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Review

Moxibustion for the treatment of osteoarthritis: An updated systematic review and meta-analysis

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ABSTRACT

The aim of this study was to update previous reviews and examine recent evidence from randomised clinical trials (RCTs) of the use of moxibustion for osteoarthritis (OA). Twelve databases were searched from inception through to September 2016 with no language limits applied. Data extraction and risk-of-bias assessments were performed by two independent reviewers. A total of 19 RCTs met all inclusion criteria and were evaluated. Three RCTs compared the effects of moxibustion with those of sham moxibustion in patients with knee OA (KOA) and found favourable effects of moxibustion on pain reduction (n = 305; SMD, −0.46; 95% CI: −0.86 to −0.06, P = 0.02, I^2 = 65%), including at follow-up (n = 305; SMD, −0.36; 95% CI: −0.70 to −0.01, P = 0.04, I^2 = 54%). Eleven RCTs compared the effects of moxibustion with those of conventional oral drug therapies. Eight RCTs reported a total symptom score and the meta-analysis showed superior effects of moxibustion compared with drug therapies for this measure (n = 691; SMD, −0.24; 95% CI: −0.78 to 0.29; P = 0.37, I^2 = 91%) and response rate (n = 758 knees; RR, 1.10; 95% CI: 1.05–1.16, P < 0.0001, I^2 = 0%). Three RCTs found superior or equivalent effects of moxibustion on symptom score compared with intra-articular injection or topical drug therapy. The existing trial evidence is sufficiently convincing to suggest that moxibustion, compared with sham moxibustion and oral drugs, is effective for pain reduction and symptom management in KOA. The level of evidence is moderate, given the high risk of bias and small sample size.

Contents

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1. Introduction

Osteoarthritis (OA), is a common chronic progressive joint disease [1], which affects primarily the joints of the knee, hip and the hand [2]. OA is associated with pain often accompanied with functional limitation and a decreased quality of life [3,4]. The incidence of symptomatic OA is likely to increase given the upsurge in elderly and obese populations, thus serving as a leading health complaint [5,6]. OA is highly prevalent worldwide, and the economic global burden is large [7]. OA patients often use pharmacological treatments [8] that may be only marginally effective for short-term relief of pain with potentially long-term side effects, such as stomach pain [9]. OA patients often consider combining pharmacological and non-pharmacological interventions [10,11]. Non-pharmacological interventions are perceived to be essential to the treatment and management of OA and may be as important as pharmacological interventions [11–14].

Moxibustion is widely used in China and East Asian countries. Moxibustion is "a traditional therapeutic procedure involving ignited material (usually the dried and processed leaf of Artemisia argyi) to apply heat to certain points or areas of the body surface for the treatment of disease" [15]. Generally, the application of moxa can be divided into direct or indirect moxibustion depending on whether the moxa substance is in direct contact with the skin or not during its application [16]. A recent bibliometric analysis reported that up to 364 diseases can be treated with moxibustion, including knee OA (KOA), temporomandibular joint pain, soft tissue injury, and heel pain [17]. Current evidence supports the positive effects of acupuncture for OA [10,18–20]. Given that moxibustion is an adjunct therapy to acupuncture, it seems pertinent to evaluate the effectiveness of moxibustion as a treatment for OA.

There are four systematic reviews related with this topic (Table 1) [21–24]. One recent review showed effects of moxibustion for KOA based on 12 trials as having high or moderate risk of bias. However, this review pooled the data regardless of research design and the results maybe erroneous [23]. Another recent review restricted the publication language to only English and failed to show comprehensiveness of results [22]. The third systematic review included complex interventions in addition to the use of moxibustion and utilized incomplete information [21]. In this fourth review, we searched databases from their inception through to July 2011 and identified only eight RCTs that examined the use of moxibustion as a treatment for OA [24]. For this review, we updated the evidence by including the results of studies published between August 2011 and August 2016 to the evidence reported in the previous study and further reviewed the research that utilized randomized clinical trials (RCTs) of moxibustion as a treatment for OA patients. Here, we report the updated and extended analyses on the effects of moxibustion for OA.

2. Methods

2.1. Data sources

The following databases were searched from inception through to September 2016: PubMed, EMBASE, AMED, the Cochrane Library, seven Korean medical databases (Korean Studies Information, DBPIA, Oriental Medicine Advanced Searching Integrated System (OASIS), Research Information Service System (RISS), KoreaMed, The Town Society of Science Technology and the Korean National Assembly Library), and one Chinese medical database (China National Knowledge Infrastructure (CNKI)). The search terms included osteoarthritis AND moxibustion in Korean, Chinese, and English (Supplement 1). In addition, the reference lists of all of the obtained eligible papers were searched. Hard copies of all of the articles were obtained and read in full.

2.2. Inclusion criteria

2.2.1. Types of studies

RCTs and quasi-RCTs (RCTs employing sequence generation method including alternation, case record numbers, birth dates, etc.) were included in this systematic review. We excluded trials in which moxibustion was part of a complex intervention as well as case studies, case series, qualitative studies and uncontrolled trials. Trials that failed to provide detailed results were also excluded. Trials published in the form of dissertations and abstracts were included. No language restrictions were imposed.

2.2.2. Types of participants

We included studies that involved patients with OA in any skeletal articulation joint. Studies that included a mixture of different rheumatic patients were included only if it was possible to extract the data concerning each patient population separately.

2.2.3. Types of intervention

Studies that used any type of moxibustion (direct or indirect) for treating OA in any of the peripheral joints were included. Studies were included if moxibustion was used as the sole intervention or as an adjunct therapy in conjunction with another standard treatment for OA. We also included trials if the control group received the same concomitant treatments as the moxibustion group. We included controls of no treatment, sham moxibustion or relevant standard therapies for OA, including conventional drug medications, exercise and rehabilitation therapies. Trials were excluded if they had designs that did not allow for an evaluation of the effectiveness of moxibustion (e.g., by using a treatment for unproven efficacy in the control group or a comparison of two different forms of moxibustion) or if they adopted comparisons between

Table 1
Summary of the published systematic reviews of moxibustion on osteoarthritis.

First Author (Year) Country	Number of primary studies Total sample size Database search data Quality of primary studies	Overall conclusion	Limitations
Song (2016) [23] China	12 1615 November 2015 High and moderate	". . . moxibustion treatment is equal to the oral drugs and intra-articular injections and may be an alternative in treating patients with KOA."	Meta-analysis was conducted regardless of research designs and the results are inaccurate.
Li (2016) [22] China	4 746 October 2015 Moderate	". . . moxibustion can to some extent alleviate the symptoms of KOA"	The search language was restricted to English, therefore, it is possible that not all of the relevant studies were located. Total number of included trials were only 4.
Yu (2015) [21] China	15 1228 February 2014 Poor	". . . moxibustion shows certain therapeutic effect for KOA, better than traditional moxibustion."	This review included complex treatments with moxibustion. Furthermore, the information provided on the included studies was incomplete.
Choi (2012) [24] Korea	8 720 July 2011 Mostly poor	". . .moxibustion may be effective in symptom management in patients with KOA"	Search date is out of date

KOA: knee osteoarthritis.

treatments or groups that were expected to have similar effects to moxibustion (e.g., acupuncture).

2.2.4. Types of outcomes

Primary outcomes concerned the pain and function of joint as measured by validated instruments including WOMAC, Lequesne score, response rate and specific pain scales including visual analogue score (VAS), and numeric rating scale (NRS). Secondary outcomes were adverse events (AEs) and quality of life (QoL).

2.3. Selection of studies and data extraction

One author searched the database and two authors (TYC and JIK) independently screened potentially eligible studies after reading the title and abstract of identified studies. After the initial screening, which was conducted by assessing titles and abstracts, a more thorough investigation was performed using full-text access. All articles were read by two independent reviewers (TYC and JIK) who extracted data according to pre-defined criteria. Disagreements between the two authors were resolved by discussion or where necessary, arbitrated by a third author (MSL). Information, such as the participants, interventions, outcomes and results, were obtained from each report. For the extraction of intervention-related information, the revised STRICTOM items were used to describe the details of moxibustion treatments used in the study context [25].

2.4. Assessing risk of bias

Two authors (TYC and JIK) independently extracted the data from the included trials. The Cochrane risk of bias tool [26] was used to assess the internal validity of each study. The following characteristics were assessed: (1) was the allocation sequence adequately generated?; (2) was the allocation adequately concealed?; (3) was knowledge of the allocated interventions adequately presented during the study?; (4) were incomplete outcome data adequately addressed?; (5) were the study reports free of the suggestion of selective outcome reporting?; and (6) was the study free of other problems that could introduce a risk of bias? This review used 'L', 'U', and 'H' as keys for these judgments where 'Low' (L) indicated a low risk of bias, 'Unclear' (U) indicated that the risk of bias was uncertain, and 'High' (H) indicated a high risk of bias. Disagreements were resolved by discussion between all of the authors (TYC, JIK, CZ, MSL).

2.5. Data analysis

All statistical analyses were conducted using the Cochrane Collaboration's software program, Review Manager (RevMan), Version 5.3.0 for Windows (Copenhagen, The Nordic Cochrane Center). For studies with insufficient information, we contacted the primary authors to acquire and verify data when possible. Differences between the intervention and control groups were assessed. For dichotomous data, we present the treatment effect as relative risk (RR) with 95% confidence intervals (CIs). For continuous data, we used the mean difference (MD) with 95% CIs to measure the treatment effect. In the case of outcome variables with different scales, we used the standardized mean difference (SMD) with 95% CIs. The chi-square test for heterogeneity and I^2 test were used to evaluate the heterogeneity of the included studies. Meta-analysis was performed according to study design, participants, interventions, control, and outcome measures using a random effects model. We attempted to do subgroup analysis according to treatment duration, but several included trials had insufficient information to allow this. Where possible, we assessed publication bias using a funnel plot. However, the low number of trials prevented the assessment of publication bias.

