Evidence-Based Complementary and Alternative Medicine

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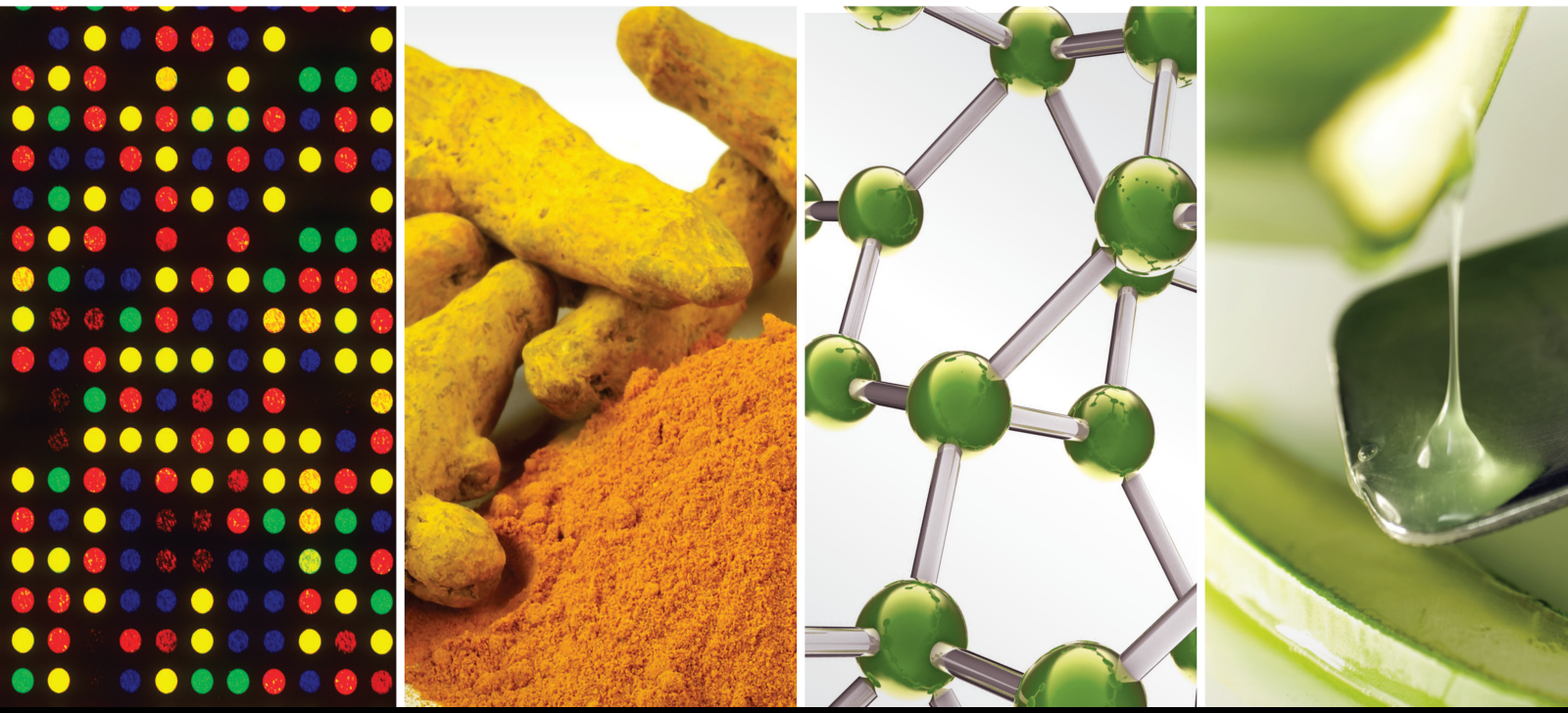

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Contents

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Review Article

The Efficacy and Safety of Zhengqing Fengtongning for Knee Osteoarthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Background. Zhengqing Fengtongning release tablet (ZQFTN) is a proprietary Chinese medicine preparation of sinomenine, the main active component of the traditional Chinese medicine (TCM) *Sinomenium acutum*. It is used in China as a complementary and alternative medicine (CAM) for knee osteoarthritis (KOA). The objective of this study was to evaluate the clinical efficacy and safety of ZQFTN in KOA treatment. *Method.* Randomized controlled trials of ZQFTN in KOA treatment were searched in PubMed, Cochrane Library, China National Knowledge Infrastructure, Chinese Scientific Journals Database, and Wanfang database. Two reviewers independently conducted the screening, extracted the data, and assessed the methodological quality. Statistical analysis was performed using RevMan 5.3 software. *Results*. Eighteen studies were assessed that included 1512 participants (757 in the treatment group and 755 in the control group). The results showed that compared with the control group, the Visual Analogue Scale (standardized mean difference (SMD) = −0.87, 95% confidence interval (CI): [−1.08, −0.66], $P < 0.001$), Western Ontario and Mc Master University (WOMAC) Osteoarthritis Index pain score (SMD = −0.67, 95% CI: [−0.88, −0.46], $P < 0.001$), WOMAC stiffness score (SMD = −0.53, 95% CI: [−0.86, −0.20], $P = 0.001$), WOMAC function score (SMD = −0.76, 95% CI: [−0.97, −0.55], $P < 0.001$), serum interleukin-1β level (SMD = −4.36, 95% CI: [−6.41, −2.31], $P < 0.001$), and serum tumor necrosis factor-α level (SMD = −8.45, 95% CI: [−11.20, −5.69], $P < 0.001$) of the ZQFTN treatment group were lower, and the total effective rate was higher relative risk ($RR = 1.15$, 95% CI [1.07, 1.23], $P < 0.001$). There was no significant difference in the incidence of adverse reactions between the two groups ($RR = 0.96$, 95% CI: [0.69, 1.35], $P = 0.82$). *Conclusion*. ZQFTN can effectively relieve knee pain, morning stiffness, and daily activity function disorders, reduce the expression of inflammatory factors in serum, and improve the total clinical response rate without increasing the incidence of adverse reactions. Therefore, ZQFTN has considerable potential as a CAM for KOA. However, due to the limitation of the quality of the included studies, the strength of this conclusion is affected. In the next step, multicenter, large sample, high-quality randomized controlled studies are needed to further confirm the present conclusion.

1. Introduction

Knee osteoarthritis (KOA) is a degenerative disease that occurs in the knee joint, with chronic joint pain, swelling, stiffness, and dysfunction as the main manifestations. With the increase in life expectancy and aging of the global population, its incidence is increasing and the burden on countries around the world is consequently becoming greater [1]. At present, the drugs used to treat KOA mainly include analgesics, intraarticular corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and symptomatic slow acting drugs for osteoarthritis (SYSADOA) [2–4].

Although these drugs have certain effects on the pain and disease relief of osteoarthritis (OA) patients, they also increase the incidence of gastrointestinal ulcers and cardiovascular events, affecting their use by some patients [5]. Therefore, the need for a safe and effective option for OA treatment has transferred the focus of research from conventional drugs to complementary and alternative medicines (CAMs). Over time, ever increasing evidence has shown that traditional Chinese medicine (TCM) therapies, including acupuncture, galbanum oil, sesame oil, and Qigong, have favorable therapeutic potential as CAMs in OA treatment [6–9].

