13)	Combination group	200	100 (41/59)	58.58±10.57	–	Acupuncture + CHM	10 days	ORR
	Control group		100 (39/61)	59.21±10.54		CHM		
Ma X, 2009 (14)	Combination group	140	70 (–/–)	–	–	CHM + acupuncture + topical washing + ultrashort wave therapy + computerized medium frequency therapy + direct current induction therapy	15 days	ORR
	Control group		70 (–/–)			Ibuprofen extended-release capsules		
Feng Z, 2014 (15)	Combination group	100	50 (22/28)	56±9.8	–	CHM + acupuncture + topical application	14 days	ORR and HSS
	Control group		50 (19/31)	54±10.1		CHM		
Liu XM, 2016 (16)	Combination group	80 (42/38)	40	55±6.7	1.2±0.5	CHM + acupuncture + massage	3 weeks	ORR
	Control group		40			Nobumetone capsules		
Gui HQ, 2019 (17)	Combination group	100	50 (32/18)	53.89±2.56	4.01±0.45	Acupuncture + CHM	10 days	ORR, functional improvement time, inflammatory factors, and joint function score
	Control group		50 (31/19)	53.25±2.24	4.03±0.42	CHM		

**Table 2** (continued)

Table 2 (continued)

Articles	Group	Pooled sample size (n)	Gender (male/female)	Age (years)	Disease course (years)	Interventions	Treatment course	Response evaluation criteria
Ma YH, 2017 (18)	Combination group	81 (30/51)	45	49–75	–	Acupuncture + CHM	28 days	ORR
	Control group		36	52–69	CHM			
Chen LS, 2017 (19)	Combination group	168	84 (35/49)	54.2	7.3	Acupuncture + CHM	5 weeks	ORR
	Control group		84 (38/46)	53.8	7.1	Diclofenac sodium dual release enteric coated capsules (orally administered) + diclofenac sodium (topically applied)		
Ou ZL, 2017 (20)	Combination group	92	46 (19/27)	61.34±3.46	3.56±1.03	Acupuncture + CHM	4 weeks	ORR, joint swelling index, joint pressure pain index, and ESR
	Control group		46 (17/29)	60.57±3.71	3.60±1.08	Compound ossotide injection + CHM decoction		
Ma P, 2011 (21)	Combination group	166	83 (42/41)	51.2	7.5 months	CHM + acupuncture + ibuprofen extended-release capsules	30 days	ORR
	Control group		83 (44/39)	52.5	7.2 months	Ibuprofen extended-release capsules		
Ge XT, 2009 (22)	Combination group	200	150 (49/101)	55.8 (39/ 85)	30 days–12 years	CHM + acupuncture + medium-frequency electrotherapy	60 days	ORR
	Control group		50 (25/25)	41–82	29 days–13 years	Diclofenac sodium sustained-release tablets + huoxue zhitong capsules		
Sun ZJ, 2013 (23)	Combination group	280	140	–	–	CHM + acupuncture + massage	2 weeks	ORR and pain scale scores
	Control group		140			Nobumetone capsules	3 weeks	
Zhu LY, 2020 (24)	Combination group	60	30 (15/15)	61.50±6.85	1.29±0.26	CHM + acupuncture/ massage + meloxicam + sodium hyaluronate	4 weeks	ORR and Lysholm score
	Control group		30 (14/16)	62.11±7.11	1.34±0.25	Oral meloxicam capsule + intra-articular injection of sodium hyaluronate		
Wang RJ, 2019 (25)	Combination group	100	50 (30/20)	49.7±5.2	8.3±4.3	CHM + acupuncture + sparrow-pecking moxibustion	–	ORR, degree of knee joint motion, and knee pain score
	Control group		50 (27/23)	50.8±6.2	9.3±3.3	CHM		

Table 2 (continued)

Table 2 (continued)