2.6. Assessing the overall quality of the evidence

We assessed the overall quality of the evidence for the primary outcome using the Grading of Recommendations Assessment, Development and Evaluation GRADEproGDT (online version) approach. The GRADE approach considers five reasons, namely, risk of bias, imprecision, inconsistency, indirectness and publication bias, for downgrading the overall quality of evidence. The 'Summary of findings' tables present the main findings of a review in a tabular format.

Table 2
Summary of the randomized clinical studies of moxibustion for knee osteoarthritis.

First Author (Year) (Ref)	Sample Size (M/F); Diagnostic criteria Age (yrs); Duration	Intervention Group (regimen), follow-up	Control Group (regimen)	Main Outcomes	Intergroup Differences	Adverse Events
Ren (2015) [27]	136 (43/93); ACR 65.6/64.0; 6.5/6.2	(A) Moxa (20 min, 3 times weekly for 6 wks, n = 69), 12 wks	(B) Sham moxa (3 times weekly for 6 wks, n = 67)	QoL (SF-36)	NS for all subscale except GH after treatment; NS for all subscale except VT, GH after 12 wks	Blister(A, 22)
Ren (2011) [28]	59 (19/40); ACR 64.0/62.6; 6.8/7.2	(A) Moxa (n.r., 3 times weekly for 6 wks, n = 31), 12 wks	(B) Sham moxa (n.r., 3 times weekly for 6 wks,n = 28)	1) WOMAC 2) Time for 46 m walking	1) Pain: P < 0.01, P < 0.05 (6wks); stiffness: P < 0.05, P < 0.05 (6wks); PF: P < 0.05, P < 0.05 (6wks) 2) NS	n.r.
Zhao (2014) [29]	110 (37/73); ACR 65.8/64.6; <5: 67/>5: 43	(A) Moxa (20 min, 3 times weekly for 6 wks, n = 55), 12 and 24 wks	(B) Sham moxa (3 times weekly for 6 wks,n = 55)	WOMAC	Pain: P < 0.001, P = 0.001 (12wks), P = 0.002 (24wks); PF: P = 0.015, P < 0.001 (12wks), NS (24wks)	Skin flushing (A:10)
Yuan (2015) [30]	148 (54/94); CMA 63.0/63.0; 5.8/5.9	(A) Moxa (10 ~ 15 min, daily for 30 days, n = 74), 12 wks	(B) Drug (Oral: Diclofenac sodium, 2/d, 30 days, n = 74)	1) WOMAC 2) Pain (VAS) 3) Response rate	1) Total: P < 0.01, P < 0.01 (12wks); pain: P < 0.01; stiffness: P < 0.01; PF: NS 2) P < 0.01, P < 0.01 (12wks) 3) P < 0.05, NS (12wks)	Nausea (B:1); stomach pain (B:1)
Deng (2015) [31]	70 (27/43); CMA 61.0/59.0; 7.4/7.1	(A) Moxa (3 times weekly for 4 wks, n = 35), none	(B) Drug (Oral: Diclofenac sodium, 0.3 g, 2/d, 7 days, for 4 wks, n = 35)	1) WOMAC 2) Response rate	1) Total: P < 0.05; pain: P < 0.05; stiffness: P < 0.05; PF: P < 0.05 2) NS	n.r.
Song (2013) [32]	80 (100knees) (37/43); CMA; 59.3/60.7; 4.2/4.7	(A) Moxa (n.r., daily for 20 days, n = 40, 56 knees), 8 wks	(B) Drug (Oral: Diclofenac sodium, 75 mg, 1/d, 20 days, n = 40, 54 knees)	1) WOMAC 2) Response rate	1) Pain: NS; stiffness: P < 0.05; PF: P < 0.05 2) P = 0.02 (8 wks)	n.r.
Cheng (2008) [33]	120 (27/93); ACR 57.8/58.8; 4.8/5.1	(A) Moxa (n.r., once every 2 days for 40 days, n = 60), none	(B) Drug (Oral: Diclofenac sodium, 75 mg, 1/d, 15 days, n = 60)	1) Pain (NRS) 2) Pain (VRS) 3) Response rate	1) NS 2) NS 3) P < 0.01	n.r.
Sun (2008) [34]	56 (80knees) (23/33); GPCRND-KOA 59.9/61.7; 4.3/4.6	(A) Moxa (n.r., daily for 20 days, n = 29, 41 knees), none	(B) Drug (Oral: Diclofenac sodium, 75 mg, 1/d, 20 days, n = 29, 39 knees)	1) Response rate 2) GPCRND-KOA scores(−)	1) NS 2) Morning stiffness: P < 0.05; pain: P < 0.05	n.r.
Yang (2008) [35]	64 (82knees) (25/39); GPCRND-KOA 59.3/59.3; n.r.	(A) Moxa (n.r., daily for 20 days, n = 33, 41 knees), 8 wks	(B) Drug (Oral: Diclofenac sodium, 75 mg, 1/d, 20 days, n = 31, 41 knees)	1) Response rate 2) GPCRND-KOA scores (−)	1) NS, NS (8 wks) 2) Total score: NS, P < 0.05 (8 wks)	n.r.
Ren (2010) [36]	128 (37/63); GPCRND-KOA n.r.; n.r	(A) Moxa (30 min, 5 times weekly for 30 days, n = 50,84 knees), none	(B) Drug (Oral: Diclofenac sodium, 75 mg, 1/d, 20 days, n = 50,80 knees)	Response rate	P = 0.01	n.r.
Zhou (2010) [37]	70 (98knees) (27/43); GPCRND-KOA 59.0/61.0; 4.2/4.6	(A) Moxa (n.r., daily for 20 days, n = 35, 50 knees), 8 wks	(B) Drug (Oral: Diclofenac sodium, 75 mg, 1/d, 20 days, n = 35,48 knees)	1) Pain (NRS) 2) GPCRND-KOA scores (−) 3) Response rate	1) NS 2) P < 0.05, P < 0.05 (8 wks) 3) NS, NS (8 wks)	n.r.

Table 2 (*Continued*)

First Author (Year) (Ref)	Sample Size (M/F); Diagnostic criteria Age (yrs); Duration	Intervention Group (regimen), follow-up	Control Group (regimen)	Main Outcomes	Intergroup Differences	Adverse Events
Zhang (2015) [38]	185(47/138); CMA 60–87;3.3/3.2/3.6 3.7	(A) Moxa (30 ~ 40 min, 3 times weekly for 30 days, n = 48) (B) Moxa plus (C) (n = 43)	(C) Drug (Oral: Celecoxib 200 mg, 1/d, 30 days, n = 48) (D) Rehabilitation (daily for 30 days, n = 46)	1) WOMAC 2) Pain (VAS)	1) A vs. C: P < 0.0001; A vs. D: NS; B vs. C: 2) A vs. C: P < 0.0001; A vs. D: NS; B vs. C:	n.r.
Zhou (2014) [39]	105 (27/78); GPCRND-KOA; 40–75; n.r.	(A) Moxa (30 ~ 40 min, 7 times weekly for 4 wks, n = 39), none	(B) Drug (Oral: Celecoxib 200 mg, 1/d, 4 wks, n = 22) *(C) EA (n = 44)*	1) Pain (VAS) 2) GPCRND-KOA scores (+)	1) P = 0.04 2) P = 0.009	n.r.
Zhang (2011) [40]	60 (22/38); ACR n.r.; n.r.	(A) Moxa (30 min, 7 times weekly for 6 wks, n = 30), none	(B) Drug (Oral: Celecoxib 200 mg, 1/d, 6wks, n = 30)	Response rate	NS	n.r. in details (B, 3)
Chen (2015) [41]	432 (266/166); GPCRND-KOA 55.0/53.0/56.0 <5 y: 73/5–10 y: 40/>10 y: 31	(A) Moxa (Conventional moxa, 45 min, 7 times weekly for 6 wks, n = 144) (B)Moxa (Heat-sensitive moxa, 30 ~ 60 min, twice a day in the first week (5 times weekly) and once a day from the second week to 6 week, n = 144), 7 month	(C) Drug (Intra-articular injection: Sodium hyaluronate 2 mL, once daily 6 days, total 5 times, n = 144)	GPCRND-KOA scores (−)	A vs. C: P < 0.00001; B vs. C: P < 0.00001	None
Wu (2011) [42]	50 (22/28); GPCRND-KOA 47.3/46.9;0.91/0.85	(A) Moxa (20 min, 7 times weekly for 3 wks, n = 24), none	(B) Drug (Intra-articular injection: Sodium hyaluronate 2 mL, once daily for 3 week, n = 26)	1) Response rate 2) GPCRND-KOA scores (+)	1) NS 2) NS	n.r.
Zhang (2009) [43]	60 (25/35); n.r. n.r.; n.r.	(A) Moxa (20 min, once daily, 7 times/session, rest 1 day,total 2 sessions, n = 30), none	(B) Drug (Topical: Diclofenac diethylamine emulgel,1 g, 1/d, 2 wks, n = 30)	1) Response rate 2) Lequesne index	1) NS 2) NS	n.r.
He (2009) [44]	60 (31/29); ACR 59.2/62.1; 8.2/8.9	(A) Moxa (5 min, once daily, 6 times/session, rest for 1 day between sessions, total 3 sessions, n = 30) plus (B), none	(B) Drug (Oral: Diclofenac sodium, 25 mg, 3/d, 20 days, n = 30)	Response rate	P = 0.04	n.r.
Kim (2014) [45]	212 (33/179); ACR n.r.; n.r.	(A) Moxa (n.r., 3 times weekly for 4 wks, n = 102) plus (B), 5 and 13 wks	(B) Usual care (educational leaflet containing basic information about KOA such drug treatment and self-exercise, n = 110)	1) WOMAC 2) QOL (SF-36) 3) Pain (NRS)	1) All subscales and total score: P < 0.01, P < 0.01 (13 wks) 2) PCS, OF, BP, SF: P < 0.05; PCS, BP: P < 0.01 (13 wks); other subscales: NS 3) P < 0.01, P < 0.01 (13 wks)	Burns (A. 119; 1st degree:6; 2nd degree: 113); pruritus and fatigue (A,2)

ACR: American College of Rheumatology; BDI: Beck Depression Inventory; BP: bodily pain; CMA: Chinese Medical Association; f/u: follow-up; GH: general health; GPCRND: Guiding principles of clinical research on new drugs of traditional Chinese medicine; KOA: Knee osteoarthritis; MD: Mean Difference; n.r.: not reported; NRS: numeric rating scale; NS: not significant; PCS: physical component summary; PF: physical function; QOL: quality of life; RR: Risk Ratio; VAS: visual analogue scale; VRS: verbal rating scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; wks: wks; Sham moxa (Device provided insulation from the heat, the patients did not feel hot; (+) high points means improvement; (−) low points means improvement.

