

Efficacy, residual effectiveness and safety of diacerein in the treatment of knee osteoarthritis

A meta-analysis of randomized placebo-controlled trials

Guangting Li, MD^{a,d}, Zhongming Zhang, MD^a, Yingying Ye, MD^b, Huiping Li, BD^c, Hanwen Luo, PhD^b, Kaijiang Tang, MD^d, Yongrong Lai, PhD^{a,*}

Abstract

Background: Osteoarthritis (OA) is the leading cause of disability in the elderly. Prevention and treatment of OA have become an urgent global demand. The pharmacologic role of diacerein in the treatment of osteoarthritis is controversial. We systematically reviewed the efficacy, safety, and residual effectiveness of diacerein.

Objectives: To estimate the symptomatic efficacy, residual effect and safety of diacerein in the treatment of knee osteoarthritis, using a meta-analysis of published randomized controlled trials (RCTs).

Methods: On December 1, 2021, we searched PubMed Medline, Web of Science, Cochrane Library databases, Wan Fang Medical Database, and National Knowledge Infrastructure. This study followed the inclusion criteria of the principle P(Population), I(Intervention), C(Comparison), O(Outcome), S (Study design) principle. All studies were randomized controlled trials of knee osteoarthritis. Cochrane bias risk assessment tool was used to assess the risk of bias. Meta-analyses were performed using a random-effects model. To explore sources of heterogeneity, subgroup analysis, sensitivity analysis, regression analysis and publication bias analysis were performed. Drug side effects with complete data were extracted from the included articles and then a combined analysis of these data was performed.

Results: Eight studies were eligible and were included in our analysis (N = 1277 participants). All studies were randomized controlled trials of knee osteoarthritis. There was no significant difference in reduction of joint pain and improvement of function between diacerein and the control group. However, subgroup analysis suggested, compared with the placebo group, diacerein treatment yielded an improved mean reduction in visual analogue scale score of -0.44% (95% confidence interval [CI]-0.79 to 0.09), an improved the western Ontario and McMaster universities (physical function) score of -0.44% (95% CI-0.72 to -0.12). Follow-up analysis after discontinuation showed that diacerein treatment had a significant residual effect (95% CI-0.81 to -0.24). Data on drug side effects described in the included articles were extracted for statistical analysis. There was an increased risk of diarrhea with diacerein (Risk Ratio [RR] = 1.95 [1.03 to 2.47]) and withdrawal event from therapy (RR = 0.93 [0.75 to 1.15]).

Conclusion: Diacerein might be considered an effective drug for the treatment of patients with KOA, showing short-term residual effectiveness. Although it is associated with an increased risk of diarrhea, the adverse event is mostly tolerable.

Abbreviations: CI = confidence interval, NSAIDs = Non-steroidal anti-inflammatory drugs, OA = osteoarthritis, RCT = randomized controlled trial, RR = Risk Ratio, SMD = standardized mean difference, VAS = visual analogue scale, WOMAC = the western Ontario and McMaster universities.

Keywords: diacerein, knee, meta-analysis, NSAIDs, osteoarthritis

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The datasets generated during and/or analyzed during the current study are publicly available.

This systematic review and meta-analysis do not require ethics approval as it does not collect any primary data from patients.

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^a Department of Hematology, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China, ^b Department of Joint Osteopathy, The Fourth Affiliated Hospital of Guangxi Medical University, Liuzhou, Guangxi, China, ^c Department of Outpatient, Liuzhou People's Hospital, Liuzhou, Guangxi, China, ^d Department of Rheumatology and Immunology, The Fourth Affiliated Hospital of Guangxi Medical University, Liuzhou, Guangxi, China.

* Correspondence: Yongrong Lai, Department of Hematology, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530000, China (e-mail: laiyongrong@hotmail.com).

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1. Introduction

Osteoarthritis (OA) is a progressive disorder of synovial joints of the hand, knee, and hip, especially knee osteoarthritis most affects the quality of life and work of patients. The main clinical manifestations are joint pain, short-term morning stiffness, and limited range of motion.^[1] Due to the prolonged life expectancy of human beings, the incidence of OA and the burden of OA have been increasing.^[2] It is common in adults > 65 years old and is the main cause of global disability.^[3] Frustratingly, OA is incurable because there is presently no medication that can cease or reverse cartilage or bone loss.^[4] Globally, the age-standardized point prevalence and annual incidence rate of OA in 2017 were 3754.2 (95% UI 3389.4 to 4187.6) and 181.2 (95% UI 162.6 to 202.4) per 100 000, an increase of 9.3% (95% UI 8% to 10.7%) and 8.2% (95% UI 7.1% to 9.4%) from 1990, respectively.^[5] More than 700,000 primary TKRs (total knee replacements) and 330,000 primary THRs (total hip replacements) are done annually in the US.^[6] Model projections suggest that over 50% of persons in the US with symptomatic knee OA undergo TKR over their lifetimes.^[7] A significant number of patients with advanced KOA require knee arthroplasty and this procedure is expected to increase by 143% from 2012 to 2050.^[8] Persons with hip and knee OA have more than 20% excess mortality as compared with age-matched controls.^[6] Prevention and treatment of OA have become an urgent global demand.

