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REVIEW

Effect of Moxibustion on Inflammatory Cytokines for Low Back Pain: A Systematic Review, Meta-Analysis and Meta-Regression

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Background and Objective: Moxibustion is effective for low back pain (LBP), and inflammatory cytokines may play an important role in the mechanism of moxibustion treatment. The purpose of this meta-analysis was to explore the mechanism of moxibustion in LBP in terms of inflammatory cytokines.

Methods: We searched China National Knowledge Infrastructure, Wanfang database, Cochrane Central Register of Controlled Trials, Ovid MEDLINE, Embase, PubMed, and Web of Science to identify eligible randomized controlled trials (RCTs). There was no restriction on the publication date.

Results: Thirty RCTs measuring interleukin (IL-) 1, IL-1β, IL-6, IL-12, IL-17, IL-23, and tumor necrosis factor (TNF-) α were included in this meta-analysis. Compared to controls: single moxibustion could effectively decrease levels IL-6 and IL-23 (SMD, −0.71, 95% CI: −1.25 to −0.17, $p = 0.01$; SMD, −1.61, 95% CI: −2.20 to −1.03, $p < 0.01$, respectively); combined moxibustion had significant effects on IL-1, IL-1β, IL-6, IL-12, IL-17, and TNF-α ($p < 0.05$). Overall, for LBP, single or combined moxibustion could effectively down-regulate levels of pro-inflammatory cytokines ($p = 0.007$ and $p < 0.00001$, respectively). For safety of moxibustion, the incidence rate of side effects was similar to that of controls (RD, −0.01, 95% CI: −0.02 to 0.01, $p = 0.59$). Sensitivity analysis showed that the pooled estimates were robust, and publication bias analysis showed there was a significant small study effect (Egger's test $p = 0.0000$). High statistical heterogeneity existed between included RCTs, meta-regression showed there was no potential factor explaining the source of heterogeneity.

Conclusion: For LBP, moxibustion can effectively decrease levels of IL-1, IL-1β, IL-6, IL-12, IL-17, IL-23, and TNF-α to achieve analgesia. Because the side effects of moxibustion are transient, it is relatively safe for clinical use. However, based on high heterogeneity in this meta-analysis, rigorously designed RCTs are required to further confirm the results in this review.

Keywords: low back pain, moxibustion, cytokines, tumor necrosis factors, interleukins

Introduction

Low back pain (LBP) is an extremely common problem worldwide experienced by people of all ages.[1] People with LBP often complain of varying degrees of pain. In addition, the recurrence and severity of LBP usually result in dysfunction and poor quality of life,[1] which brings great distress to patients. LBP is predominantly caused by intervertebral disc degeneration (IDD),[2] and the primary cause of IDD is the production of pro-inflammatory mediators.[2] This means inflammatory responses are important events during LBP. Inflammatory responses are induced by inflammatory cytokines, such as interleukin (IL-) 1β, IL-6, IL-17, IL-23, and tumor necrosis factor (TNF-) α, and these cytokines have been proved to be strongly associated with the progression of LBP.[3–5] Currently, many Western drugs used in LBP have been proved to take effect by regulating inflammatory cytokines,[6–8] however, a range of side effects caused by Western drugs (eg, gastrointestinal and cardiovascular adverse events) remain a concern for patients.[9] Therefore, alternative therapies without side effects to treat LBP have been increasingly getting attention.

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Traditional Chinese medicine (TCM) as a mainstream alternative therapy has its own characteristics in treating LBP and has various therapeutic forms, of which moxibustion is the most widely used in China.[10] Moxibustion is an external therapy based on the theory of TCM. It takes effect by burning of mugwort (moxa, Artemisia argyi) to facilitate healing over specific acupuncture points and meridians.[11] Although previous studies have suggested that moxibustion can relieve pain and dysfunction in patients with LBP[12] and other related diseases, such as lumbar disc herniation (LDH)[13,14] and IDD,[15] the mechanism of its analgesic effect remains unclear.

Previous studies have found that moxibustion could relieve pain and dysfunction in rheumatoid arthritis by down-regulating pro-inflammatory cytokines and up-regulating anti-inflammatory cytokines.[16] What is more, inflammatory cytokines were also associated with pain intensity and progression of LBP.[17] Whether moxibustion is able to treat LBP by the same mechanism (modulating inflammatory cytokines) deserves further research. Not only that, moxibustion has an advantage over acupuncture and Western drugs in regulating pain of LBP,[10] but it is unclear if moxibustion still has an advantage in the inflammatory response. Due to inconsistent findings of moxibustion on regulating inflammatory cytokines in LBP,[18,19] there is a need for a systematic review to summarize this evidence of moxibustion on inflammatory cytokines in patients with LBP. Thus, the purpose of this study is to systematically assess and meta-analyze the efficacy of moxibustion on inflammatory cytokines in patients with LBP from randomized controlled trials (RCTs).

Methods

This study protocol was registered in PROSPERO, the International Prospective Registry of Systematic Reviews (registration no. CRD42022357108). When conducting and reporting this systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[20]

Selection Criteria

We strictly limited the inclusion and exclusion criteria according to PICOS (P-participant, I-intervention, C-comparison, O-outcome, S-study design) framework to ensure clinical homogeneity as far as possible.

For participant: patients with LBP or any other disorders that lead to LBP were included, such as LDH, IDD, lumbar spinal stenosis (LSS), sciatica, ankylosing spondylitis (AS), and failed back surgery syndrome (FBSS).

For intervention: we only included studies that used moxibustion alone or in combination with other treatments; that is, no more than two forms of treatment in the experimental group.

For comparison: there was no restriction on control groups.

For outcome: the primary outcomes considered were inflammatory cytokines, including TNF-α, interferon (IFN-) α, IFN-γ, IL-1, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-17, etc. The secondary outcome was the incidence rate of side effects related to moxibustion.

We excluded studies that LBP was caused by trauma, tumor, or infection. We also excluded studies if moxibustion was combined with other therapies, making it difficult to distinguish the effect of moxibustion; for example, a study comparing moxibustion plus acupuncture with another type of treatment (eg, Chinese herbal medicine). Studies comparing the effectiveness of different types of moxibustion were also excluded (eg, heat-sensitive moxibustion vs manual moxibustion).

Search Strategy

We identified RCTs from an electronic search of several databases: China National Knowledge Infrastructure (CNKI), Wanfang database, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Embase, PubMed, and Web of Science. There was no restriction on language or publication date. Besides, a manual search of related reviews and studies' reference lists was conducted. The search filter was set to limit search results to studies focused on clinical trials. The search process was conducted by two reviewers.

The search term format, guided by the PICO framework, included keywords, terms, and Medical Subject Headings (Mesh) related to LBP (Participant), moxibustion (Intervention), and inflammatory cytokines (Outcome). The search strategy of PubMed is shown in Table 1. A Supplementary Material: Search Key Terms and Strategy describing the comprehensive search term framework is attached.