TCM has a long history, has the advantages of an accurate curative effect, safety and stability, and is a major research topic in the treatment of many difficult diseases [10]. Sinomenine (chemical structure: C19H23NO4, Mw 329.18) is a monomer alkaloid extracted from the TCM *Sinomenium acutum*, which has anti-inflammatory, analgesic, and immunomodulatory effects [11–14]. It can be used in the treatment of musculoskeletal diseases, neuropathy, cancer, and other diseases [15–19]. At present, Zhengqing Fengtongning release tablets (ZQFTN), sinomenine tablets, and sinomenine hydrochloride injection are used clinically in China [20]. To date, many clinical studies have been reported on the treatment of KOA with ZQFTN [21–38], but there remains a lack of relevant evidence-based medical studies on its efficacy and safety. Because there is no systematic review of oral ZQFTN for KOA treatment, whether ZQFTN can be used as a CAM for clinical KOA treatment remains inconclusive, which complicates the clinician's decision. Therefore, we conducted a meta-analysis on the efficacy and safety of ZQFTN in KOA treatment using evidence-based medicine for guidance.

2. Materials and Methods

The systematic review protocol was developed with guidance from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and is registered in PROSPERO (CRD42021284282).

2.1. Search Strategy. Randomized controlled trials (RCTs) of ZQFTN in the treatment of KOA were searched in PubMed, Cochrane Library, China National Knowledge Infrastructure, Chinese Scientific Journals Database, and Wanfang database. The retrieval time is from a database construction to August 31, 2021. The retrieval strategy adopted the combination of subject words and free words. The key words were as follows: "Osteoarthritis" "knee osteoarthritis" "KOA" "Zhengqing Fengtongning release tablets" "Zhengqing Fengtongning" "Sinomenine," and "Sinomenium". The search strategy was as follows, taking PubMed as an example:

(1) "Osteoarthritis" [Title/Abstract] OR "knee osteoarthritis" [Title/Abstract] OR "KOA" [Title/Abstract]

(2) "Zhengqing Fengtongning release tablets" [Title/Abstract] OR "Zhengqing Fengtongning" [Title/Abstract] OR "Sinomenine" [Title/Abstract] OR "Sinomenium" [Title/Abstract]

(3) "Randomized controlled trial" [Title/Abstract] OR "random trials" [Title/Abstract] OR "Controlled clinical trial" [Title/Abstract]

(4) (1) and (2) and/or (3)

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria. The inclusion criteria were as follows: (1) Study type: RCTs, no language limitation. (2) Participants: patients should be clearly diagnosed with KOA. No restrictions on country, race, age, or gender. (3) Experimental group: in the treatment group, ZQFTN was taken orally alone or combined with other therapies. (4) Control group: any type of control group, including NSAIDs and SYSADOA among others. (5) Outcomes: total effective rate, Visual Analog Scale (VAS), Western Ontario and Mc Master University (WOMAC) Osteoarthritis Index, serum interleukin-1β (IL-1β) level, serum tumor necrosis factor-α (TNF-α) level, and adverse events.

2.2.2. Exclusion Criteria. The exclusion criteria were as follows:

(1) Repeated publications

(2) Full-text literature is not available

(3) Studies with incomplete data and information

2.3. Literature Screening and Data Extraction. Two reviewers (Zeling Huang and Xiao Mao) searched the literature and screened it independently according to the inclusion and exclusion criteria. We used standard data extraction methods to extract data. The basic information, sample characteristics, intervention measures, outcome, and other data, which were included in the article, were extracted by two reviewers (Zeling Huang and Xiao Mao). In the case of any inconsistency occurring in the result, this was further discussed by the two researchers or scrutinized by the third reviewer (Zhenqiang Hong).

2.4. Quality Assessment of the Included Studies. A bias risk assessment was conducted by two reviewers (Zeling Huang and Xiao Mao) based on the bias risk assessment tool recommended in the Cochrane manual [39, 40]. The details that were assessed were as follows: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) others. Make high risk, low risk, or unclear judgments for each item. Any disagreements were resolved by the third reviewer (Zhenqiang Hong).

2.5. Statistical Analysis. Review Manager (RevMan) (Computer program), version 5.3 (the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen,

Denmark, 2014), was used to analyze the collected clinical research data. The enumeration data were evaluated using the relative risk (RR) and 95% confidence interval (CI), and the measurement data were combined using the standardized mean difference (SMD) and 95% CI. Analysis was performed using a fixed or random effects model according to the heterogeneity. The percentage of heterogeneity in the study was determined by the I^2 statistic; if the $I^2 < 50\%$, the heterogeneity among the included studies was considered to be small and the fixed effect model was adopted. If $I^2 \geq 50\%$, the heterogeneity among the included studies was considered significant, and the random effect model was adopted [41]. Subgroup analysis was conducted according to different treatments in the treatment group, and sensitivity analysis was also used to analyze the sources of heterogeneity. A value $P < 0.10$ was considered to suggest statistical heterogeneity and prompted random effects modeling.

3. Results

3.1. Literature Search Results. We initially retrieved 341 articles (Figure 1). We subsequently removed 178 duplicate articles manually, leaving 163 articles. Of these 163 articles, 118 were excluded after reading the title and abstract. Of the remaining articles, two lacked full text, and 25 were excluded because they failed to meet the inclusion criteria for complete reading. The present study eventually included 18 articles [21–38].

3.2. Characteristics of the Included Studies. The study of all included papers was a single-center, randomized controlled trial undertaken in China. In total, there were 757 cases in the experimental group and 755 cases in the control group. Except for three studies [28, 31, 33] that did not indicate drug sources, ZQFTN in the other fifteen studies was all produced by Hunan Zhengqing Pharmaceutical Group Co., Ltd. (Huaihua, Hunan, China). The included studies on the ZQFTN dosage are not uniform. Six studies [25, 26, 28, 34, 37, 38] defined ZQFTN alone as the experimental group, with a total of 209 patients, while the control group used SYSADOA, with a total of 209 patients. In seven studies [22, 23, 27, 31–33, 35], ZQFTN combined with SYSADOA was defined as the experimental group, with 318 patients in total, and SYSADOA was used by the control group, with 315 patients in total. In three studies [21, 24, 29], ZQFTN combined with NSAIDs was defined as the experimental group, with a total of 145 patients, and NSAIDs were used by the control group, with a total of 146 patients. In two studies [30, 36], 85 patients were treated with ZQFTN combined with sodium hyaluronate injection as the experimental group, and 85 patients were treated with sodium hyaluronate injection in the control group. The characteristics of the included studies are presented in Table 1.

3.3. Methodological Quality of Included Studies. Most of the included studies were of low quality because of unclear randomization, inefficient allocation concealment, inadequate blinding, or described withdrawals and dropouts. Nine studies [24, 25, 30–33, 35–37] were grouped by the random number table method (low risk), and nine studies [21–23, 26–29, 34, 38] did not indicate a specific randomization method (unclear). Eighteen studies [21–38] did not implement allocation hiding (high risk) or blinding (high risk), while sixteen studies [23, 24, 26–38] had complete data (low risk). Because none of the eighteen studies had clinical trial registration in advance, the results of selective reporting were unclear, and none of the eighteen studies found other sources of bias (low risk). The risk of bias assessment is summarized in Figure 2.

3.4. Treatment Effects

3.4.1. Total Effective Rate. The total effective rate is an important indicator for assessing the effect of treatment, which is mainly based on the changes in the patient's clinical symptoms before and after treatment. A total of seventeen of the included studies reported the total effective rate, but their criteria for judging the treatment effect included the WOMAC score, Lequesne index, and hospital for special surgery knee score. To enhance the strength of the results, we only performed meta-analysis on the six studies that used WOMAC scores to determine the total effective rate, involving a total of 534 patients, with 267 in the experimental group and 267 in the control group. The results of heterogeneity analysis showed good homogeneity among the included studies ($P = 0.46$, $I^2 = 0\%$), and the fixed effect model was used for analysis. The results showed that the total effective rate of the experimental group was higher than that of the control group ($RR = 1.15$, 95% CI: [1.07, 1.23], $P < 0.001$). The analysis was divided into three subgroups according to different treatment methods of the experimental group. The results of the subgroup analysis showed that the total effective rate of ZQFTN alone was equivalent to that of SYSADOA alone (MD = 1.13, 95% CI: [0.99, 1.28], $P = 0.06$). The total effective rate of ZQFTN combined with SYSADOA was higher than that of SYSADOA alone (RR = 1.18, 95% CI: [1.07, 1.30], $P < 0.001$). The total effective rate of ZQFTN combined with NSAIDs was equivalent to that of NSAIDs alone (RR = 1.06, 95% CI: [0.85, 1.33], $P = 0.03$) (Figure 3).

