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A Systematic Review of CheeZheng Pain Relieving Plaster for Musculoskeletal Pain: Implications for Oncology Research and Practice

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Abstract

Background: Musculoskeletal pain is a common and debilitating condition for cancer patients. Existing therapies for these pain conditions have substantial limitations. To identify an integrative approach to pain management, we conducted a systematic review to evaluate the safety and efficacy of a Tibetan herbal-based topical agent, CheeZheng Pain Relieving Plaster (PRP), for the treatment of osteoarthritis (OA) pain. **Methods:** We extracted citations from PubMed and Chinese databases (CNKI, WanFang Data, and CQVIP). We included randomized clinical trials evaluating the effectiveness and safety of CheeZheng PRP compared to conventional OA pain treatments. **Results:** Twenty-two randomized clinical trials (n = 2556 participants) compared CheeZheng PRP against nonsteroidal anti-inflammatory drugs (11), glucosamine (2), intraarticular corticosteroid (2), hyaluronic acid injections (6), and acetaminophen (1). Ten studies found a statistically greater effectiveness (assessed by ≥30% reduction in symptom severity) of CheeZheng PRP in improving OA pain (measured by the Visual Analogue Scale), stiffness, and function compared to control. Ten studies reported that 4.8% of participants experienced application site skin irritation that resolved after discontinuing the plaster. Randomization was not sufficiently described in most studies, and no placebo-controlled trials were identified. **Conclusions:** There is promising evidence for the safety and clinical effectiveness of CheeZheng PRP to treat OA; however, lack of placebo control and unclear descriptions of randomization increase the potential risk for bias. Future randomized, placebo-controlled trials are needed to establish the safety and efficacy of CheeZheng PRP for pain management in oncology settings.

Keywords

cancer pain management, chronic pain, topical pain patch, herbal patch analgesic, pain management

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Introduction

As of 2019, there were an estimated 16.9 million cancer survivors in the United States alone, a number projected to reach 26.1 million by 2040.[1] One in every 3 of these survivors suffers from high-impact chronic pain that restricts daily function, a rate double that of the general population.[2] For these patients, pain can result either directly from the cancer itself or as a sequela of treatment (ie, surgery, radiation, or chemotherapy),[3] which can cause various musculoskeletal conditions such as connective tissue fibrosis, osteoporotic fractures, aseptic necrosis of the femoral head, and degenerative arthritis.[4,5] These chronic pain conditions are often poorly addressed and pose a high symptom burden for cancer survivors as they can substantially affect daily function and quality of life.

The current standard for pain management in cancer patients involves commonly used analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy, and opioids and coanalgesics in escalated cases.[6-9] However, long-term NSAID use is associated with increased

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risk of gastrointestinal bleeding, cardiovascular side effects, and NSAID-induced nephrotoxicity.[10-14] Opioid treatments not only have side effects,[7,15] but also long-term use in cancer survivors is particularly concerning for opioid dependence, addiction, abuse, and overdose.[16-18] Furthermore, 20% of patients with cancer pain do not respond to standard analgesics and require second-line agents or nonpharmacological interventions.[19] It is estimated that 5.4 million cancer survivors are still living with poorly managed chronic pain despite increased pain control efforts.[2] This underscores the unmet needs of the oncologic community and the demand for integration of novel therapeutic approaches for pain management into comprehensive cancer care.

