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Cupping therapy for treating knee osteoarthritis: The evidence from systematic review and meta-analysis

Jin-Quan Li [a, 1], Wen Guo [b, 1], Ze-Gan Sun [a], Qing-Song Huang [a], En Yeong Lee [c], Ying Wang [d], Xiao-Dong Yao [a, *]

[a] Department of Orthopedics, Fuzhou General Hospital of Nanjing Command, PLA, FuZhou 350025, China
[b] Department of Endocrinology, Fuzhou General Hospital of Nanjing Command, PLA, FuZhou 350025, China
[c] School of Health and Biomedical Sciences, Royal Melbourne Institute of Technology University, Bundoora, Victoria, Australia
[d] Department of First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu Province 210023, China

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ABSTRACT

Objective: Cupping therapy is widely used in East Asia, the Middle East, or Central and North Europe to manage the symptom of knee osteoarthritis (KOA). The purpose of this systematic review was to evaluate the available evidence from randomized controlled trials (RCTs) of cupping therapy for treating patients with KOA.

Methods: The following databases were searched from their inception until January 2017: PubMed, Embase, the Cochrane Central Register of Controlled Trials and four Chinese databases [WanFang Med Database, Chinese BioMedical Database, Chinese WeiPu Database, and China National Knowledge Infrastructure (CNKI)]. Only the RCTs related to the effects of cupping therapy on KOA were included in this systematic review. A quantitative synthesis of RCTs will be conducted using RevMan 5.3 software. Study selection, data extraction, and validation was performed independently by two reviewers. Cochrane criteria for risk-of-bias were used to assess the methodological quality of the trials.

Results: Seven RCTs met the inclusion criteria, and most were of low methodological quality. Study participants in the dry cupping therapy plus the Western medicine therapy group showed significantly greater improvements in the pain [MD = −1.01, 95%CI (−1.61, −0.41), $p < 0.01$], stiffness [MD = −0.81, 95% CI (−1.14, −0.48), $p < 0.01$] and physical function [MD = −5.53, 95%CI (−8.58, −2.47), $p < 0.01$] domains of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) compared to participants in the Western medicine therapy group, with low heterogeneity ($Chi^2 = 0.00$ $p = 1.00$, $I^2 = 0\%$ in pain; $Chi^2 = 0.45$ $p = 0.50$, $I^2 = 0\%$ in stiffness; $Chi^2 = 1.09$ $p = 0.30$, $I^2 = 9\%$ in physical function). However, it failed to do so on a Visual Analog Scale (VAS) [MD = −0.32, 95%CI (−0.70, 0.05), $p = 0.09$]. In addition, when compared with Western medicine therapy alone, meta-analysis of four RCTs suggested favorable statistically significant effects of wet cupping therapy plus western medicine on response rate [MD = 1.06, 95%CI (1.01, 1.12), p = 0.03; heterogeneity: $Chi^2 = 1.13$, $p = 0.77$, $I^2 = 0\%$] and Lequesne Algofunctional Index (LAI) [MD = −2.74, 95%CI (−3.41, −2.07), p < 0.01; heterogeneity: $Chi^2 = 2.03$, $p = 0.57$, $I^2 = 0\%$].

Conclusion: Only weak evidence can support the hypothesis that cupping therapy can effectively improve the treatment efficacy and physical function in patients with KOA.

Contents

* Corresponding author. Department of Orthopedics, Fuzhou General Hospital of Nanjing Command, PLA, FuZhou 350025, China.
E-mail address: yaoxiaodongmd@163.com (X.-D. Yao).

[1] Please clarify that Jin-Quan Li and Wen Guo contributed equally to this article.

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1. Introduction

Knee osteoarthritis (KOA) is a common chronic degenerative disorder of unknown etiology affecting approximately 19.4% of the Chinese elderly [1,2]. It can be the consequence of a pathological process characterized by progressive loss of articular cartilage, periarticular muscle wasting, subchondral bone thickening, bone hypertrophy, and new bone formation [3]. KOA most frequently presents with clinical symptoms which include loss of physical function accompanied by pain, stiffness, muscle weakness, deformity and instabilities [4]. In addition, with the disease progression, KOA impaired patients' normal quality of life, and increased their heavy economic burden [5].

To date, international and local guidelines recommended that the use of oral nonsteroidal anti-inflammatory drugs (NSAIDs) can be highly beneficial for the management of KOA [6,7]. However, according to recent researches, these agents only help to slightly reduce short-term pain and do not modify the natural history or progression of KOA [8]. Moreover, these drugs are frequently associated with some undesired side effects, and increase the risk of serious adverse events (AEs) involving the cardiovascular, gastrointestinal (GI), and renal systems [9,10]. Therefore, as with most chronic musculoskeletal diseases, KOA patients usually tend to seek complementary and alternative treatment (CAM) therapies for help in managing their pain and discomfort [11].