Table 1 PubMed Search Strategy

Steps	Search Terms
#1	"moxa" [Title/Abstract] OR "moxibustion"[Title/Abstract]
#2	"pain" [Title/Abstract] AND ("back" [Title/Abstract] OR "lumbar" [Title/Abstract] OR "spine"[Title/Abstract])
#3	"lumbar disc herniation" [Title/Abstract] OR "discogenic pain"[Title/Abstract]
#4	"Back Pain" [MeSH Terms] OR "Low Back Pain" [MeSH Terms] OR "Failed Back Surgery Syndrome" "[MeSH Terms] OR" Spinal Stenosis "[MeSH Terms] OR spondylitis, ankylosing" [MeSH Terms]
#5	"backache" [Title/Abstract]
#6	"intervertebral disc degeneration" [MeSH Terms]
#7	#2 OR #3 OR #4 OR #5 OR #6
#8	"Cytokines" [MeSH Terms]
#9	"mechanism" [Title/Abstract] OR "TNF" [Title/Abstract] OR "IL"[Title/Abstract] OR "IFN"[Title/Abstract]
#10	#8 OR #9
#11	#7 AND #10

Study Selection Process

All the records retrieved from the databases and websites were first exported to EndNote X9 for removing of duplication. First, titles and abstracts of the records were screened by two independent reviewers for eligibility, and in the absence of an abstract, records were retained for full-text review. Second, the same reviewers assessed the full text of potential studies to determine ultimate inclusion in this review. Finally, in case of any disagreement, a decision would be made by consensus with a senior researcher.

Data Collection

Two reviewers independently extracted information based on preset standards, including the first author, publication year, location, condition, sample size, population characteristics, intervention details, control details, and outcomes. A third reviewer checked these data. If key information was missing from the study report, we would contact the report authors to obtain the information. In case of any disagreement, we would use the Kappa score to assess interrater agreement. As Cochrane described, a Kappa score of 0 to 0.2 was considered a slight agreement, 0.21 to 0.40 as fair agreement, 0.41 to 0.60 as moderate agreement, 0.61 to 0.80 as substantial agreement and 0.81 to 1.00 as almost perfect (https://s4be.cochrane.org/blog/2016/05/13/kappa-value/).

Assessment of Risk of Bias in Included Studies

Two independent reviewers assessed the risk of bias (RoB) according to the guidelines of the Cochrane Back Review Group.[21] In case of any disagreement, the authors discussed and reached a consensus. The RoB assessment tool has 13 independent criteria; with a judgement of "yes", "unsure", or "no". As described in the guidelines,[21] the types of biases assessed are as follows: selection bias (criteria 1, 2, 9), performance bias (criteria 3, 4, 10, 11), attrition bias (criteria 6, 7), detection (or measurement) bias (criteria 5, 12) and reporting bias (criterion 8). The last criterion, "Other" (criteria 13), is reserved for any type of potential bias that is not detected by the previous items. According to the Cochrane Handbook for Systematic Reviews of Interventions,[22] the overall RoB for each study was assessed as follows:[23]

- Low RoB if the trial was judged to be at low risk of bias for all domains for this result;
- Moderate RoB if the trial was judged to raise some concerns in at least one domain for this result but not to be at high risk of bias for any domain;
- High RoB if the trial was judged to be at high risk of bias in at least one domain for this result, or the trial was judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Data Synthesis and Analysis

We used Review Manager (RevMan) (V.5.3) to perform meta-analyses of clinically homogeneous studies, where we could not combine data for clinical heterogeneity, and a narrative synthesis of results would be presented. Since the studies on moxibustion treatment alone and in combination would be included, we first analyzed the effect of moxibustion used alone on inflammatory cytokines, and then analyzed the joint effect of moxibustion on inflammatory cytokines. Inflammatory cytokines were considered as continuous outcomes, so mean difference (MD) with 95% confidence interval (CI) would be employed to estimate the combined effect sizes. If different measurement units were used to measure the same outcome across separate studies, standardized mean difference (SMD) would be used. For incidence rate of side effects (dichotomous outcome), risk ratio (RR) with 95% CI would be employed to estimate the combined effect sizes. If zero-events existed in dichotomous outcomes, risk difference (RD) with Mantel–Haenszel methods would be employed.[24]

For any pooled data, we used I^2 statistics to assess statistical heterogeneity, as described in Cochrane Handbook of Systematic Reviews of Interventions, a rough interpretation of heterogeneity is as follows: 0% to 25%: insignificant heterogeneity; 25% to 50%: low heterogeneity; 50% to 75%: moderate heterogeneity; and 75% to 100%: high heterogeneity. If I^2 <50%, a fixed-effect model would be used; otherwise, a random-effect model would be performed. When high heterogeneity existed, subgroup analysis would be conducted according to the prosperity of inflammatory cytokines. The robustness of the pooled estimates was assessed by sensitivity analysis. If sufficient data were available, a random-effect meta-regression would be performed to explore the potential sources of heterogeneity, such as settings of subgroups, condition of participants, types of moxibustion, and types of controls. Publication bias and small study effects were assessed with the Egger test. We considered a *p-value* of 0.05 or less to be statistically significant. Sensitivity analysis, meta-regression, and publication bias would be analyzed with Stata 16.0.

Results

Study Selection

The flow of study selection was according to the PRISMA 2020 statement.[20] A total of 500 articles were identified through electronic databases (93 articles from CNKI, 350 from Wanfang, 2 from CENTRAL, 5 from Ovid MEDLINE, 19 from Embase, 12 from PubMed, and 19 from Web of Science). After removing of duplication, 419 records were left. 378 records were excluded on the basis of title and abstract screening. Hence, after assessing full-text articles, only 30 records fulfilled the inclusion criteria. The flow of study selection and reasons for exclusion is presented in Figure 1.

Study Characteristics

30 RCTs[14,18,19,25–50] with a total of 2560 participants satisfied our inclusion criteria and were included in this review. The characteristics of the included studies are presented in Table 2. All trials were conducted in Chinese public hospital. The LBP subjects included in this review were chronic non-specific LBP (1 RCT), LDH (14 RCTs), lumbar muscle strain (4 RCTs), ankylosing spondylitis (8 RCTs), LBP (1 RCT), and sciatica (2 RCTs). Except for pure moxibustion, there were five specific types of moxibustion involved in this review: bamboo circle salt moxibustion (1 RCT), long snake moxibustion (13 RCTs), heat-sensitive moxibustion (3 RCTs), seed-sized moxibustion (1 RCT), and vesicular moxibustion (1 RCT). All of these are ancient moxibustion therapies widely used in the treatment of LBP in China. In addition, seven studies[18,19,25,29,41,50,51] reported the effects of moxibustion alone on LBP inflammatory cytokines, while others reported the joint effects of moxibustion. Except for Du meridian that is specifically used in long snake moxibustion, the most commonly used acupoints for moxibustion were Shenshu (BL23) and Weizhong (BL40), which were used in nine and eight RCTs, respectively. Five studies used Dachangshu (BL25), Jiaji (EX-B2), Mingmen (GV4), Huantiao (GB30), Yanglingquan (GB34), and Ashi point. The most frequently used acupoints and locations are presented in Table 3.