At present, there is no very effective treatment method to improve the treatment of OA. Therefore, the main purpose is to relieve pain and prevent loss of function depending on the drugs treatments. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed drugs for the treatment of OA pain and are recommended as first-line drugs in various guidelines.^[9] However, NSAIDs cause serious gastrointestinal and vascular adverse events,^[10] and will not improve articular cartilage damage. After the drug is stopped, joint pain is prone to relapse, and the side effects become more obvious with longer use. Disease-modifying OA drugs need to be strengthened in research to slow down disease progression and reduce the patients' symptoms. There are many pieces of evidence that diacerein has both asymptomatic and a structural effect on cartilage, and clinical trials indicate that diacerein therapy significantly decreases OA symptoms when compared to placebo, and diacerein is comparable to analgesic effects of NSAIDs.^[11] However, another article pointed out that diacerein might lead to a slight reduction in pain but probably won't improve functionality among patients with knee osteoarthritis and can frequently present diarrhea as an adverse effect.^[12] There was a meta-analysis article published in 2010 of diacerein in the treatment of osteoarthritis, but the studies included in this article were relatively heterogeneous.^[13] For example, combined analysis of data for 3 years of treatment and 2 or 3 months of treatment, the intervention group has combined drugs, compared hand osteoarthritis with knee osteoarthritis.

However, the overall impact varies across studies, showing heterogeneity. Due to the existing meta-analysis of diacerein in the treatment of osteoarthritis, the clinical efficacy is inconsistent, and the heterogeneity of different trials on the effect size has not been fully resolved. Whether diacerein has sequelae effects is controversial. Therefore, the question of this paper was formulated in view of the different studies reported on RCT of diacerein in the treatment of knee osteoarthritis. We conducted a systematic review and meta-analysis of all available randomized controlled trials (RCTs) to determine the efficacy, safety, and residual effects of diacerein on KOA.

2. Methods

Reporting was guided by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The entire review process (study selection and risk-of-bias

assessment) was undertaken using the Cochrane bias risk assessment tool.^[14]

2.1. Data sources and search strategies

We searched Medline, Web of Science, Cochrane central register of controlled trials (CENTRAL), Wan Fang medical database, and national knowledge infrastructure. No retrieval date restrictions were applied, while the end date for the search was December 1, 2021. We did not obtain target data for some conference abstracts during the retrieval process when we tried to contact the author via email. The language of the studies in the literature search was restricted to English and Chinese. The complete search used for PubMed was: (Osteoarthritis [MeSH Terms] OR osteoarthrosis [Text Word] OR degenerative arthritides [Text word] AND diacetylrhein [MeSH Terms] OR diacerein [Text word]). In addition, we did not use any methodological search filters, aiming to increase comprehensiveness.

2.2. Selection of studies

Firstly, we set keywords, such as diacerein, Osteoarthritis, knee joint, randomized, double-blind, controlled trial. And then 2 reviewers conducted a preliminary screening of the search results in terms of titles and abstracts (GL, YY). In this step, the standards related to the aftereffects and adverse reactions of the drug after drug withdrawal are not considered, because studies that mainly focus on the therapeutic effect may not report data on the aftereffects and adverse reactions of the drug in the abstract; therefore, all trials that only mention effect information are retrieved in this step. After this step, the 2 investigators (GL and YY) continue to independently evaluate the qualifications of the full-text article. The review authors recorded the reasons for the exclusion of rejected studies. All differences of opinion regarding the selection of articles between 2 review authors (GL and YY) were discussed until a consensus was achieved with the consultation of a third review author (YL) if needed.

2.3. Criteria for considering studies for this review

We included studies as follows: Including only randomized controlled trials; The intervention group trials diacerein as an intervention drug; Interventions in the control group were placebo or non-steroidal anti-inflammatory drugs; and Provide detailed visual analogue scale (VAS), the western Ontario and McMaster universities (WOMAC) evaluation data and side effects data after treatment.

We excluded reviews, case series, systematic reviews, and meta-analyses. We also excluded meeting abstracts or meeting minutes reports that cannot download the full text. Finally, we excluded studies in the intervention group that have combined anti-OA medications during the trial, except for paracetamol and acetaminophen during rescue treatment.

2.4. Data extraction

Two investigators (GL, YY) independently extracted the data and resolved disagreements by consensus. And the 2 investigators had a Kappa score of 0.8. We extracted the following data from the eligible studies: study characteristics: first author, year of publication, study design, age of the patients, number of patients, country of origin, demographic baseline variables, study duration, dosage, attrition, study objective and design; The core data of each study include the sample size of the control group and the intervention group, the evaluation value of the main outcome indicators, the number of adverse events in each group, the evaluation value of the follow-up at the end of the study, or the change score.