Herbal medicine has long been used in traditional Chinese medicine alone or in combination with conventional medicine to treat chronic pain conditions. CheeZheng Pain Relieving Plaster (PRP) is an herbal-based topical analgesic manufactured by Tibet CheeZheng Tibetan Medicine Co Ltd. Since its introduction into the market in 1993, CheeZheng PRP has been studied and used extensively throughout China as an analgesic for acute soft tissue injury and chronic musculoskeletal conditions such as spondylosis, disc herniation, and osteoarthritis (OA). In addition to China, this plaster is currently available in the United States as an over the counter therapy for the temporary relief of minor aches and pains of muscles and joints. The formulation of CheeZheng PRP contains the following herbs: camphor 3% (active ingredient), *Zanthoxylum bungeanum* Maxim. (Chuan Jiao), *Lamiophlomis rotata* (Benth.) Kudo (Du Yi Wei), *Curcuma longa* L. (Jiang Huang), *Myricaria germanica* (L.) Desv. (Shui Bai Zhi), *Carthamus tinctorius* L. (Hong Hua), and *Oxytropis falcata* Bunge (Ji Dou). In vitro and in vivo studies have found that its therapeutic effect in treating pain is achieved by reducing inflammation and inhibiting nociceptive response.[20,21]

Osteoarthritis is a common chronic pain condition characterized by the degeneration of cartilage tissue in joints. Currently, a large body of Chinese literature supports the use of CheeZheng PRP for treating chronic pain conditions such as OA. However, the quality of this evidence is unclear, and limitations of the current literature have not been identified. To inform the appropriate research of PRP for pain management in oncology settings, we undertook this systematic review of randomized controlled trials to evaluate the safety and effectiveness of PRP in improving symptoms in patients with OA compared to conventional treatments. Better defining the current evidence base and identification of limitations can help design more rigorous trials of PRP in cancer patients.

Methods

Identification of Studies

We searched PubMed and the Chinese databases China National Knowledge Infrastructure, WanFang Data, and Chongqing VIP up to May 2019. Key search terms include CheeZheng, pain relieving plaster, and Xiaotong Tiegao (Chinese translation). We did not place any limits or filters on searches or apply any language or publication-type restrictions.

Study Selection

Type of Study. Randomized clinical trials (RCTs) that evaluated the clinical efficacy and safety of CheeZheng PRP for the treatment of OA were included. RCTs on CheeZheng PRP for other indications (ie, soft tissue injury, disc herniation, spondylosis, and trauma) were excluded.

Type of Intervention. Randomized clinical trials that evaluated the efficacy of CheeZheng PRP against or in combination with conventional therapies such as NSAIDs, COX-2 inhibitor, and intraarticular injections were included. RCTs that compared CheeZheng PRP with nonconventional treatments such as massage, acupuncture, and other herbal analgesics were excluded, as the efficacy of these comparator treatments is not fully established outside China and would be difficult to interpret.

Type of Comparison. Both active control and placebo-controlled studies were eligible. Trials that did not provide detailed comparison data were excluded.

Types of Outcome Measures. Studies with standardized outcome measures were included, while studies with subjective outcome measures were excluded. The primary outcomes were pain intensity and physical functioning, after completion of treatment course. Standardized outcome measures that were used in the included studies with regard to therapeutic effectiveness included the following: Visual Analogue Scale (VAS), Clinical Effective Rate (CER), Western Ontario and McMaster Universities Arthritis Index (WOMAC), Hospital for Special Surgery (HSS) Knee Score, Lysholm Scale, and Lesquene Index. The outcome measure used in the included studies to evaluate safety was reported adverse events (AEs).

Visual Analogue Scale. A psychometric measurement (0-10 scale) to assess statistically measurable and reproducible classification of pain severity,[22-25] with a higher score indicating more severe pain.

Clinical Effective Rate. A cumulative score for pain, stiffness, and joint disability obtained pre- and posttreatment. Outcome is categorized based on posttreatment symptom score reduction: very effective ($\geq$66% reduction), effective ($\geq$30% reduction), and not effective ($<$30% reduction). CER is the percentage of patients that demonstrate $\geq$30% reduction in the symptom score.

Western Ontario and McMaster Universities Arthritis Index. A validated 24-item questionnaire (total score = 96) used to evaluate hip and knee OA based on subcategories: pain, stiffness, and physical function.[26-28] Higher scores indicate worse pain, stiffness, and physical function.