In terms of interventions in control groups, western medicine, acupuncture, tuina, cupping therapy, herbal medicine, exercise, catgut embedding and traction were involved in this review. All of the included studies reported outcomes at post-intervention, among them, only two studies reported drop-out rates. In Zhang's et al study,[19] the drop-out reasons were job transfer (1 case) and receiving other treatments for a cold (1 case), and Cui et al, did not report drop-out reasons.[26] The outcome measures of inflammatory cytokines reported in the included studies were IL-1, IL-1β, IL-6, IL-12, IL-17, IL-23, and TNF-α. All of these

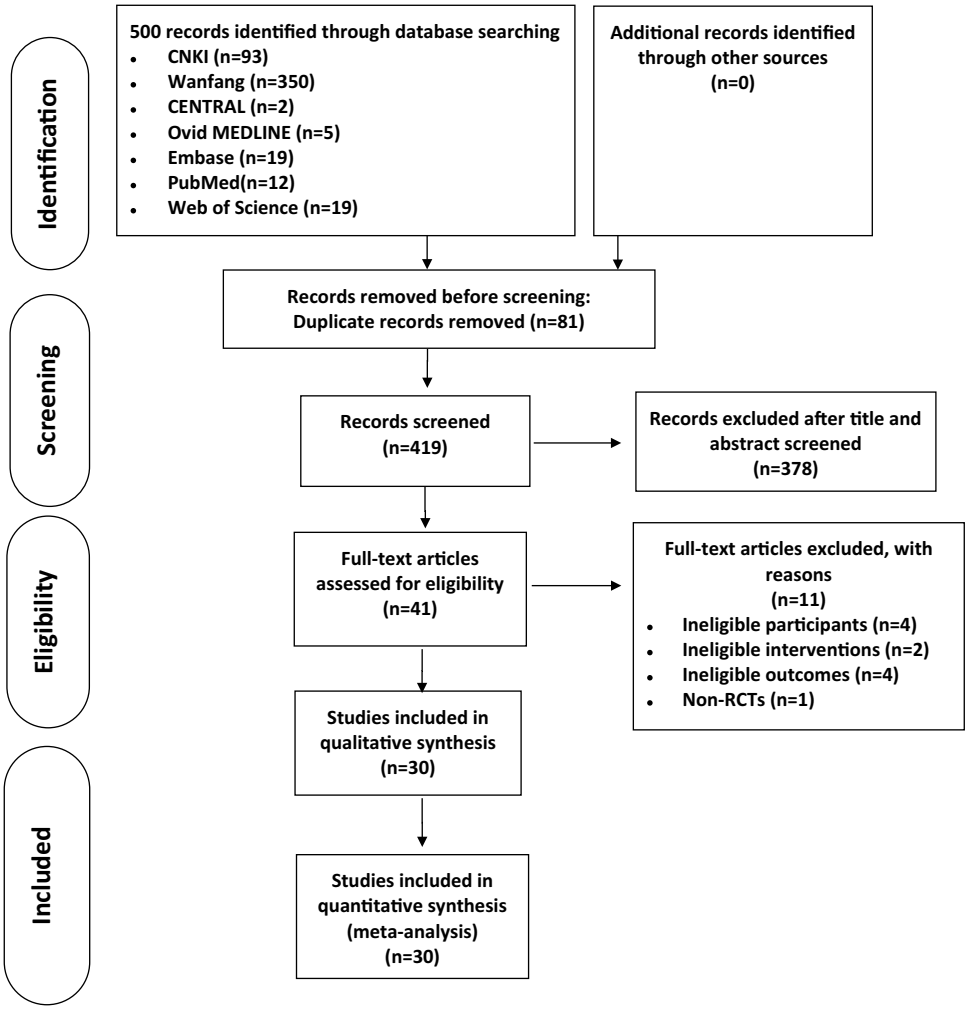

Figure 1 Flow diagram of study selection adapted from PRISMA.

were pro-inflammatory cytokines, and no study reported anti-inflammatory cytokines as outcomes. In addition, eight studies reported incidence of side effects of moxibustion.[19,26,27,31,36,42,44,48]

Risk of Bias Assessment

The RoB assessment of all the included studies is presented in Table 4. According to the evaluation rules reported in the Methods section, we found 2 RCTs (7%) were classified as low RoB, 20 RCTs (66%) as moderate RoB, and 8 RCTs (27%) as high RoB.

The main methods limitations across the included RCTs were that 8 RCTs (27%) did not report the randomization process, and 29 RCTs (97%) did not use or inform about concealed allocation. In terms of missing outcome data, 28 RCTs (93%) did not inform about missing data, only 2 RCTs reported the details of drop-out and did not use intention-to-treat (ITT) analysis. Because of the nature of interventions, it was difficult to blind therapists and participants, and only 2 RCTs (7%) provided details about blinding. Due to inflammatory cytokines and side effects were observer-reported outcomes not involving judgment, we classified these studies as moderate RoB regarding the influence of the non-blinding of the assessor.

Outcome Analysis

Effects of Single Moxibustion on Inflammatory Cytokines

Six pro-inflammatory cytokines including IL-1, IL-1β, IL-6, IL-17, IL-23, and TNF-α were measured in selected studies, and no anti-inflammatory cytokines were measured. Meta-analyses (see Figure 2) showed that moxibustion alone had

Table 2 Characteristics of Included Studies

Study	Location	Condition	Sample Size	Age, Years (Mean ± SD)	EG	Acupoints	CG	Frequency	Duration	Outcomes
Zhang et al, 2021[19]	Fujian	CNLBP	N=78: EG=34; CG=34	EG=52.55±4.70; CG=51.36±4.37	Moxibustion[a]	Mingmen; Yaoyangguan; Shenshu	Western medicine	1 time/day	1 week	TNF-α; IL-1β; Side effects
Jiang et al, 2020[29]	Jiangxi	LDH	N=80: EG=40; CG=40	EG=24 to 65; CG=25 to 66	Moxibustion[b]	Du meridian	Acupuncture	1 time/2 days	2 weeks	IL-6
Gong et al, 2020[28]	Shandong	LDH	N=104: EG=52; CG=52	EG=45.37±3.56; CG=44.73±3.53	Moxibustion[c] + Tuina	Shenshu; Dachangshu; Ashi; Weizhong; Guanyuan	Tuina	1 time/day	4 weeks	TNF-α
Yang et al, 2020[44]	Guangdong	LMS	N=60: EG=30; CG=30	EG=41.22±7.06; CG=41.27±7.11	Moxibustion + Cupping therapy	Ashi	Cupping therapy	1 time/day	10 days	TNF-α; IL-6; Side effects
Hu et al, 2020[18]	Jiangxi	LDH	N=80: EG=40; CG=40	EG=39.80; CG=38.03	Moxibustion[b]	Du meridian	Acupuncture	1 time/ week	4 weeks	TNF-α; IL-1β
Fan et al, 2019[27]	Shanxi	AS	N=100: EG=50; CG=50	EG=33.22±10.65; CG=33.89±10.71	Moxibustion[b] + Western medicine	Du meridian	Western medicine	1 time/ week	3 months	IL-6; TNF-α; Side effects
Li et al, 2019[32]	Henan	BP	N=100: EG=50; CG=50	EG=56.14±6.25; CG=55.42±6.89	Moxibustion[d] + Western medicine	Shenshu; Mingmen; Ganshu; Baliao	Western medicine	3 times/ week	3 weeks	TNF-α
Lyu Mingfang et al, 2018[35]	Jiangxi	AS	N=80: EG=40; CG=40	EG=41.38±9.46; CG=41.79±9. 89	Moxibustion[b] + Western medicine	Du meridian	Western medicine	1 time/ week	3 months	TNF-α
Lyu Shiqi et al, 2018[36]	Shandong	LDH	N=186: EG=93; CG=93	EG=70.9±4.3; CG=73.7±4.9	Moxibustion[c] + Herbal medicine	Shenshu; Dachangshu; Ashi; Weizhong; Guanyuan	Herbal medicine	1 time/day	30 days	IL-6; TNF-α; Side effects
Kong et al, 2014[30]	Henan	AS	N=60: EG=30; CG=30	EG=28.83±8.16; CG=28.10±8.07	Moxibustion[b] + Western medicine	Du meridian	Acupuncture + Western medicine	1 time/ week	12 weeks	IL-17; IL-1β
Xu et al, 2012[41]	Ningxia	LDH	N=60: EG=30; CG=30	EG=41.1±11.6; CG=40.1±10.1	Moxibustion	Guanyuan	Acupuncture	1 time/day	3 weeks	IL-6
Zhang et al, 2012[47]	Jiangxi	LDH	N=103: EG=52; CG=51	EG=18 to 72; CG=16 to 71	Moxibustion[c] + Herbal medicine	Zhiyang; Guanyuan; Weizhong	Herbal medicine	1 time/day	30 days	IL-6
Li et al, 2020[33]	Zhongshan	AS	N=100: EG=50; CG=50	EG=21 to 37; CG=20 to 36	Moxibustion[b] +Western medicine	Du meridian	Western medicine	2 times/ week	12 weeks	IL-1β
Hong et al, 2016[51]	Fujian	LDH	N=104: EG=52; CG=52	EG=53.91±7.05; CG=53.42±7.62	Moxibustion[e]	Yaoyangguan; Shenshu; Mingmen	Acupuncture	1 time/day	3 times	IL-1; IL-6
Niu et al, 2022[38]	Zhengzhou	LDH	N=100: EG=50; CG=50	EG=50.11±7.46; CG=49.98±5.06	Moxibustion[b] + exercise	Du meridian	Exercise	1 time/ week	6 weeks	IL-6; TNF-α;