Articles	Group	Pooled sample size (n)	Gender (male/female)	Age (years)	Disease course (years)	Interventions	Treatment course	Response evaluation criteria
Zhu JH, 2010 (26)	Combination group	100	50	65.13	6 months–10 years	Acupuncture + CHM + functional rehabilitation	4 weeks	Lysholm score
	Control group		50			Acupuncture + CHM		
Lai ZS, 2011 (27)	Combination group	40	20	56.2±2.5	3.1	CHM (orally and topically) + acupuncture	4 weeks	ORR
	Control group		20			Intra-articular injection of sodium hyaluronate		
Li ZH, 2010 (28)	Combination group	100	50 (13/37)	48–75	3 months–5 years	Acupuncture + CHM	1 month	ORR
	Control group		50 (14/36)	47–72	4 months–4 years	Intra-articular injection of sodium hyaluronate		
Wu DP, 2008 (29)	Combination group	60	30 (14/16)	64.1	5.7	Acupuncture + CHM	1 month	ORR
	Control group		30 (13/17)	61.8	5.5	Diclofenac		
Sun Y, 2013 (30)	Combination group	120 (69/51)	40	50.4	3.4	CHM + acupuncture + sparrow-pecking moxibustion	2 months	ORR
	Control group		40			CHM		
	Two control groups		40			Acupuncture		
Yin QD, 2009 (31)	Combination group	120	60 (31/29)	57	15	CHM + acupuncture + topical application	4 weeks	ORR and VAS
	Control group		60 (32/28)	56	16	Topical application with diclofenac-diethylamine gel		
Ding WM, 2013 (32)	Combination group	50 (26/24)	25	51.46±13.26	–	CHM + acupuncture + topical application (topical)	–	ORR
	Control group		25			Ibuprofen		
Qiu YQ, 2013 (33)	Combination group	146 (84/62)	112	67.3±3.1	–	CHM (oral + topical) + acupuncture/massage	6 months	ORR, knee function score, pain level, and functional recovery time
	Control group		34			Glucosamine hydrochloride capsules + diclofenac (topical)		
Jiao FD, 2017 (34)	Combination group	140	70 (33/37)	58.8±1.6	5.1±0.7	CHM + acupuncture/massage + teng therapy (heat spreading therapy) + akupotomy	1.5 months	ORR and WOMAC
	Control group		70 (34/36)	58.7±1.8	5.2±0.6	Intra-articular injection of sodium hyaluronate + oral administration of glucosamine hydrochloride		

Table 2 (continued)

Table 2 (continued)

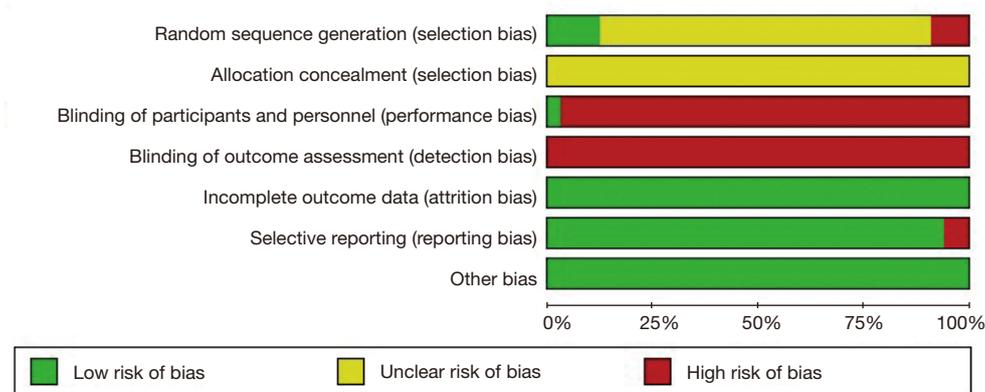
Articles	Group	Pooled sample size (n)	Gender (male/female)	Age (years)	Disease course (years)	Interventions	Treatment course	Response evaluation criteria
Huang XW, 2018 (35)	Combination group	80	40 (17/23)	57.3±7.61	–	CHM + acupuncture + massage	2 months	ORR + joint pressure and pain sensation score, joint swelling score, and arthritis index
	Control group		40 (14/24)	58.1±7.62		Acupuncture + massage		
Bai Y, 2017 (36)	Combination group	104	52 (27/25)	63.2±5.1	7.1±3.2	Intra-articular injection of sodium hyaluronate + CHM + acupuncture	1 month	ORR
	Control group		52 (23/29)	65.5±4.7	6.3±3.1	Sodium hyaluronate		
Yu ZX, 2017 (37)	Combination group	112	56 (30/26)	59.7±7.2	22.7±11.9	CHM + acupuncture + massage	–	ORR
	Control group		56 (32/24)	58.2±6.5	23.5±12.5	Acupuncture + massage		
Chen SY, 2015 (38)	Combination group	210	120 (74/46)	62	9.8	CHM decoctions, fumigation and soaking therapy, massage, small akupotomy, acupuncture, symptomatic pain relief, and intra-articular injection of sodium hyaluronate	–	ORR
	Control group		90 (51/39)	61.50±6.85	10.1	Intra-articular injection of sodium hyaluronate + oral administration of NSAIDs		
Niu GY, 2011 (39)	Combination group	80	40	51.2	4.6	Acupuncture + CHM	30 days	ORR
	Control group	(33/47)	40			Meloxicam		