3.4.2. VAS. Four studies [30, 31, 35, 38] reported a pain VAS after treatment, involving a total of 294 patients, 147 in the experimental group, and 147 in the control group. Heterogeneity analysis results showed good homogeneity among the included studies ($P = 0.17$, $I^2 = 40\%$), and the fixed effect model was used for analysis. Results showed that the VAS of the experimental group was lower than that of the control group after treatment (SMD = −0.87, 95% CI: [−1.08, −0.66], $P < 0.001$). The results of subgroup analysis showed that the VAS of ZQFTN alone was lower than that of SYSADOA after treatment (SMD = −0.83, 95% CI: [−1.28, −0.38], $P < 0.001$). The VAS of the ZQFTN combined with the SYSADOA group was lower than that of SYSADOA

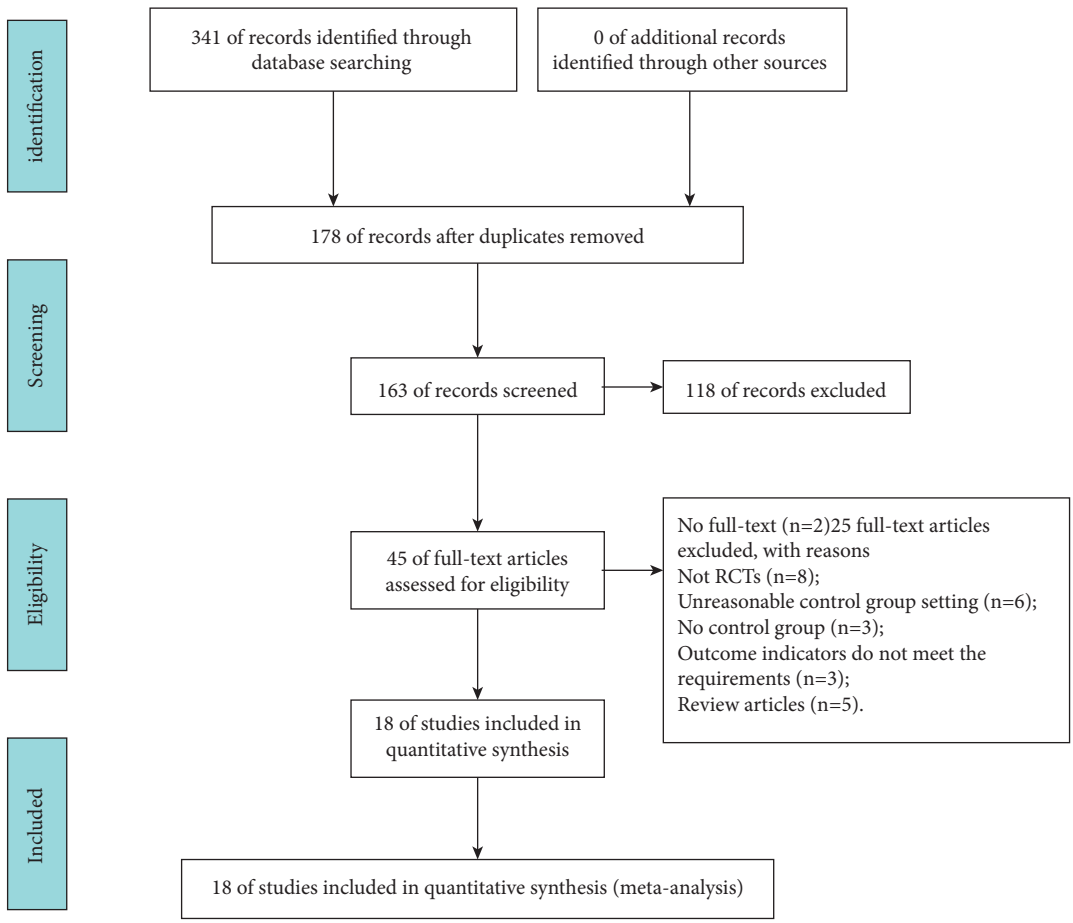

Figure 1: Process of searching and screening studies.

Table 1: Characteristics of the included studies.

Author, year	Sample size		Sex (male/female)		Age (years)		Treatment		Treatment cycle	Outcomes
	EG	CG	EG	CG	EG	CG	EG	CG		
Lin ZX, 2008 [21]	53	54	15/38	16/38	63.5 ± 8.7	65.7 ± 9.2	ZQFTN 120 mg bid + CG	Diclofenac sodium sustained-release tablets	6 months	TER, AE
Tang C, 2010 [22]	33	30	18/15	16/14	58.5 ± 8.3	59.8 ± 8.1	ZQFTN 60 mg bid + CG	Glucosamine sulfate capsules	6 weeks	TER
Liu YL, 2011 [23]	40	40	19/21	22/18	63 ± 8	62 ± 8	ZQFTN 60 mg tid + CG	Glucosamine hydrochloride capsules	3 months	TER, WOMAC, AE
Zhao HY, 2011 [24]	40	40	-	-	59.975 ± 11.077	61.200 ± 10.649	ZQFTN 120 mg bid + CG	Celecoxib	8 weeks	TER, AE
Xu YX, 2013 [25]	35	35	18/17	17/18	52	53	ZQFTN 60 mg bid	Diacerein capsules	8 weeks	TER, AE
Zhu FX, 2013 [26]	43	43	12//31	13/30	65.17 ± 8.73	64.93 ± 9.12	ZQFTN 60 mg bid	Glucosamine hydrochloride capsules	12 weeks	TER, WOMAC, IL-1β, TNF-α, AE
Zheng CE, 2014 [27]	40	40	11//29	9/31	60.8 ± 6.6	61.2 ± 5.8	ZQFTN 60 mg bid + CG	Glucosamine sulfate capsules	1 months	TER, AE

Table 1: Continued.