HSS Knee Score. Seven categories (total points = 100) that assess pain, function, range of motion, muscle strength, flexion deformity, instability, and subtractions.[29] Approximately 50% of the score is based on a patient interview and the remaining on physical examination. The higher the score, the better the outcome.

Lysholm Scale. An 8-item questionnaire (total score = 100) that measures pain (25 points), instability (25 points), locking (15 points), swelling (10 points), limp (5 points), stair climbing (10 points), squatting (5 points), and need for support (5 points).[30-32] A higher score indicates a better outcome with fewer symptoms of disability.

Lesquene Index. Combines pain, walking ability, and activities of daily living into a questionnaire with 11 parameters (0-24 scale) that assesses pain or discomfort, maximum distance walked, and activities of daily living.[33] A higher score indicates more severe handicap.

Adverse Events. Adverse events from CheeZheng PRP use were reported as the percent of patients who experienced patch-related application-site irritation, as well as the duration and degree of skin irritation (ie, redness, pain, itchiness, and blistering of the skin).

Data Extraction and Quality Assessment

Two reviewers (CC, QL) independently screened the extracted articles in accordance to established inclusion and exclusion criteria. Both investigators independently extracted data including manuscript title, author, publication date, patient population characteristics, sample size, type of intervention, and outcome. Methodological quality of the eligible studies was assessed independently by reviewers using the Cochrane risk of bias assessment tool for randomized trials.[34] The Cochrane tool assesses the likelihood of selection, reporting, performance, detection, and attrition bias using 7 categories: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We defined other bias as trials in which baseline characteristics between intervention groups were not similar. Quality items were graded as low risk, high risk, or uncertain risk for each study. In case of disagreement, consensus was reached after discussion with a third reviewer (LZ). We reserved the decision on whether to conduct a collective outcome analysis for after evaluating whether or not the included studies would provide clinically meaningful effect sizes.

Results

Literature Identification and Screening

A total of 175 relevant citations were retrieved from 4 databases, of which 76 were excluded after screening titles and abstracts based on exclusion criteria. We conducted a full-text review of 99 articles and 22 met the eligibility criteria of our study. Reporting of our study was in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Figure 1 further shows the PRISMA flow diagram depicting our search process and study selection.

Baseline Characteristics of Eligible Studies

We included 22 RCTs conducted between 2009 and 2019 with a total of 2556 participants in this review. All studies were conducted and published in China. Studies included 1473 females and 973 males ranging in age from 30 to 86 years old. OA joint involvement included knee (19 studies), elbow (2 studies), and ankle (1 study). CheeZheng PRP was compared to 5 conventional treatments for OA in the included trials: NSAIDs (11 studies; 4 oral, and 7 topical), glucosamine (1 study), glucosamine and NSAID (1 study), intraarticular corticosteroid (2 studies), hyaluronic acid injections (6 studies), and acetaminophen (1 study; Table 1).

Outcomes

Compared to NSAIDs. In the 11 RCTs comparing CheeZheng PRP to NSAIDs, CheeZheng PRP was superior in 9 and equivalent in 2 studies for treatment of ankle, elbow, and knee OA. The median length of treatment was 7 days (range = 5 to 42 days). Compared to NSAIDs, improvement in pain as measured by VAS score reduction was found to be significantly greater for CheeZheng PRP in 4 studies and equivalent in 1 study (Table 2). Improvement in WOMAC outcomes of pain, stiffness, and functionality was superior for CheeZheng PRP compared to NSAIDs in 3 studies. Six studies found a significantly greater number of patients who achieved a CER—as measured by a ≥30% score improvement in pain, tenderness, and functionality—using CheeZheng PRP compared to NSAIDs. One RCT comparing 1 week of CheeZheng PRP to 1 week of diclofenac sodium 25 mg 3 times a day found CERs of 86.7% and 84.4%, respectively. The study concluded that there was no significant difference in effectiveness between CheeZheng PRP and NSAIDs ($P > .05$).

