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Tibetan herbal pain-relieving plaster for low back pain: A systematic review and meta-analysis

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Abstract

Ethnopharmacological relevance: Tibetan traditional medicine CheeZheng Pain-Relieving Plaster (CZPRP) is frequently used as an over-the-counter external analgesic for musculoskeletal pain; however, its evidence for low back pain (LBP) has not been evaluated.

Aim of the study: This study aims to assess the efficacy and safety of CZPRP for both acute, subacute and chronic LBP through a systematic review and meta-analysis of clinical trials.

Materials and methods: PubMed, CENTRAL, CNKI, CQVIP, and Wanfang databases were searched through April 20, 2020 for randomized controlled trials of CZPRP for LBP. Eligible comparators were placebo, active treatment, or usual care. Clinical outcomes included pain severity, lower back function score, pain-free rate, and adverse events (AEs). Qualitative evaluations were conducted using the Cochrane risk of bias assessment tools. Quantitative analyses were conducted using a random-effects model.

Results: This study includes 1674 LBP patients from nine clinical studies. Pooled analyses among subjects with acute LBP show 1) significant pain reductions (mean difference − 0.84, 95% confidence interval[CI] − 1.31, − 0.37) in CZPRP plus diclofenac versus diclofenac, 2) significant improvements in lower back function (standard mean difference − 1.50, 95% CI − 2.16, − 0.85) in CZPRP versus diclofenac, and 3) a higher pain-free rate in CZPRP alone (risk ratio 1.48, 95% CI

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CRediT authorship contribution statement

JJM conceived the study. MY designed the study protocol. MY and SQL collected the data. MY and SQL performed statistical analyses. MY wrote the paper. MY, CMS, YLZ, TB, and JJM critically revised the paper. MY created the tables and figures. All authors approved the final version of the article, including the authorship list. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2021.111727.

1.16, 1.89; I^2 = 61%) or CZPRP plus nonsteroidal anti-inflammatory drugs (NSAIDs) (risk ratio 1.66, 95% CI 1.14, 2.40; I^2 = 0%) versus NSAIDs. However, in a heterogeneous population with mixed LBP subtypes, there was no significant difference in pain outcomes between CZPRP and diclofenac. Additionally, CZPRP use did not increase AEs compared with no CZPRP (p = 0.40). All nine studies are associated with moderate to high risk of bias.

Conclusions: The use of CZPRP is associated with improved acute LBP outcomes compared to diclofenac. However, due to the moderate to high risk of bias of the studies, future rigorous randomized controlled trials are needed to evaluate the effects of CZPRP for acute and chronic LBP.

Keywords

Low back pain; Tibetan herbal formula; Camphor-based external analgesic; CheeZheng pain-relieving plaster; Efficacy

1. Introduction

Low back pain (LBP) is a common musculoskeletal disorder that poses a major public health challenge. It is estimated that over 80% of adults experience acute LBP at some point of their lives, while the prevalence of chronic LBP is 23% [1,2]. LBP, a leading cause of disability worldwide, is associated with a 52% increase in years lived with disability from 1997 to 2017, contributing to ever-growing disease burden and medical cost [3–5]. In clinical practice, the goal of LBP management has greatly evolved from overly focusing on spine abnormality to an emphasis on the promotion of activity and function. Clinical practice guidelines recommend a biopsychosocial framework-guided, non-pharmacological strategy as the initial treatment for LBP, and prudent use of medication, imaging, and surgery [6]. In recent years, several complementary and alternative medicine (CAM) interventions have been recommended by guidelines for the treatment of LBP, and herbal medicine is frequently used by people with LBP [6,7].

In the Asia-Pacific region and the U.S., CheeZheng Pain-Relieving Plaster (CZPRP)—one Tibetan medicine-based herbal product made with camphor, turmeric, and other herbal ingredients—is widely utilized as an over-the-counter external analgesic for the relief of musculoskeletal pain [8]. Pharmacology studies indicated that the bioactive chemicals extracted from CZPRP—including iridoid glycoside, diphenylheptanone, sesquiterpene, and luteolin—may inhibit proinflammatory factor expression in skin and restore SP-R, c-fos, and GFAP expression in neurons and, therefore, ameliorate peripheral and central hyperalgesia [9]. Systematic reviews of randomized clinical studies suggested that CZPRP could safely reduce pain, improve joint function, shorten stay-in-bed time, and decrease pain medication use among people with acute soft tissue injuries, knee osteoarthritis, lumbar disc herniation, and other chronic musculoskeletal disorders [10,11]. Although literature has indicated that CZPRP is effective for LBP, its efficacy and safety have not been systematically assessed.

In recent years, clinical trials conducted to evaluate the efficacy of CZPRP for LBP yielded contradictory results [12–15]. One clinical study showed that a 4-week CZPRP treatment did not induce significant pain reduction among patients with LBP when compared to

topical diclofenac gel at week 4/day 28, although the pain-free rate significantly improved at day 14 [12]. In contrast, several randomized controlled studies indicated that CZPRP was associated with both short- and long-term pain reductions among LBP patients when compared to diclofenac or ibuprofen [13–15]. As the LBP subtypes and length of CZPRP treatment varied from study to study, the exact duration of CZPRP treatment for different subtypes of LBP is still unknown. A comprehensive examination of current clinical evidence is, therefore, necessary to provide answers to the questions LBP patients and clinicians have on the effect of CZPRP for LBP. However, no systematic review or meta-analyses has ever been conducted on CZPRP for LBP. To better inform clinical decision making and identify potential research gaps, we conducted this study (PRSOPERO CRD42020178011) to assess the efficacy and safety of CZPRP for LBP, both acute, sub-acute and chronic subtypes, through a systematic review and meta-analysis of randomized controlled trials (RCTs).

2. Materials and methods

2.1. Study inclusion criteria

The review included parallel-group RCTs with no restriction on publication language, trial status, origin of study, or publication year. Crossover trials and quasi-RCTs were excluded.