2.5. Assessment of methodological quality

Two review authors (HL, ZZ) independently and in duplicate assessed the methodological quality using the Cochrane bias risk assessment tool and solved disagreements by consensus. Any disagreement that could not be resolved by consensus was submitted to a third author (YL). The

following characteristics were evaluated^[15,16]:

- (1) Random sequence generation (selection bias).
- (2) Allocation concealment (selection bias).
- (3) Blinding of participants and personnel (performance bias).
- (4) Blinding of outcome assessment (detection bias).
- (5) Incomplete outcome data (attrition bias).

- (6) Selective reporting (reporting bias).
- (7) Other bias.

2.6. Statistical analysis and data synthesis

We used results from the ITT analysis if possible. Since the methods used to evaluate the knee joint VAS score and WOMAC score were different, the mean and standard deviation were quite a gap, we converted to standardized mean difference (SMD) for analysis. The risk ratio (RR) was used as the outcome measure for diarrhea and withdrawal events, as the RR is on average more consistent than the Risk

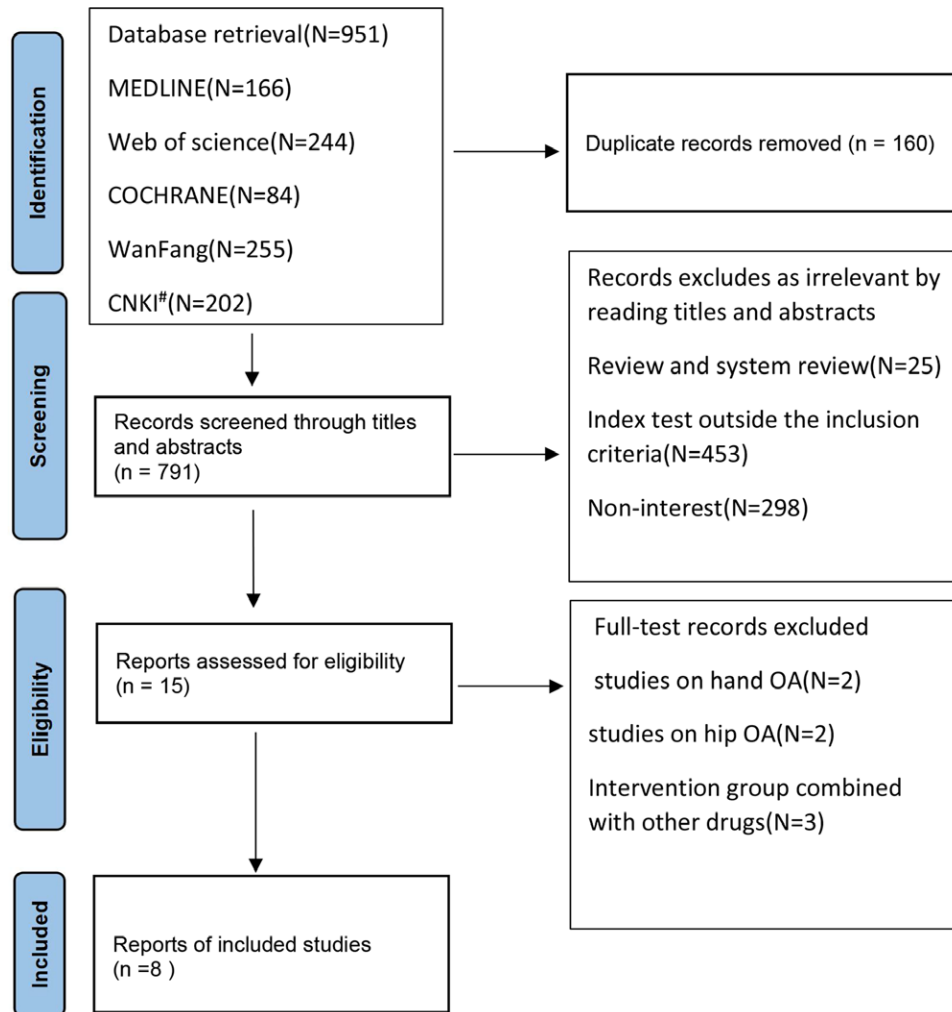


Figure 1. PRISMA flow diagram.

Table 1
Characteristics of eligible trials.