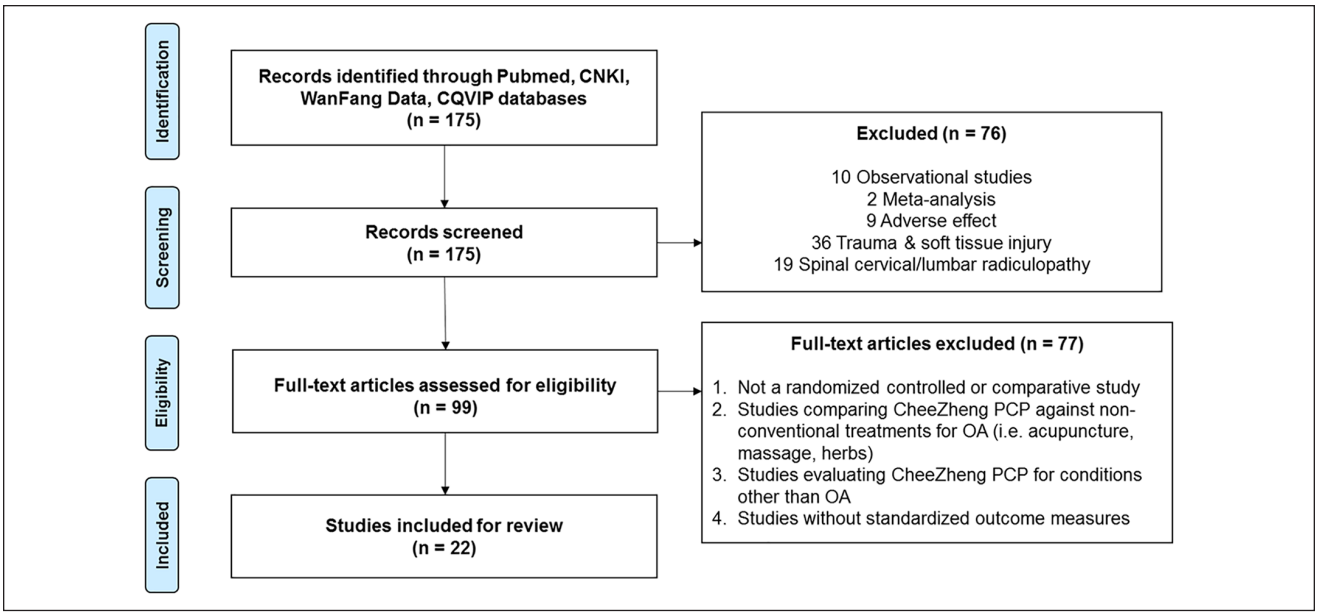

Figure 1. PRISMA flow diagram of selection process.

Table 1. Characteristics of Included Studies.

Total studies	**22**
Total participants	2556
Mean age (range)	30-86
Gender	27.8
Female	1473
Male	973
Joint involvement, n (%)	
Knee	19 (86%)
Elbow	2 (9%)
Ankle	1 (5%)
Comparator, n (%)	
Oral NSAID	5 (22%)
Topical NSAID	6 (27%)
Sodium hyaluronate injections	6 (27%)
Corticosteroid injections	2 (9%)
Glucosamine	1 (5%)
Acetaminophen	1 (5%)
NSAID + glucosamine	1 (5%)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

Compared to Acetaminophen. One study compared 1 week of CheeZheng PRP in combination with 900 mg once daily acetaminophen to acetaminophen alone in 200 patients with knee OA (Table 2). The study found that the magnitude of VAS and WOMAC score improvement was significantly greater when CheeZheng PRP was used in combination with acetaminophen.