Patient: Trials with participants that met the diagnostic criteria of either acute, subacute or chronic LBP (regardless of their age, gender, race, sex, ethnicity, economic status, or educational background) were considered eligible for inclusion. Pregnant or lactating women and study participants with severe diseases who should not receive CZPRP were excluded.

Intervention: The patented Tibetan herbal medicine CZPRP (Tibet Cheezheng Tibetan Med Co Ltd., Tibet Autonomous Region, China) was included as the experimental intervention. Studies in which CZPRP was combined with non-pharmacotherapy therapies such as acupuncture, massage, or exercise; and studies that compared the efficacy of different CZPRP doses or administration methods.

Comparator: Eligible comparators were placebo, active treatment, or usual care.

Outcome: The following clinical outcomes were considered eligible: 1) pain severity measured by validated pain instruments, such as the Visual Analog Scale (VAS), the Numerical Rating Scale (NRS), the Brief Pain Inventory (BPI), etc.; 2) lower back function measured by validated tools, for example, the Japanese Orthopedic Association score, the Oswestry Low Back Disability Questionnaire, or the Roland-Morris Disability Questionnaire; 3) pain-free rate (defined as proportion of patients who had complete pain relief after treatment (post-treat VAS score = 0)); and 4) adverse events (AEs) associated with CZPRP.

Setting: No restrictions were set for the trial setting. Studies conducted in an academic-oriented research setting or in clinics (inpatient and outpatient) were eligible.

2.2. Search strategy, study selection, and data extraction

Two English databases—PubMed and Cochrane CENTRAL—and three Chinese databases—the China National Knowledge Infrastructure (CNKI), the Chongqing VIP database (CQVIP), and Wanfang database—were searched for RCTs of CZPRP for LBP (Supplementary material 1) through April 20, 2020 with no language restrictions. The ClinicalTrials.gov registry was searched for ongoing trials. Additionally, reference lists from published systematic reviews were compared with the results of the database searches to identify any missing studies. Two reviewers (MY and SQL) independently assessed the eligibility of each record, according to a study screening standard operating procedure (SOP). Initially, only the title and abstract were screened. Non-clinical trials and those that did not focus on LBP were excluded at this stage. Additional studies were excluded after reading the full text. Specific reasons for exclusion were recorded, and any disagreements were resolved by a discussion between two reviewers.

A modified Cochrane data-extraction form was used by two reviewers (MY and SQL) back-to-back to extract detailed data (study origin, year of publication, patient demographics, intervention, comparator, outcome and results, time, setting, adverse events, etc.) from each study [16]. The groups were determined and reported according to the intervention administered, such as CZPRP group, Diclofenac group, etc. When CZPRP was used as in combination with conventional drugs, the group would be a ‘CZPRP + drug (drug name)’ group. The extracted data were cross-checked to ensure consistency and accuracy. Data missing ‘at random’ were predetermined by contacting the corresponding person of the study and only available data would be used in further data synthesis. Otherwise, data not missing ‘at random’ were obtained through contacting the corresponding person of a specific study or referring to related review studies. Data required for meta-analysis was transferred from the extraction from to the RevMan software (version 5.3) in a double-entry manner. Any discrepancy or disagreement was resolved through discussions.

Additionally, assessment of the overall quality of evidence was not performed as the focus of the present study is to identify methodological limitations and research gaps rather than provide clinical recommendations. Further, the clinical outcome observed was only reported by a limited number of studies, so the overall quality of evidence may not provide additional information.

2.3. Risk of bias assessment

The Cochrane Risk of Bias assessment tool version 2.0 (RoB 2) was used for qualitative assessment [17]. RoB 2 is is the recommended tool to assess the risk of bias in randomized trials included in Cochrane Reviews. RoB 2 replaces the first version of the Risk of Bias Assessment tool, originally published in Version 5 of the Cochrane Handbook in 2008, and updated in 2011. Version 1 of the tool evaluates the risk of bias for each trial based on different risk domains, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Unlike the precedent version, the RoB 2 assessment of bias is specific to clinical outcomes and is therefore outcome-based. The RoB was rated as high, some concerns or low according to the Cochrane handbook and the technical guidance document of RoB 2 tool (https://www.riskofbias.info/welcome/rob-2–0-tool/current-version-

of-rob-2) [33]. Two reviewers (MY and SQL) independently assessed the risk of bias for each study, and any disagreements were resolved by discussion.

2.4. Statistical analysis

RevMan 5.3 was used for synthesis and meta-analysis of the efficacy data. Continuous and dichotomous data were summarized using the mean difference (MD) and the relative risk or risk ratio (RR), respectively. A 15-mm reduction of VAS score for pain severity or a 30% change from baseline in low back function scales for pain-related function may be considered clinically meaningful improvement [34]. For continuous data, when different instruments/scales were used to measure one clinical outcome, the effect size would be reported using the standard mean difference (SMD); For dichotomous data, when rare instances such as zero cases in an outcome event were reported, the Peto odds ratio model or the risk difference model was used to merge dichotomous data. For each pooled analysis, a heterogeneity test was performed using the chi-square statistic. $p < 0.10$ indicated statistical significance according to the Cochrane Handbook [33]. I^2 was used to quantify the proportion of total variations of all studies caused by heterogeneity rather than change. The Cochrane Handbook classified the I^2 statistics into the following four categories: 0–40%, might not be important; 30–60%, may represent moderate heterogeneity; 50–90%, may represent substantial heterogeneity; 75–100%, considerable heterogeneity [33]. Meta-analysis was performed with a random-effects model when $I^2 > 50\%$. Subgroup or sensitivity analysis was performed to identify the cause of substantial heterogeneity. A descriptive analysis was given if the source of heterogeneity was unclear.

2.5. Quality control

Reviewers need to uphold consistency and accuracy, especially during eligibility determination, data extraction, and risk of bias assessment. Therefore, each reviewer underwent three systematic review methodology training sessions on SOPs—at the beginning of study screening, during data extraction, and at the end of risk of bias assessment. Additional quality monitoring, including double entry, data monitoring, and cross-validation, was performed.