Table 3
Appraisal of moxibustion procedure based on the revised STRICTOM criteria.

First author (year) (Ref)	Moxa rationale	Moxa details							Treatment Regime (Total session)	Other components of treatment	Control intervention	Practitioner background	Precaution measures
		Type of moxa	Names of acupoints*	Materials used for moxa	Moxa time per point	Procedure and technique for moxa	Responses sought	Patient posture and treatment environment					
Ren (2015) [27]	TCM theory	Indirect.	Partially individualized: ST35, EX-LE4, Ashi points	Moxa cone. (Nanyang Hanyi Moxa Company, Ltd., Nanyang, Henan, China)	3	Moxa pillar	Y	n.r.	6 weeks. (18 sessions)	NA.	Sham moxa.	n.r.	n.r.
Ren (2011) [28]	TCM theory	Indirect.	Partially individualized:. ST35, EX-LE4, Ashi points	Moxa cone (Nanyang Hanyi Moxa Company, Ltd., Nanyang, Henan, China)		Moxa pillar	n.r	n.r.	6 wks (18 sessions)	NA	Sham moxa	n.r.	n.r.
Zhao (2014) [29]	TCM theory	Indirect	Partially individualized: ST35, EX-LE4, Ashi point	Moxa cone (Nanyang Hanyi Moxa Company, Ltd., Nanyang, Henan, China)	3	Moxa pillar	n.r.	n.r.	6 wks (18 sessions)	NA	Sham moxa	n.r.	n.r.
Yuan (2015) [30]	TCM theory	Indirect	Partially individualized: ST35, SP9, ST36, EX-LE2, Ashi points	Moxa stick (n.r.)	1	Heat-sensitive moxa	Y	Y	30 days (30 sessions)	NA	Drug	n.r.	n.r.
Deng (2015) [31]	TCM theory	Indirect	Partially individualized: ST35, EX-LE4, EX-LE5, LR8, EX-LE2, GB3, Ashi points, KI3, SP9, GB39, ST36, SP9, SP10 in 4 points were chosen at every treatment	Moxa floss (n.r.)	1	Salt cake-separated moxa	n.r.	Y	4 wks (12 sessions)	NA	Drug	n.r.	Y
Song (2013) [32]	TCM theory	Indirect	Partially individualized: SP10, ST34, EX-LE2, EX-LE4, EX-LE5, SP9, GB34, Ashi points in 4 points were chosen at every treatment	Moxa floss (n.r.)	5	Panax notoginsengs cake-separated moxa	Y	n.r.	20 days (20 session)	NA	Drug	n.r.	n.r.
Cheng (2008) [33]	TCM theory	Indirect	Partially individualized: EX-LE4, EX-LE5, EX-LE2, SP9, GB34, GV14, SP10, BL23	Moxa floss (n.r.)	5	Ginger, panax notoginsengs cake-separated moxa or aconite cake-separated moxa	Y	n.r.	30 days (30 sessions)	NA	Drug	n.r.	n.r.
Sun (2008) [34]	TCM theory	Indirect	Partially individualized: EX-LE4, ST35, SP9, GB34, SP10, ST34, EX-LE2, BL18, BL23 in 2–4 points were chosen at every treatment	Moxa floss (n.r.)	5	Aconite cake-separated moxa	Y	n.r.	20 days (20 sessions)	NA	Drug	n.r.	n.r.
Yang (2008) [35]	TCM theory	Indirect	Partially individualized: EX-LE5, EX-LE2, SP9, GB34, SP10, ST36 in 2–4 points were chosen at every treatment	Moxa floss (n.r.)	5	Panax notoginsengs cake-separated moxa	Y	n.r.	20 days (20 sessions)	NA	Drug	n.r.	Y

Table 3 (*Continued*)

First author (year) (Ref)	Moxa rationale	Moxa details							Treatment Regime (Total session)	Other components of treatment	Control intervention	Practitioner background	Precaution measures
		Type of moxa	Names of acupoints*	Materials used for moxa	Moxa time per point	Procedure and technique for moxa	Responses sought	Patient posture and treatment environment					
Ren (2010) [36]	TCM theory	Indirect	Partially individualized: EX-LE4, EX-LE5, ST34, SP10, ST35, SP9, GB34 in 4 points were chosen at every treatment	Moxa floss (n.r.)	3	Herbal cake-separated moxa	Y	n.r.	20 days (20 sessions)	NA	Drug	n.r.	n.r.
Zhou (2010) [37]	TCM theory	Indirect	Partially individualized: EX-LE4, EX-LE5, EX-LE2, SP9, GB34, SP10, ST36, Ashi-points in 2–4 points were chosen at every treatment	Moxa floss (n.r.)	5	Panax notoginsengs cake-separated moxa	Y	n.r.	20 days (20 sessions)	NA	Drug	n.r.	Y
Zhang (2015) [38]	TCM theory	Indirect	Partially individualized: EX-LE4,EX-LE5, EX-LE2,ST34,BL40, SP9, GB34, Ashi points, CV4, BL23	Moxa stick (n.r.)	1	Moxa box	n.r.	Y	30 days (15 sessions)	NA	Rehabilitation or drug	n.r.	n.r.
Zhou (2014) [39]	TCM theory	Indirect	Fixed: CV8, EX-LE4, ST35, SP10, ST34	Moxa stick (n.r.)	1	Moxa box	n.r.	Y	4 wks (12 sessions)	NA	Drug	n.r.	n.r.
Zhang (2011) [40]	TCM theory	Indirect	Partially individualized: SP10, ST34, BL40, GB34, etc.	Moxa stick (n.r.)	1	Moxa box	Y	Y	6 wks (30 sessions)	NA	Drug	n.r.	Y
Chen (2015) [41]	TCM theory	Indirect	Fixed: (A) SP9, GB34, ST34, SP10 Fixed: (B) EX-LE5, EX-LE2	Moxa stick (diameter 22 mm, length 120 mm, Jiangxi provincial TCM Hospital, china)	1	Heat-sensitive moxa	Y	Y	6 wks (35 sessions)	NA	Drug	Y	n.r.
Wu (2011) [42]	TCM theory	Indirect	Partially individualized: Ashi points, EX-LE4, EX-LE5, SP9, GB34, SP10, ST34	Moxa stick (n.r.)	1	Heat-sensitive moxa	Y	Y	3 wks (18 sessions)	NA	Drug	n.r.	n.r.
Zhang (2009) [43]	TCM theory	Indirect	Fixed: EX-LE4, EX-LE5, GB33, GV3	Moxa stick (n.r.)	1	Moxa box	n.r.	Y	2 wks (14 sessions)	NA	Drug	n.r.	n.r.
He (2009) [44]	TCM theory	Indirect	Fixed: ST36, EX-LE4, EX-LE5,	Moxa stick (n.r.)	n.r.	Moxa box	n.r.	n.r.	3 wks (18 sessions)	Drug	Drug	n.r.	n.r.
Kim (2014) [45]	TKM literature and clinical and research experience	Indirect	Partially individualized: ST36, ST35, ST34, SP9, EX-LE4, SP10, Ashi points	Moxa cone (Manina moxibustion, Haitnim Bosung Inc., South Korea)	3	Moxa pillar	n.r.	Y	4 wks (12 sessions)	Usual care	Usual care	Y	Y

moxa: moxibustion; n.r.: not reported; TCM, traditional Chinese medicine; TKM: traditional Korean medicine; NA: not applicable; Y, Yes.
*Moxibustion method was classified into 3 categories on the basis of the levels of individualization: "fixed" means all patients receive the same treatment at all sessions, "partially individualized" means using a fixed set of points to be combined with a set of points to be used flexibly, and "individualized" means each patient receives a unique and evolving diagnosis and treatment.