Author, year	Sample size		Sex (male/female)		Age (years)		Treatment		Treatment cycle	Outcomes
	EG	CG	EG	CG	EG	CG	EG	CG		
Liu QY, 2016 [28]	40	40	18/22	15/25	68.15 ± 7.8	65.28 ± 1.20	ZQFTN 60 mg bid	Glucosamine hydrochloride capsules	10 weeks	TER, WOMAC, IL-1β, TNF-α, AE
Wu B, 2017 [29]	52	52	36/16	34/18	62.19 ± 7.20	62.24 ± 7.15	ZQFTN 20 mg tid + CG	Meloxicam	4 weeks	TER, IL-1β, TNF-α, AE
Wang CC, 2017 [30]	45	45	16/29	18/27	49.59 ± 5.70	51.63 ± 5.12	ZQFTN 120 mg bid + CG	Sodium hyaluronate injection	10 weeks	VAS, TNF-α, AE
Luo HC, 2018 [31]	60	60	21/39	25/35	61.28 ± 10.12	59.97 ± 11.03	ZQFTN 60 mg bid + CG	Diacerein capsules	8 weeks	TER, VAS, WOMAC, AE
Luo HC, 2019 [32]	49	49	13/36	14/35	57.49 ± 10.52	59.92 ± 10.89	ZQFTN 60 mg bid + CG	Glucosamine hydrochloride capsules	12 weeks	TER, IL-1β, TNF-α, AE
Mi ZY, 2019 [33]	50	50	22/28	19/31	62.7 ± 5.3	60.9 ± 5.0	ZQFTN 60 mg bid + CG	Diacerein capsules	2 months	TER
Wang GL, 2019 [34]	30	30	16/14	17/13	32.2 ± 8.4	40.5 ± 8.2	ZQFTN 60 mg bid	Diacerein capsules	8 weeks	TER
Zhang Q, 2019 [35]	46	46	18/28	16/30	58.91 ± 5.63	58.72 ± 5.81	ZQFTN 120 mg bid + CG	Diacerein capsules	8 weeks	TER, VAS, AE
Zhang Y, 2019 [36]	40	40	22/18	21/19	52.6 ± 2.5	52.7 ± 2.4	ZQFTN 60 mg bid + CG	Sodium hyaluronate injection	5 weeks	TER, AE
Yang J, 2021 [37]	20	20	14//6	13//7	62.45 ± 4.25	62.50 ± 4.00	ZQFTN 60 mg tid	Glucosamine hydrochloride capsules	10 weeks	TER, AE
Yu Z, 2021 [38]	41	41	23/18	24/17	60.78 ± 8.51	61.42 ± 8.23	ZQFTN 120 mg bid	Diacerein capsules	3 months	TER, VAS, AE

EG: experimental group; CG: control group; -: not mentioned; ZQFTN: Zhengqing Fengtongning release tablets; TER: total effective rate; VAS: Visual Analog Scale; WOMAC: Western Ontario and Mc Master University Osteoarthritis Index; IL-1β: serum IL-1β level; TNF-α: serum TNF-α level; AE: adverse events.

alone after treatment (SMD = −0.72, 95% CI: [−1.00, −0.45], $P < 0.001$). The VAS of ZQFTN combined with sodium hyaluronate injection was lower than that of sodium hyaluronate injection alone after treatment (SMD = −1.30, 95% CI: [−1.76, −0.85], $P < 0.001$) (Figure 4).

3.4.3. WOMAC Pain Score. Four studies [23, 26, 28, 31] reported the WOMAC pain score after treatment, involving 366 patients (183 in the experimental group and 183 in the control group). Heterogeneity analysis showed good homogeneity among the included studies ($P = 0.90$, $I^2 = 0\%$), and the fixed effect model was used for the analysis. The results showed that after treatment, the WOMAC pain score in the experimental group was lower than that in the control group (SMD = −0.67, 95% CI: [−0.88, −0.46], $P < 0.001$). The results of subgroup analysis showed that the WOMAC pain score of ZQFTN alone was lower than that of SYSADOA after treatment (SMD = −0.60, 95% CI: [−0.91, −0.28], $P < 0.001$). The WOMAC pain score of ZQFTN combined with SYSADOA was lower than that of SYSADOA alone after treatment (SMD = −0.73, 95% CI: [−1.02, −0.45], $P < 0.001$) (Figure 5).

3.4.4. WOMAC Stiffness Score. Four studies [23, 26, 28, 31] reported the WOMAC stiffness score after treatment, involving 366 patients (183 in the experimental group and 183 in the control group). The results of the heterogeneity analysis showed that there was significant heterogeneity among the included studies ($P = 0.06$, $I^2 = 59\%$), and the random effect model was used to analyze the results. After treatment, the WOMAC stiffness score in the experimental group was lower than that in the control group (SMD = −0.53, 95% CI: [−0.86, −0.20], $P = 0.001$). Subgroup analysis showed that there was no significant difference in the WOMAC stiffness score between the ZQFTN and SYSADOA groups after treatment (SMD = −0.24, 95% CI: [−0.55, −0.06], $P = 0.12$). The WOMAC stiffness score of ZQFTN combined with SYSADOA was lower than that of SYSADOA alone after treatment (SMD = −0.82, 95% CI: [−1.10, −0.53], $P < 0.001$) (Figure 6).

3.4.5. WOMAC Function Score. Four studies [23, 26, 28, 31] reported the WOMAC function score after treatment, involving 366 patients (183 in the experimental group and 183 in the control group). Heterogeneity analysis showed good

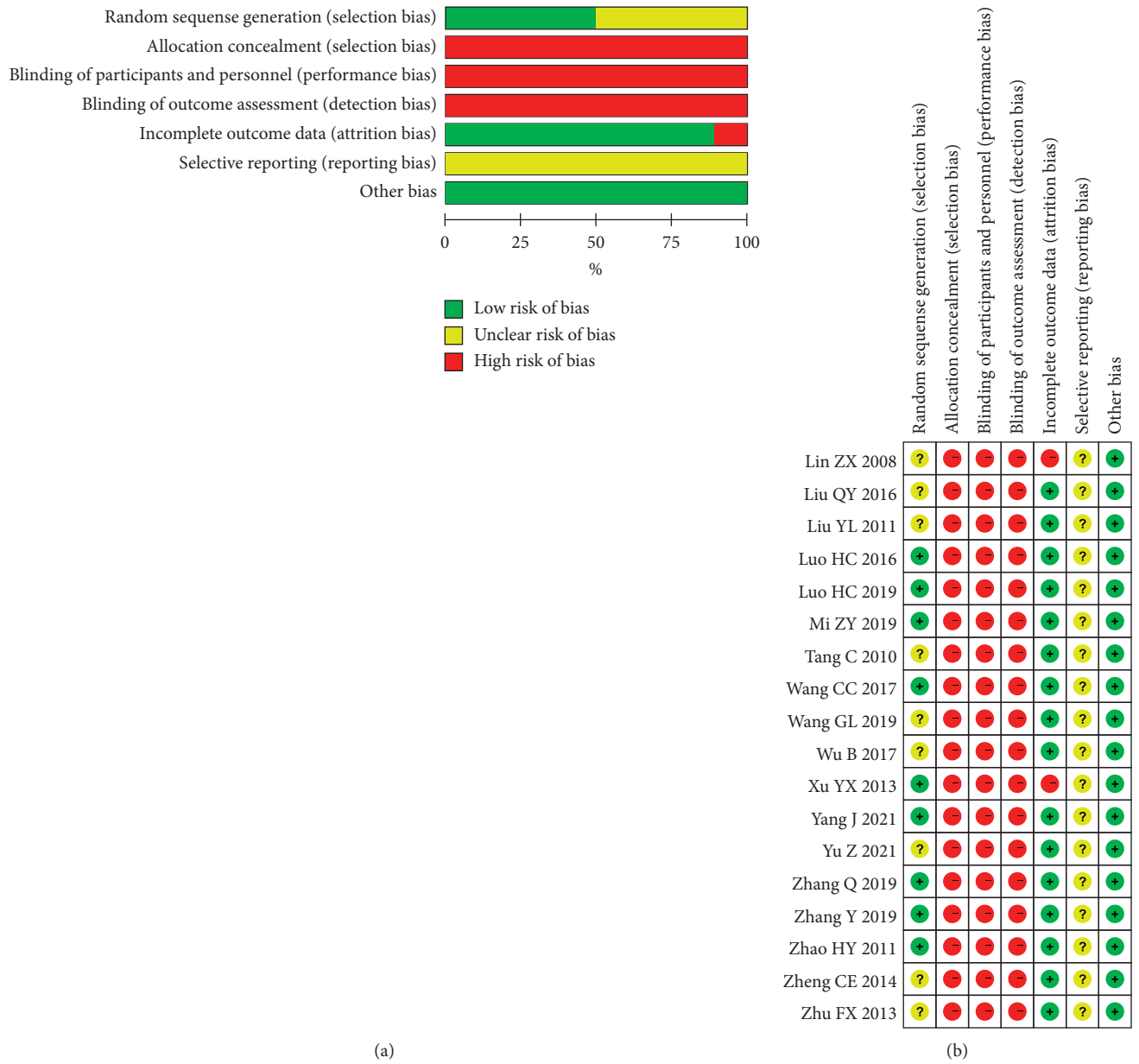

Figure 2: Risk of bias summary and risk of bias graph.