Study	Year	Age (yr)	Nt	Nc	Trial duration (mo)	Dose of diacerein	Control group	Outcomes indicators	Study design
Brahmachari, B	2009	49.3 ± 11.2	28	27	2	50 mg bid	Placebo	VAS/WOMAC/AE	RCT
Pelletier, JP	2000	64.4 ± 8.3	80	80	4	50 mg bid	Placebo	VAS/AE	RCT
Zheng, WJ	2006	58.8 ± 8.5	106	107	3	50 mg bid	Diclofenac 25mg tid	VAS/WOMAC/AE	RCT
Pavelka, K	2007	63.6 ± 8.2	82	83	3	50 mg bid	Placebo	VAS/WOMAC/AE	RCT
Louthrenoo, W	2007	54.0 ± 6.6	82	79	4	50 mg bid	Piroxicam	VAS/WOMAC/AE	RCT
Pelletier, JP	2020	63.9 ± 6.3	140	148	6	50 mg qd/first month; then, 50 mg bid	Celecoxib 200 mg QD	VAS/WOMAC/AE	RCT
Chen, EH	2015	56.5 ± 5.5	18	18	3	50 mg qd/first month; then, 50 mg bid	Celecoxib 200 mg qd	VAS/AE	RCT
Ye, FT	2015	40–65	180	180	4	50 mg bid	Piroxicam	VAS/AE	RCT

bid = twice a day, Nc = no. of control group, Nt = no. of diacerein treatment group, qd = once a day, RCT = randomized controlled trial, WOMAC = the western Ontario and McMaster universities.

Difference. Due to the expected large differences between the experimental results, the random-effects model was used for meta-analysis, and the statistical heterogeneity was analyzed considering the I^2 generated by STATA software (12.0 version)($I^2 < 50\%$: low to moderate; $I^2 \geq 50\%$: substantial;

$I^2 > 75\%$ considerable heterogeneity). The results were shown in a forest plot. For the analysis of heterogeneity, subgroup analysis, sensitivity analysis, regression analysis and publication bias analysis were carried out on the main indicators.

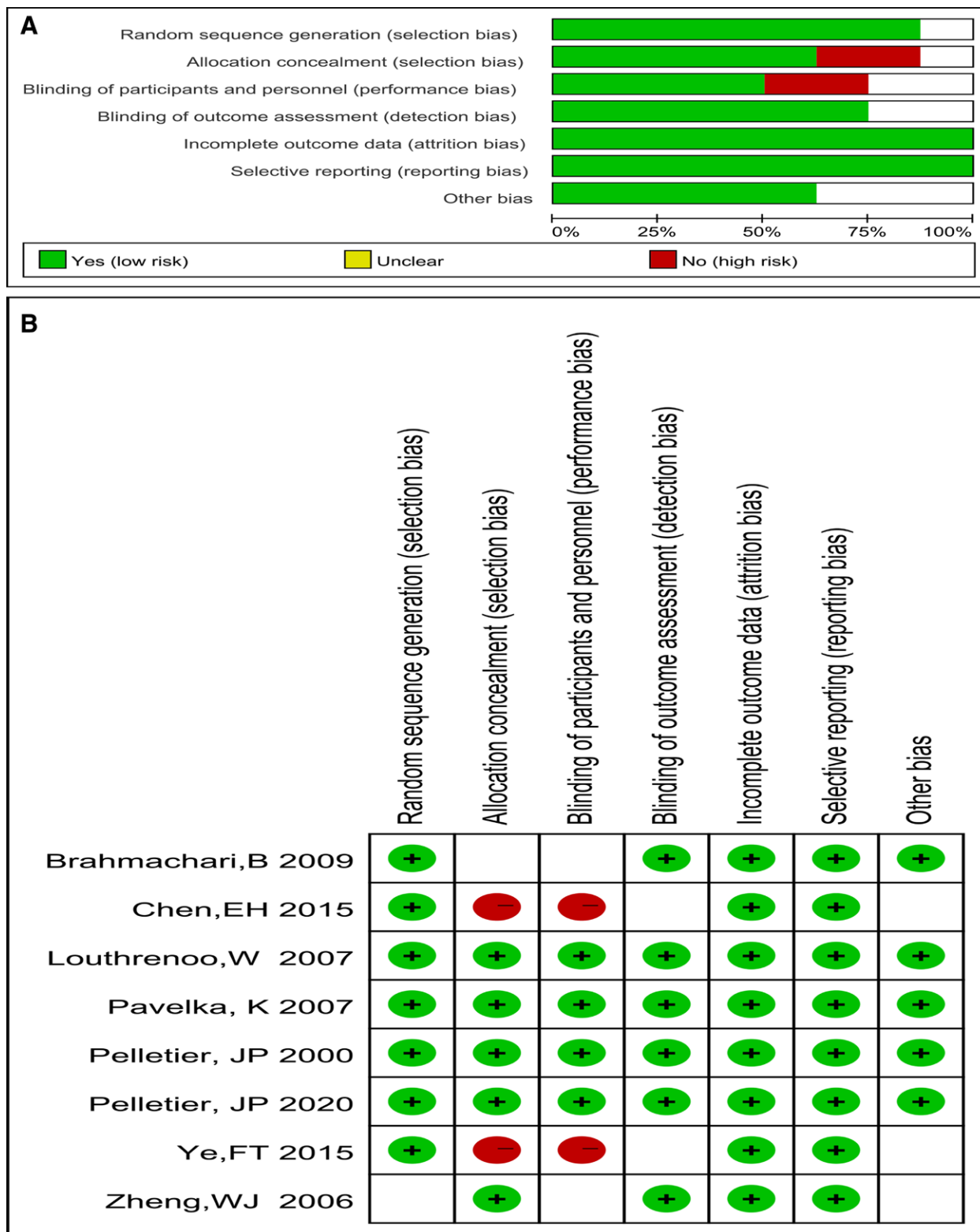


Figure 2. Risk of bias for the studies included in the meta-analysis. (a) Risk of bias graph. (b)Risk of bias summary.