CHM, Chinese herbal medicine; NSAID, non-steroidal anti-inflammatory drugs; VAS, Visual Analogue Scale; LKSS, Lysholm knee score; ORR, overall response rate; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; HSS, hospital for special surgery knee score; ESR, erythrocyte sedimentation rate.

$I^2=100\%$ ), so the random-effects model was used [MD = -13.05 and its 95% CI was (-21.70, -4.41);  $Z=2.96$ ;  $P=0.003$ ]. Meta-analysis showed that the combination group had a larger decrease in WOMAC score after treatment than the control group. In particular, acupuncture combined with orally administered CHM had a significantly higher decrease in WOMAC score compared with other treatment methods. Thus, the combination could effectively relieve knee pain and stiffness in KOA patients and improve their daily living difficulties.

#### Lysholm score after treatment

Lysholm score was mentioned in 2 articles (Figure 8). The heterogeneity among studies was high ( $P=0.007$ ;  $I^2=86\%$ ), so the random-effects model was used [MD = 10.47 and its 95% CI was (5.21, 15.72);  $Z=3.91$ ;  $P<0.0001$ ]. Meta-analysis showed that the combination group had a higher Lysholm score after treatment than the control group. In particular, acupuncture combined with orally administered CHM significantly increased the Lysholm score compared with other treatment methods. Thus, the combination could



**Figure 2** Bar chart for bias risks of the included studies.

effectively relieve knee pain, stiffness, and swelling in KOA patients, and improve the quality of life.

### Adverse reactions

Adverse reactions were mentioned in two studies (Figure 9). In one study, the incidence of adverse reactions was 1.92% (mild swelling of the lower extremities in one case) and 3.85% (diarrhea in one case and dizziness in one case), respectively, in the control group and the combination group, showing no significant difference ( $P > 0.05$ ). In another study, two patients in the combination group experienced mild gastrointestinal discomfort and abdominal distension, which disappeared after stopping the CHM. Three patients showed gastrointestinal reactions in the control group, manifested as nausea, vomiting, abdominal pain, and constipation, which resolved after stopping the CHM. There were no significant changes in the findings of routine blood tests, routine urine tests, and liver/kidney function tests before and after treatment in both groups.

### Discussion

KOA is a common degenerative disease of the knee joint, with the main symptoms being knee stiffness, pain, and movement disorders. Currently, the commonly used Western medical treatments, including Western drugs or surgery, still cannot cure KOA and are often associated with adverse effects (40). Therefore, the role of TCM in treating KOA has been increasingly recognized, particularly the combination of acupuncture with orally administered CHM. The clinical efficacy of acupuncture has long been

demonstrated. When used in combination with liver- and kidney-tonifying drugs, wind-, cold-, and dampness-dispelling drugs, and blood circulation-activating drugs, acupuncture can alleviate KOA and reduce its recurrence. It also helps increase the patient's quality of life and improve the economic/psychological burden of patients and their families.