homogeneity among the included studies ($P = 0.15$, $I^2 = 43\%$), and the fixed effect model was used for the analysis. The results showed that after treatment, the WOMAC function score in the experimental group was lower than that in the control group (SMD = −0.76, 95% CI: [−0.97, −0.55], $P < 0.001$). The results of the subgroup analysis showed that the WOMAC function score of ZQFTN alone was lower than that of SYSADOA after treatment (SMD = −0.78, 95% CI: [−1.09, −0.46], $P < 0.001$). The WOMAC function score of ZQFTN combined with SYSADOA was lower than that of SYSADOA alone after treatment (SMD = −0.75, 95% CI: [−1.04, −0.46], $P < 0.001$) (Figure 7).

3.5. Serum IL-1β Level. Four studies [15, 16, 24, 28] reported the serum IL-1β level after treatment, involving 368 patients (184 in the experimental group and 184 in the control group). The results of the heterogeneity analysis showed that there was significant heterogeneity among the included studies ($P < 0.001$, $I^2 = 97\%$), and the random effect model was used to analyze the results. The results showed that the serum IL-1β level of the experimental group was lower than that of the control group after treatment (SMD = −4.36, 95% CI: [−6.41, −2.31], $P < 0.001$). The results of subgroup analysis showed that the serum IL-1β level of ZQFTN alone was lower than that of SYSADOA after treatment (SMD = −5.43, 95% CI: [−6.11, −4.76], $P < 0.001$). The serum

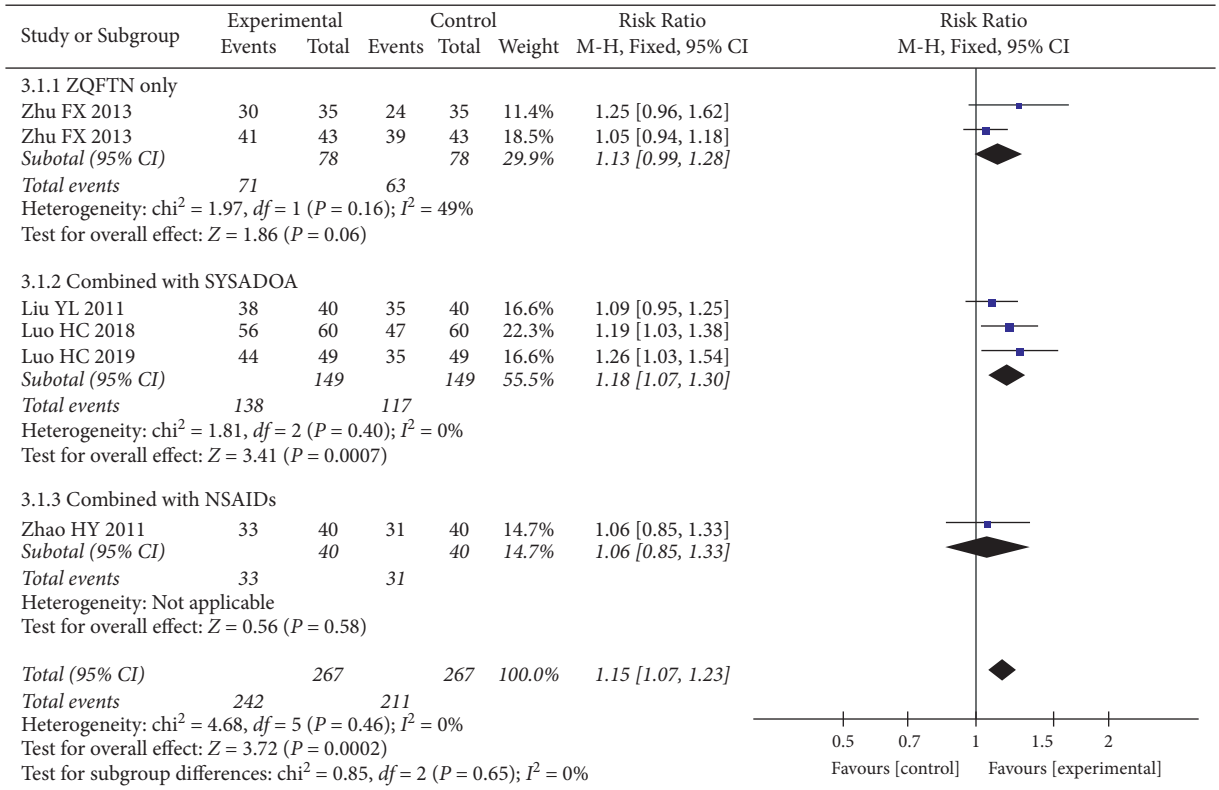

Figure 3: Forest plot of total effective rate.

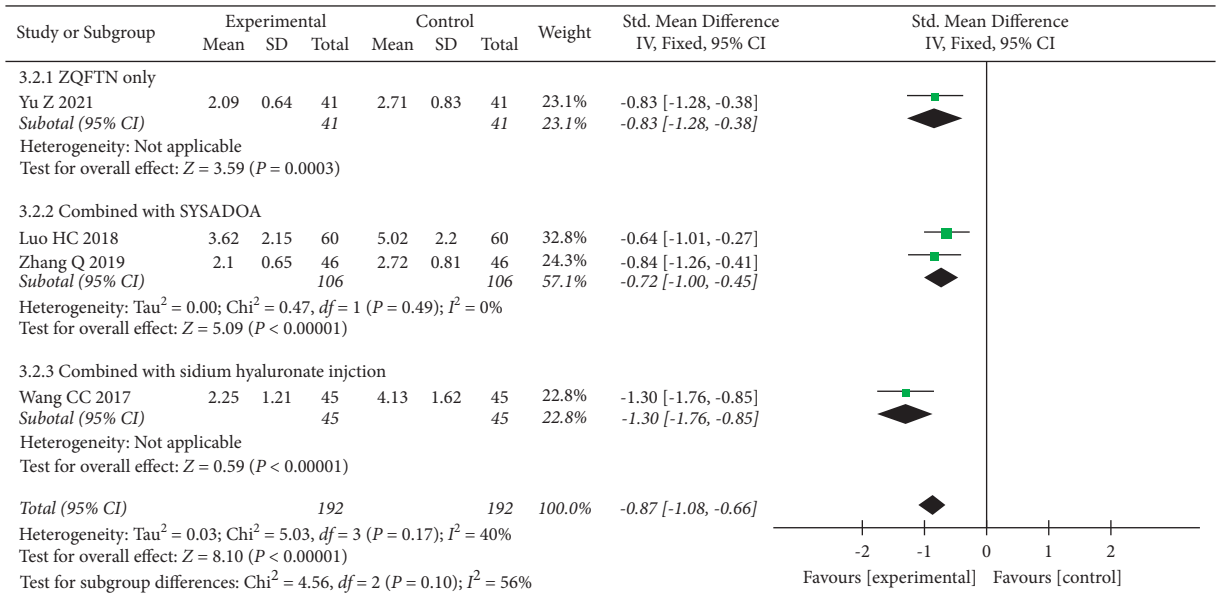

Figure 4: Forest plot of VAS.