3. Results

3.1. Results of literature search

The search yielded 989 titles for review, of which 427 were duplicate records and 505 were excluded. The full texts of 57 articles were assessed, and 48 were excluded (Supplementary material 2). Reasons for exclusion are detailed in Fig. 1. In summary, only nine eligible clinical studies were included in this review [12–15,18–22].

3.2. Characteristics of included studies

All of the studies originated from China and were published in Chinese between 2010 and 2014. All participants were from primary/secondary health centers or hospitals, and the overall age of the patients ranged from 27 to 79 years with the majority being young/middle-aged adults. They all had a clinical diagnosis of non-specific LBP: four of these studies included acute (<4 weeks) / subacute (4–12 weeks) LPB patients [14,15,19,20], among

which two studies were related to pain caused by acute soft tissue injury [19,20] and one study was conducted in lumbar disc herniation populations [14]; one study included chronic LBP patients [22]; two studies included a heterogenous LBP population (acute/subacute and chronic LBP were included) [18,21], and two studies didn't specify the LBP subtype [12,13]. The duration of LBP ranged from 3.6 h to 16 years.

Of the included studies, five studies compared CZPRP to diclofenac head-to-head [12,13,18–20], three compared CZPRP plus non-steroidal anti-inflammatory drugs (NSAIDs, e.g., diclofenac and fenbid) with NSAIDs [14,15,21], and one study compared CZPRP plus ultrashort wave therapy (UWT) versus UWT [22] (Table 1). The treatment course ranged from 1 to 4 weeks. None of these studies was designed with a placebo control.

3.3. Risk of bias of included studies

Overall, the included trials were rated as having moderate to high risk of bias. We reported the results of qualitative assessment for each outcome according to the reporting standards of the RoB 2 device. 1) For pain severity, two-thirds of the studies had high risk of bias, whereas one-third had moderate risk of bias. The risk of bias summary graph shows major bias from random sequence generation, deviation from intended intervention, and incomplete outcome data (Fig. 2a). 2) For lower back function score, half of the studies had high risk of bias, whereas the other half had moderate risk of bias. Noticeable bias was found in the randomization process and incomplete outcome data (Fig. 2b). 3) For pain-free rate, 62.5% of the studies had high risk of bias, whereas only 37.5% had moderate risk of bias. Major bias was found in the randomization process, invalid outcome measurement, and incomplete outcome data (Fig. 2c).

3.4. Effects of interventions

3.4.1. Pain severity measured by VAS—Three studies measured the pain severity changes with VAS. For acute LBP, one study showed that the CZPRP as an adjunct to diclofenac significantly reduced pain severity (MD − 0.84, 95% CI − 1.31, − 0.37) compared to diclofenac alone [14]. However, the pain reduction didn't reach a clinically meaningful improvement. Among the mixed LBP population where the LBP subtype was unspecified, one study found that compared with topical diclofenac gel, the CZPRP did not result in a significant pain reduction ($p = 0.065$) [12] at day 28/week 4; however, another study demonstrated that compared to oral diclofenac capsules, the CZPRP significantly decreased pain severity by − 2.70 points (95% CI − 3.68, − 1.72) at the end of a 10-day CZPRP treatment and the effect maintained for over 6 months (MD − 3.0, 95% CI − 4.35, − 1.65) [13]. Pooled analysis showed that the CZPRP produced marginally significant pain reductions (MD − 1.11, 95% CI − 2.22, 0.01) compared with diclofenac ($p = 0.05$), with significant statistical heterogeneity ($I^2 = 93\%$) (Fig. 3a). Sensitivity analysis showed that heterogeneity was well explained by removing studies with the mixed LBP subtypes.

3.4.2. Functional status—Pooled analyses of two studies showed that compared to topical diclofenac, the CZPRP was associated with significant improvements in the lower back function status (SMD − 1.50, 95% CI − 2.16, − 0.85) among patients with acute LBP, with statistical heterogeneity (I2 = 91%) [18,20] (Fig. 3b). The heterogeneity was explained

by the mixed subtypes of acute soft tissues injuries. Another study done among acute and chronic LBP patients showed that the CZPRP was comparable to tropical diclofenac in improving lower back function (SMD − 0.05, 95% − 0.28, 0.18; $p = 0.40$) [12]. Same as pain severity, the functional improvement also didn't reach a clinically meaningful improvement.

3.4.3. Pain-free rate—Further analyses showed that the CZPRP was associated with a significantly increased pain-free rate at the end of a one-to-four weeks treatment among patients with acute/chronic LBP when compared with diclofenac (RR 0.72, 95% CI 0.49, 1.05), with significant statistical heterogeneity ($I^2 = 93\%$) [12,13,18–20]. Sensitivity analysis showed that by excluding study data of patients with chronic LBP or other types of acute soft tissue injury, the heterogeneity was reduced to <50% [12, 19]. Subgroup analysis among subjects with acute LBP showed that the CZPRP led to a significantly increased pain-free rate compared to diclofenac (RR: 0.64, 95% CI 0.30, 1.35), with significant statistical heterogeneity ($I^2 = 97\%$) [18–20]. Within subjects with mixed LBP subtypes, the use of CZPRP did not significantly increase the pain-free rate compared with diclofenac (RR 0.80, 95% 0.66, 0.97; $I^2 = 0\%$) [12,13]. (Fig. 4a) Moreover, CZPRP combined with NSAIDs (diclofenac and fenbid) also produced a significantly higher pain-free rate (RR 0.75, 95% 0.61, 0.92) among acute LBP patients when compared to NSAIDs alone, and the heterogeneity was not statistically significant ($I^2 = 0\%$) [14,15] (Fig. 4b). One study showed that among chronic LBP patients, CZPRP combined with UWT was associated with a significantly increased pain-free rate (RR 0.14, 95% CI 0.04, 0.57) compared with UWT alone. A summary of the effect size was provided in Table 2.