The acupuncture points mentioned in the literature included neixiyan, waixiyan, zusanli, xuehai, liangqiu, yinlingquan, yanglingquan, weizhong, and ashi point, which are around the knee joint. Acupuncture at these points helps alleviate knee pain and regulate qi and blood. Acupuncture can enhance muscle strength, adjust soft tissue tension around the knee, improve joint stress, eliminate swelling and relieve pain. And promote local blood circulation, accelerate metabolism, benefit the absorption of inflammatory substances in the joint, enable the damaged tissue to repair, relieve the resting pain of the knee joint, swelling, pain from up and down stairs, stiffness and the improvement of joint mobility. The TCM orally administered Radix Angelicae Pubescentis, parasite scurrula, Radix Cyathulae, Poria, Radix Saposhnikoviae, Rhizoma Ligustici Chuanxiong, Radix Codonopsis, Radix Angelicae Sinensis, Radix Paeoniae Alba, Radix Rehmanniae Preparata, Radix Aconiti Preparata, and Eupolyphaga Seu Steleophaga. They were mainly liver- and kidney-tonifying drugs and blood circulation-activating drugs. It has modern pharmacological effects such as anti-inflammatory, analgesia, expanding blood vessels, improving circulation and regulating immune functions. The Chinese herbs with the actions of activating blood flow and removing blood stasis, and strengthening the muscles

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bai Ye 2017	?	?	-	-	+	+	+
Chen Honglin 2011	-	?	-	-	+	+	+
Chen Lusha 2017	?	?	-	-	+	+	+
Chen Shiyong 2015	?	?	-	-	+	+	+
Ding Weirnin 2013	?	?	-	-	+	+	+
Feng Zhi 2014	?	?	-	-	+	+	+
Ge Xingtao 2009	?	?	-	-	+	+	+
Gui Huaqing 2019	?	?	-	-	+	+	+
Guo Pengfei 2010	-	?	-	-	+	+	+
Huang Xiarwen 2018	?	?	-	-	+	+	+
Jiao Fuda 2017	?	?	-	-	+	+	+
Lai Zhanshao 2011	?	?	-	-	+	+	+
Lihongtao 2020	-	?	-	-	+	+	+
Liu Xiaomei 2016	?	?	-	-	+	+	+
Lizhenhua 2010	?	?	-	-	+	+	+
Ma Ping 2011	?	?	-	-	+	+	+
Ma Xin 2009	?	?	+	-	+	+	+
Ma Yinghui 2017	?	?	-	-	+	+	+
Mo Luli 2013	?	?	-	-	+	-	+
Niu Gengyu 2011	?	?	-	-	+	+	+
Ou Zhenglong 2017	+	?	-	-	+	+	+
Qiu Yuanqiang 2013	?	?	-	-	+	+	+
Sun Jian 2014	?	?	-	-	+	-	+
Sun Yan 2013	?	?	-	-	+	+	+
Sun Zhujuan 2013	?	?	-	-	+	+	+
Wang Ruijie 2019	?	?	-	-	+	+	+
Wu Dapeng 2008	?	?	-	-	+	+	+
Yin Qundang 2009	+	?	-	-	+	+	+
Yu Zhandang 2017	?	?	-	-	+	+	+
Zhang Boyu 2017	+	?	-	-	+	+	+
Zhang Hong 2015	?	?	-	-	+	+	+
Zhu Jianhuan 2010	?	?	-	-	+	+	+
Zhu Lanyong 2020	+	?	-	-	+	+	+

**Figure 3** Bias risk assessment of the included studies. +, low risk; ?, unknown; -, high-risk.

and bones were applied to the affected sites and irradiation by the spectrograph can promote the local absorption of medicines. Herbs with the effects of activating blood flow and removing blood stasis can ameliorate hemodynamical state, promote the microcirculation and improve the hypercoagulability to relieve blood stasis. Moreover, the herbs effective to nourish the kidney and strengthen effective to bones, activate blood flow and remove blood stasis can inhibit chondral degeneration and promote the auto-repairment of the cartilages TCM. Thus, they can exert very well effects in treating and preventing the KOA. The combination treats the disease via both oral and topical approaches, and from local and systemic perspectives. Strengthening the tendons, bones, and joints relieves knee pain and improve the quality of life in KOA patients.