Cupping therapy is a major integral part of CAM. It is described as a technique that involves a glass, plastic or bamboo cup to create localized pressure on the patient's skin over precise acupuncture points, painful area, or a reflex zone [12]. To date, cupping therapy has widely been utilized and practiced in different cultures like East Asia, the Middle East, or Central and North Europe. In general, wet and dry cupping are the two main types of cupping therapy [13]. Wet cupping, also called *Hijama* in the Middle East, was the most popular cupping method of all by CAM practitioners. Before suction, CAM practitioners conducted bleeding cupping technique (involves incision, lancing or scarification of the skin) in order to drain excess blood, fluids or toxins, which were considered the source of disease, from the body [14]. In dry cupping, which stimulate the skin by applying cups with a vacuum pressure; the difference lies in whether the skin is punctured to allow blood and other body fluids to flow [15]. In addition to two main types of cupping therapy, other subtypes of cupping therapy include retained cupping, quick-cupping, moving cupping, shaking-cupping and balance-cupping.

In comparison to acupuncture, cupping therapy has not attracted much attention in the West, which is partly due to the lack of sufficient modern scientific evidence. Recently, a bibliometrics analysis of papers published from 1950 to 2010 in China, showed that Cupping therapy has been widely used in the treatment of a wide spectrum of chronic musculoskeletal diseases, especially KOA [16]. Nowadays, numerous systematic reviews have investigated the effects of cupping therapy on stroke rehabilitation [17], hypertension [18], herpes zoster [19] and pain conditions [20]. Nevertheless, there was no systematic review specifically focusing on the cupping therapy of KOA.

Therefore, the aim of this study is to update and critically evaluate the evidence from randomized controlled trials (RCTs) that have tested the efficacy and safety of cupping therapy in treating KOA.

2. Materials and methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. In addition, the protocol of this systematic review has been registered in PROSPERO funded by the UK National Institute for Health Research (Registration Number: CRD42017057483).

2.1. Data sources

The following databases were searched from their inception until January 2017: PubMed, Embase, the Cochrane Central Register of Controlled Trials and four Chinese databases [WanFang Med Database, Chinese BioMedical Database, Chinese WeiPu Database, and China National Knowledge Infrastructure (CNKI)]. Search strategies are presented in Appendix 1, and these search terms were slightly modified for other databases. Additionally, we also searched the reference lists of review articles and identified RCTs for any possible titles matching the inclusion criteria. Furthermore, in order to identify the grey literature/unpublished studies, we also identified relevant studies via a review of Registry ClinicalTrials.gov, Chinese Clinical Trial, and WHO International Clinical Trials Registry Platform (ICTRP).

2.2. Selection of studies

Only the RCTs related to the effects of cupping therapy in KOA were included in this systematic review. Trials published in the

form of dissertations were also selected as eligible studies. All studies included met the following inclusion criteria with the PICOS principle (population, intervention, comparison, and outcome). No language restrictions will be imposed.

P (population): patients aged over 18 diagnosed with KOA using definitive American College of Rheumatology (ACR) diagnostic criteria were included.

I (intervention): Studies were included if cupping therapy was used as the sole intervention or as an adjunct therapy in conjunction with Western medicine therapy for KOA. Therefore, we excluded studies in which other CAM therapies (e.g. acupuncture, moxibustion, massage, Chinese herbals, Chinese patent medicine) were utilized as an adjunct treatment in conjunction with the Western medicine therapy.

C (comparison): A sham cupping device/placebo or Western medicine as controls was included. Conventional Western medicine therapy was used as a reference standard therapy for KOA in the control group. Studies were excluded if the control group treatments were not relevant to Western medicine therapy or other CAM therapies (e.g. acupuncture, moxibustion, massage, Chinese herbals, Chinese patent medicine) were used as an adjunct treatment in conjunction with the Western medicine therapy.

O (outcomes): The outcome measures were the clinical efficacy measurement (Guiding Principles of Clinical Research on New Drugs-response rate, GPCRND-response rate), pain (visual analog scale, VAS) and physical function (Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC; Lequesne Algofunctional Index, LAI). ① GPCRND-response rate: Similar to the international standardized evaluation of clinical efficacy, GPCRND-response rate is a reliable and valid Chinese Culture-specific assessment of KOA, which includes pain intensity associated with the affected joint, morning stiffness, the maximum distance walked, and activities of daily living (ADL). To date, several CAM evidence-based medicine researchers (Choi TY [21], Wang Y [22] and Song GM [23]) have been successfully applied this indicator to detect the efficacy of moxibustion in treating KOA. ② VAS: Initially developed in 1976, the VAS has been revealed to be a suitable measure of pain, which is widely used in the Clinical Research Center(CRC). This measurement contains a 10-cm line anchored at each end. The left-hand anchor represents 'no pain' and the right-hand anchor represents 'worst possible pain'; the patient marks a line to show their degrees of pain intensity. Higher scores indicate worse pain [24]. ③ WOMAC: As a validated patient-reported questionnaire recommended by the U.S. Food and Drug Administration (FDA), WOMAC is used to assess patients with KOA in the clinical settings [25]. This questionnaire includes 24 items in three dimensions (pain 5 items; stiffness 2 items; and physical function 17 items). For each item, we have five possible response options: none, mild, moderate, severe and extreme. The equivalent scores are 0, 1, 2, 3 and 4, respectively. Therefore, the scores for items in each dimension (pain, stiffness, physical function) are summed to acquire dimension scores (score range for pain 0–20, stiffness 0–8, physical function 0–68). Higher scores can indicate worse pain, more stiffness, and greater functional limitation.④ LAI: The LAI is an internationally used validated questionnaire to determine the physical function of KOA [26]. This questionnaire consists of 11 items in three dimensions (pain or discomfort 5 items; maximum walking distance 2 items; and physical function disability 4 items). Each dimension has a score ranging from 0 to 8, resulting in a total score between 0 and 24. Higher scores indicate the presence of poorer health and greater physical function limitations.