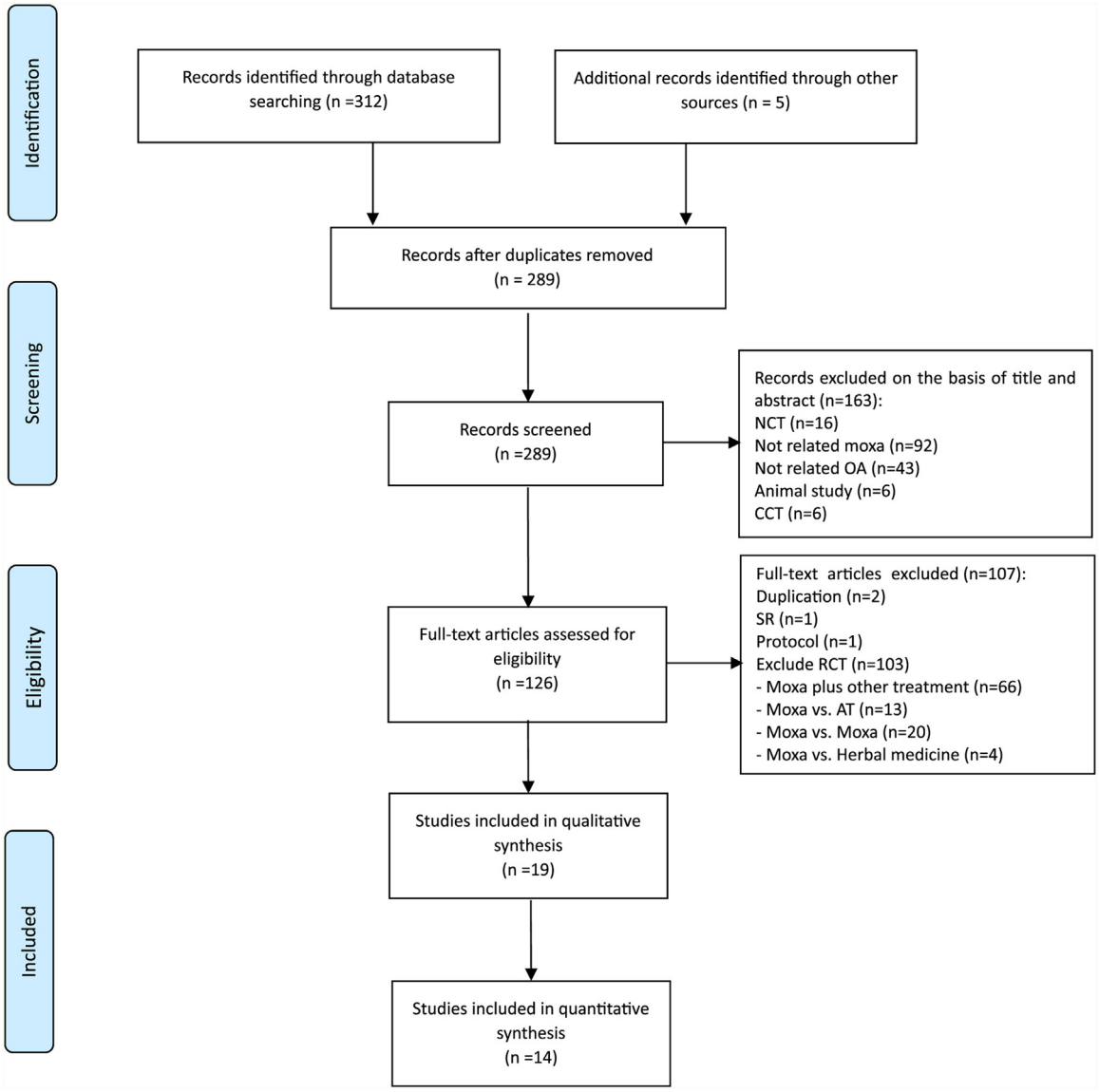

Fig. 1. PRISMA diagram for the included studies. AT: acupuncture; CCT: controlled trials; NCT: non clinical trials; OA: osteoarthritis; RCTs: randomized clinical trials; SR: systematic review.

3. Results

3.1. Description of studies

The literature search revealed 317 articles, and 298 studies were excluded. The study selection flow diagram is presented in Fig. 1. A total of 19 trials representing 2196 participants met the inclusion criteria and were analysed in the review. Key data from the 19 RCTs are summarized in Table 2 [27–45]. All of the RCTs originated in China except one from South Korea [45]. The number of participants in the studies varied from 56 to 212. Participants in studies were diagnosed with KOA according to American College Rheumatology (ACR) criteria in seven trials [27–29,33,40,44,45], Chinese Medical Association (CMA) criteria in four trials [30–32,38] and the Guiding Principles of Clinical Research on New Drugs for Traditional Chinese Medicine (GP-TCM) in seven trials [34–37,39,41,42]. All trials used indirect moxibustion. Four studies used moxa pillar [27–29,45], seven studies used cake-separated moxa [31–37], five studies used moxa box [38–40,43,44], and three studies used heat-sensitive moxa [30,41,42]. Three of the studies compared moxibustion with a sham moxibustion device [27–29]. Eleven studies used an oral drug [30–40], two used intra-articular injection [41,42], and one used a topical drug [43]. Two studies employed moxibustion plus oral diclofenac [44] and moxibustion plus usual care [45] as control groups. Moxibustion acupoint selection was based on TCM theory in all of the included RCTs. The treatment period of the other studies varied from 2 weeks to 6 weeks for 12–35 sessions. The details of the treatment regimens are summarized in Table 3.

3.2. Risk of bias

The Cochrane risk of bias (ROB) is presented in Figs. 2. Eleven of the included trials reported appropriate sequence generation methods for the randomization process [27–31,34,37,41–43,45], whereas three RCTs used inappropriate methods [33,35,44]. Two RCTs were described as ‘randomized’, but none of these reported the method of random sequence generation [32,40]. Only five RCTs describe the methods of allocation concealment [27–29,41,45], and the remaining trials did not describe the methods of allocation concealment. The majority of trials compared acupuncture and conventional oral drug therapies; thus, blinding could not be applied for patients and researchers. Sixteen RCTs had a high ROB

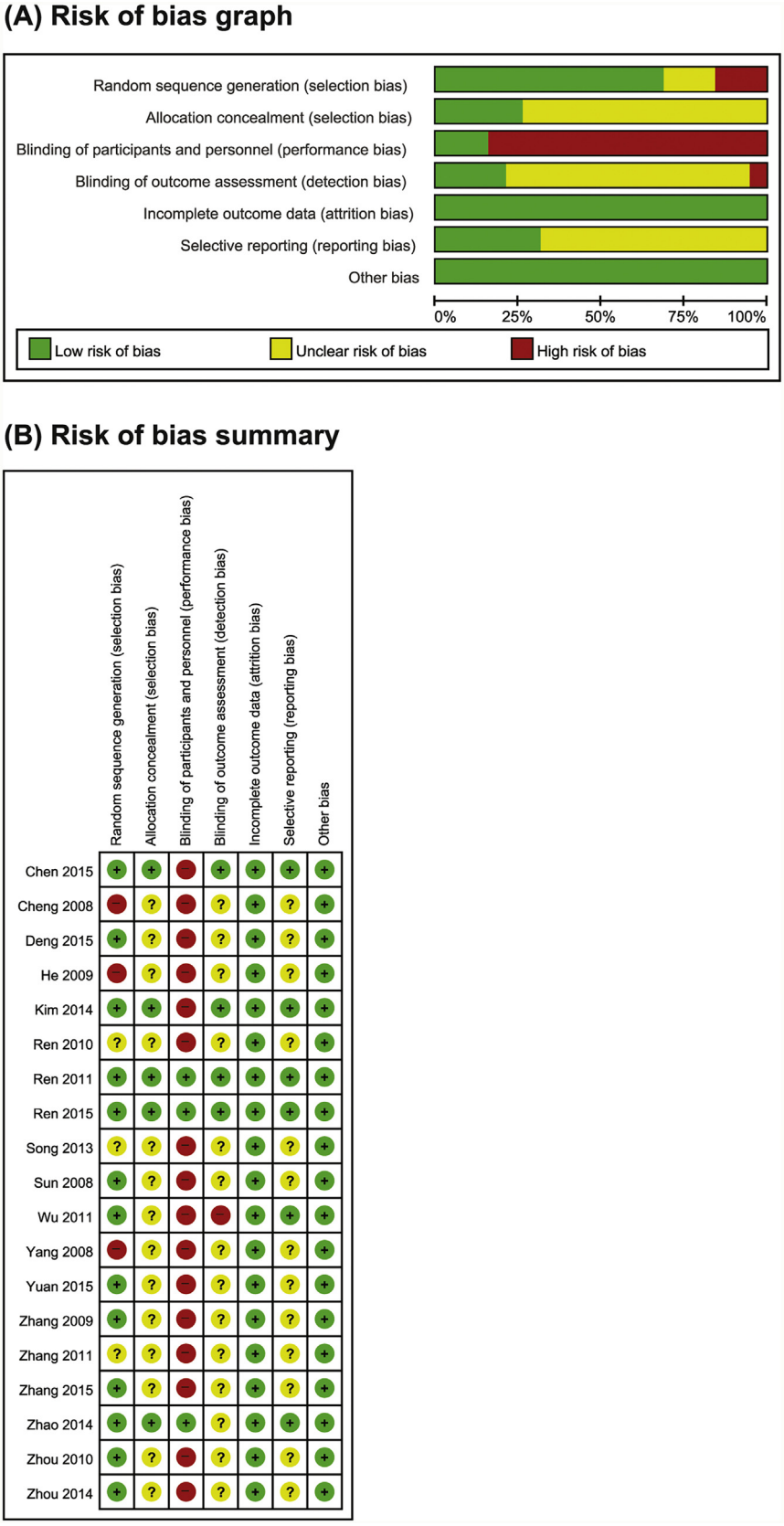

Fig. 2. Risk of bias. (A) Risk of bias graph: review authors' judgments about each item's risk of bias item presented as percentage across all included studies. (B) Risk of bias summary: review authors' judgments about each item's risk of bias for each included study. +: low risk of bias; –: high risk of bias;?: unclear.

for the item of participant and personnel blinding due to the nature of the treatment [30–45]. Only three RCTs made comparisons with sham moxibustion [27–29]. Four RCTs reported outcome assessor blinding [27,28,41,45]. All 19 RCTs had low ROBs in incomplete outcome data. Only five RCTs had published protocols or reported trial registration [27–29,41,45], and all except five RCTs had a high risk of bias in selective reporting of outcomes. All RCTs reported patient baseline characteristics, and all RCTs had low ROBs for other sources of bias.