Qin et al, 2012[40]	Guizhou	Sciatica	N=60: EG=30; CG=30	EG=55.5±16.97; CG=59.0±13.91	Moxibustion +Acupuncture	Jiaji; Huantiao; Weizhong; Yanglingquan; Chengshan	Acupuncture	1 time/day	10 days	IL-6
Zhao et al, 2021[48]	Henan	AS	N=106: EG=53; CG=53	EG=52.18±6.37; CG=53. 69±9. 05	Moxibustion[b] + Catgut embedding	Du meridian	Catgut embedding	1 time/ week	8 weeks	TNF-α; Side effects
Yao et al, 2019[45]	Tangshan	LMS	N=90: EG=45; CG=45	EG=35±9; CG=35±10	Moxibustion + Western medicine	Mingmen Eight Array Points	Western medicine	1 time/day	4 weeks	TNF-α; IL-6
Zhu et al, 2019[49]	Nanchang	AS	N=92: EG=46; CG=46	EG=18-55; CG=20-54	Moxibustion[b] + Western medicine	Du meridian	Western medicine	2 times/ week	3 months	IL-12
Zuo et al, 2018[50]	Yunnan	AS	N=60: EG=30; CG=30	EG=27±1; CG=28±1	Moxibustion[b]	Du meridian	Western medicine	2 times/day	4 weeks	IL-17; IL-23; IL-6; TNF-α
Yan et al, 2015[43]	Tangshan	LBP	N=65: EG=33; CG=32	EG=33±2; CG=33±2	Moxibustion[b]	Du meridian	Traction + Tuina	6 times/ week	3 weeks	TNF-α
Lyu et al, 2019[37]	Zhejiang	LMS	N=98: EG=49; CG=49	EG=55.98±10.98; CG=56.15±11.03	Moxibustion + Acupuncture	Shenshu; Dachangshu; Weizhong; Mingmen; Yaoyangguan; Ashi; Jiaji	Acupuncture	1 time/2 days	3 months	IL-6; TNF-α
Li et al, 2021[31]	Henan	LDH	N=100: EG=50; CG=50	EG=45.23±3.11; CG=45.96±2.88	Moxibustion + Acupuncture	Jiaji; Dachangshu; Shenshu; Huantiao; Yanglingquan; Ashi	Acupuncture	1 time/day	20 days	TNF-α; IL-6; Side effects
Liu et al, 2020[34]	Liaoning	Sciatica	N=50: EG=25; CG=25	EG=55.40±16.81; CG=55.42±16.83	Moxibustion + Acupuncture	Weizhong; Huantiao; Yanglingquan; Chengshan	Acupuncture	1 time/day	10 days	IL-6
Cui et al, 2019[26]	Hebei	LDH	N=84: EG=42; CG=42	EG=46.87±4.91; CG=47.12±5.04	Moxibustion + Acupuncture	Jiaji	Acupuncture	1 time/2 days	42 days	IL-6; TNF-α; Side effects
Xu et al, 2013[42]	Guangdong	LDH	N=60: EG=30; CG=30	EG= 36.0±5.6; CG= 37±6.6	Moxibustion + Acupuncture	Ashi	Acupuncture	1 time/day	15 days	IL-1β; IL-6; TNF-α; Side effects
Cao et al, 2013[25]	Henan	AS	N=60: G1=20 G2=20; G3=20	G1=19 to 37; G2=22 to 34; G3=17 to 40	G1=moxibustion[b] + acupuncture; G3=moxibustion[b]	Du meridian	G2=acupuncture;	1 time/ week	4 weeks	IL-1; IL-6; TNF-α
Qin et al, 2021[39]	Henan	LDH	N=80: EG=40; CG=40	EG= 51.73±9.12; CG= 50.96±11.3	Moxibustion[b] + Traction	Du meridian	Traction	1 time/ week	6 weeks	IL-1β; TNF-α
Yin et al, 2008[46]	Hubei	LDH	N=60: EG=30; CG=30	21 to 62	Moxibustion + Acupuncture	Jiaji; Shenshu; Huantiao; Weizhong; Yanglingquan; Chengshan; Kunlun	Acupuncture	1 time/day	20 days	IL-6
Lu et al, 2021[14]	Shanghai	LMS	N=100: EG=50; CG=50	EG=54.6±5.4; CG=55.1±5.8	Moxibustion + Acupuncture	Dachangshu; Shenshu; Huantiao; Xuehai; Weizhong; Yanglingquan	Acupuncture	1 time/day	20 days	TNF-α; IL-6

Notes: [a]Bamboo circle salt moxibustion. [b]Long snake moxibustion / Du moxibustion / Huolong moxibustion. [c]Heat sensitive moxibustion. [d]Seed-sized moxibustion. [e]Vesicular moxibustion.

Abbreviations: CNLBP, chronic non-specific low back pain; LDH, lumbar disc herniation; LMS, lumbar muscle strain; AS, ankylosing spondylitis; BP, back pain; N, number; EG, experimental group; CG, control group; G, group; IL, interleukin; TNF, tumor necrosis factor.