IL-1β level of the ZQFTN combined with SYSADOA group was lower than that of SYSADOA alone after treatment (SMD = −4.73, 95% CI: [−5.51, −3.94], $P < 0.001$). The serum IL-1β level of ZQFTN combined with NSAIDs was lower than that of NSAIDs alone after treatment (SMD = −1.86, 95% CI: [−2.33, −1.40], $P < 0.001$) (Figure 8).

3.6. Serum TNF-α Level. Five studies [15, 16, 24, 28, 30] reported the serum TNF-α level after treatment, involving 458 patients (229 in the experimental group and 229 in the control group). The results of the heterogeneity analysis showed that there was significant heterogeneity among the included studies ($P < 0.001$, $I^2 = 99\%$), and the random

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.2.1 ZQFTN only								
Liu QY 2016	3.5	1.3	40	4..2	1	40	22.1%	-0.60 [-1.05, -0.15]
Zhu FX 2013	3.6	1.6	43	4.5	1.4	43	23.8%	-0.59 [-1.03, -0.16]
Subtotal (95% CI)			*83*			*83*	*45.9%*	*-0.60 [-0.91, -0.28]*
Heterogeneity: chi^2 = 0.00 *df* = 1 (*P* = 0.99); I^2 = 0%								
Test for overall effect: *Z* = 3.75 (*P* = 0.0002)								
3.2.2 Combined with SYSADOA								
Liu YL 2011	4.9	3.4	40	7.2	3.5	40	21.9%	-0.66 [-1.11, -0.21]
Luo HC 2018	6.49	3.11	60	9.01	3.28	60	32.2%	-0.78 [-1.16, -0.41]
Subtotal (95% CI)			*100*			*100*	*54.1%*	*-0.73 [-1.02, -0.45]*
Heterogeneity: chi^2 = 0.17 *df* = 1 (*P* = 0.68); I^2 = 0%								
Test for overall effect: *Z* = 5.01 (*P* < 0.00001)								
Total (95% CI)			*183*			*183*	*100.0%*	*-0.67 [-0.88, -0.46]*
Heterogeneity: chi^2 = 0.58, *df* = 3 (*P* = 0.90); I^2 = 0%								
Test for overall effect: *Z* = 6.23 (*P* < 0.00001)								
Test for subgroup differences: chi^2 = 0.41, *df* = 1 (*P* = 0.52); I^2 = 0%								

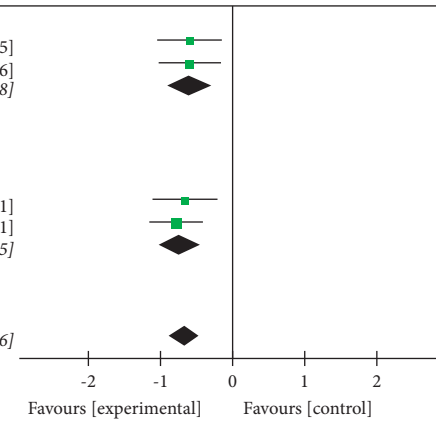

Figure 5: Forest plot of WOMAC pain score.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.4.1 ZQFTN only								
Liu QY 2016	0.6	0.4	40	0.7	0.2	40	24.1%	-0.31 [-0.75, 0.13]
Zhu FX 2013	0.7	0.5	43	0.8	0.6	43	25.0%	-0.81 [-0.60, 0.24]
Subtotal (95% CI)			*83*			*83*	*49.1%*	*-0.24 [-0.55, 0.06]*
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.18, *df* = 1 (*P* = 0.67); I^2 = 0%								
Test for overall effect: *Z* = 1.56 (*P* = 0.12)								
3.4.2 Combined with SYSADOA								
Liu YL 2011	1.1	0.7	40	1.7	0.8	40	23.4%	-0.79 [-1.25, -0.33]
Luo HC 2018	3.69	1.91	60	5.38	2.12	60	27.5%	-0.83 [-1.21, -0.46]
Subtotal (95% CI)			*100*			*100*	*50.9%*	*-0.82 [-1.10, -0.53]*
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.02, *df* = 1 (*P* = 0.89); I^2 = 0%								
Test for overall effect: *Z* = 5.53 (*P* < 0.00001)								
Total (95% CI)			*183*			*183*	*100.0%*	*-0.53 [-0.86, -0.20]*
Heterogeneity: Tau^2 = 0.07; Chi^2 = 7.31, *df* = 3 (*P* = 0.06); I^2 = 59%								
Test for overall effect: *Z* = 3.18 (*P* = 0.001)								
Test for subgroup differences: Chi^2 = 7.11, *df* = 1 (*P* = 0.008); I^2 = 85.9%								

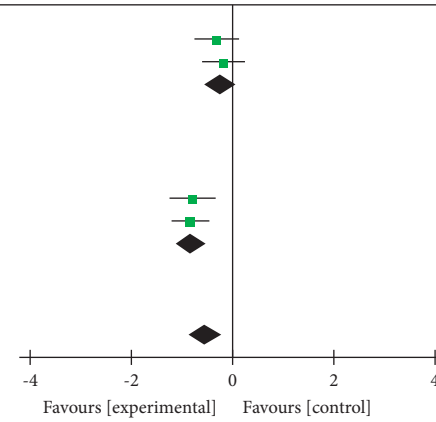

Figure 6: Forest plot of WOMAC stiffness score.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.5.1 ZQFTN only								
Liu QY 2016	8.8	5.8	40	13.8	5.5	40	21.5%	-0.88 [-1.34, -0.42]
Zhu FX 2013	9.9	6.1	43	14.1	6	43	24.0%	-0.69 [-1.12, -0.25]
Subotal (95% CI)			*83*			*83*	*45.5%*	*-0.75 [-1.09, -0.25]*
Heterogeneity: Chi^2 = 0.34, *df* = 1 (*P* = 0.56); I^2 = 0%								
Test for overall effect: *Z* = 4.82 (*P* < 0.00001)								
3.5.2 Combined with SYSADOA								
Liu YL 2011	13.8	10.3	40	17.2	7.8	40	23.3%	-0.37 [-0.81, 0.07]
Luo HC 2018	19.97	9.13	60	29.27	8.83	60	31.2%	-1.03 [-1.41, -0.65]
Subotal (95% CI)			*100*			*100*	*54.5%*	*-0.75 [-1.04, -0.46]*
Heterogeneity: Chi^2 = 4.91, *df* = 1 (*P* = 0.03); I^2 = 80%								
Test for overall effect: *Z* = 5.07 (*P* < 0.00001)								
Total (95% CI)			*183*			*183*	*100.0%*	*-0.76 [-0.97, -0.55]*
Heterogeneity: Chi^2 = 5.27, *df* = 3 (*P* = 0.15); I^2 = 43%								
Test for overall effect: *Z* = 6.99 (*P* < 0.00001)								
Test for subgroup differences: Chi^2 = 0.02, *df* = 1 (*P* = 0.89); I^2 = 0%								

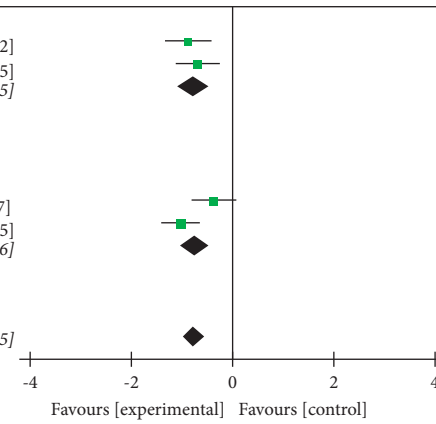

Figure 7: Forest plot of WOMAC function score.