3.3. Outcomes measurements

3.3.1. Moxibustion vs. sham moxibustion

Three RCTs compared the effects of moxibustion with sham moxibustion, which uses a device that insulates KOA patients from the radiant heat produced during moxibustion [27–29]. Two RCTs showed positive effects of moxibustion for reducing pain in WOMAC after treatments and follow-up, whereas the other RCT failed to demonstrate effects on body pain for QoL. The meta-analysis showed favourable effects of moxibustion on pain level after the last session of treatment (n = 305; SMD, −0.46; 95% CI: −0.86 to −0.06, P = 0.02, I^2 = 65%) (Fig. 3A) and at follow-up (n = 305; SMD, −0.36; 95% CI: −0.70 to −0.01, P = 0.04, I^2 = 54%) (Fig. 3B).

Two RCTs also reported the positive effects of moxibustion on physical function [28,29], whereas one RCT failed to do so [27]. The meta-analysis failed to show superior effects of moxibustion on physical function (n = 305; SMD, −0.23; 95% CI: −0.62 to 0.17, P = 0.26, I^2 = 65%) (Fig. 3C) and follow-up (n = 305; SMD, −0.31; 95% CI: −0.69 to 0.07, P = 0.11, I^2 = 62%) (Fig. 3D).

One RCT showed the effects of moxibustion improvement in SF-36 subscales, including general health and vitality, compared with sham moxibustion immediately after treatment and at 12 weeks of follow-up [27].

3.3.2. Moxibustion vs. oral drug therapy

Eleven RCTs tested the effects of moxibustion compared with conventional oral drug therapies [30–40]. Nine RCTs exhibited superior effects of moxibustion on at least one main outcome [30–37,39], whereas the other 2 trials showed equivalent or inferior results compared with drug therapies [38,40]. Eight RCTs reported the total symptom score with WOMAC or GPCRND-KOA. Four trials showed favourable effects of moxibustion on total symptom score compared with oral drug therapy (diclofenac sodium) [30–33,37], whereas the other two reported equivalent effects [34,35]. The meta-analysis showed superior effects of moxibustion on total symptom score compared with diclofenac sodium (n = 534; SMD, −0.46; 95% CI: −0.73 to −0.19; P = 0.0009, I^2 = 58%) (Fig. 4A) [30–32,34,35,37]. One RCT showed superior effects of moxibustion on total symptom score compared with celecoxib [39], whereas the other one trial failed to do so [38].

Eight RCTs reported the effects of moxibustion on response rate compared with drug therapies [30,31,33–37,40]. Three of them showed favourable effects of moxibustion on the response rate compared with drug therapies [30,33,36], and the other 5 RCTs reported equivalent effects [31,34,35,37,40]. The meta-analysis showed favourable effects of moxibustion on response rate (n = 758 knees; RR, 1.10; 95% CI: 1.05–1.16, P < 0.0001, I^2 = 0%) (Fig. 4B). Subgroup analysis also showed favourable effects of moxibustion compared with diclofenac sodium (n = 619 knees; RR, 1.11; 95% CI: 1.06–1.17, P < 0.0001, I^2 = 0%) (Fig. 4B). Three RCTs tested the effects of moxibustion on the response rate after 8 weeks [32,35,37] and one RCT after 12 weeks [30]. The meta-analysis showed favourable effects of moxibustion on follow-up response rate (n = 426 knees; RR, 1.12; 95% CI: 1.04–1.21, P = 0.002, I^2 = 0%) (Fig. 4C).

Eight RCTs assessed the effects of moxibustion on pain level compared with drug therapies [30–34,37–39]. Four studies showed the significant reduction of pain in moxibustion [30,31,34,39], whereas the other four reported equivalent [32,33,37] or inferior effects [38] compared with drug therapies. The meta-analysis showed superior effects of moxibustion on pain reduction compared with diclofenac sodium (n = 628 knees; SMD, −0.42; 95% CI: −0.81 to −0.03, P = 0.03) with high heterogeneity (I^2 = 83%) (Fig. 4D) [30–34,37].

3.3.3. Moxibustion vs. intra-articular injection

Two RCTs tested the effect of moxibustion on KOA compared with intra-articular injection [41,42]. One trial which compared the effects of heat-sensitive moxibustion and a type of routine application of moxibustion with sodium hyaluronate injection reported superior effects for both types of moxibustion on OA symptom scores [41]. The other trial showed equivalent effects of moxibustion compared with intra-articular injection for response rate and OA symptom scores [42].

3.3.4. Moxibustion vs. topical drug therapy

One RCT investigated the effect of moxibustion on response rate and Lequesne scores and showed equivalent effects of moxibustion with topical drug therapy [43].

3.3.5. Moxibustion plus oral drug therapy vs. oral drug therapy alone

Two RCTs compared the effect of moxibustion plus drug therapy on WOMAC, pain or response rate with drug therapy alone [44]. The results showed favourable effects of moxibustion on the response rate.

3.3.6. Moxibustion plus usual care vs. usual care alone

One RCT compared moxibustion plus usual care with usual care alone on WOMAC, SF-36, and pain [45]. The results showed favourable add-on effects of moxibustion on all three outcomes.

3.4. Adverse events

Six RCTs [27,29,30,40,41,45] reported AEs. Three RCTs reported no AEs with moxibustion, whereas three RCTS reported that 5 patients experienced AEs with drug therapy, which involved nausea and stomach pain. No detailed report was provided in two of the three RCTs. In the other three studies, 22 patients experienced blisters of varying sizes [27], and 10 patients reported skin flushing associated with the moxibustion [29]. A total of 102 participants reported 119 burn wounds, and 2 patients reported pruritus and fatigue (121 AEs associated with a total of 1158 treatments, 10.45%) [45]. Most adverse effects disappeared within 3 days without obtaining medical care.

4. Discussion

This updated systematic review suggests that moxibustion may be an effective treatment for reducing pain and total symptoms of OA compared with sham moxa and conventional drug therapy. The levels of evidence and risk of bias were moderate in all of the included trials (Tables 4 and 5). Hence, the evidence is sufficient to conclude that moxibustion is beneficial to treat the symptoms of patients with KOA.

Our review aimed to update and complete the evidence by including recent RCTs. Compared with our previous review, we identified eleven new RCTs [27–32,38,39,41,42,45]. Recently, two new systematic reviews were published during the updating of our previous review [22,23]. We also successfully updated these reviews [22,23] with seven new RCTs [28,30–32,38,43,44]. All of the previous systematic reviews demonstrated that moxibustion may be effective or exhibit equivalent effects to drug therapies. The

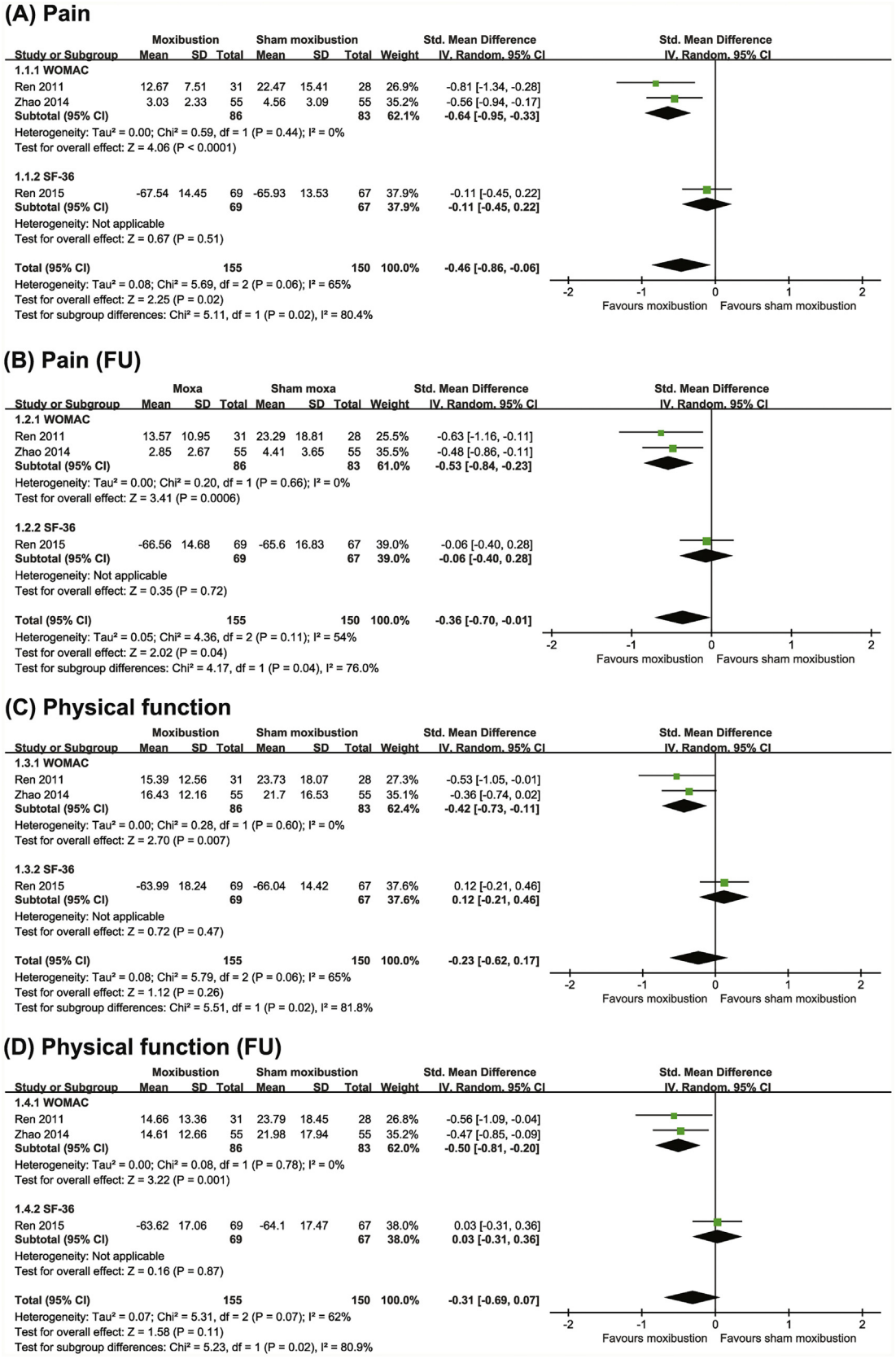

Fig. 3. Forest plot of moxibustion compared with sham moxibustion on (A) Pain; (B) Pain (FU); (C) Physical function; (D) Physical function (FU). FU: follow-up; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