Compared to Intraarticular Treatments. Six studies compared CheeZheng PRP with sodium hyaluronate injections. The median length of treatment was 5 weeks for intraarticular treatments and 1 week for CheeZheng PRP; all studies involved the knee. Among these studies, 3 found that the use of CheeZheng PRP in combination with sodium hyaluronate was more effective in improving pain, swelling, and function than sodium hyaluronate alone. Two studies found CheeZheng PRP alone to be significantly more effective in improving pain and function than sodium hyaluronate. One RCT comparing CheeZheng PRP daily with sodium hyaluronate injections once a week for 4 weeks found no significant difference between the effectiveness of the 2 stand-alone therapies, with a significant reduction in pain, stiffness, and joint disability found in both groups posttreatment (Table 2).

Two studies compared CheeZheng PRP to corticosteroid injections. One of these studies compared the use of CheeZheng PRP for 1 week in combination with prednisone injections 20 mg (once a week) over the course of 5 weeks to prednisone 20 mg alone for the treatment of knee OA. The study found that the adjunct of CheeZheng PRP led to a statistically greater improvement in the VAS pain score as well as overall CER compared to prednisone alone. Another study found that the combination of CheeZheng PRP with 1-mL betamethasone achieved a greater improvement in the VAS pain score and Lysholm score in the treatment of knee OA (Table 2).

Compared to Glucosamine. In one study, 10 days of CheeZheng PRP once a day combined with glucosamine hydrochloride (0.48 g) 3 times a day for 6 weeks resulted in a significantly greater improvement in VAS and HSS scores compared to glucosamine alone. Another study

Table 2. Effectiveness of CheeZheng PRP Versus Comparators[a].

Author, Year	Treatment Duration (days)	CheeZheng PRP (N), Control (N)	Outcome (Treatment vs Control)	
Li et al. 2013[35]	112	CheeZheng PRP N = 30, Diclofenac topical gel N = 30	Δ VAS 5.05 vs 1.22	P<0.05
Wang et al. 2013[36]	13	CheeZheng PRP N = 43, Diclofenac topical gel N = 43	Δ HSS 13.86 vs 8.24	P<0.05
Li et al. 2011[37]	5	CheeZheng PRP N = 30, Diclofenac topical gel N = 30	CER 93.88% vs 66.7%	P<0.05
Li et al. 2011[38]	7	CheeZheng PRP N = 30, Diclofenac sodium (75 mg) N = 32	CER 86.67% vs 84.4%	P>0.05
Chen et al. 2011[39]	5	CheeZheng PRP N = 309, Diclofenac topical gel N = 168	CER 78% vs 39.75%	P<0.05
Jiang et al. 2011[40]	14	CheeZheng PRP N = 40, Diclofenac topical gel N = 40	Δ HSS 13.08 vs 9.50	P<0.01
Jia et al. 2011[41]	unspecified	CheeZheng PRP N = 43, Diclofenac topical gel N= 40	VAS pre, post: 66.6, 27.2 vs pre, post: 67.2, 29.8	P<0.05
Xin et al. 2011[42]	5	CheeZheng PRP N = 100, Topical Indomethacin N = 100	CER 92% vs 84%	P<0.05
Lu et al. 2011[43]	5	CheeZheng PRP N = 80, Diclofenac sodium (100 mg) N = 80	VAS pre, post: 7.8, 2.8 vs pre, post: 7.7, 4.2	P<0.05
Guo et al. 2011[44]	15	CheeZheng PRP N = 90, Diclofenac sodium (150 mg) N = 90	CER: 91.9% vs 78%	P<0.05
Yu et al. 2009[45]	56	CheeZheng PRP N = 60, Celecoxib (200 mg) N = 60	WOMAC pain pre, post: 12.9, 7.2 vs pre, post: 12.3, 6.01	P<0.01
Wu et al. 2011[46]	10, 42 (CheeZheng, Glucosamine)	CheeZheng PRP + Glucosamine N = 40, Glucosamine (1.44 g) N = 30	VAS pre, post: 67.3, 18.5 vs pre, post: 65.4, 30.2	P<0.05
Zhang et al. 2010[47]	84	CheeZheng PRP N = 32, Nimesulide (200 mg) Glucosamine (1.44 g) N = 28	Lequesne pre, post: 3.64, 0.35 vs pre, post: 3.7, 3.7	P<0.05
Li et al. 2019[48]	35	CheeZheng PRP + Sodium hyaluronate N = 40, Sodium hyaluronate N = 40	Δ WOMAC 6.58 vs 3.70	P<0.05
Peng et al. 2011[49]	35	CheeZheng PRP N = 43, Sodium hyaluronate N = 43	CER 93.02% vs 88.37%	P<0.05
Zhang et al. 2011[50]	42	CheeZheng PRP + Sodium hyaluronate N = 36, Sodium hyaluronate N = 44	CER 93.1% vs 85.7%	P<0.05
Gao et al. 2011[51]	35	CheeZheng PRP + Sodium hyaluronate N = 44, Sodium hyaluronate N = 44	HSS pre, post: 64.9, 85.31 vs 64.9, 78.1	P<0.01
Chen et al. 2010[52]	28	CheeZheng PRP N = 40, Sodium hyaluronate N = 40	CER 85% vs 82.5%	P>0.05
Guo et al. 2010[53]	21, 35 (CheeZheng, Sodium hyaluronate)	CheeZheng PRP N = 40, Sodium hyaluronate N = 40	CER: 97% vs 91%	P<0.05
Yuan et al. 2010[54]	Not reported	CheeZheng PRP + Betamethasone N = 30, Betamethasone N = 30	VAS pre, post: 5.41, 3.42 vs pre, post: 5.32, 2.70	P<0.05
Zhao et al. 2009[55]	7, 35 (CheeZheng, Prednisone)	CheeZheng PRP + Prednisone N = 35, Prednisone N = 33	CER: 86% vs 61%	P<0.05
Li et al. 2012[56]	7	CheeZheng PRP + acetaminophen N = 100, Acetaminophen (900 mg) N = 100	Δ VAS 4.5 vs 2.5 Δ WOMAC 11.3 vs 9.5	P<0.05