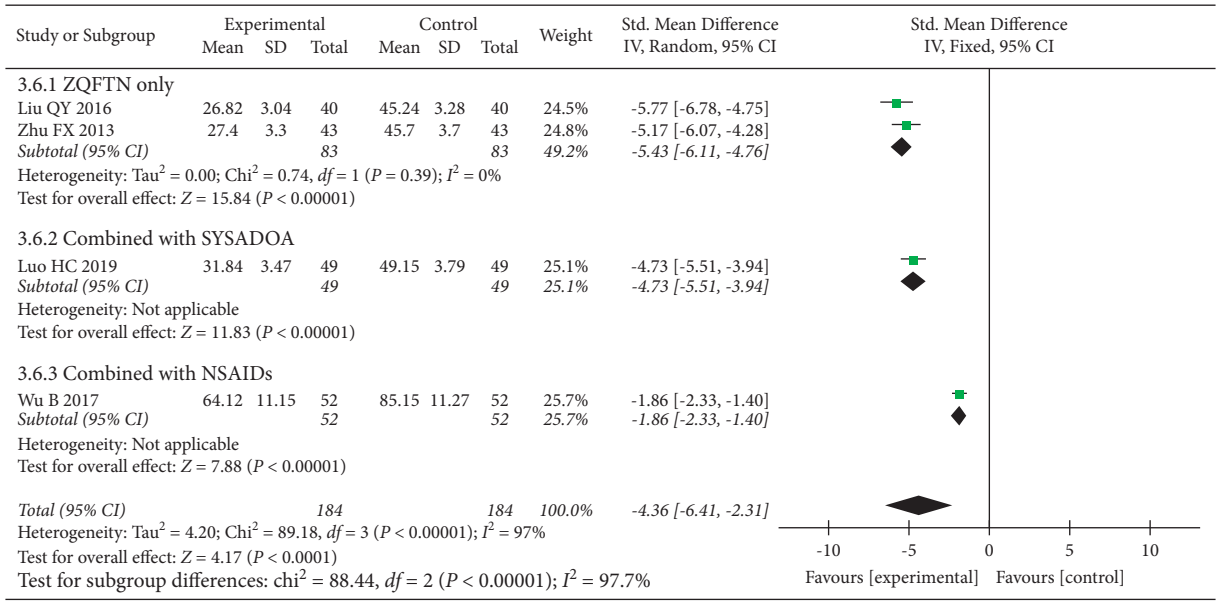

Figure 8: Forest plot of serum IL-1β level.

effect model was used to analyze the results. The results showed that the serum TNF-α level of the experimental group was lower than that of the control group after treatment (SMD = −8.45, 95% CI: [−11.20, −5.69], $P < 0.001$). The results of the subgroup analysis showed that the serum TNF-α level of ZQFTN alone was lower than that of SYSADOA after treatment (SMD = −24.30, 95% CI: [−41.18, −7.43], $P = 0.005$). The serum TNF-α level of the ZQFTN combined with SYSADOA group was lower than that of SYSADOA alone after treatment (SMD = −0.91, 95% CI: [−1.32, −0.49], $P < 0.001$). The serum TNF-α level of ZQFTN combined with NSAIDs was lower than that of NSAIDs alone after treatment (SMD = −1.50, 95% CI: [−1.94, −1.06], $P < 0.001$). The serum TNF-α level of ZQFTN combined with sodium hyaluronate injection was lower than that of sodium hyaluronate injection alone after treatment (SMD = −3.15, 95% CI: [−3.78, −2.52], $P < 0.001$) (Figure 9).

3.7. Adverse Events. Fifteen studies [21, 23–32, 35–38] reported the adverse events after treatment, involving 1285 patients (644 in the experimental group and 641 in the control group). Heterogeneity analysis showed good homogeneity among the included studies ($P = 0.42$, $I^2 = 3\%$), and the fixed effect model was used for the analysis. The results showed that there was no significant difference between the experimental group and the control group ($RR = 0.96$, 95% CI: [0.69, 1.35], $P = 0.82$). The results of the subgroup analysis showed that ZQFTN alone had less adverse events than SYSADOA alone ($RR = 0.45$, 95% CI: [0.21, 0.95], $P = 0.04$). There was no significant difference between the ZQFTN combined with SYSADOA group and the SYSADOA group ($RR = 1.04$, 95% CI: [0.61, 1.78], $P = 0.87$). There was no significant difference in adverse events between ZQFTN combined with NSAIDs and NSAIDs alone (SMD = 1.44, 95% CI: [0.73, 2.83], $P = 0.30$). There was no significant difference in adverse events between ZQFTN combined with sodium hyaluronate injection and sodium hyaluronate injection alone ($RR = 1.49$, 95% CI: [0.51, 4.31], $P = 0.46$) (Figure 10).

3.8. Publication Bias. The inverted funnel plot of publication bias was generated with the adverse reactions as indicators, and the scatter point distribution of each study was asymmetric, suggesting the possibility of publication bias in this study (Figure 11).

4. Discussion

Sinomenium acutum is the vine stem of the *Asteraceae* plant and Chinese *Anseraceae* plant among others. It is a TCM, which has the function of dispelling wind dampness, channelling channels and collaterals, and relieving urination, and is often used to treat rheumatoid arthritis, OA, and gout arthritis [42]. Sinomenine is an alkaloid extracted from *Sinomenium acutum* and is the main active ingredient of *Sinomenium acutum*. Experimental studies have found that sinomenine has clear anti-inflammatory and analgesic effects. Its anti-inflammatory effect mainly results from its selective inhibition of cyclooxygenase-2 activity, whereby capillary permeability is reduced by downregulating prostaglandin E synthesis, or preventing histamine-induced capillary permeability increase by inhibiting the release of various inflammatory mediators, thus blocking inflammatory infiltration and exudation. Sinomenine also has anticoagulation and antiembolism effects and reduces tissue damage [20]. Studies have shown that sinomenine can reduce synovial inflammation and cartilage degeneration by inhibiting the expression of inflammatory factors and chondrocyte apoptosis, thus delaying the progression of osteoarthritis [43]. ZQFTN as an oral preparation of