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Table 3 Acupoints Commonly Used for LBP

Acupoint Name	Location
Shenshu (BL23)	At the level of the lower border of the spinous process of the second lumbar vertebra, 1.5 cun lateral to spinal midline
Weizhong (BL40)	At the midpoint of the transverse crease of the popliteal fossa, between the tendons of the biceps femoris muscle and the semitendinosus muscle
Dachangshu (BL25)	At the level of the lower border of the spinous process of the fourth lumbar vertebra, 1.5 cun lateral to spinal midline
Jiaji (EX-B2)	On either side of the vertebral column and 15 mm below the spinal processes from T1 to L5 and totaling 17 pairs
Mingmen (GV4)	On the posterior midline, in the depression below the spinous process of the L2
Huantiao (GB30)	At the junction of the lateral third and medial two thirds of the distance between the greater trochanter and the sacral hiatus
Yanglingquan (GB34)	On the lateral side of the leg, in the depression of the anteroinferior fibular head
Ashi point	Pain site

Table 4 Risk of Bias Assessment

Study	Criteria of RoB													Overall risk of bias
	1	2	3	4	5	6	7	8	9	10	11	12	13	
Zhang et al, 2021[19]	Y	Y	U	U	Y	Y	N	Y	Y	Y	Y	Y	Y	L
Jiang et al, 2020[29]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Gong et al, 2020[28]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Yang et al, 2020[44]	N	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	H
Hu et al, 2020[18]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Fan et al, 2019[27]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Li et al, 2019[32]	N	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	H
Lyu Mingfang et al, 2018[35]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Lyu Shiqi et al, 2018[36]	N	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	H
Kong et al, 2014[30]	Y	U	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	L
Xu et al, 2012[41]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Zhang et al, 2012[47]	N	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	H
Li et al, 2020[33]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Hong et al, 2016[51]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Niu et al, 2022[38]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Qin et al, 2012[40]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Zhao et al, 2021[48]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Yao et al, 2019[45]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Zhu et al, 2019[49]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Zuo et al, 2018[50]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Yan et al, 2015[43]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Lyu et al, 2019[37]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Li et al, 2021[31]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Liu et al, 2020[34]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Cui et al, 2019[26]	N	U	U	U	U	N	N	Y	Y	Y	Y	Y	Y	H
Xu et al, 2013[42]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Cao et al, 2013[25]	Y	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	M
Qin et al, 2021[39]	N	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	H
Yin et al, 2008[46]	N	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	H
Lu et al, 2021[14]	N	U	U	U	U	N	Y	Y	Y	Y	Y	Y	Y	H

Notes: 1 Was the method of randomization adequate? 2 Was the treatment allocation concealed? 3 Was the patient blinded to the intervention? 4 Was the care provider blinded to the intervention? 5 Was the outcome assessor blinded to the intervention? 6 Was the drop-out rate described and acceptable? 7 Were all randomized participants analyzed in the group to which they were allocated? 8 Are reports of the study free of suggestion of selective outcome reporting? 9 Were the groups similar at baseline regarding the most important prognostic indicators? 10 Were co-interventions avoided or similar? 11 Was the compliance acceptable in all groups? 12 Was the timing of the outcome assessment similar in all groups? 13 Are other sources of potential bias unlikely?
Abbreviations: Y, yes; N, no; U, unsure; L, low; M, moderate, H, high.

a significant effect on pro-inflammatory cytokine level over controls (SMD, −0.42, 95% CI: −0.72 to −0.11, $p = 0.007$; $I^2 = 81\%$). Among these pro-inflammatory cytokines, subgroup analysis showed that there was no significance was found between moxibustion group and controls in IL-1 (SMD, −0.00, 95% CI: −0.42 to 0.41, $p = 0.99$; $I^2 = 24\%$), IL-1β (SMD,

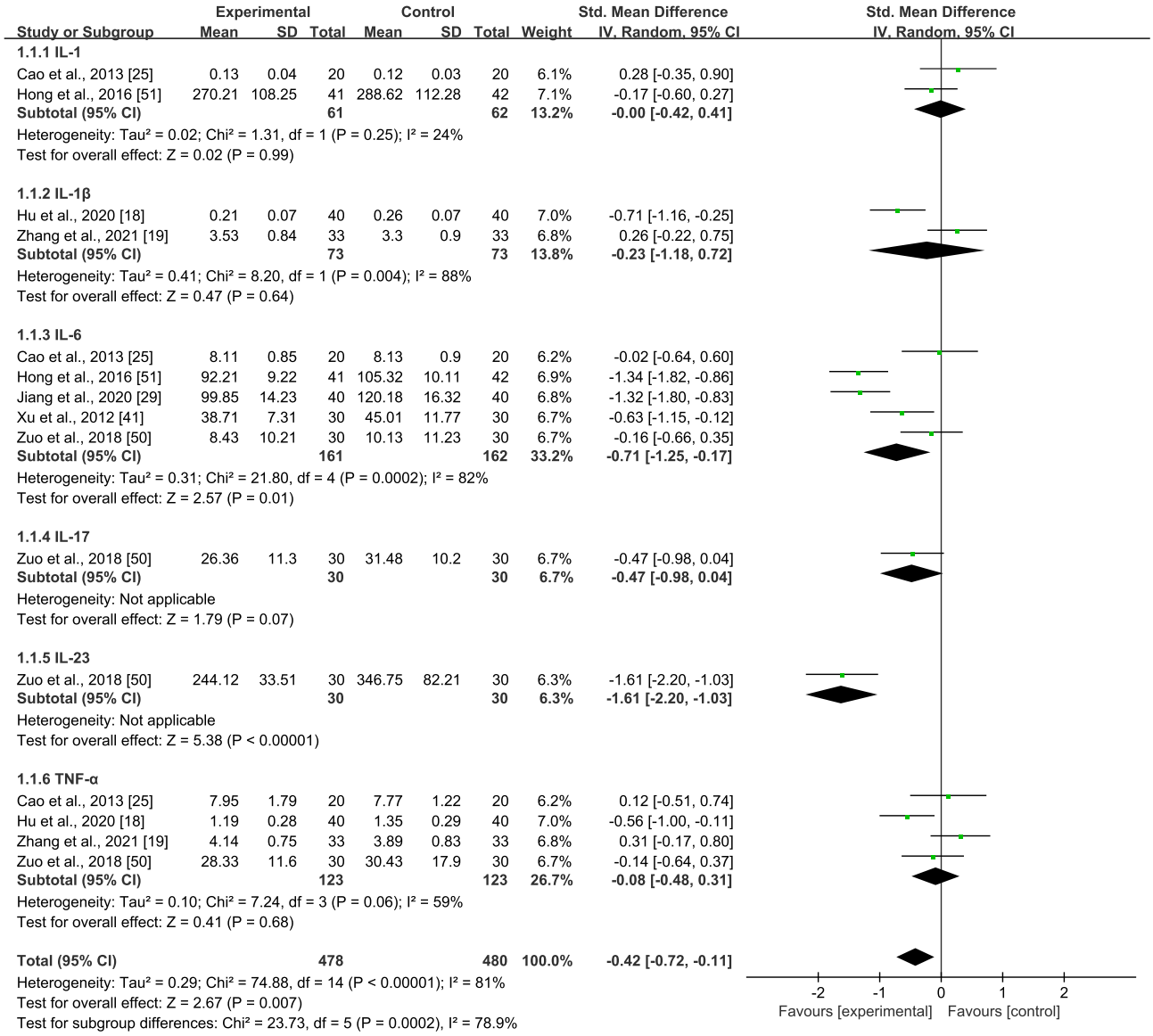

Figure 2 Forest plot for single moxibustion on pro-inflammatory cytokines.

−0.23, 95% CI: −1.18 to 0.72, $p = 0.64$; $I^2 = 88\%$), IL-17 (SMD, −0.47, 95% CI: −0.98 to 0.04, $p = 0.07$; $I^2 = NA$), and TNF-α (SMD, −0.08, 95% CI: −0.48 to 0.31, $p = 0.68$; $I^2 = 59\%$). However, for inflammatory cytokine IL-6 and IL-23, moxibustion alone had a significant effect over controls (SMD, −0.71, 95% CI: −1.25 to −0.17, $p = 0.01$; $I^2 = 82\%$; SMD, −1.61, 95% CI: −2.20 to −1.03, $p < 0.01$; $I^2 = NA$, respectively).