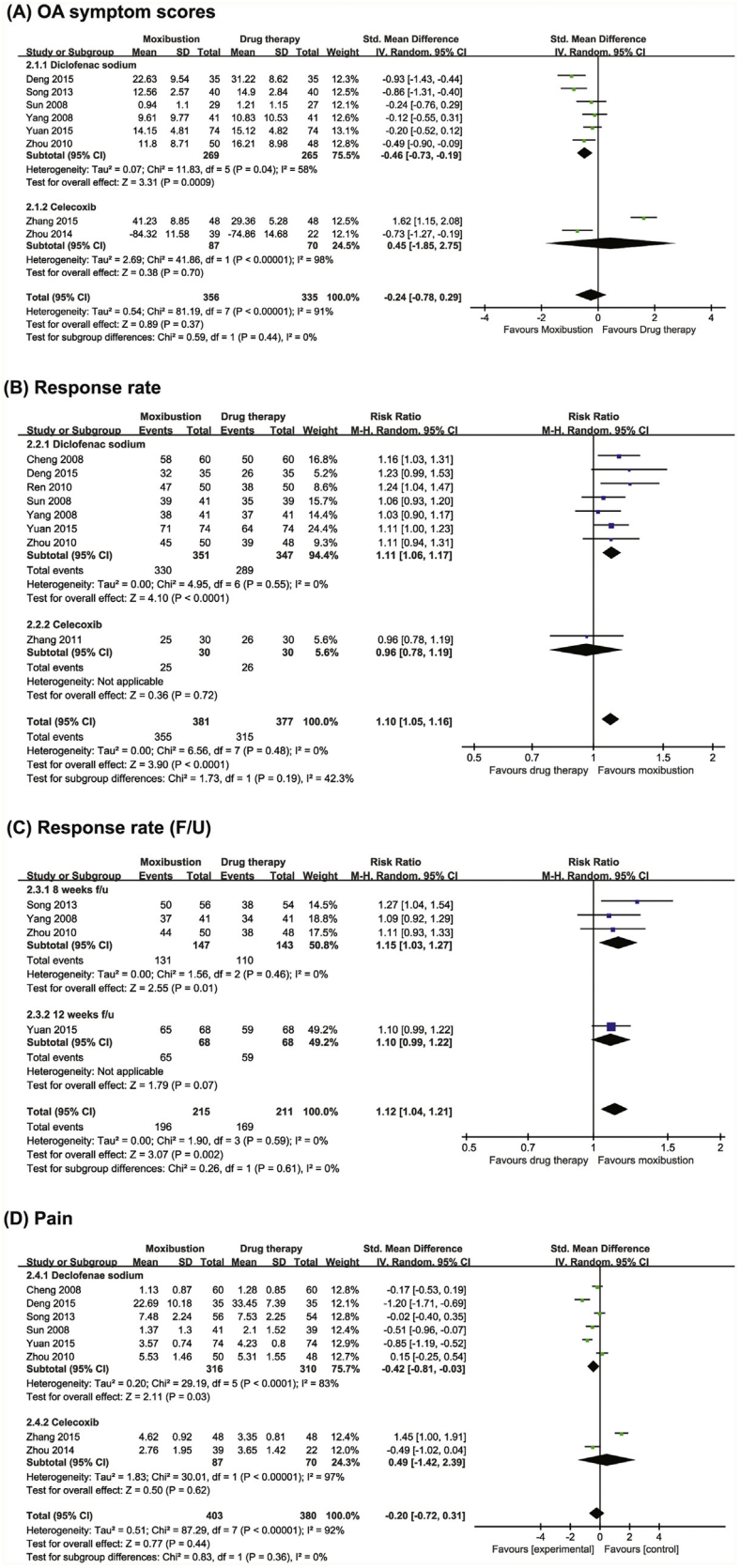

Fig. 4. Forest plot of moxibustion compared with oral drug therapy on (A) OA symptom score; (B) Response rate; (C) Response rate (FU); (D) Pain. FU: follow-up.

newly added trials offer supportive evidence for the use of moxibustion for OA compared with previous reviews. The findings from RCTs of moxibustion for treatment KOA are mixed according to moxibustion type and therapeutic regimens. This review concluded that moxibustion exhibits equivalent or possible positive benefits compared with oral drugs and intra-articular injections in patients

Table 4
Summary of findings for moxibustion vs. sham moxibution for OA.

Moxibustion compared to sham moxibustion for Knee osteoarthritis						
Patient or population: Knee osteoarthritis	Intervention: Moxibustion		Comparison: Sham moxibustion			
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Sham moxibustion	Corresponding risk Moxibustion				
Pain		The mean pain in the intervention groups was **0.46 standard deviations lower** (0.86–0.06 lower)		305 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Pain – WOMAC		The mean pain – womac in the intervention groups was **0.64 standard deviations lower** (0.95–0.33 lower)		169 (2 studies)	⊕⊕⊕⊖ **moderate**[2]	
Pain – SF-36		The mean pain – sf-36 in the intervention groups was **0.11 standard deviations lower** (0.45 lower to 0.22 higher)		136 (1 study)	⊕⊕⊕⊖ **moderate**[2]	
Pain(12weeks)		The mean pain(12weeks) in the intervention groups was **0.36 standard deviations lower** (0.7–0.01 lower)		305 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Pain(12weeks) – WOMAC		The mean pain(12weeks) – womac in the intervention groups was **0.53 standard deviations lower** (0.84–0.23 lower)		169 (2 studies)	⊕⊕⊕⊖ **moderate**[2]	
Pain(12weeks) – SF-36		The mean pain(12weeks) – sf-36 in the intervention groups was **0.06 standard deviations lower** (0.4 lower to 0.28 higher)		136 (1 study)	⊕⊕⊕⊖ **moderate**[2]	
Phyiscal function		The mean phyiscal function in the intervention groups was **0.23 standard deviations lower** (0.62 lower to 0.17 higher)		305 (3 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Phyiscal function – WOMAC		The mean phyiscal function – womac in the intervention groups was **0.42 standard deviations lower** (0.73–0.11 lower)		169 (2 studies)	⊕⊕⊕⊖ **moderate**[2]	
Phyiscal function – SF-36		The mean phyiscal function – sf-36 in the intervention groups was **0.12 standard deviations higher** (0.21 lower to 0.46 higher)		136 (1 study)	⊕⊕⊕⊖ **moderate**[2]	
Phyiscal function(12weeks)		The mean phyiscal function(12weeks) in the intervention groups was **0.31 standard deviations lower** (0.69 lower to 0.07 higher)		305 (3 studies)	⊕⊕⊖⊖ **low**[1]	
Phyiscal function(12weeks) – WOMAC		The mean phyiscal function(12weeks) – womac in the intervention groups was 0.5 standard deviations lower (0.81–0.2 lower)		169 (2 studies)	⊕⊕⊕⊖ **moderate**[2]	
Phyiscal function(12weeks) – SF-36		The mean phyiscal function(12weeks) – sf-36 in the intervention groups was **0.03 standard deviations higher** (0.31 lower to 0.36 higher)		136 (1 study)	⊕⊕⊕⊖ **moderate**[2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **f/u:** follow-up; **OA:** osteoarthritis; **RR:** Risk ratio; **VAS:** visual analogue scale**; WOMAC:** Western Ontario and McMaster Universities Osteoarthritis Index
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[1] Statistical heterogeneity is high.
[2] Sample size too small.
[3] Risk of bias are high or uncertain in several domain of most of trials.

with KOA. The level of evidence is moderate and low in general. Furthermore, the number of trials and total sample size included in our analysis were not sufficient to draw firm conclusions.

Three sham moxibustion methods were used to assess the efficacy of moxibustion for OA, including a sham moxibustion device which provides insulation from the radiant heat, the patients did not feel the heat, and the procedure was similar to the verum moxibustion group. One trial showed favourable effects on QOL general health [27] and WOMAC pain [28,29] for scores of verum moxibustion compared with sham moxibustion for KOA. Two RCTs showed specific effects of moxibustion for pain reduction and function improvement with WOMAC [28,29], but one trial did not show favourable effects of moxibustion on pain and physical function concerning the SF-36 [27]. The failure to demonstrate specific effects may be due to the validity of the outcome measurement instrument, which is not a disease-specific outcome measure. The

Table 5
Summary of findings for moxibustion vs. drug therapy for OA.