3. Results

3.1. Results of the search

An overview of our literature search is shown in Figure 1. The literature search identified 791 references after the removal of duplicates. The search of conference abstracts did not yield any effective study data. Through an initial selection of titles and abstracts, we evaluated 15 references for full text. We retrieved the full texts of the remaining 15 studies and assessed them for eligibility. Ultimately, 8 studies that were eligible according to the inclusion criteria provided data for the review. Non-inclusion and exclusion in the full-text screening stage of the reasons are outlined in the PRISMA flow diagram provided in Figure 1.

3.2. Characteristics of included studies

We included a total of 8 studies and 1277 patients in the qualitative analysis. The main characteristics of the included studies are summarized in Table 1. The included studies were published between 2000 and 2020. Three studies were published after 2015,^[17-19] and 5 pieces of literature were published before 2010.^[20-24] All studies are randomized controlled trials on knee osteoarthritis. The intervention group uses diacerein alone for the intervention study, and the control group uses placebo or non-steroidal anti-inflammatory drugs. The intervention time included in the studies was 2 to 6 months, and at least 1-month follow-up was carried out after stopping the drug.

3.3. The methodological quality of the included studies

We appraised the quality of the studies using the Cochrane bias risk assessment tool. We concluded the overall risk of bias and applicability concerns of the studies in Figure 2. Since the article does not describe in detail allocation concealment and double-blind implementation, we judged the risk of bias of patient selection (Cochrane bias risk assessment, domain 2,3) to be high in 2 studies.^[17,18] Regarding the reference standard assessment (Cochrane bias risk assessment, domain 7), we considered 4 studies to be at unclear risk of bias because there is not enough information to explain.^[17,18,20,24] Finally, Regarding the Cochrane bias risk assessment tool, there are 4 studies with detailed information, and all evaluated items are rated as low-risk.^[21-23,25]

3.4. Efficacy

In a summary analysis of the VAS scores of all 8 trials, diacerein in the intervention group was not statistically significant compared with the control group (SMD -0.97, 95% confidence interval [CI] -0.27 to 0.13, I^2 68.2%), with statistically significant between-study heterogeneity, but the subgroup analysis showed that the intervention group was significantly better than the placebo group in reducing pain (SMD -0.44, 95%CI -0.79 to -0.09, I^2 60.6%) (Fig. 3a). Compared with NSAIDs, the VAS score after diacerein treatment is not statistically significant. Subgroup analysis suggests that the placebo group's I^2 is 60.6%, the NSAIDs group's I^2 is 0%, speculated that the intervention is a possible source of heterogeneity. Further sensitivity analysis with no signifying between-study heterogeneity (95%CI -0.31 to 0.1) (Fig. 4a). The WOMAC (physical function) score of diacerein compared with placebo or NSAIDs for knee osteoarthritis is similar to the VAS score (Fig. 3b).

A pooled analysis of 5 studies that evaluated the follow-up VAS scores of patients in the intervention group after treatment stopped showed that compared with the control group, the pain scores of the intervention group patients were significantly lower, which was statistically significant, with the heterogeneity between the studies was statistically significant (SMD -0.53, 95%CI -0.81 to -0.24, I^2 76.6%) (Fig. 3c). Further sensitivity