Abbreviations: PRP, pain relieving plaster; VAS, Visual Analogue Scale; HSS, Hospital for Special Surgery; CER, Clinical Effective Rate; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

[a]VAS, WOMAC, HSS Knee Score, Lysholm Scale, Lesquene Index, and CER: percentage of patients that demonstrated ≥30% reduction in symptom severity.

comparing CheeZheng PRP with 12 weeks of nimesulide (100 mg) twice a day and glucosamine hydrochloride (480 mg) 3 times a day found a greater statistically significant improvement in the Lequesne index post treatment.

Methodological Characteristics and Risk Assessment of Bias

As there were no placebo-controlled studies, the included RCTs demonstrated high risk of performance bias due to

Table 3. Cochrane Risk of Bias Assessment.

Author, Year	Random Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of Outcome Assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other Bias
Li 2013[35]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Wang 2013[36]	High Risk	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Li 2011[37]	Uncertain	Uncertain	High Risk	Uncertain	High Risk	Low Risk	Low Risk
Li 2011[38]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Chen 2011[39]	High Risk	Uncertain	High Risk	Uncertain	High Risk	High Risk	Low Risk
Jiang 2011[40]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Jia 2011[41]	Uncertain	Uncertain	High Risk	Uncertain	Uncertain	Low Risk	Low Risk
Xin 2011[42]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Lu 2011[43]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Guo 2011[44]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Yu 2009[45]	High Risk	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Wu 2011[46]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Zhang 2010[47]	Low Risk	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Li 2019[48]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Peng 2011[49]	Uncertain	Uncertain	High Risk	Low Risk	Low Risk	Low Risk	Low Risk
Zhang 2011[50]	Low Risk	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Gao 2011[51]	Uncertain	Uncertain	High Risk	Uncertain	High Risk	High Risk	Low Risk
Chen 2010[52]	Low Risk	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Guo 2010[53]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Yuan 2010[54]	Low Risk	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Zhao 2009[55]	High Risk	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk
Li 2012[56]	Uncertain	Uncertain	High Risk	Uncertain	Low Risk	Low Risk	Low Risk