Moxibustion compared to drug for Knee osteoarthritis						
Patient or population: patients with Knee osteoarthritis		Intervention: Moxibustion		Comparison: Drug		
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Drug	Corresponding risk Moxibustion				
OA symptoms score		The mean OA symptoms score in the intervention groups was **0.24 standard deviations lower** (0.78 lower to 0.29 higher)		691 (8 studies)	⊕⊕⊖⊖ **low**[1,3]	
OA symptoms score – Diclofenac sodium		The mean OA symptoms score – diclofenac sodium in the intervention groups was **0.46 standard deviations lower** (0.73–0.19 lower)		534 (6 studies)	⊕⊕⊖⊖ **low**[1,3]	
OA symptoms score – Celecoxib		The mean OA symptoms score – celecoxib in the intervention groups was **0.45 standard deviations higher** (1.85 lower to 2.75 higher)		157 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
Response rate	**Study population**		**RR 1.1** (1.05–1.16)	758 (8 studies)	⊕⊕⊕⊖ **moderate**[1]	
	833 per 1000	**916 per 1000** (875–966)				
	Moderate					
	849 per 1000	**934 per 1000** (891–985)				
Response rate – Diclofenac sodium	**Study population**		**RR 1.11** (1.06–1.17)	698 (7 studies)	⊕⊕⊕⊖ **moderate**[1]	
	833 per 1000	**924 per 1000** (883–974)				
	Moderate					
	833 per 1000	**925 per 1000** (883–975)				
Response rate – Celecoxib	**Study population**		**RR 0.96** (0.78–1.19)	60 (1 study)	⊕⊕⊖⊖ **low**[1,2]	
	867 per 1000	**832 per 1000** (676–1000)				
	Moderate					
	867 per 1000	**832 per 1000** (676–1000)				
Response rate(f/u)	**Study population**		**RR 1.12** (1.04–1.21)	426 (4 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
	801 per 1000	**897 per 1000** (833–969)				
	Moderate					
	811 per 1000	**908 per 1000** (843–981)				
Response rate(f/u) – 8 weeks f/u	**Study population**		**RR 1.15** (1.03–1.27)	290 (3 studies)	⊕⊕⊖⊖ **low**[1,2]	
	769 per 1000	**885 per 1000** (792–977)				
	Moderate					
	792 per 1000	**911 per 1000** (816–1000)				
Response rate(f/u) – 12 weeks f/u	**Study population**		**RR 1.1** (0.99–1.22)	136 (1 study)	⊕⊕⊖⊖ **low**[1,2]	
	868 per 1000	**954 per 1000** (859–1000)				
	Moderate					
	868 per 1000	**955 per 1000** (859–1000)				
Pain		The mean pain in the intervention groups was 0.2 standard deviations lower (0.72 lower to 0.31 higher)		783 (8 studies)	⊕⊕⊖⊖ **low**[1,3]	
Pain – Declofenae sodium		The mean pain – declofenae sodium in the intervention groups was **0.42 standard deviations lower** (0.81–0.03 lower)		626 (6 studies)	⊕⊕⊖⊖ **low**[1,3]	
Pain – Celecoxib		The mean pain – celecoxib in the intervention groups was **0.49 standard deviations higher** (1.42 lower to 2.39 higher)		157 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **f/u:** follow-up; **OA:** osteoarthritis; **RR:** Risk ratio; **VAS:** visual analogue scale**; WOMAC:** Western Ontario and McMaster Universities Osteoarthritis Index.
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
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Very low quality: We are very uncertain about the estimate.
[1] Statistical heterogeneity is high.
[2] Sample size too small.
[3] Risk of bias are high or uncertain in several domain of most of trials.

high heterogeneity in the meta-analysis may originate from the use of different measurement instruments for the same outcome. The use of disease-specific measurement tools may be important to investigate the effects of moxibustion or other interventions.

This evidence may suggest the possibility of non-inertness of sham moxibustion, which is different from placebo effects of conventional drugs. However, the superiority of moxibustion compared with conventional drugs supports the possible interpretation of specific effects of moxibustion for this condition.

Overall, most included trials had a moderate risk of bias across the domains. Three RCTs did not report the random sequence generation methods [32,36,40]. Only five used allocation concealment [27–29,41,45]. Three studies employed patient blinding [27–29] and only four studies employed accessor blinding [27,28,33,45]. Given the nature of intervention, practitioner blinding may not be achievable. RCTs with inadequate or unclear blinding and allocation concealment may be subject to selection bias and would therefore be likely to produce an overestimation of treatment effects and generate an underestimation of the effect [46]. Only five RCTs had published protocols or trial registration [27–29,41,45]. Selective reporting of missing or partially reported harm-related outcomes indicates that the quality of the reporting of harm outcomes must be improved for both primary studies and systematic reviews [47]. In the future, collective efforts should be made to increase adherence to the CONSORT statement [48] and STRICTOM guidelines [25] to facilitate improvement in the reporting quality of the RCTs of moxibustion and to ensure the veracity and reliability of the conclusions.

Moxibustion involves the burning of moxa material on the skin and can potentially cause scars of 1–2 cm. The temperature was approximately 65 °C on the skin surface and 45 °C in the subcutaneous layer [49] when moxa was lit on or above the acupoints thus potentially producing various AEs, such as burn wounds, blister and pruritus [50]. In this review, only three of the reviewed studies reported several type of AEs [27,29,45] and two of the included trials noted no adverse events related to moxibustion [30,40]. Most AEs did not require particular medical intervention. Moxibustion is not entirely risk free because it can potentially cause adverse events. Several studies required further detailed information. For example, only two of the included trials reported the practitioner background/experience [38,41] and only five of the trials reported precautionary measures [31,35,37,40,45]. Moxibustion produces heat, tar and smoke that may increase the risk of several of AEs occurring. Improving practitioner skill, standardizing the moxa procedure, and taking precautionary measures can reduce the incidence of adverse reactions and improve the safety of moxibustion [50,51]. Therefore, adverse events should be reported in future studies, and STRICTOM guidelines regarding study reporting should be followed.

This review has several limitations. First, we searched a large number of databases without publication language restrictions. We are confident that our search strategies located all relevant data; however, some degree of uncertainty remains. Second, with one exception [45], all of the RCTs were conducted in China, where it has previously been reported that few negative studies have been published [52]. Thus, the generalization of the results to other countries might be limited. Third, most trials did not use internationally recognized reliable and valid outcome measures. Furthermore the response rate cannot avoid possible bias by the practitioner. Future trials on the evaluation of treatment effects in compliance with international standards could resolve this issue.

In conclusion, the existing trial evidence is sufficiently convincing to suggest that moxibustion compared with oral drugs is effective for managing patients with KOA. This systemic review and meta-analysis provide suggestive evidence for the superiority of moxibustion compared with oral drugs for treating KOA. However, the level of evidence is moderate and low given the high risk of bias and small sample size. In the future more rigorously designed RCTs with large sample size are warranted.

Contributors

T-YC and MSL conceived and designed the experiments.

T-YC and JIK searched the literature and selected studies and then extracted the data and analyzed the data.

T-YC wrote the first draft of the manuscript.

MSL and CZ critically revised the manuscript.

All authors contributed to the refinement of the manuscript and take public responsibility for its content. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

[1] D. Bhatia, T. Bejarano, M. Novo, Current interventions in the management of knee osteoarthritis, J. Pharm. Bioall. Sci. 5 (1) (2013) 30–38.
[2] J. Bijlsma, F. Berenbaum, F. Lafeber, Osteoarthritis: an update with relevance for clinical practice, Lancet 377 (9783) (2011) 2115–2126.
[3] WHO Scientific Group on the Burden of Musculoskeletal Conditions at the Start of the New Millennium, The burden of musculoskeletal conditions at the start of the new millenium: report of a WHO scientific group. 2003 (Accessed 03 February 2016).
[4] National Clinical Guideline Centre, National institute for health and clinical excellence: Guidance, Osteoarthritis: Care and management in adults, National Institute for Health and Care Excellence (UK) London, 2014.
[5] L. Murphy, T.A. Schwartz, C.G. Helmick, J.B. Renner, G. Tudor, G. Koch, A. Dragomir, W.D. Kalsbeek, G. Luta, J.M. Jordan, Lifetime risk of symptomatic knee osteoarthritis, Arthritis Rheum. 59 (9) (2008) 1207–1213.
[6] Y. Zhang, J. Niu, M. Kelly-Hayes, C.E. Chaisson, P. Aliabadi, D.T. Felson, Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: the Framingham Study, Am. J. Epidemiol. 156 (11) (2002) 1021–1027.
[7] A. Chen, C. Gupte, K. Akhtar, P. Smith, J. Cobb, The global economic cost of osteoarthritis: how the UK compares, Arthritis 2012 (2012) 698709.
[8] K. Bennell, D. Hunter, R. Hinman, Management of osteoarthritis of the knee, BMJ 345 (2012) e4934.
[9] A.M. Wood, T.M. Brock, K. Heil, R. Holmes, A. Weusten, A review on the management of hip and knee osteoarthritis, Int. J. Chron. Dis. 2013 (2013) 845015.
[10] T. Manyanga, M. Froese, R. Zarychanski, A. Abou-Setta, C. Friesen, M. Tennenhouse, B.L. Shay, Pain management with acupuncture in osteoarthritis: a systematic review and meta-analysis, BMC Complement. Altern. Med. 14 (2014) 312.
[11] L. Brosseau, P. Rahman, K. Toupin-April, S. Poitras, J. King, G. De Angelis, L. Loew, L. Casimiro, G. Paterson, J. McEwan, A systematic critical appraisal for non-pharmacological management of osteoarthritis using the appraisal of guidelines research and evaluation II instrument, PLoS One 9 (1) (2014) e82986.
[12] E. Manheimer, K. Cheng, K. Linde, L. Lao, J. Yoo, S. Wieland, D.A. van der Windt, B.M. Berman, L.M. Bouter, Acupuncture for peripheral joint osteoarthritis, Cochrane Database Syst. Rev. 1 (2010), Cd001977.
[13] C.M. Witt, S. Jena, B. Brinkhaus, B. Liecker, K. Wegscheider, S.N. Willich, Acupuncture in patients with osteoarthritis of the knee or hip: a randomized, controlled trial with an additional nonrandomized arm, Arthritis Rheum. 54 (11) (2006) 3485–3493.
[14] M.S. Sridhar, C.D. Jarrett, J.W. Xerogeanes, S.A. Labib, Obesity and symptomatic osteoarthritis of the knee, J. Bone Joint Surg. Br. 94 (4) (2012) 433–440.
[15] World Health Organization Western Pacific Region, WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region. Manila, 2007.
[16] J. Xu, H. Deng, X. Shen, Safety of moxibustion: a systematic review of case reports, Evid. Based Complement. Alternat. Med. 2014 (2014) 783704.