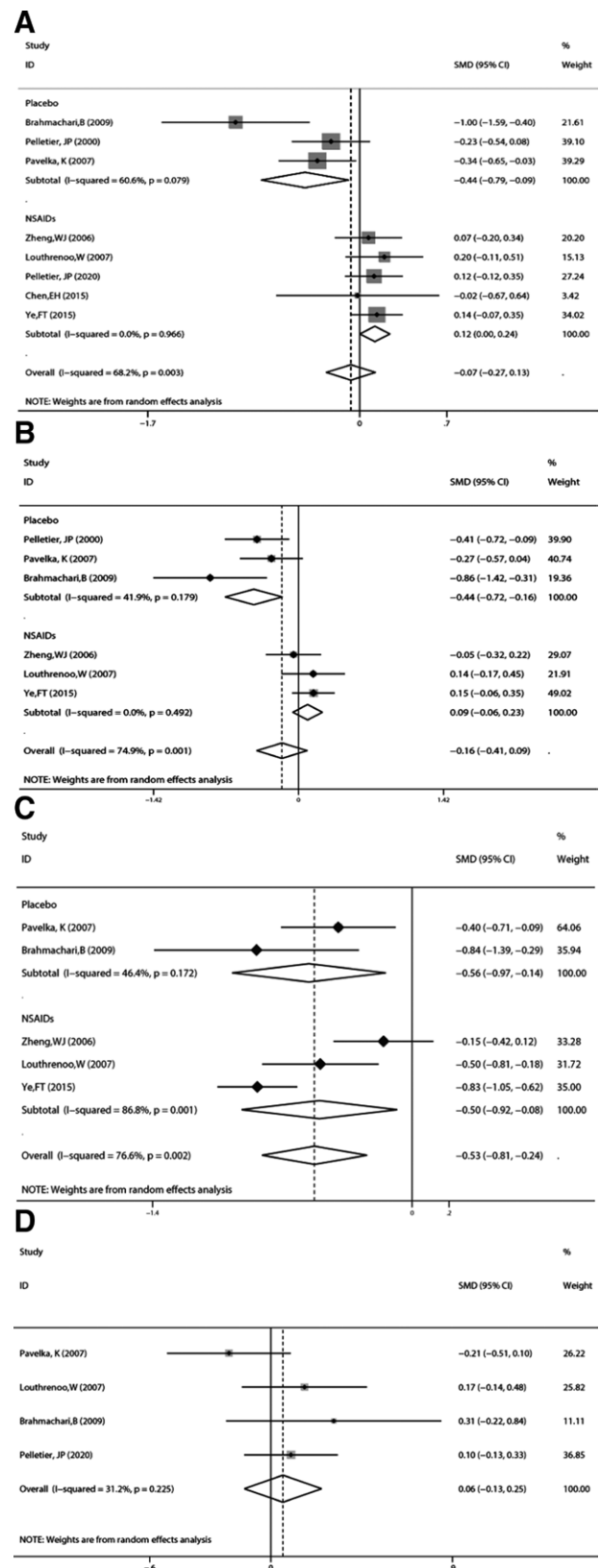


Figure 3. Meta-analyses of diacerein treatment versus placebo or NSAIDs, comparing VAS score and WOMAC (physical function and stiffness) score. Outcomes assessed are (a)VAS score at the end of treatment, (b) WOMAC (physical function) score at the end of treatment, (c) VAS score at discontinuation follow-up, and (d) WOMAC (stiffness) score at the end of treatment. For each estimate, the gray shaded area is the weight of the estimate in proportion to the overall effect. NSAIDs = Non-steroidal anti-inflammatory drugs, WOMAC = the western Ontario and McMaster universities.

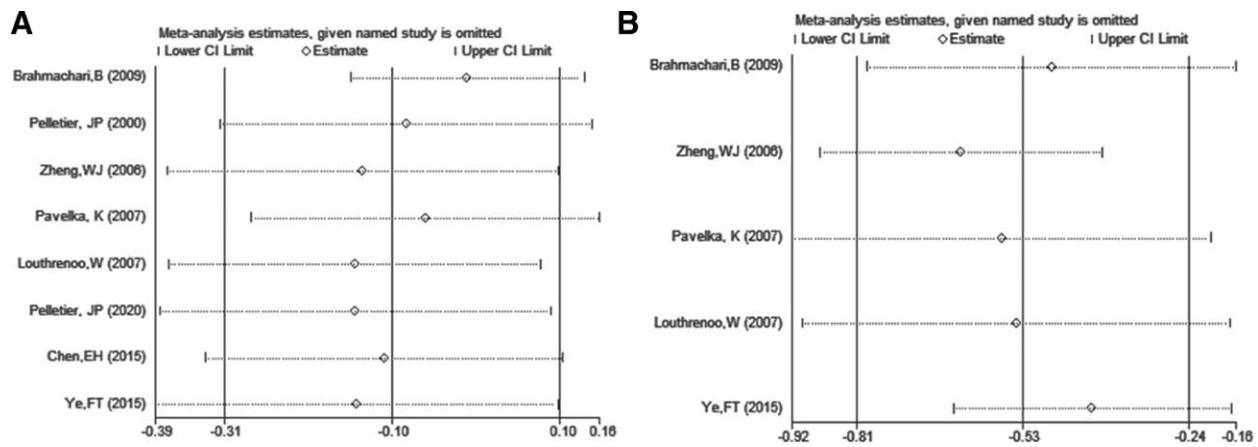


Figure 4. (a) Sensitivity analysis of VAS score after treatment;(b) Sensitivity analysis of VAS score during follow-up.

analysis with no signifying between-study heterogeneity (95% CI -0.81 to -0.24) (Fig. 4b). Then we performed regression analysis and publication bias, both of which were not statistically significant (Figure S1, Supplemental Digital Content, <http://links.lww.com/MD/H896> and Table 2).