2.3. Data extraction, quality and validation

The complete text of each included article was read by two independent reviewers (Lee and Kim) who extracted relevant data based on the predetermined criteria. The following data were extracted from the original manuscripts: (1) Author and year; (2) sample size; (3) Therapeutic intervention (types of cupping therapy, duration of treatment, treatment acupuncture points, Acupoints' rational theory); (4) Control groups (types of NSAIDs, methods of administration, and the duration of treatment); (5) Follow-up (6) Main outcomes (7) AEs. The Cochrane risk-of-bias tool [27] was used to evaluate the methodological quality of each included trial, and each RCT was assessed for the following characteristics: (1) selection bias; (2) performance bias; (3) detection bias; (4) attrition bias; (5) reporting bias. The terms 'Low', 'Unclear', and 'High' referred to *low*, *uncertain*, and *high* risks of bias, respectively. In most cases, disagreements were settled by discussion between the two reviewers. If disagreement remained after discussion, a third reviewer (Wang) was consulted before taking the final decision on the disagreements.

2.4. Quantitative data synthesis

In our review, meta-analysis was performed using software RevMan 5.3 Cochrane Collaboration, Oxford, UK, obtainable from the website for free: http://www.ccims.net/revman/download [27]. For dichotomous data, we presented results as risk ratio (RR) with 95% confidence intervals (CIs). For continuous data, mean difference (MD) was included in the meta-analysis. In each meta-analysis, the chi-square and I^2 tests were used to evaluate statistical heterogeneity [28]. Given $I^2<50\%$ and $p>0.1$, a fixed effect model was applied. On the other hand, the random effect model was used if articles were thought clinically similar enough [28]. If a sufficient number of studies were available (at least 10 studies), we attempted to assess publication bias using a funnel plot [29].

3. Results

3.1. Trial flow and study characteristics

The literature search of databases generated 220 citations. After excluding the duplicate manuscripts, titles and abstract, we analyzed 47 full text articles. Of these 47 articles, 40 were excluded as they did not meet the inclusion criteria, leaving 7 eligible RCTs [30–36] involving 661 participants for the systematic review (Fig. 1). Seven included RCTs originated in German and China, and had relatively small sample size. Three trials compared a co-intervention of dry cupping therapy and Western medicine with a control of Western medicine alone [30–32]. In addition, Wet cupping therapy combined with Western medicine was used in other four studies [33–36]. Moreover, the duration of the interventions was mostly 4 weeks, and the site of cupping therapy varied according to traditional Chinese medicine (TCM) theory for six of the all included RCTs [30,32–36]. Details regarding the seven RCTs [30–36] included in our meta analysis are shown in Table 1 and Table 2.

3.2. Risk of bias

The Cochrane risk-of-bias was presented in Figs. 2 and 3. Three of the included trials [30,31,33] reported appropriate sequence-generation methods for the randomization, whereas the remaining trials [32,34–36] did not describe the methods of sequence generation. Two of the included trials [30,31] conducted concealment of allocation by sealed envelopes, while three RCTs [32,34,35] used inappropriate methods and the remaining trials [33,36] did not describe the methods of sequence generation. In addition, the authors reported that none of the included trials employed patient-