lack of participant blinding. Outcome assessor blinding was not mentioned in most studies, posing an uncertain risk of detection bias. All studies referred to randomization; however, only 2 trials reported the use of computer-generated randomization, while the remaining studies did not report details of randomization. Furthermore, description of randomization and allocation concealment were unclear in many studies and thus had uncertain selection bias. Most studies accounted for all study subjects by reporting a consistent number of subjects in outcome data as number enrolled and thus had a low risk of attrition bias. Most studies reported no statistical differences in baseline characteristics between compared groups and were thus considered to be low risk under the predefined other bias category. We have reported the risk of bias assessment for each study in Table 3 and the overall quality results in Figure 2.

Adverse Events

Five studies did not mention AEs. Seven studies reported no AEs with use of CheeZheng PRP. Of the 10 studies with reported AEs, 4.8% of participants experienced localized application-site redness, pain, itchiness, or blistering of the skin that resolved after discontinuation of plaster.

Discussion

Poorly addressed chronic pain leads to debilitating physical symptoms and psychosocial issues that can significantly affect quality of life, lower adherence to treatment, and incur higher health care costs. This is the first systematic review of 22 RCTs spanning 2556 participants to evaluate the clinical effectiveness and safety of an herbal-based topical analgesic for the treatment of OA. When compared to NSAIDs and intraarticular treatments, CheeZheng PRP was found to be superior in reducing the VAS pain score and improving joint stiffness and function. Furthermore, overall, PRP was well tolerated with 4.8% of reported AEs demonstrating localized dermatitis that resolved on discontinuation of the patch. Comparably, incidence of application-site irritation for other commonly used topical analgesics such as diclofenac is 7.7% to 36%.[57-59]

There is currently a paucity of novel therapeutic approaches that effectively treat chronic pain among cancer patients. Although pharmaceutical advancements have improved pain management, many are limited by significant side effects. Furthermore, prevalent opioid use has led to rising rates of abuse and overdose.[60-62] As cancer and its treatments leave patients in a higher state of fragility, therapeutic safety is of particular concern when treatments are used long-term to treat chronic and degenerative pain conditions. The US Food and