To summarize and compare the WOMAC stiffness scores of 4 studies on treatment, the 2 groups were not statistically significant (SMD 0.06, 95% CI -0.13 to 0.25, I^2 31.2%) (Fig. 3d). The heterogeneity test I^2 was 31.2%. (Figure S2, Supplemental Digital Content, <http://links.lww.com/MD/H897>).

3.5. Safety

The side effects reported in the included studies included diarrhea, abdominal pain, dyspepsia, dizziness, urine color changes, and edema. Among these side effects, diarrhea was obvious, and the included literatures had relatively complete data on diarrhea. In this paper, relatively complete data such as diarrhea and withdrawal events due to drug side effects were selected for pooled analysis. Six studies (N = 1423 participants) evaluated the relative risk of any diarrhea event during treatment. The data of these studies showed that compared with the control group, the RR (95% CI 1.03 to 2.47) of diacerein treatment was significantly different, and the heterogeneity between the studies was statistically significant (Fig. 5a). Subgroup analysis showed that the heterogeneity of the NSAIDs group was relatively high. Six studies (N = 1242 participants) evaluated the relative risk of withdrawal event during the trial. The data of these studies showed that compared with the control group, the RR (95% CI 0.75 to 1.15) of diacerein treatment was not significantly different, and the heterogeneity between the studies was not statistically significant (Fig. 5b).

4. Discussion

Our research results show that compared with placebo, diacerein treatment of knee osteoarthritis can significantly relieve pain and improve joint physical function. Diacerein has the same effect as NSAIDs in relieving knee pain and improving joint function. In addition, compared with NSAIDs or placebo groups, diacerein treatment has sequelae effects. Therefore, these data supported that diacerein might be used as an effective drug for the treatment of knee osteoarthritis and may be recommended as an alternative therapy to NSAIDs.

In the management of osteoarthritis, the realization of the goals of relieving joint pain and maintaining joint function is limited by existing treatment methods.^[26] With the use of NSAIDs (such as diclofenac sodium, celecoxib), the risk of gastrointestinal diseases and cardiovascular adverse events will

Table 2

Regression analysis of VAS score during follow-up.

ES	Coef.	Std. Err.	t	P	95% CI	Adj R ²
Drug	-0.074	0.324	-0.23	0.83	-1.11 0.958	-40.92%
Trials duration	-0.37	0.73	-0.51	0.84	-2.70 1.95	-27.92%

CI, confidence interval, ES = effect size, VAS = visual analogue scale.

increase. Other drugs (such as glucosamine) have no obvious anti-inflammatory and pain relief effects, due to inflammation being considered to have an important role in the pathogenic and development of osteoarthritis.^[27] The common structural characteristics of osteoarthritis are cartilage degradation, subchondral bone remodeling, osteophyte formation, and changes in the synovium and joint capsule. Recent studies have highlighted the involvement of immune cells and inflammatory cytokines in the development and progression of osteoarthritis.^[28] Early release of inflammatory cytokines such as interleukin 1 β (IL-1 β), IL-6, TNF- α et cetera, induces activation of signaling pathways such as the activation of the nuclear factor kappa-light chain enhancer (NF- κ B) that activates B cells,^[29] phosphate inositol 3-kinase/protein kinase B (PI3K/AKT),^[30] and mitosis-activated protein kinase (MAPK), which in turn leads to the release of more inflammatory molecules to induce the release of collagenase-like matrix metalloproteinase, which mediates the degradation of the extracellular matrix and changes the anatomy and physiological function of the joint.^[31] Finding drugs that have anti-inflammatory effects and protect joint function has become an urgent problem in clinical work. Diacerein has been shown to inhibit the production and activity of the cytokine interleukin-1 (IL-1) in vitro and in vivo, thereby protecting cartilage.^[32-34] A further potential advantage of using diacerein in OA treatment is that diacerein does not cause gastrointestinal mucosal damage and cardiovascular events. Osteoarthritis is characterized by long-term recurring pain and irreversibility and requires long-term anti-inflammatory treatment.^[4] Diacerein has been postulated as a novel strategy that can potentially reconcile this management by inhibiting IL-1 while reducing joint pain.