Here we systematically evaluated the efficacy of the combination in treating KOA. A meta-analysis was conducted on the retrieved studies. Data were extracted from studies without significant heterogeneity and pooled with appropriate statistical methods to draw comprehensive conclusions, which to a certain extent can yield more reliable clinical data. The results suggested that the combination could effectively increase the ORR and reduce disease recurrence. However, most of the included articles were of low quality, as they failed to strictly follow the requirements of randomized control trials (e.g., blinding), and some of them were biased. The limitations of our current analysis are summarized as follows: (I) due to insufficient relevant foreign language literature, the included articles were all small-sample, single-center randomized controlled trials published in China, which could lead to selection bias; (II) most of the studies did not mention allocation concealment and blinding, which may have some influence on the results due to the risk of bias; (III) the duration of treatment, follow-up time, and specific acupuncture points/CHM varied among different studies, so there was statistical heterogeneity; (IV) while the vast majority of randomized controlled trials focusing on the combination of acupuncture and CHM in treating KOA were included in our current analysis, only a few studies on the combinations with warm acupuncture, small needle knife, and Western medicine were retrieved for comparisons, which may result in a certain risk of bias; and (V) the three indicators, including WOMAC score, VAS score, and Lysholm score, were adopted in only a small number of studies used, and were highly heterogeneous among these studies due to differences in treatment course, interventions in control group, and grouping