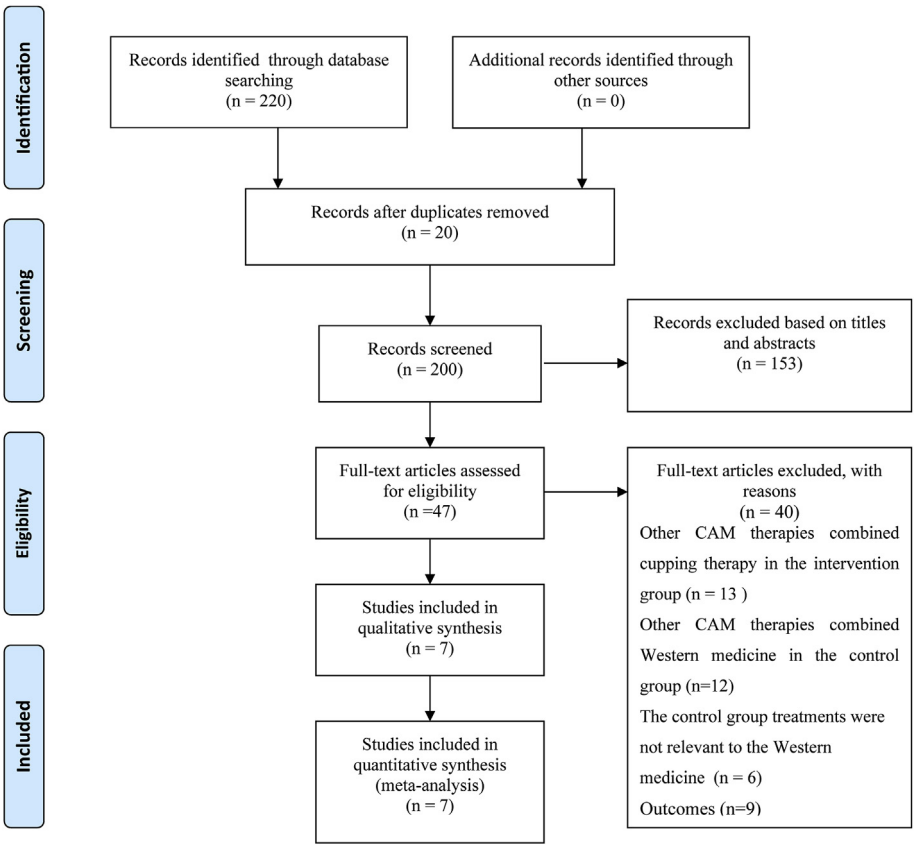

Fig. 1. Flowchart of the trial selection process.

blinding methods, whereas the assessor blinding was unclear in 5 RCTs [32–36]. Of the 8 included RCTs, three RCTs [30,31,33] stated the risk of bias for participant dropout or withdrawal. Considering other biases, the sources of funding were shown in 4 RCTs [30,31,33,36]. The sources of direct funding were medical university or Ministry of Health research foundations; these trials were deemed to be free from the risk of bias posed by a financial conflict of interest.

3.3. Meta-analysis outcomes

3.3.1. Western medicine vs western medicine Plus Dry cupping therapy

3.3.1.1. VAS. Three RCTs [30–32] (involving 271 patients) were identified with the outcome measurement of pain. The meta-analysis showed superior effects of cupping therapy plus the Western medicine therapy on pain when compared with Western medicine alone [MD = −0.32, 95%CI (−0.70, 0.05), $p = 0.09$], (Fig. 4).

3.3.1.2. WOMAC. There were three RCTs [30–32] (involving 271 patients) which used WOMAC as an outcome for improvement of KOA after treatment. Study participants in the cupping therapy plus the Western medicine therapy group showed significantly greater improvements in the pain [MD = −1.01, 95%CI (−1.61, −0.41), $p < 0.01$], stiffness [MD = −0.81, 95%CI (−1.14, −0.48), $p < 0.01$] and physical function [MD = −5.53, 95%CI (−8.58, −2.47), $p < 0.01$] domains of WOMAC compared to participants in the Western medicine therapy group, with low heterogeneity ($Chi^2 = 0.00$ $p = 1.00$, $I^2 = 0\%$ in pain; $Chi^2 = 0.45$ $p = 0.50$, $I^2 = 0\%$ in stiffness; $Chi^2 = 1.09$ $p = 0.30$, $I^2 = 9\%$ in physical function) (Fig. 5).

3.3.2. Western medicine vs western medicine Plus Wet cupping therapy

3.3.2.1. Response rate. Four RCTs [33–36] (involving 390 patients) were identified with the outcome measurement of response rate. The pooled results displayed favorable significant effects of cupping therapy plus the Western medicine therapy on response rate when compared with the Western medicine therapy alone [MD = 1.06, 95%CI (1.01, 1.12), p = 0.03] with low heterogeneity ($Chi^2 = 1.13$, $p = 0.77$, $I^2 = 0\%$) (Fig. 6).

3.3.2.2. LAI. Four RCTs [33–36] (involving 390 patients) measured LAI as the outcome. The meta-analysis showed superior effects of cupping therapy plus the Western medicine therapy on LAI when compared with the Western medicine therapy alone [MD = −2.74, 95%CI (−3.41, −2.07), $p < 0.01$] with low heterogeneity ($Chi^2 = 2.03$, $p = 0.57$, $I^2 = 0\%$) (Fig. 7).

3.4. Sensitivity analysis

According to the VAS index forest plot, the result of Teut et al. [31] was markedly different to all of the other included trials. By removing the trial of Teut et al. [31], statistical heterogeneity of analysis for the effect size of VAS ($I^2 = 44\%$) was substantially decreased ($I^2 = 0\%$). Moreover, when omitting the heterogeneity contributed by Teut et al. study [31], our pooled results [MD = 0.06, 95% CI (0.01,0.14), $p = 0.11$] were consistent with those [MD = −0.22, 95% CI (−0.61,0.17), $p = 0.27$] in the previous analysis; suggesting the stability of results in our current meta-analysis.

Table 1
Summary of the randomized controls trials of cupping therapy for KOA.