3.4.4. Safety—Six studies reported AEs. AEs associated with CZPRP or topical diclofenac gel are mostly skin allergic reactions such as itchiness, redness, and blister. Stomach discomfort was also reported for oral diclofenac [13]. A pooled analysis of the safety data showed that the occurrence of AEs in patients who received CZPRP was not significantly different from those who did not receive CZPRP (Risk Difference 0.01, 95% CI − 0.02, 0.04, $P = 0.63$, $I^2 = 64\%$) (Fig. 5).

4. Discussion

4.1. Summary of the finding

This study evaluated the efficacy and safety of Tibetan herbal analgesic CZPRP among 1674 LBP patients through a systematic review and meta-analysis of RCTs. The results showed that CZPRP used alone or in combination with conventional analgesics was associated with significant improvements in pain and function, as well as pain-free rate, among patients with acute LBP when compared to conventional analgesics. However, in a heterogenous LBP population including both acute and chronic LBP patients, there was no significant difference in pain outcomes between CZPRP and diclofenac. Nevertheless, CZ PRP use did not increase the odds of AEs. These clinical outcomes are associated with moderate to high risk of bias in studies that include diverse forms of LBP and the differences are of questionable clinical relevance. The findings have important clinical and research implications for using CZPRP in the management of LBP.

4.2. Clinical implications

Currently, non-pharmacologic interventions were recommended for both acute and chronic LBP [23,24]. Many traditional medicine/CAM therapies including massage, Yoga, Tai Chi, and acupuncture are recommended by clinical practice guidelines and widely consumed by LBP patients [23]. However, herbal medicine is not recommended for LBP due to a paucity of pertinent clinical evidence [25]. In the present study, we summarized the clinical evidence on Tibetan herbal medicine CZPRP for LBP. This study suggests that CZPRP might be associated with greater pain reduction and function improvement than NSAIDs when used alone or as an adjunct to NASIDs among acute LBP patients. However, the magnitude of change in pain and function was relatively small, which warrants further verification in better powered studies. It is also unclear whether the effects of CZPRP for acute LBP persist. Moreover, as psychological distress and other concurrent symptoms also increase the risk of persistent disabling LBP, future studies are needed to examine the effect of CZPRP on mental distress and other comorbidities of LBP in order to prevent the chronicity of LBP [26].

Our study also contributed important clinical information regarding the effect of CZPRP for chronic LBP. The results showed that, although CZPRP was associated with efficacy in acute LBP patients, the between-group differences were no longer significant when chronic LBP patients were mixed in, indicating heterogenous effects of CZPRP for acute and chronic LBP. This finding may help explain the contradictory effects of CZPRP for LBP observed in different studies. However, this should not be interpreted as the sole reason, given the heterogeneity in intervention delivery and the choice of comparator. More importantly, current evidence may not support firm conclusions on the effect of CZPRP for either acute or chronic LBP, due to limitations in statistical power and methodological inadequacy. Therefore, in clinical practice if preferred by patients, CZPRP might be used as a supplement to conventional non-pharmacologic/pharmacologic treatment for acute LBP and, could be considered if LBP were inadequately resolved with conventional interventions.

4.3. Research implications

Our study highlights the importance of rigorous methodology in determining the clinical benefits of CZPRP for LBP. First, using explicit diagnostic criteria to differentiate acute and chronic LBP is critical to ensure the homogeneity of the study population [27]. Clarifying which LBP subtype CZPRP is effective for may potentially change current clinical recommendations for treating LBP with CZPRP. Second, validated clinical measurements for pain and function are required to accurately capture the clinical improvement induced by CZPRP. LBP-related mental distress and other comorbidities may be considered as important secondary clinical outcomes to understand the comprehensive effects of CZPRP. Third, a valid control arm, placebo plaster in particular, should be included in future prospective trials to evaluate the specific efficacy of CZPRP for LBP. Lastly, the potential synergetic effect of including CZPRP as a first-line recommended treatment and the long-term therapeutic effect for LBP should be further determined in pragmatic trials.

4.4. Pharmacological relevance

Mechanism of how CZPRP might be effective in treating LBP is not yet fully understood. Previous pharmacology studies identified bioactive components such as iridoid glycoside, diphenylheptanone, sesquiterpene, and luteolin from the herbs used in CZPRP [28,29]. Their anti-carcinogenic, anti-inflammatory, and anti-oxidative actions are essential to the property of CZPRP. A study in an animal model of muscular inflammation showed that topical use of CZPRP substantially decreased C-fiber afferent spontaneous firing in the nerve innervating the inflamed muscle, suggesting that CZPRP may reduce the nociceptive input from inflamed muscles via a reflex mechanism by activating the cutaneous nociceptive afferents [30]. Another study showed that the anti-inflammatory effects of CZPRP possibly are related to the reduction of inflammatory cytokines (TNF-α and IL-1β), inducible inflammatory enzyme (COX-2), and its metabolite PGE_2 via the NF-κB signal pathway [31]. It also suggested that CZPRP extracts inhibited the production of leukotrienes B_4, indicating that CZPRP inhibited the 5-lipoxygenase pathway, which may be the other mechanism for its anti-inflammatory action. In addition, CZPRP also decreased blood flow velocity and facilitated edema absorption to improve closed soft tissue injuries [32]. Additionally, it remains unknown how non-specific effects contributes to the difference observed between groups. More studies are required to elucidate the mechanism of the analgesic and tissue-repairing actions of CZPRP.

4.5. Strengths and limitations

Study limitations need to be considered. First, all included studies are conducted in a Chinese population. The generalizability of current evidence is limited. Future studies should test the efficacy and safety of CZPRP in a Western or other population. Second, the small-study effect cannot be ruled out from meta-analyses, due to insufficient studies to allow for the performance of the Egger's test or Funnel plot analysis. Third, the long-term follow-up and data from ongoing trials were not available. Lastly, further subgroup analyses or meta-regression were not conducted due to the small number of studies included. With these limitations, the results should be interpreted with caution. The overall strengths of this study include: 1) a comprehensive appraisal of up-to-date evidence on the effect of CZPRP for LBP; and 2) a differentiation of the clinical benefits of CZPRP for acute and chronic LBP.