As shown in Figures 3 and 4, we conducted a meta-analysis, compared with the control group, the VAS score and WMOAC (physical function) score of the diacerein group had not significantly reduced during the treatment period, with statistically significant between-study heterogeneity. We conducted a subgroup analysis and discovered that compared with the placebo group, the VAS score and WMOAC (physical function) score of the diacerein group were significantly lower, and there was no difference from the NSAIDs group. The source of heterogeneity

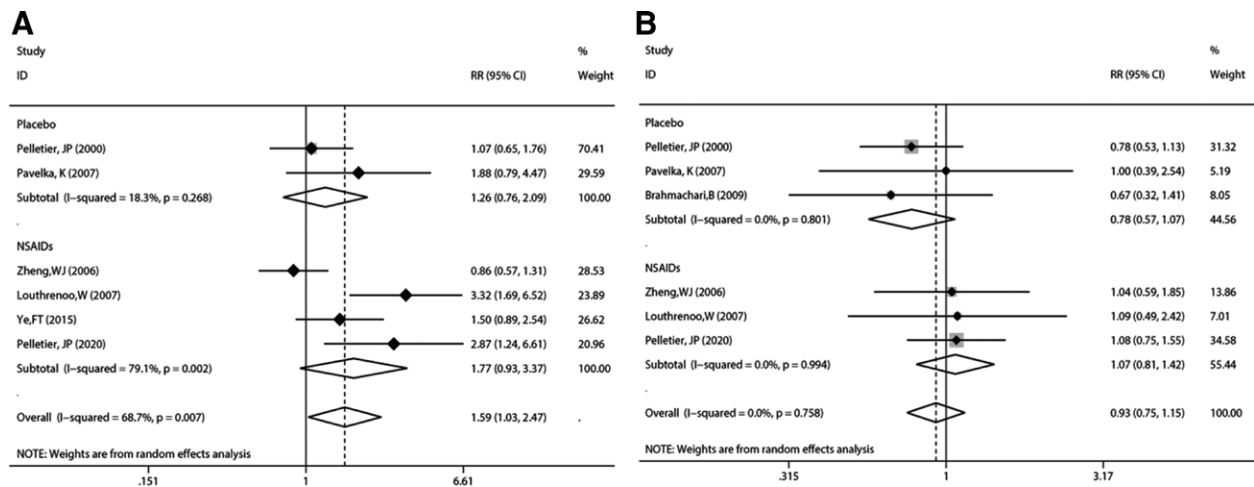


Figure 5. Meta-analyses of diacerein treatment versus placebo or NSAIDs, comparing diarrhea and withdrawal event. Outcomes assessed are (a) diarrhea, (b) withdrawal event. NSAIDs = Non-steroidal anti-inflammatory drugs.

may be the grouping factor. And then, the sensitivity analysis shows no significant difference, indicating that the results are relatively reliable. These results suggest that diacerein is as effective as NSAIDs in analgesia and joint function improvement and is better than placebo. As shown in Figure 3, combined analysis of 5 documents, our results suggest that the VAS score of diacerein is still better than the control group at the 1-month follow-up of drug withdrawal, suggesting that there is a sequelae effect. Although there is significant heterogeneity, the sensitivity analysis shows no significant difference. Subgroup analysis showed that whether compared with placebo or NSAIDs, diacerein reduced the VAS score better than the control group, and the results of the subgroup analysis were consistent with the results of the combined analysis. After the above analysis, we believe that the results are relatively reliable. Many studies^[9,35] have proved that NSAIDs have a significant analgesic effect in the treatment of osteoarthritis, and as the first-line drugs recommended by clinics and guidelines. The results of this study suggest that diacerein and NSAIDs have the same pain relief effect, and residual effect as diacerein, showing that the analgesic effect of diacerein is not only small. This is very beneficial for the management of osteoarthritis.

Meta-analysis indicated that diacerein does increase the risk of experiencing diarrhea. Although there is heterogeneity, the results of these documents tended to be consistent. We noticed that none of the studies attempted to characterize or grade reported loose stools (frequency, water sample/formation, severity, prognosis, etc.). However, the included literature suggested that most of the adverse reactions were mild to moderate, and there were no serious adverse reactions. Researching on withdrawal events found that there was no statistical significance.

A limitation of this analysis is that the long-term durability of diacerein treatment is uncertain; included trials ranged in duration from 2 months to 6 months. Although a study confirmed that compared with placebo, treatment with diacerein for 3 years had a significant structural modification effect, coupled with good safety.^[36] We still need more research to explore the long-term effects of diacerein, whether it is RCT research or real-world research. Second, this meta-analysis is all included in RCT studies on knee osteoarthritis, which may be at risk of selection bias. Third, more studies are needed to determine the duration of the sequelae effects of long-term use of the diacerein.

5. Conclusion

There is moderate to high-quality of evidence that the use of diacerein in the treatment of patients with knee osteoarthritis

can relieve pain and improve joint function and shows a residual effect. However, the effect size was too small to be clinically significant. Further high-quality studies are needed to demonstrate the long-term efficacy, residual effect and safety of the diacerein.

Author contributions

Conceptualization: Guangting Li, Kaijiang Tang, Yongrong Lai.
Data curation: Guangting Li, Yingying Ye.
Formal analysis: Guangting Li, Kaijiang Tang.
Funding acquisition: Hanwen Luo.
Investigation: Guangting Li.
Software: Huiping Li.
Writing – original draft: Guangting Li, Yingying Ye.
Writing – review & editing: Zhongming Zhang, Huiping Li, Hanwen Luo.

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