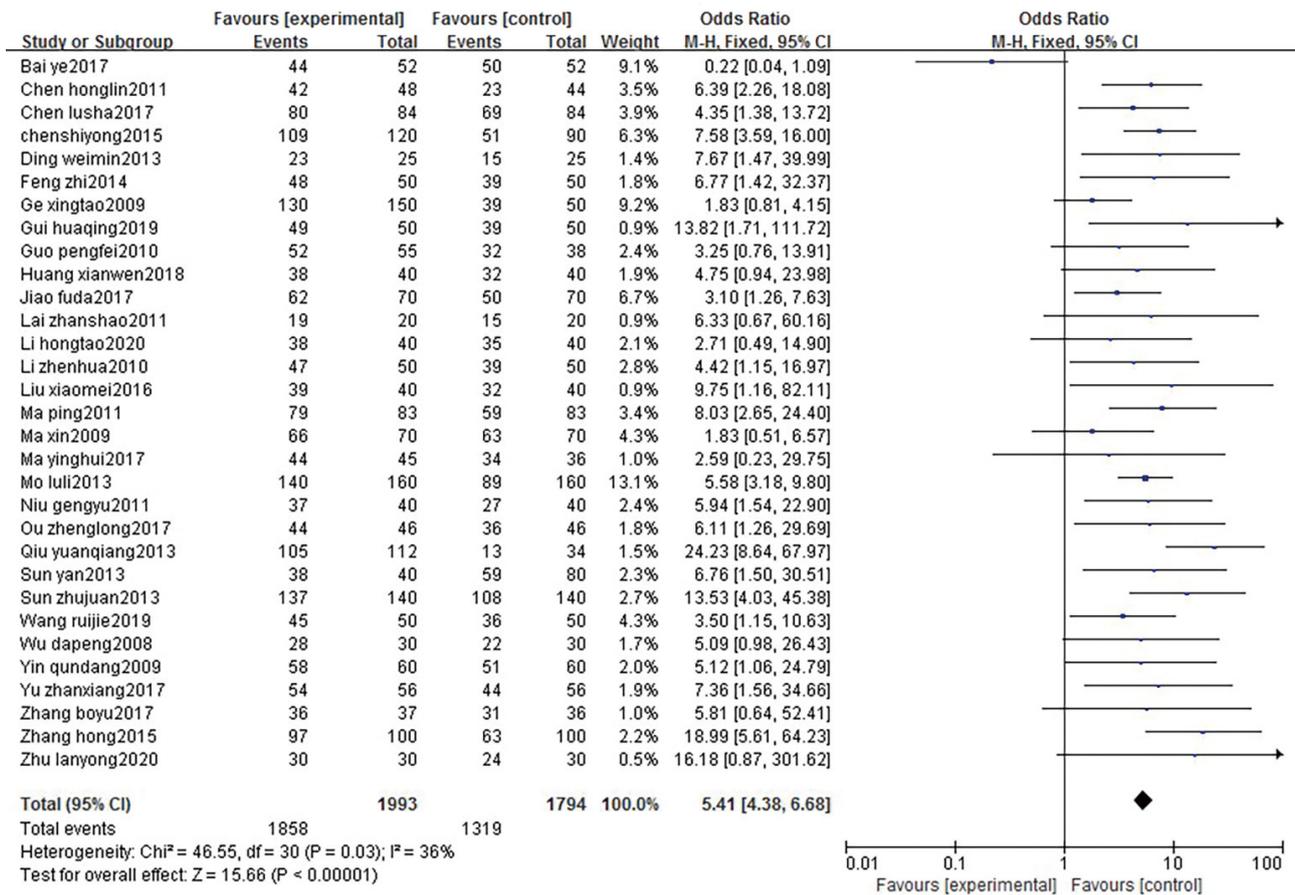


Figure 4 Forest plot of the meta-analysis of ORR. ORR, overall response rate.

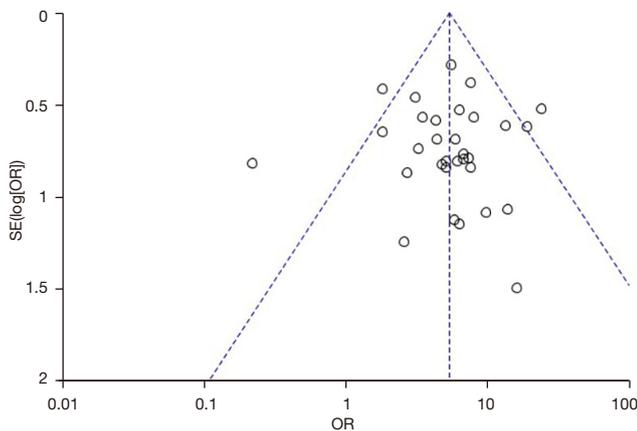


Figure 5 Funnel plot of the meta-analysis of ORR. ORR, overall response rate; OR, odds ratio; SE, standard error.

protocols, which undermined the reliability of the results (41,42).

**Limitations and heterogeneity**

The limitations of meta-analysis: 33 studies were included, mostly randomized methods and random assignment, some had only overall efficiency, too-old or self-contained efficacy criteria; most literature lacked long-term follow-up data to evaluate patients’ disease recurrence, long-term survival quality and specific adverse effects. Evaluation indicators were limited, the outcome indicators only analyzed efficiency, VAS, WOMAC score and Lysholm joint function score, such as HSS score, Inflammatory factor and adverse events were not included in the analysis. On systematic review, the article has some bias in systematic review, selection bias, incomplete or not objective; in research level, there may be publication bias, positive results are easy to publish, negative results are not acceptable, in outcome level, researchers have reporting bias, Selective reports of favorable results.

The article on the source of heterogeneity to consider

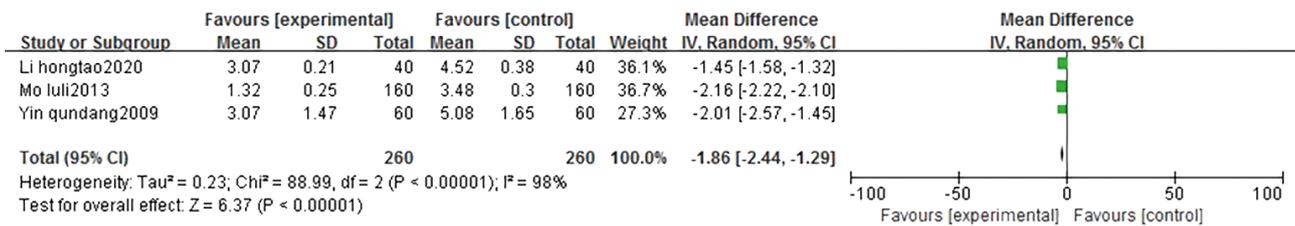


Figure 6 Forest plot of meta-analysis of VAS score after treatment. VAS, Visual Analogue Scale.