5. Conclusion

This study suggests that use of CZPRP is associated with greater reduction in pain and greater improvement in function when compared to diclofenac/NSAID, however the clinical relevance is questionable. Randomized placebo-controlled trials with long-term follow-ups are warranted to assess the effect of CZPRP for acute and chronic LBP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JJM reports grants from Tibet CheeZheng Tibetan Medicine Co. Ltd. and from Zhongke Health International LLC outside the submitted work. MY, SQL, CMS, YLZ, and TB declare no conflict of interest.

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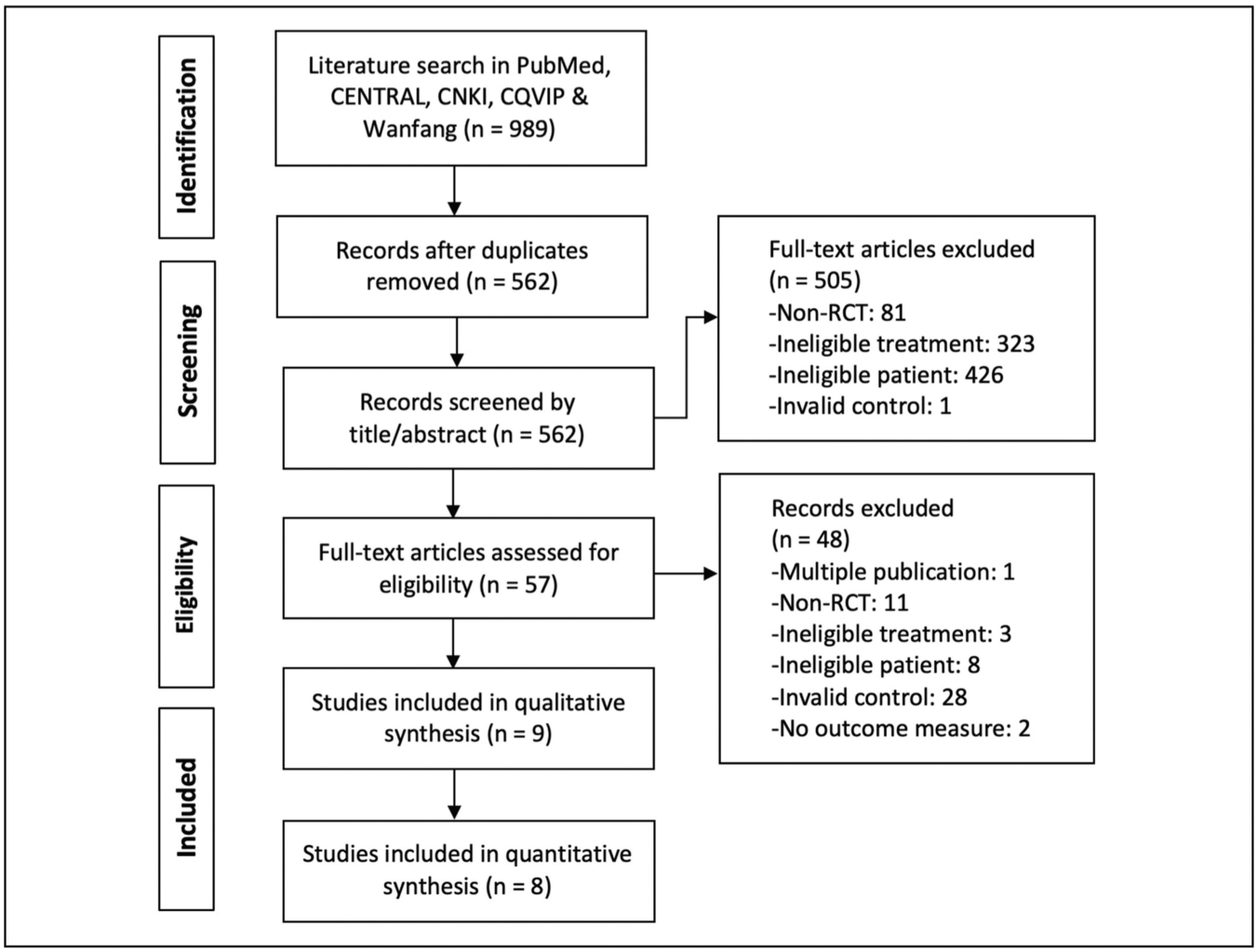

Fig. 1. Flow diagram of systematic review

This chart illustrates the flow of the review process from the initial literature search to the final meta-analysis. At each stage, the number of studies and the reasons for study inclusion and exclusion were detailed. (Figure not to be printed in color).