[17] Q.F. Huang, H.G. Wu, J. Liu, J. Hong, Bibliometric analysis of diseases spectrum of moxibustion therapy, J. Acupunct. Tuina Sci. 10 (2012) 342–348.
[18] M.S. Corbett, S.J. Rice, V. Madurasinghe, R. Slack, D.A. Fayter, M. Harden, A.J. Sutton, H. Macpherson, N.F. Woolacott, Acupuncture and other physical treatments for the relief of pain due to osteoarthritis of the knee: network meta-analysis, Osteoarthr. Cartil. 21 (9) (2013) 1290–1298.
[19] T.K. Selfe, A.G. Taylor, Acupuncture and osteoarthritis of the knee: a review of randomized, controlled trials, Fam. Commun. Health 31 (3) (2008) 247–254.
[20] Y.D. Kwon, M.H. Pittler, E. Ernst, Acupuncture for peripheral joint osteoarthritis: a systematic review and meta-analysis, Rheumatology (Oxford) 45 (11) (2006) 1331–1337.
[21] J. Yu, J. Xiong, Systematic evaluation and meta analysis of clinical effectiveness of heat-sensitive moxibustion for knee osteoarthritis, J. Guangzhou Univ. TCM 01 (2015).
[22] A. Li, Z.J. Wei, Y. Liu, B. Li, X. Guo, S.Q. Feng, Moxibustion treatment for knee osteoarthritis: a systematic review and meta-analysis, Medicine (Baltimore) 95 (14) (2016) e3244.
[23] G.M. Song, X. Tian, Y.H. Jin, Y.H. Deng, H. Zhang, X.L. Pang, J.G. Zhou, Moxibustion is an alternative in treating knee osteoarthritis: the evidence from systematic review and meta-analysis, Medicine (Baltimore) 95 (6) (2016) e2790.
[24] T.Y. Choi, J. Choi, K.H. Kim, M.S. Lee, Moxibustion for the treatment of osteoarthritis: a systematic review and meta-analysis, Rheumatol. Int. 32 (10) (2012) 2969–2978.
[25] C. Cheng, S. Fu, Q. Zhou, T. Wu, H. Shang, X. Tang, Z. Liu, J. Liu, Z. Lin, L. Lao, A. Lü, B. Zhang, B. Liu, Z. Bian, Extending the CONSORT statement to moxibustion, J. Integr. Med. 11 (1) (2013) 54–63.
[26] J. Higgins, D. Altman, J. Sterne, Chapter 8: assessing risk of bias in included studies, in: J. Higgins, S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 510, The Cochrane Collaboration, 2011.
[27] X. Ren, C. Yao, F. Wu, Z. Li, J. Xing, H. Zhang, Effectiveness of moxibustion treatment in quality of life in patients with knee osteoarthritis: a randomized, double-blinded, placebo-controlled trial, Evid. Based Complement. Alternat. Med. 2015 (2015) 569523.
[28] W.M. Ren, J.J. Cao, X.Y. Shen, L.Z. Wang, L. Zhao, F. Wu, H.M. Zhang, Knee osteoarthritis treated with moxibustion: a randomized controlled trial, Chin. Acupunct. Moxibust. 31 (12) (2011) 1057–1061.
[29] L. Zhao, K. Cheng, L. Wang, F. Wu, H. Deng, M. Tan, L. Lao, X. Shen, Effectiveness of moxibustion treatment as adjunctive therapy in osteoarthritis of the knee: a randomized, double-blinded, placebo-controlled clinical trial, Arthritis Res. Ther. 16 (3) (2014) R133.
[30] Q.D. Yuan, X. Guo, Y.C. Han, J.Q. Zhang, X.D. Feng, Observations on the therapeutic effect of heat-sensitive point thunder-fire moxibustion on knee osteoarthritis, Shangh. J. Acup. Moxi. 34 (7) (2015) 665–667.
[31] J.M. Deng, Y. Chen, S.X. Wang, Salt insulation moxibustion in the treatment of knee osteoarthritis: analysis of 35 cases, J. Clin. Acup. Moxi. 31 (3) (2015) 14–17.
[32] Y.C. Song, D.C. Liu, J.C. Zhu, Clinical research of treating knee osteoarthritis by gesan qibing moxibustion, J. Clin. Acup. Moxi. 29 (9) (2013) 40–42.
[33] H.L. Cheng, W. Han, P.J. Hu, J. Yang, Clinical study of differential selection of objects separated moxibustion for treatment of knee osteoarthritis, Clin. J. Tradit. Chin. Med. 20 (2) (2008) 114–116.
[34] K. Sun, Y.H. Yang, Z.L. Zhou, Clinical observations on the treatment of primary genual osteoarthritis of liver-kidney depletion type by aconite cake-separated moxibustion, Shangh. J. Acup. Moxi. 27 (4) (2008) 9–10.
[35] Y.H. Yang, K. Sun, G.H. Su, C.L. Zhou, Clinical study panax notoginsengs cake separated moxibustion treatment of qi stagnation blood stasis type for primary knee osteoarthritis, Clin. J. Tradit. Chin. Med. 20 (1) (2008) 53–55.
[36] X.M. Ren, S.L. Song, Y. Shi, Observations on the therapeutic effect of herbal cake-separated moderate moxibustion on knee osteoarthritis of 50 cases, Zhejiang J. Tradit. Chin. Med. 45 (10) (2010) 759.
[37] Z.L. Zhou, K. Sun, H.L. Cheng, D.C. Liu, J. Yang, Observations on the therapeutic effect of herbal cake-separated moxibustion on knee osteoarthritis of blood stasis type, Shangh. J. Acup. Moxi. 29 (1) (2010) 45–47.
[38] J. Zhang, Y. Shen, G. Huang, Clinical observation of moxibustion combined with knee joint rehabilitation for the treatment of knee osteoarthritis, J. Clin. Acup. Moxi. 31 (8) (2015) 7–9.
[39] Y.L. Zhou, J. Li, W.G. Hou, C.L. Bao, Q. Zhang, S.S. Wang, H.G. Wu, Clinical observation of moxibustion in treatment of knee osteoarthritis, Shangh. J. Acup. Moxi. 33 (12) (2014) 1086–1088.
[40] Q.J. Zhang, L.H. Cao, Z.D. Li, S.C. Wang, Y.H. Ma, J.C. Su, C.C. Zhang, N. Du, The clinical effects and safety of moxibustion and celecoxib for obteoarthritis of knee, Chin. J. Tradit. Med. Trauma Orthop. 19 (1) (2011) 1315.
[41] R. Chen, M. Chen, T. Su, M. Zhou, J. Sun, J. Xiong, Z. Chi, D. Xie, B. Zhang, Heat-sensitive moxibustion in patients with osteoarthritis of the knee: a three-armed multicentre randomised active control trial, Acupunct. Med. 33 (4) (2015) 262–269.
[42] F. Wu, P. Xiong, Moxibustion on heat-sensitive acupoints in the treatment of KOA (Swelling Type), J. Clin. Acup. Moxi. 27 (2011) 1–4.
[43] S. Zhang, The Clinical Observationon the Therapy of Knee Joint Osteoarthritis Using Moderate Moxibustion, Guangzhou University of Chinese Medicine, 2009, Master degree.
[44] Y. He, Y.P. Xu, X.T. Huo, Clinical research of moxibustion in treating knee joint osteoarthritis, Chin. J. Tradit. Med. Trauma. Orthop. 17 (3) (2009) 38–39.
[45] T.H. Kim, K.H. Kim, J.W. Kang, M. Lee, K.W. Kang, J.E. Kim, J.H. Kim, S. Lee, M.S. Shin, S.Y. Jung, A.R. Kim, H.J. Park, H.J. Jung, H.S. Song, H.J. Kim, J.B. Choi, K.E. Hong, S.M. Choi, Moxibustion treatment for knee osteoarthritis: a multi-centre, non-blinded, randomised controlled trial on the effectiveness and safety of the moxibustion treatment versus usual care in knee osteoarthritis patients, PLoS One 9 (7) (2014) e101973.
[46] K. Dwan, C. Gamble, P.R. Williamson, J.J. Kirkham, Systematic review of the empirical evidence of study publication bias and outcome reporting bias – an updated review, PLoS One 8 (7) (2013) e66844.
[47] M.J. Page, J.E. McKenzie, A. Forbes, Many scenarios exist for selective inclusion and reporting of results in randomized trials and systematic reviews, J. Clin. Epidemiol. 66 (5) (2013) 524–537.
[48] K.F. Schulz, D.G. Altman, D. Moher, CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials, Ann. Intern. Med. 152 (11) (2010) 726–732.
[49] S.H. Yi, Thermal properties of direct and indirect moxibustion, J. Acupunct. Merid. Stud. 2 (4) (2009) 273–279.
[50] J.E. Park, S.S. Lee, M.S. Lee, S.M. Choi, E. Ernst, Adverse events of moxibustion: a systematic review, Complement. Ther. Med. 18 (5) (2010) 215–223.
[51] J. Xu, H.Y. Deng, X.Y. Shen, Safety of moxibustion: a systematic review of case reports, Evid. Based Complement. Alternat. Med. 2013 (2014) 783704.
[52] A. Vickers, N. Goyal, R. Harland, R. Rees, Do certain countries produce only positive results? A systematic review of controlled trials, Control. Clin. Trials 19 (2) (1998) 159–166.