Study (author/year)	Sample size	Follow-up	Intervention group (regimen)	Control group (regimen)	Main outcomes	Intergroup differences
Wang (2016)[a] [30]	171	4 weeks	(A) Dry cupping (1 session = 15 min, 2 times/week, total 4 weeks, n = 89), plus (B).	(B) Drug therapy (NSAIDs, Celecoxib, 200 mg, 1/day) NSAIDs were used according to patients' conditions,n = 82	VAS WOMAC(Pain,Stiffness, Physicla fuction)	MD, −1.62 [-2.56,-0.68], P < 0.01 Pain: MD, −1.01 [-1.87, −0.15], P = 0.02; Stiffness: MD, −0.38 [1.06, 17.12], P = 0.04; Physical function: MD, −3.92[-7.18,-0.66], P < 0.01
Teut (2012) [31]	40	4 weeks	(A) Dry cupping (1 session = 10 min, 5 times/week, total 4 weeks,, n = 21), plus (B).	(B) Drug therapy (NSAIDs, Paracetamol, 200 g, 1/day) NSAIDs were used according to patients' conditions, n = 19	VAS WOMAC(Pain,Stiffness, Physicla fuction)	MD, −0.97 [-1.44,-0.50], P < 0.01 Pain: MD, −1.01 [-1.86, −0.16], P = 0.02; Stiffness: MD, −1.15 [-2.20, −0.10], P = 0.03; Physical function: MD, −9.90 [-18.64,-1.16] P = 0.03
Zhang (2013) [32]	60	1 month	(A) Dry cupping (1 session = 20 min, 3 times/week, total 4 weeks, n = 30), plus (B).	(B) Drug therapy (NSAIDs, Celecoxib, 200 mg, 1/day) NSAIDs were used according to patients' conditions, n = 30	VAS	MD, −0.26 [-0.78, 0.26], NS
Gao (2014) [33]	66	4 weeks	(A) Wet cupping (1 session = 20min, once daily, 5 days/week, total 4 weeks, n = 32), plus (B)	(B) Drug therapy (Glucosamine Hydrochloride, 240 mg, 3/day) NSAIDs were used according to patients' conditions, n = 34	Response rate LAI	RR, 1.09 [0.97, 1.94], NS MD, −3.52 [-6.36,-0.68], P = 0.02
Wang (2016)[b] [34]	74	4 weeks	(A) Wet cupping (1 session = 20min, once daily, total 4 weeks, n = 37), plus (B)	(B) Drug therapy (Glucosamine Hydrochloride, 480 mg, 3/day) NSAIDs were used according to patients' conditions, n = 37	Response rate LAI	RR, 1.00 [0.87, 1.14], NS MD, −1.95 [-3.85, −0.05], P = 0.04
Zhang (2012) [35]	110	1 months	(A) Wet cupping (1 session = 20min, once daily, total 1 month, n = 58), plus (B)	(B) Drug therapy (Diclofenac sodium, 25 mg, 2/day) NSAIDs were used according to patients' conditions, n = 52	Response rate LAI	RR, 1.07 [0.97, 1.18], NS MD, −2.61 [-3.44, −1.78], P < 0.01
Ma (2010) [36]	140	n.r.	(A) Wet cupping (1 session = 15min, 3 times/week, n = 70), plus (B)	(B) Drug therapy (Diclofenac sodium, 25 mg, 2/day) NSAIDs were used according to patients' conditions, n = 70	Response rate LAI	RR, 1.08 [0.98, 1.19], NS MD, −3.55 [-5.15, −1.95], P < 0.01

KOA: Keen Osteoarthritis; LAI Lequesne Algofunctional Index; MD mean difference; n.r. not reported; NS not significant; NSAIDs non-steroidal anti-inflammatory drugs; RR risk ratio; VAS visual analog scale; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2
Summary of the treatment points and other information related to the treatments.

Study (author/year)	Types of cupping therapy	Treatment points	Acupoints' rational theory	Adverse events
Wang (2016)[a] [30]	Dry cupping therapy	EX-LE 4, ST35,*ashi*	TCM theory: Invigorate the blood and regulate Qi	None related to cupping therapy
Teut (2012) [31]	Dry cupping therapy	n.r.	n.r.	Mild hematomas at the skin location where cupping took place
Zhang (2013) [32]	Dry cupping therapy	EX-LE 4, ST35	TCM theory: Invigorate the blood and regulate Qi	None related to cupping therapy
Gao (2014) [33]	Wet cupping therapy	*ashi*	TCM theory: Invigorate the blood and regulate Qi	n.r.
Wang (2016)[b] [34]	Wet cupping therapy	EX-LE 4, ST 32, ST 33, ST34, ST35, ST36	TCM theory: warm meridians, relieve pain and regulate Qi	None related to cupping therapy
Zhang (2012) [35]	Wet cupping therapy	BL 40	TCM theory: Invigorate the blood and regulate Qi	None related to cupping therapy
Ma (2010) [36]	Wet cupping therapy	BL 40	TCM theory: Invigorate the blood and regulate Qi	n.r.

TCM traditional Chinese medicine; n.r. not reported.

3.5. Adverse events

In one RCT [31], mild hematomas in three patients were detected in the cupping therapy group. However, the other six RCTs [30,32–36] did not report any adverse events in this research.