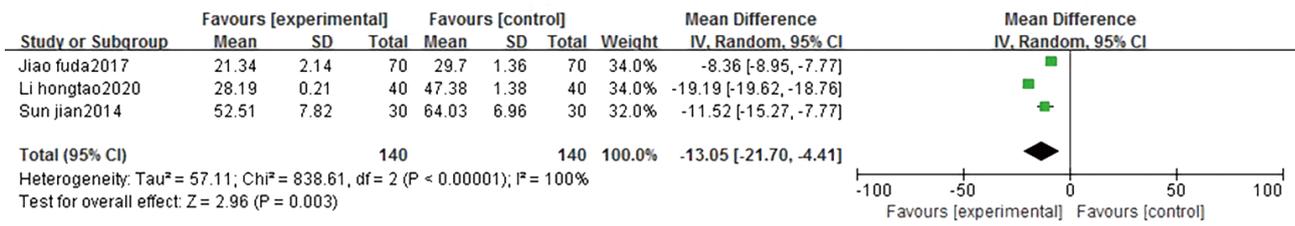


Figure 7 Forest plot of meta-analysis of WOMAC score after treatment. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

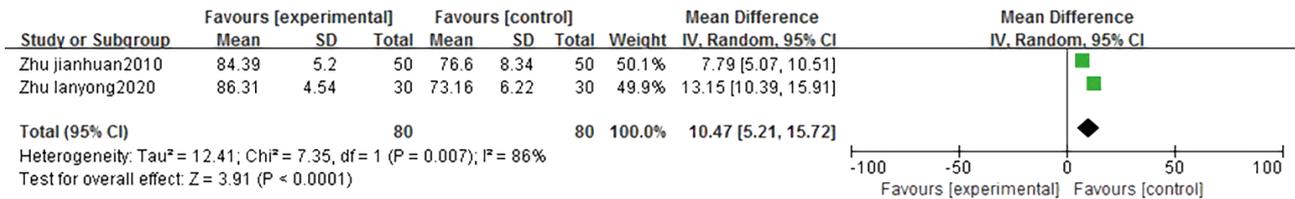


Figure 8 Forest plot of meta-analysis of Lysholm score after treatment.

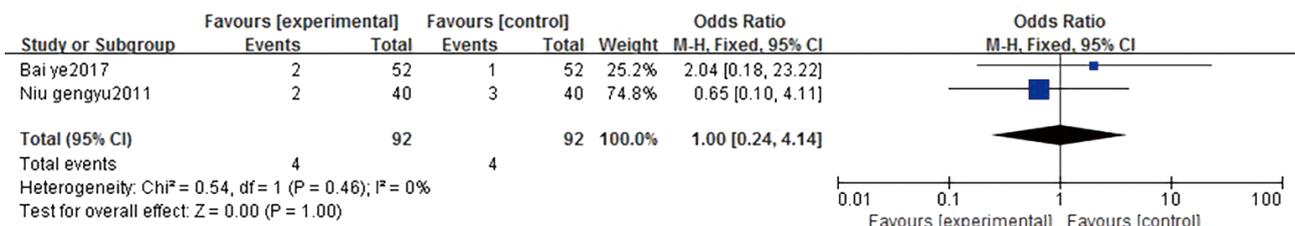


Figure 9 Forest plot of adverse reactions.

the following points: acupuncture selected acupoints are different: far away Near selection points, with the evidence selection points, meridian syndrome differentiation selection points and viscera syndrome differentiation selection points, etc.

The oral CHMs selected in the literature are also different, including tonifying the liver and kidney,

strengthening tendons and bones, promoting blood circulation and dredging collaterals, regulating qi and so on, which will also cause some heterogeneity.

In conclusion, the combination of acupuncture with CHM has significant efficacy in treating KOA, with remarkable therapeutic effects in improving ORR, increasing Lysholm score, and lowering VAS score and WOMAC score. With

a high clinical value, it may be a preferred treatment for KOA. However, as the currently available studies still had many limitations, the conclusions of our analysis still need to be further validated in more multicenter, large-sample randomized controlled trials at home and abroad. Based on our findings, future studies may increase their quality by optimizing research protocols and increasing sample sizes. In addition, the clinical value of the combination of acupuncture with CHM in treating KOA has been demonstrated, and the underlying mechanism may be a research priority (43).

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