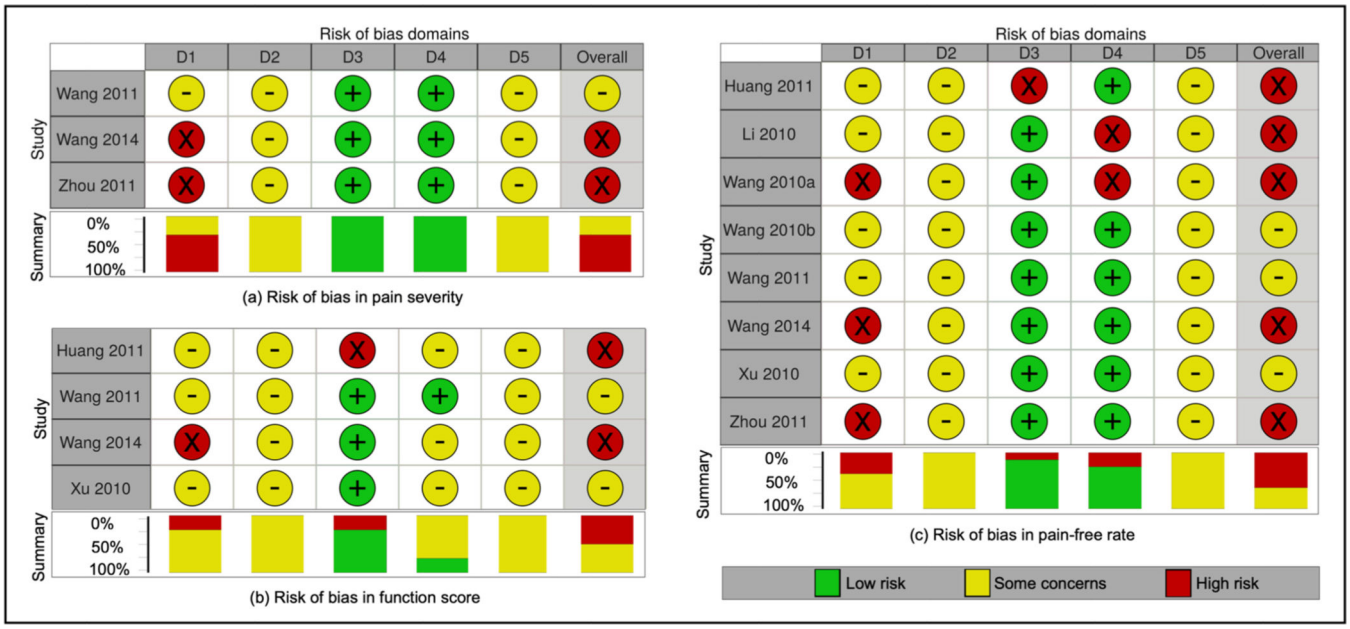

Fig. 2. Risk of bias assessment.

This figure shows the risk of bias for each outcome. Figure (a) indicates the risk of bias associated with studies reporting pain intensity; (b) demonstrates the risk of bias associated with studies reporting lower back pain function; and (c) represents the risk of bias associated with studies reporting lower back pain function. The meaning of each risk of bias domain was listed as following: D1 = Bias arising from the randomization process; D2 = Bias due to deviation from intended intervention; D3 = Bias due to missing outcome data; D4 = Bias in measurement of the outcome; D5 = Bias in selection of the reported results. (Figure to be printed in color).

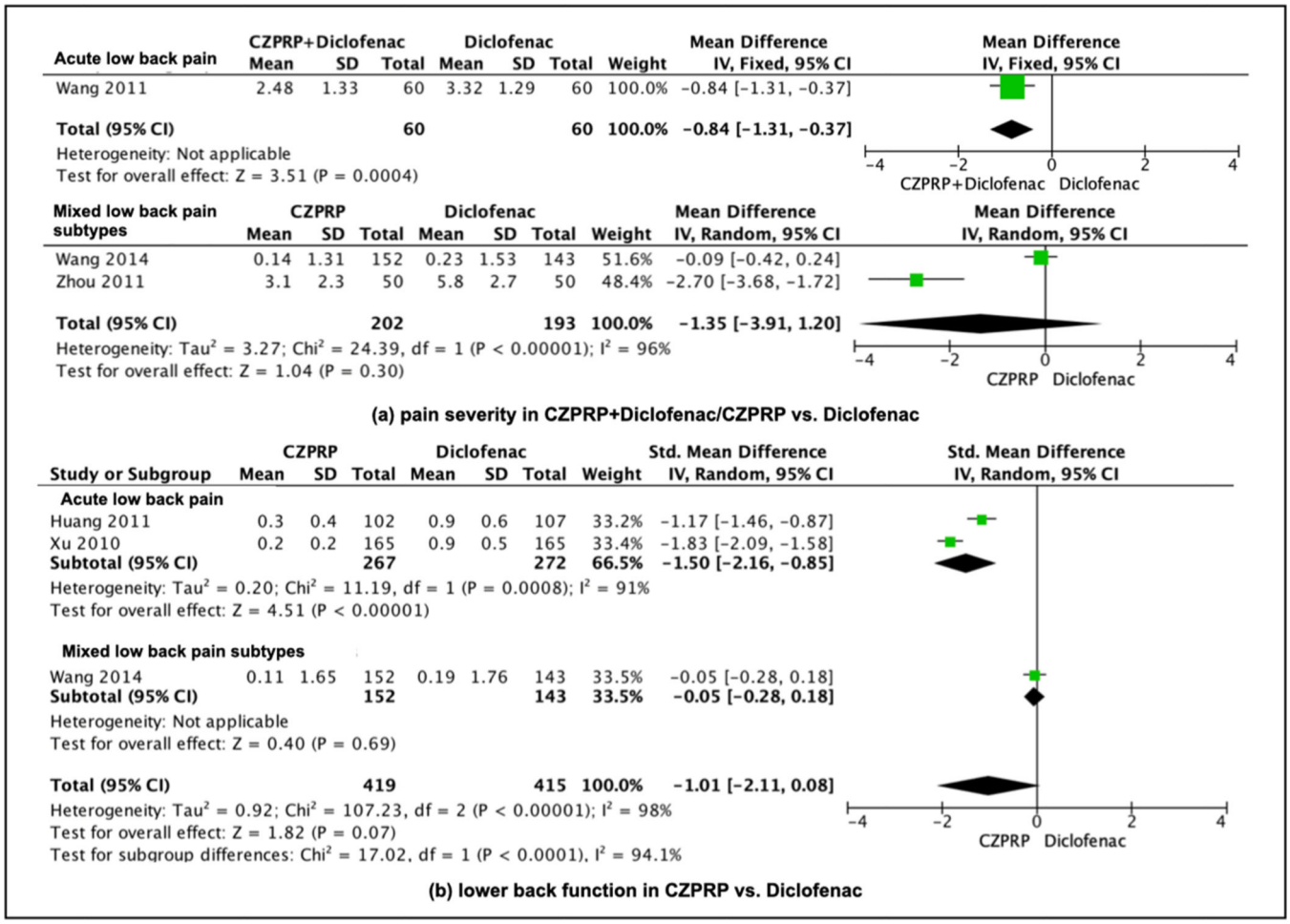

Fig. 3. Forest plot comparing changes in pain severity and lower back function of CZPRP versus control.