4. Discussion

In the current meta-analysis, the research team identified 7 RCTs covering 661 participants that involved a comparison of cupping therapy plus Western medicine therapy with Western medicine

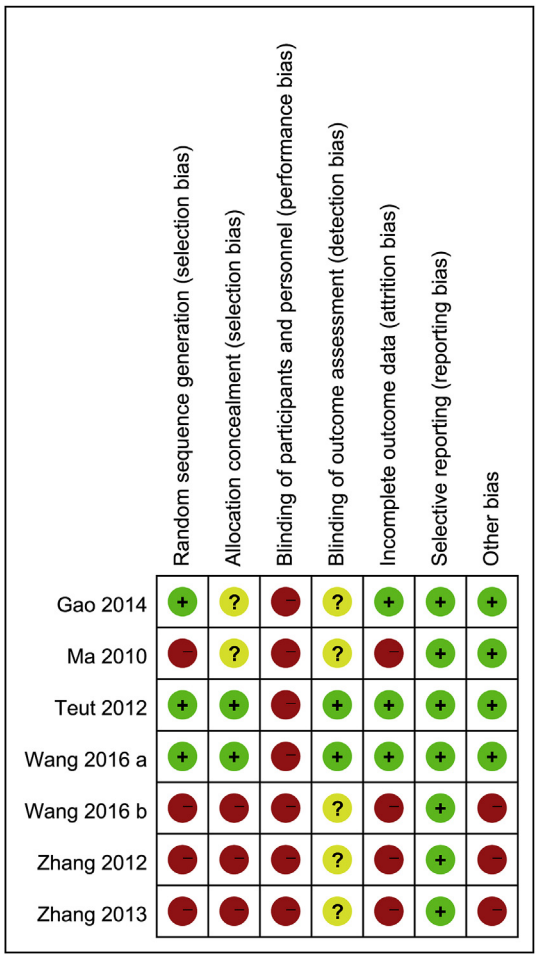

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

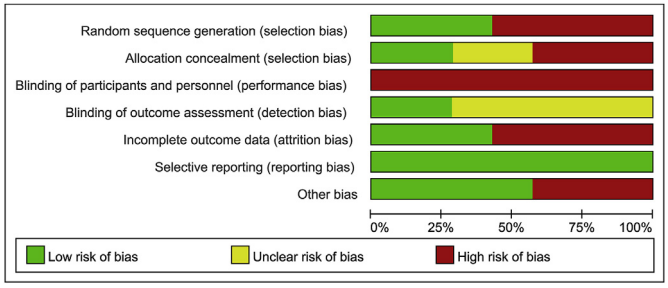

Fig. 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

therapy alone for the treatment of KOA. Overall, the combined use of cupping therapy and Western medicine therapy was considered to be superior to Western medicine therapy alone in terms of treatment efficacy (GPCRND-response rate) and physical function (WOMAC, LAI). Nevertheless, considering the high risks of bias of included trials, those results should be interpreted with caution. In addition, the intervention group using cupping therapy was not superior to the intervention group that used Western medicine therapy alone in terms of decreasing the pain intensity (VAS). To explore this issue, VAS is a generic pain-related instrument. However, this instrument is too superficial and simple to assess the complexity of a KOA patient's pain experience [37]. Moreover, according to the recent study, the use of such generic instrument can harm the validity of results in specific subpopulations [38]. Hence, in our research, the positive results from KOA patient's change in pain-related experience might be more incisively detected with the use of WOMAC pain subscale. In the future, conclusions reached in studies which applied a generic instrument to detect the pain intensity should be viewed with caution.

Previously, Cao et al. [39]carried out the systematic review to examine the effect of cupping therapy for all kinds of diseases. In that systematic review, the author only included two RCTs [36,40] to test the effect of cupping therapy on the pain intensity and physical function of KOA patients. Their findings are somewhat consistent with our research with the conclusion that cupping therapy may have a beneficial effect on reducing the pain intensity and improving the physical fuction for KOA patients. Nevertheless, the previous study [40] included one RCT that compared different CAM therapies. To the best of our knowledge, it is not appropriate for us to compare the cupping therapy with the other unknown and unproven CAM therapy. Therefore, in order to obtain a more concrete picture on the role of cupping therapy, we only included the trials that involved a comparison of cupping therapy plus Western medicine therapy with Western medicine therapy alone for the treatment of KOA patients. In addition, compared to Cao et al.'s study [39], several new RCTs [30–35] published in German and China since 2010 were also included and analysis in our research. Thus, it is important to consider that a meta-analysis should be updated periodically as new RCTs are published.

We assessed the methodological quality of RCTs using the risk of bias assessment tool described in the Cochrane Handbook. For adequate random sequence generation, high risk of bias was given to 57% of the included studies. For the allocation concealment, the group assignment was adequately concealed in only 29% of included trials and the rest of the trials were given high risk of bias or unclear risk of bias. RCTs with inadequate random sequence generation and inadequate allocation concealment may be subject to selection bias and are more likely to overestimate the results of the outcome measures [41,42]. For the attrition bias, only 43% of included trials adequately reported the incomplete outcome data, which may lead to attrition bias [43]. Finally, although subject

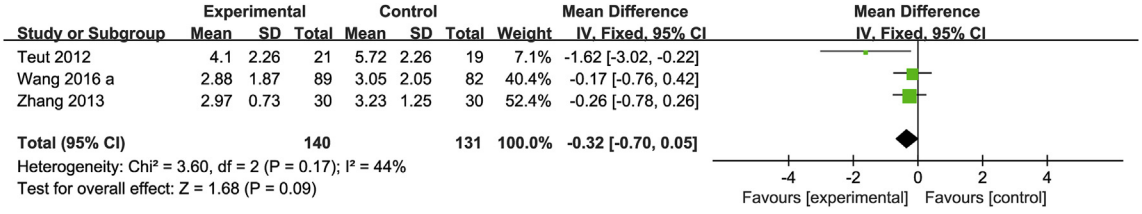

Fig. 4. Western medicine vs Western medicine Plus Dry cupping therapy on VAS.