Joint Effects of Moxibustion on Inflammatory Cytokines

Six pro-inflammatory cytokines including IL-1, IL-1β, IL-6, IL-12, IL-17, and TNF-α were measured in selected studies. Meta analysis (see Figure 3) showed that the combined moxibustion had a significant effect on pro-inflammatory cytokine level over controls (SMD, −1.56, 95% CI: −1.86 to −1.26, $p < 0.00001$; $I^2 = 93\%$). Foremove, in subgroup analysis, we found the combined moxibustion had a superior effect on IL-1 (SMD, −0.65, 95% CI: −1.29 to −0.02, $p = 0.004$; $I^2 = NA$), IL-1β (SMD, −0.98, 95% CI: −1.32 to −0.64, $p < 0.00001$; $I^2 = 48\%$), IL-6 (SMD, −2.19, 95% CI: −2.85 to −1.53, $p < 0.00001$; $I^2 = 96\%$), IL-12 (SMD, −0.67, 95% CI: −1.09 to −0.25, $p = 0.002$; $I^2 = NA$), IL-17 (SMD, −0.62, 95% CI: −1.14 to −0.11, $p = 0.02$; $I^2 = NA$), and TNF-α (SMD, −1.52, 95% CI: −1.90 to −1.15, $p < 0.00001$; $I^2 = 90\%$) than controls.

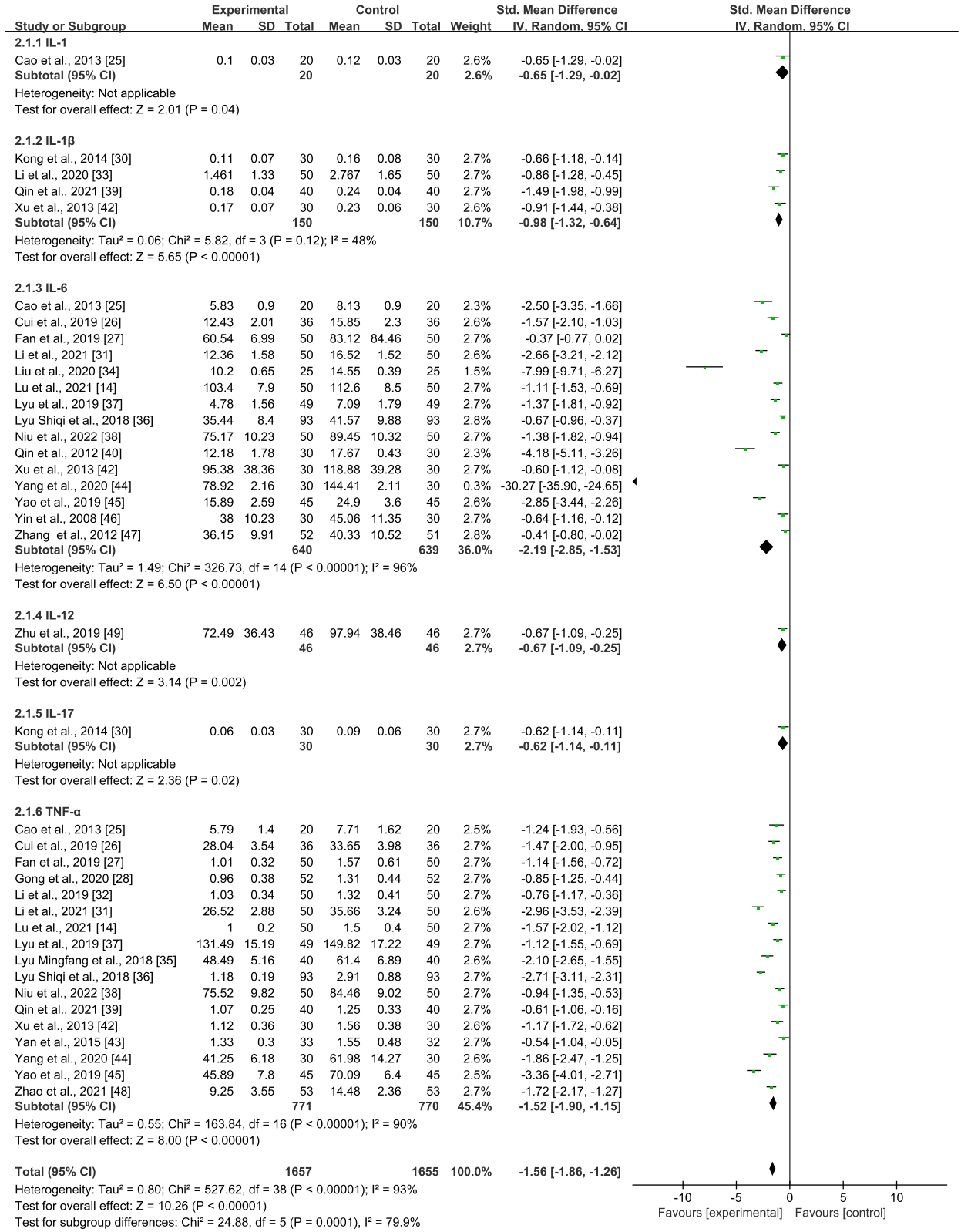

Figure 3 Forest plot for combined moxibustion on pro-inflammatory cytokines.

Incidence Rate of Side Effects of Moxibustion Vs Controls

Among 30 studies included in this review, eight studies reported side effects of moxibustion and controls, through meta-analysis (see Figure 4), we found the incidence rate of side effects of moxibustion was similar to controls (RD, −0.01,

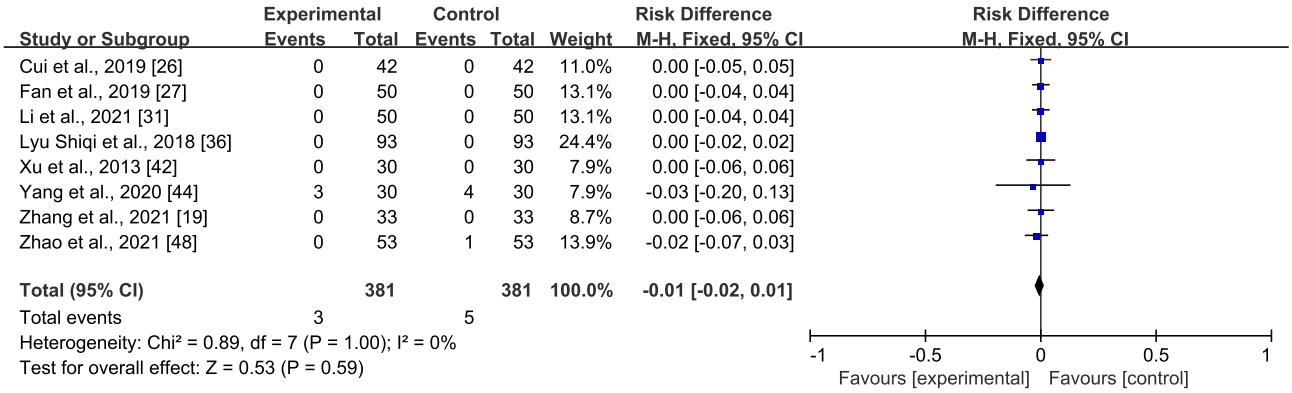

Figure 4 Forest plot for incidence rate of side effects of moxibustion vs controls.

95% CI: −0.02 to 0.01, $p = 0.59$; $I^2 = 0\%$). Side effects of moxibustion reported in Zhang's et al study were nausea (1 case), gastrointestinal upset (1 case), and local redness (1 case), all of these were transient side effects.