Fig. 3a is a forest plot comparing the pain severity changes in CZPRP versus control. Fig. 3b is a forest plot comparing the lower back function changes in CZPRP versus diclofenac. (Figure to be printed in color).

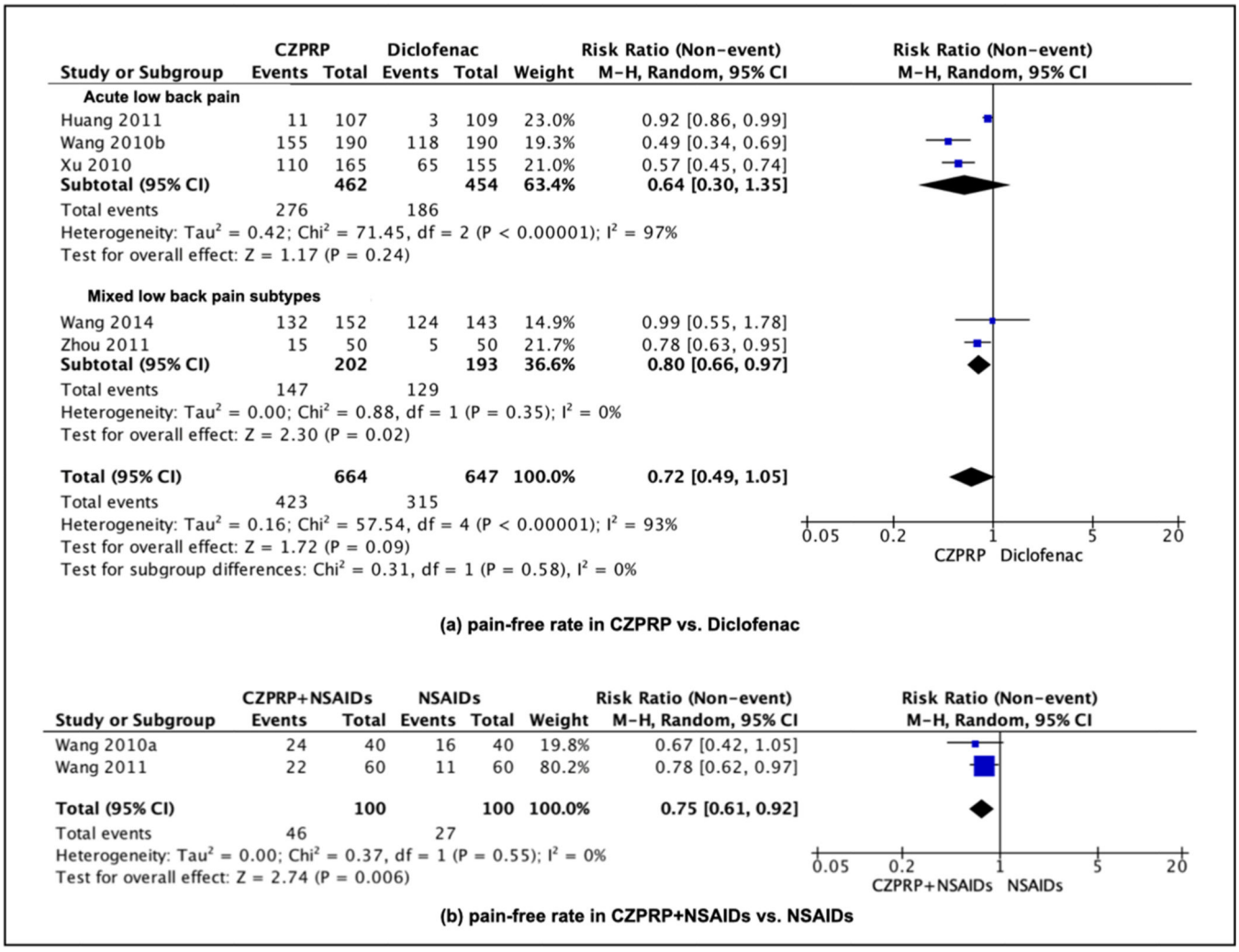

Fig. 4. Forest plot comparing the pain-free rate of CZPRP or CZPRP+NSAIDs versus NSAIDs.

Fig. 4a is the forest plot comparing the pain-free rate of CZPRP versus diclofenac. Fig. 4b is the forest plot comparing the pain-free rate of CZPRP+NSAIDs versus NSAIDs.(Figure to be printed in color).

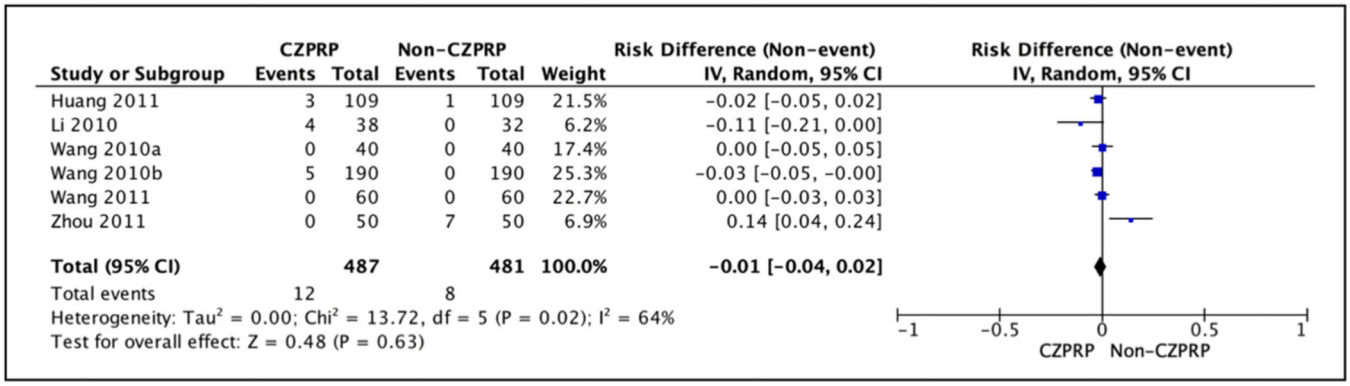

Fig. 5. Forest plot comparing AEs of CZPRP versus non-CZPRP.