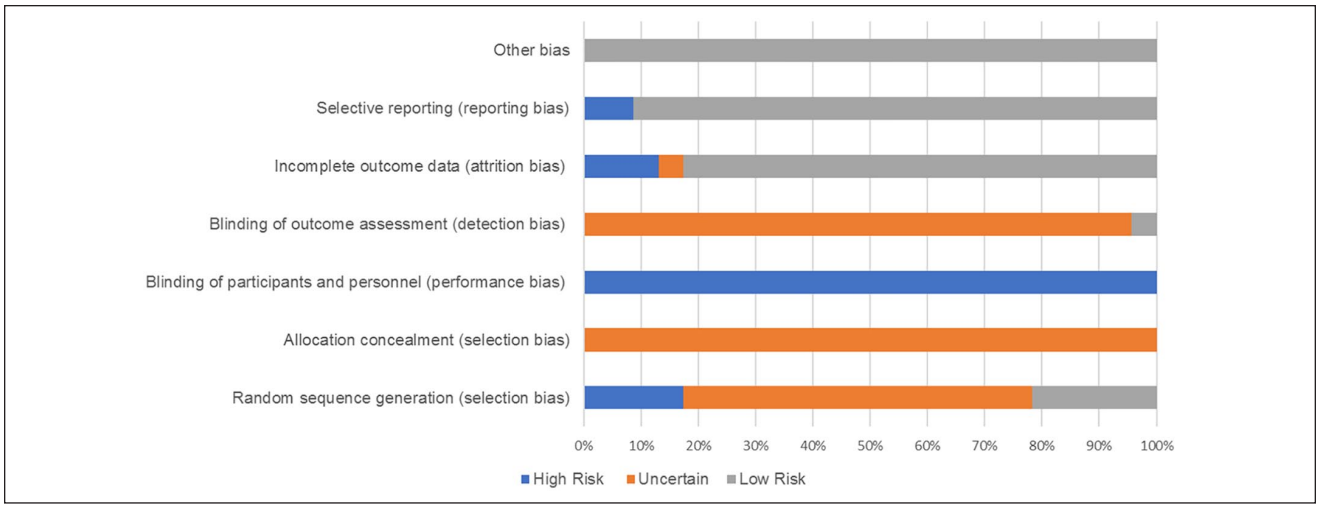

Figure 2. Cochrane risk of bias assessment.

Drug Administration has strengthened its warning about the cardiovascular risks associated with NSAIDs, particularly in cases of long-term use. As patients in the survivorship population often have multiple comorbidities, systematic adverse effects such as renal and cardiovascular toxicity could pose a significant risk in this patient group. An herbal topical analgesic that avoids these safety concerns could address the need for a safer and more targeted approach to pain management for cancer patients.

This review found that PRP has promising clinical effect for managing musculoskeletal pain such as OA with limited toxicity. Although the etiology of musculoskeletal pain in cancer patients can be multi-factorial and more complex than OA, there is an underlying component of inflammation that applies in both cases. Chronic low-grade inflammation mediated through pro-inflammatory factors and chemokines contributes to OA development and progression.[63,64] Residual tissue damage caused by cancer and its treatments (chemotherapy, radiation, and surgery) elicits somatic musculoskeletal pain in patients by inciting inflammation and stimulating nociceptive receptors in the injured bone, muscle, ligaments, and joints.[2,4,6] Preclinical research investigating the mechanistic action of PRP suggests that it inhibits nociceptive response and reduces inflammation.[20,21] One in vivo study demonstrated that application of PRP for 5 hours led to lower blood flow velocity and less edema compared to control in ear pinna of rabbits with soft tissue injury.[21] On the molecular level, CheeZheng PRP was also shown to significantly reduce levels of proinflammatory cytokines TNF-α, IL-1B, COX-2, and 5-LOX in macrophages in vitro.[65] This plausible biological mechanism along with the clinical effectiveness demonstrated through the included studies provides a basis for further clinical and translational research to optimize PRP for pain management in cancer patients.

Our systematic review identified several limitations that need to be addressed with future research. The lack of a placebo control as well as insufficient descriptions of the randomization process posed potential risk of bias across studies. Appropriate randomization is imperative, as it generates comparable groups and prevents selection bias.[66,67] Furthermore, future clinical trials should incorporate a placebo control and exclude individuals with skin sensitivities to adhesives or plant extracts to better estimate a safety profile for CheeZheng PRP. Finally, variability in outcome assessments can hinder establishment of a true efficacy for a treatment, which should be addressed with the incorporation of standardized outcome assessment in future trials to establish a true efficacy for PRP.[68] Collectively these considerations led us to conclude that the quality of the studies are moderate at best, and a meta-analysis would not provide clinically meaningful insight into the effect size.

Conclusion

Safety concerns associated with chronic analgesic use along with prevalent opioid abuse pose significant challenges for appropriate pain management in cancer patients. This phenomenon encourages the exploration of herbal therapeutics as a safe and effective way to address pain for cancer patients. In this systematic review, we found that an herbal topical agent CheeZheng PRP has promising clinical effects for managing musculoskeletal pain with minimal AEs. Future rigorously designed placebo-controlled trials are needed to establish the definitive efficacy and safety of this product for pain relief in oncology populations.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The sponsor of this review article, Tibet CheeZheng Tibetan Medicine Co Ltd, was not involved in study design,

collection, analysis, or interpretation of data. The sponsor was also not involved in the writing of this review or the decision to submit it for publication.

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