Sensitivity Analysis

For effects of single (see Figure 5) or combined moxibustion (see Figure 6) on inflammatory cytokines, we performed a sensitivity analysis by deleting individual studies one by one and evaluating the effect of each deletion on the pooled prevalence. Based on the sensitivity analysis results, none of the studies had an impact on the overall effect, indicating that our meta-analysis was statistically stable.

Meta-Regression Analysis

More than ten studies evaluated the effects of combined moxibustion on inflammatory cytokines; therefore, we conducted a multivariate meta-regression analysis to explore potential sources of high heterogeneity. And the results of regression showed settings of subgroups, conditions of participants, types of moxibustion, and types of controls were not potential factors ($p > 0.05$) that could explain the source of high heterogeneity (see Table 5).

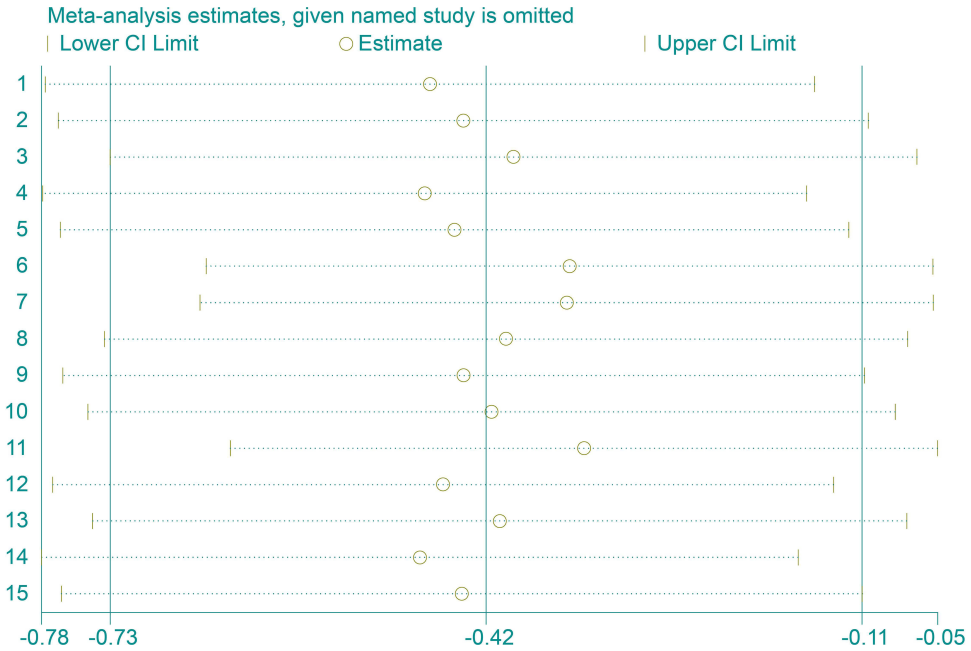

Figure 5 Sensitivity analysis for single moxibustion on pro-inflammatory cytokines.

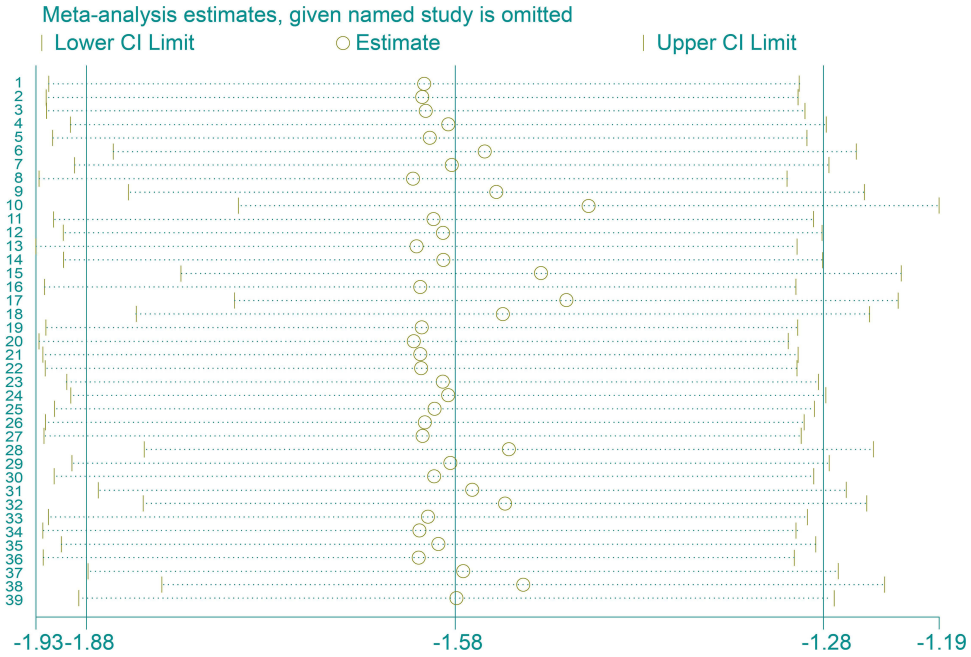

Figure 6 Sensitivity analysis for combined moxibustion on pro-inflammatory cytokines.

Publication Bias

More than ten studies evaluated the effects of combined moxibustion on inflammatory cytokines; therefore, we assessed publication bias by Egger test. And the results showed there was a significant small study effect in this meta-analysis (Egger's test $p = 0.0000$), which might indicate a publication bias of small studies being less likely to be published in moxibustion clinical trials on inflammatory cytokines.

Table 5 Multivariate Meta-Regression Analysis for Combined Moxibustion on Pro-Inflammatory Cytokines

Covariates	Coef.	Std. Err.	z	p>|z|	95% Conf. Interval	
Settings of subgroups						
IL-1	−0.4849648	5.646777	−0.09	0.932	−11.55245	10.58252
IL-1β	−0.2837299	4.215214	−0.07	0.946	−8.545398	7.977939
IL-6	−1.847518	4.128052	−0.45	0.654	−9.938352	6.243315
IL-12	0 (omitted)					
IL-17	−0.450754	5.643628	−0.08	0.936	−11.51206	10.61055
TNF-α	−0.324115	4.058702	−0.08	0.936	−8.279025	7.630795
Conditions of participants						
Ankylosing spondylitis	0 (omitted)					
Lumbar disc herniation	0.7706914	3.658786	0.21	0.833	−6.400398	7.941781
Sciatica	−2.81258	5.027132	−0.56	0.576	−12.66558	7.040417
Lumbar muscle strain	0.5745139	4.321256	0.13	0.894	−7.894992	9.04402
Back pain	−0.6204169	5.747253	−0.11	0.914	−11.88483	10.64399
Low back pain	2.037511	6.678361	0.31	0.760	−11.05184	15.12686

(*Continued*)

Table 5 (Continued).

Covariates	Coef.	Std. Err.	z	p>|z|	95% Conf. Interval	
Types of moxibustion						
Moxibustion	−1.412021	5.726559	−0.25	0.805	−12.63587	9.811828
Long snake moxibustion	−0.1129846	3.658786	−0.03	0.975	−7.284074	7.058105
Heat sensitive moxibustion	0 (omitted)					
Seed-sized moxibustion	0 (omitted)					
Types of controls						
Acupuncture	0.6722572	4.005477	0.17	0.867	−7.178334	8.522848
Western medicine	0.1745448	3.677731	0.05	0.962	−7.033675	7.382765
Traction	−1.411015	4.43984	−0.32	0.751	−10.11294	7.290912
Herbal medicine	−0.6954735	4.244955	−0.16	0.870	−9.015431	7.624485
Exercise	0 (omitted)					
Cupping therapy	0 (omitted)					
Tuina	0 (omitted)					
Catgut embedding	0 (omitted)					

Abbreviations: Coef, Coefficient; Std. Err, Standard Error; Conf, Confidence.