Fig. 5 is the forest plot comparing AEs associated with CZPRP versus non-CZPRP. The black diamond touches the null effect line, indicating that CZPRP did not significantly increase AEs compared with non-CZPRP. (Figure to be printed in color).

Table 1

Characteristics of included studies.

ID	Participants		Subtype	Sample size	Experimental	Control	Outcome	Setting	Adverse events
	Age (mean, SD) (yrs)	Disease course							
Guo 2011 [21]	Median: 63 Min: 27 Max: 79	1m to 16 y;	Lumbar disc herniation	E: 80 C: 80	CZPRP: topical use, 1 patch daily for 7d Dic: oral, 75 mg/ d 7d	Dic: oral, 75 mg/ d 7d	Effective rate	Orthopedics department	Not reported
Huang 2011 [20]	E: 32.5 (8.6) C: 29.8 (9.2)	E: 2.1 (0.6)d C: 2.6 (0.7)d	Acute LBP and other acute soft tissue sprain	E: 102 C: 107	CZPRP: topical use, 1 patch/d 10d	Dic gel: topical, 1 g t.i.d 10d	pain-free rate; functional score	Orthopedics department	E: skin allergies C: allergy
Li 2010 [22]	E: 34.3 (11.5) C: 36.4 (12.3)	E: 9.2 (2.5)m C: 8.6 (2.8)m	Lumbar strain	E: 38 C: 32	CZPRP: topical use, 1 patch/d 30d UWT: 40.7 MHz, 15 min/ session, b.i. d 30d	UWT: 40.7 MHz, 15 min/session, b.i.d 30d	pain-free rate	Orthopedics department	E: skin redness, itching
Wang 2010a [15]	E: 45(26, 65) C: 46(25, 66)	E: 1–8w C: 1–8w	LBP	E: 40 C: 40	CZPRP: topical use, 1 patch/d 5d Fenbid: oral, 1 pill/ d 5d	Fenbid: oral, 1 pill daily 5d	pain-free rate	Outpatient orthopedics clinic	None
Wang 2010b [19]	29.1(12.6)	3.8(2.9)h	Lumbar sprain and other acute soft tissue injury	E: 190 C: 190	CZPRP: topical use, 1 patch/d 5d	Dic gel: topical use, 5d	pain-free rate	Orthopedics department	E: skin allergy
Wang 2011 [14]	37.9(11.4)	1.2(3.7)d	Lumbar disc herniation	E: 60 C: 60	CZPRP: topical use, 1 patch/d 15d Dic gel: topical, twice/d 15d	Dic gel: topical, twice/d 15d	pain-free rate; VAS; functional score	Orthopedics department	None
Wang 2014 [12]	E: 43.1 (13.6) C: 44.0 (12.4)	Not reported	Acute/chronic LBP	E: 152 C: 143	CZPRP: topical use 28d	Dic gel: topical use 28d	pain-free rate; VAS; functional score	Hospitals	Not reported
Xu 2010 [18]	E: 32.5 (8.6) C: 29.8 (9.2)	E: 3.1 (0.6)m C: 2.6 (0.7)m	Lumbar strain and other acute soft tissue sprain	E: 165 C: 155	CZPRP: topical use, 1 patch/d 15d	Dic gel: topical use, q.i.d 15d	pain-free rate; functional score	Orthopedics department	Not reported
Zhou 2011 [13]	E: 44.6 (11.2) C: 46.3 (9.5)	Not reported	Lumbar strain	E: 50 C: 50	CZPRP: topical use, 1 patch/d 7d	Dic: oral, 50 mg t. i.d 10d	pain-free rate; VAS	Emergency department	C: stomach discomfort

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Note: Abbreviations: E = experimental group; C = control; h= hour; d = day; w = week; m = month; y = year; b.i.d = twice a day; t.i.d = three times a day; q.i. d = four times a day; CZPRP: CheeZheng Pain relief plaster; Dic = Diclofenac; LBP = low back pain; SD = standard deviation; UWT = ultrashort wave therapy; VAS = visual analog scale.

Table 2

The effect size associated with CheeZheng Pain-Relieving Plaster versus controls.

Clinical outcome low back pain subtype	Effect size			Comparison
Pain severity (VAS)	(Mean, 95% CI)			
Acute	−0.84 (− 1.31, − 0.37) *			(CZPRP + Dic Vs. Dic)[14]
Mixed subtypes	−1.35 (− 3.91, 1.20)			(CZPRP vs. Dic)[12,13]
Functional status	(Mean, 95% CI)			
Acute	−1.50 (− 2.16, − 0.85) *			(CZPRP vs. Dic)[18,20]
Mixed subtypes	−0.05 (− 0.28, 0.18)			(CZPRP vs. Dic)[12]
Pain free rate	(Risk Ratio, 95% CI)	Anticipated absolute effects Risk with Control	Risk difference with CZPRP	
Acute	0.64 (0.30, 1.35) *	410 per 1000	254 per 1000 (123 more to 554 more)	(CZPRP vs. Dic)[18–20]
	0.75 (0.61, 0.92) *	270 per 1000	203 per 1000 (165 more to 248 more)	(CZPRP + NSAIDs vs. NSAIDs)[14,15]
Chronic	0.14 (0.04, 0.57) *	625 per 1000	500 per 1000 (25 more to 356 more)	(CZPRP + UWT vs. UWT)[22]
Mixed subtypes	0.80 (0.66, 0.97)	668 per 1000	535 per 1000 (441 more to 647 more)	(CZPRP vs. Dic)[12,13]

Note:

* indicates $p < 0.05$. Abbreviations: CI = confidence interval; CZPRP = CheeZheng Pain-Relieving Plaster; Dic = Diclofenac; NSAIDs = nonsteroidal anti-inflammatory drugs; UWT = ultrashort wave therapy; VAS = visual analog scale.