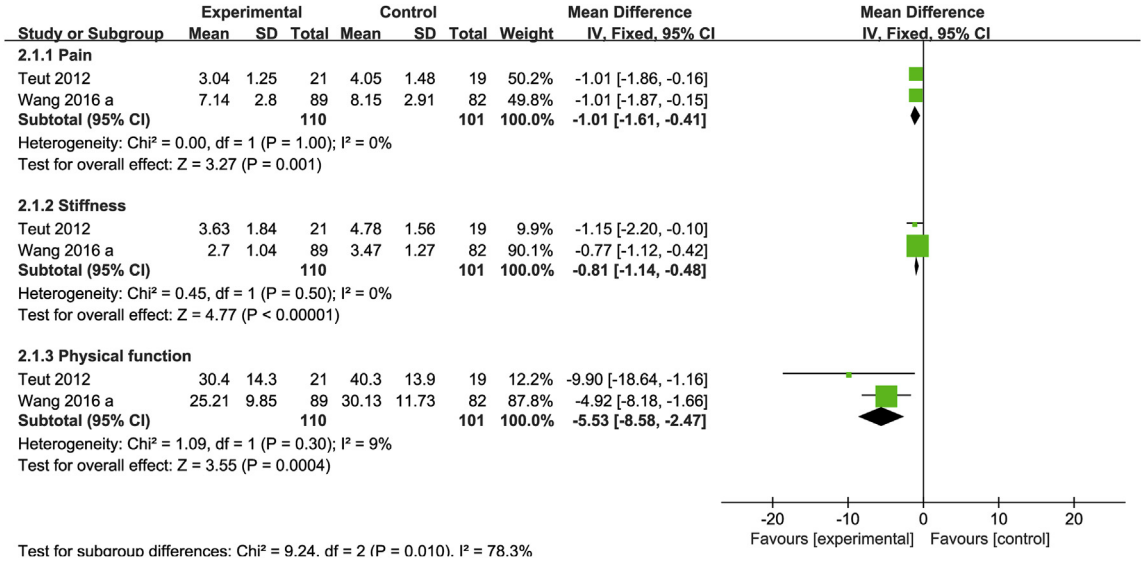

Fig. 5. Western medicine vs Western medicine Plus Dry cupping therapy on WOMAC.

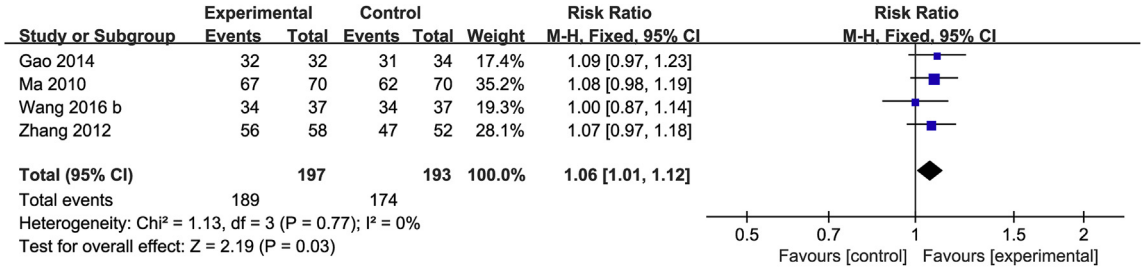

Fig. 6. Western medicine vs Western medicine Plus Wet cupping therapy on response rate.

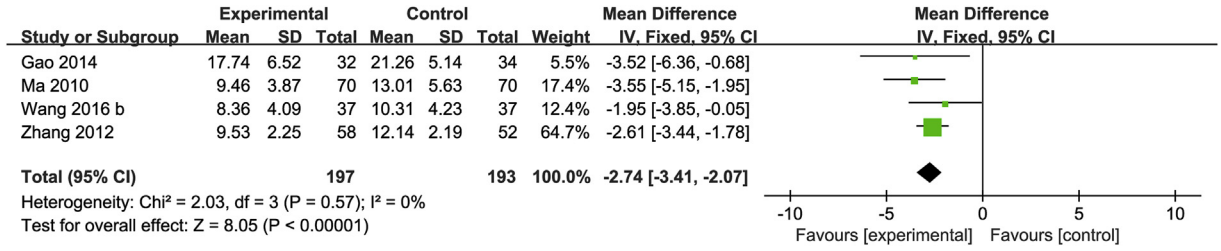

Fig. 7. Western medicine vs Western medicine Plus Dry cupping therapy on LAI.

blinding is difficult to achieve for cupping therapy, assessor blinding is possible. Unfortunately, none of the RCTs included in the systematic review adopted assessor blinding, which may result in the detection biases [41]. Overall, caution must be taken when attempting to generalize the results of our systematic review owing to the low quality of the included RCT.

On inspection of the funnel plot for the VAS measurement, one trial from Teut et al. [31] was the obvious outlier in this meta-analysis. To explore that issue, the current research team noted that the study by Teut et al. [31] administered the dry cupping therapy by a mechanical cupping device. However, the other included trials used the traditional manual dry cupping by CAM practitioners. Therefore, the use of different dry cupping methods might have contributed to the different results on the VAS measurement. By eliminating the study by Teut et al. [31] from the statistical analysis, an improvement in the heterogeneity index was observed. Furthermore, results from the VAS did not produce material differences after eliminating the study by Teut et al. [31] from the analysis.