Discussion

Main Findings

The aim of this study was to meta-analyze the effects of moxibustion on inflammatory cytokines for LBP. Thirty RCTs were reviewed with seven pro-inflammatory cytokines measured, including IL-1, IL-1β, IL-6, IL-12, IL-17, IL-23, and TNF-α. The results showed that moxibustion used alone or in combination could effectively decrease overall levels of pro-inflammatory cytokines. The incidence of side effects of moxibustion was similar to that of controls, and only a few transient side effects of moxibustion were reported. In summary, moxibustion could positively down-regulate the levels of pro-inflammatory cytokines, and could be used in clinical practice as an alternative therapy for LBP.

Possible Modern Biological Mechanism of Moxibustion

Among numerous members of pro-inflammatory cytokines, IL-1, IL-1β, and IL-17 have been proved to be major risk factors for IDD.[52–54] IDD is the predominant cause of LBP, and during the progression of LBP, IL-1β and TNF-α were considered to be the key mediators.[2] High levels of IL-1, IL-1β, IL-6, IL-17, and TNF-α were thought to accelerate the occurrence and progression of LBP.[5,55,56] In addition, other pro-inflammatory cytokines (eg, IL-12 and IL-23) have also been shown to be associated with the presence of LBP.[4,57]

Pro-inflammatory cytokines are sensitive indicators for the progression and regression of LBP, therefore, therapeutic interventions targeting pro-inflammatory cytokines may represent a novel and effective approach for LBP. And in our study, we found that moxibustion takes effect by down-regulating levels of pro-inflammatory cytokines for LBP. Similarly, for other inflammatory diseases, there was evidence that moxibustion could relieve inflammation by down-regulating pro-inflammatory cytokines.[58,59] However, the current research on the mechanism of moxibustion therapy is still not systematic and thorough. Inflammatory response is just one part of the complicated mechanism, and we still have a long way to go to explore the mechanism of moxibustion.

Comparison with Previous Systematic Reviews

To our knowledge, this is the first systematic review and meta-analysis evaluating the value of moxibustion on inflammatory cytokines for LBP. Compared to previous study, moxibustion has been proved to be effective for pain and disability for LBP,[10] and on that basis, our study further explored the mechanism of moxibustion. Similarly, high heterogeneity was found between the included studies, and the quality of the included studies was generally low. Low quality of moxibustion RCTs published in Chinese journals seems to be a common phenomenon.[60]

Previous study also conducted a meta-analysis of moxibustion on inflammatory cytokines for rheumatoid arthritis,[16] and consistent results were found for moxibustion on pro-inflammatory cytokines. There are some methodological differences that deserve mentioning: firstly, we included human rather than animal models as subjects in our study, relative to human experiments, the results of animal experiments cannot be directly applied and popularized in the human population; secondly, we conducted statistical analysis for sensitivity analysis and publication bias, compared to visual inspection, the former is more objective; finally, although high statistical heterogeneity could not be well addressed, we conducted multivariate meta-regression analysis to explore the potential factors that could explain the sources of high heterogeneity. In brief, although high statistical heterogeneity was found in this meta-analysis, we designed and conducted a rigorous methodological analysis to promote the level of evidence of this meta-analysis.

Recommendation for Research

In terms of methodology, firstly, the included RCTs were generally of low quality due to RoB, and randomization and blinding method are the main sources of high RoB. Therefore, future moxibustion RCTs should follow The Standards for Reporting Interventions in Clinical Trials of Moxibustion (STRICTOM) to reduce RoB.[61] Secondly, none of the included studies reported the method of sample size estimate. We recommend that clinical trials related to moxibustion or acupuncture follow the recommendations and guidelines of the Beijing Evidence-Based Center,[62] and perform standardized sample size estimation when designing trials.

Although this meta-analysis found the effectiveness of moxibustion on inflammatory cytokines for LBP, the targeting cytokines of moxibustion to take effect remain unclear and still deserve more research. Besides, to deeply explain the mechanism of moxibustion, more researches are still needed to explore whether moxibustion can be widely used in other inflammatory pain.

Implications for Practice

For clinicians, there are several important points of this meta-analysis that need to be mentioned. First of all, this meta-analysis involved different acupoints for LBP, the most frequently used acupoints in moxibustion were Shenshu (BL23), Weizhong (BL40), Dachangshu (BL25), Jiaji (EX-B2), Mingmen (GV4), Huantiao (GB30), Yanglingquan (GB34), and Ashi point which were similar to that in acupuncture treatment.[63] Different acupoints belong to different meridians, therapists should individualize the acupoints for treatment according to the specific situation of meridian blockage. Second, for the effects of moxibustion on inflammatory cytokines, there was a difference between single moxibustion and combined moxibustion. Moxibustion alone can reduce the level of pro-inflammatory factors in general, but the effect is diminished on IL-1, IL-1β, IL-17, and TNF-α. Therefore, when the effects of moxibustion used alone are not ideal, the combined use of moxibustion is indicated. Finally, for the safety of moxibustion, only transient side effects of moxibustion were reported in this meta-analysis, in contrast to irreversible side effects of perennial use of Western medicine (eg, NSAIDs and opioid), moxibustion seems to be a safe treatment for LBP. In China, moxibustion can be performed by clients at home, thereby care providers still need to inform clients about side effects of moxibustion, such as scald, redness, and gastric upset. If any side effects occur, moxibustion should be stopped immediately.

Inflammatory cytokines play an important role in the pain and dysfunction caused by LBP, and this meta-analysis proved that moxibustion could take effect by regulating inflammatory cytokines. Therefore, for patients who suffer from inflammatory pain, moxibustion may become an effective alternative therapy. Furthermore, the effectiveness and the relative safety also prompt moxibustion to be widely used, and when Western drugs are not indicated, patients could use moxibustion at home to relieve inflammation and inflammatory pain.

Strengths and Limitations

The present systematic review has several strengths and some limitations that should be mentioned. The strengths are as follows: first, we systematically searched several databases and grey literature, which reduced publication bias to some extent; second, we used a 13-item tool to evaluate the RoB of each included trial, and this tool has been widely used in systematic reviews focused on LBP; last, we assessed sensitivity analysis and publication bias by statistical analysis, and performed meta-regression to explore sources of heterogeneity, and the results of this meta-analysis was robust. As a limitation, due to the high statistical heterogeneity existed in this meta-analysis, the overall quality of evidence was low. High-quality RCTs are needed in the future. In addition, this meta-analysis involved several types of moxibustion, and we did not explore therapeutic differences between different types of moxibustion, and network meta-analysis may be needed in the future. Last but not least, we failed to detect the effectiveness of moxibustion on anti-inflammatory cytokines, more research is needed to overcome the limitations of the existing evidence.

Conclusions

This meta-analysis measured moxibustion on IL-1, IL-1β, IL-6, IL-12, IL-17, IL-23, and TNF-α for LBP. We found that moxibustion used alone or in combination can reduce the overall level of pro-inflammatory cytokines for LBP. Due to the high statistical heterogeneity and limited studies in this meta-analysis, further meticulous RCTs are needed to explore the mechanism and safety of moxibustion for LBP.

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Disclosure

The authors report no conflicts of interest in this work.

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