The inclusion of a placebo or sham cupping therapy group that can be compared with an actual cupping therapy group may be crucial when conducting an RCT measuring the effects of cupping therapy. However, in all included RCTs, none examined the different effects between the sham cupping therapy and the specific effects of cupping therapy. Recently, a placebo cupping device developed by Lee et al. [44] may open the open the door to achieved patient-blinding in RCTs. In order to test the reliability of this sham device, Lauche et al. [45] conducted the same sham cupping procedure for patients with the fibromyalgia syndrome. Unfortunately, the majority of participants in their research were able to determine what cupping they had received. This is in contrast to findings from Lee et al. [44]. Hence, some discrepancies may be ongoing in terms of

the credibility of this sham cupping device. In the future, more rigorous trials will be warranted to testify this sham cupping device.

The safety of cupping therapy is another important issue that we should discuss in our research. In this study, only one RCT [31] reported that mild hematomas in three patients were found in the cupping therapy group. Therefore, it seems that cupping therapy may be a relatively safe treatment for KOA. However, the common AEs of cupping therapy including erythema, edema, ecchymosis and factitial panniculitis have been well reported in the previous systematic review [46]. Moreover, it is worth noting that applying cupping therapy may still result in some severe AEs. In a retrospective study by Jing et al. [47], due to skin burns induced by cupping therapy, 14 outpatients and inpatients were visited to a burn center in northeast china. In another research, cupping therapy procedure was thought to be a risk of transfer of blood-borne pathogens (human immunodeficiency virus, hepatitis B, and hepatitis C) [48]. Thus, in the future, several details about the AEs associated with cupping therapy safety assessment should be reported in the RCTs.

The mechanism of action of cupping therapy is still not clear, and various theories have been proposed. In modern research, the primary speculation about cupping therapy is that it acts through the system neural network and releases some neurotransmitters and endogenous opioids (nitric oxide, beta endorphins adenosine triphosphate,etc.), which gives euphoria so this may ease the nociceptive painful reception and make patients feel comfortable [49]. Moreover, it was reported that cupping therapy could modulate the inflammatory reactions through the degranulation of the level of tumor necrosis factor in patients who suffered from a headache [50]. Furthermore, Boris et al. [51] and Suleyman et al. [52] revealed that cupping therapy may regulate the immune system via removing oxidants and reducing the cytotoxicity of natural killer cell numbers. Thus, the above basic modern scientific researches may partly account for the possible mechanism of cupping therapy, and provide a better understanding of the mechanism of cupping therapy.

5. Limitation

Our meta-analysis has several important gaps that should be mentioned. First, all of the included RCTs were associated with a high risk of bias, which seemed to cause the positive results we found. Thus, in the future, in order to improve the quality of included trials, RCTs concerning cupping therapy should be reported following the CONSORT statements [53]. Second, the number of studies included in our systematic review and meta-analysis were small. As more RCTs are available in the literature, we will update our systematic review in the future. Third, the sample size of included studies was very small and thus small sample size effects may be generated. The power of our systematic review based on small sample size effects may be exaggerated [54]. Fourth, the follow-up period for all included trials were less than 1 month, warranting the analyses of long-term data on trial outcomes in the future. Fifth, a potential source of bias of this systematic review may originate from the search strategy. More potential trials might be captured if the search was expanded. Sixth, due to the number of pooled studies was too small, it was not appropriate for us to formally test the asymmetry in the funnel plot. Last but not least, most of included RCTs were conducted on Chinese populations, limiting the results specifically to this subset of Asian populations. In the future, more large-scale, rigorously designed, multicenter, randomized, placebo-controlled, double-blind trials are warranted in the western countries.

6. Conclusions

Overall, as a potential low cost therapy, only weak evidence can support the hypothesis that cupping therapy can effectively improve the treatment efficacy and physical function in patients with KOA. In the future, results from RCTs with more rigorous standards must be carried out to overcome the limitations of our existing data, and reach more reliable conclusions.

Conflict of interest

No conflict of interest declared.

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Appendix A

Search strategies
MEDLINE

1 exp osteoarthritis/
2 osteoarthriti$.ti,ab,sh.
3 osteoarthro$.ti,ab,sh.
4 gonarthriti$.ti,ab,sh.
5 gonarthro$.ti,ab,sh.
6 coxarthriti$.ti,ab,sh.
7 coxarthro$.ti,ab,sh.
8 arthros$.ti,ab.
9 arthrot$.ti,ab.
10 ((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab.
11 ((knee$ or hip$ or joint$) adj3 stiff$).ti,ab.
12 or/1–15
13 exp Cupping therapy/
14 *Hijamah*.tw.
15 dry cupping.tw.
16 wet cupping.tw.
17 or/13–16
18 12 and 17
19 controlled clinical trial.pt.
20 Randomized controlled trials/
21 random allocation.sh.
22 double blind method.sh.
23 single-blind method.sh.
24 or/19–23
25 exp animals/not human/
26 24 not 25
27 18 and 26

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