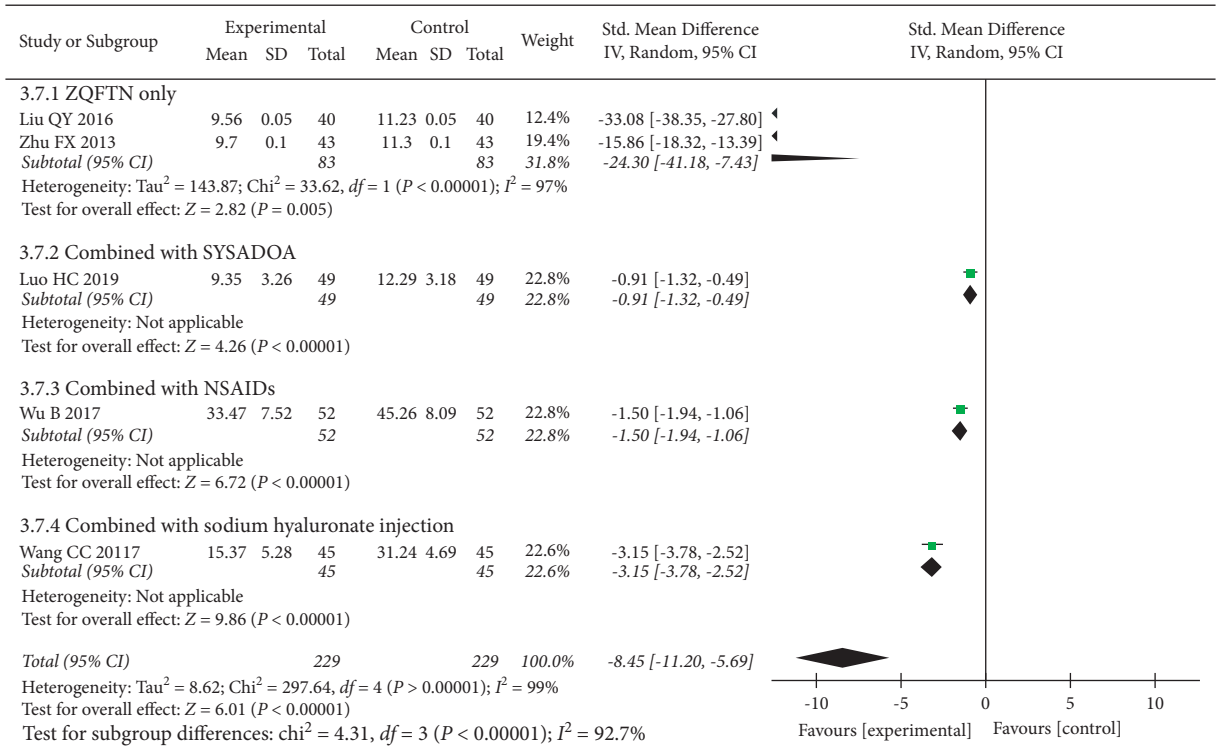

Figure 9: Forest plot of serum TNF-α level.

sinomenine has been used ever more frequently in the clinical treatment of OA.

4.1. Effectiveness of ZQFTN in Treating KOA. Through a literature search, it was found that ZQFTN could be used as a complementary drug in combination with SYSADOA, NSAIDs, or sodium hyaluronate, or used alone as an alternative drug for KOA. The results showed that ZQFTN has good efficacy, but due to the influence of inconsistent treatment methods, insufficient sample size, and other factors, the conclusions were frequently unconvincing and the evidence basis was not strong. To determine the effectiveness of oral ZQFTN in KOA treatment, 18 RCTs were included in the present study, including 1512 KOA patients. The results of the meta-analysis showed that ZQFTN could effectively relieve knee pain, morning stiffness, and daily activity disturbance. The VAS and WOMAC scores were lower than the control group, and the total clinical effectiveness rate was higher than the control group, indicating that ZQFTN had significant clinical efficacy as a CAM for KOA. The results of serum IL-1β and TNF-α showed that their respective levels in the experimental group were lower than those in the control group, suggesting that the mechanism of ZQFTN in treating KOA may be associated with its ability to reduce inflammation.

4.2. Safety of ZQFTN in Treating KOA. Adverse events related to drug treatment were recorded in 15 studies, and meta-analysis results showed that there was no significant difference in the incidence of adverse reactions between the experimental and control groups. The reported adverse reactions were mainly gastrointestinal, including nausea and diarrhea, and allergic reactions, such as pruritus and rash, which were consistent with the adverse events recorded in the instructions of ZQFTN, SYSADOA, and NSAIDs. Eight studies monitored the changes of blood routine and liver and kidney functions during medication, including 737 KOA patients. The results showed that a total of five patients in the experimental groups displayed a slight increase in transaminases, while a further seven patients in control groups showed a slight increase in transaminases, which returned to normal after symptomatic treatment. These results indicated that the use of ZQFTN did not increase the risk for adverse events and that it was safe as a CAM for KOA.

4.3. Limitations of the Study. Through a comprehensive analysis of the included literature, the following problems were found to generally exist in this literature: (1) There was no allocation concealment or blind method in all studies, and strict and careful experimental design was lacking. (2) The sample size of some of the literature was small, and the calculation basis of sample size was not given. (3) There were differences in medication duration and dosage in the included studies, which were not conducive to the formation of standardized medication guidance. (4) Because there is no standardized ZQFTN in other countries, all analyzed studies were performed in China, which may have led to a certain bias.

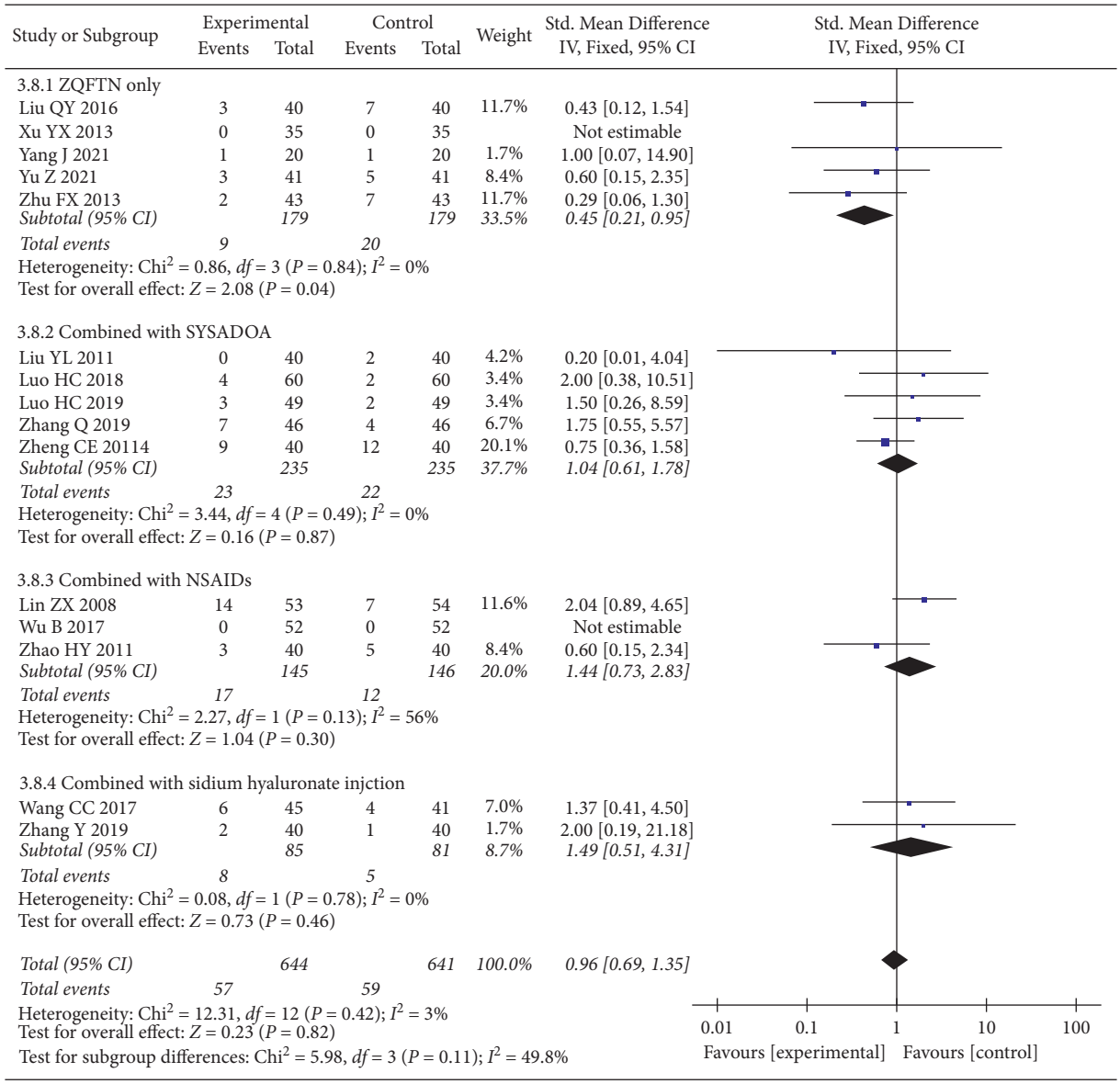

Figure 10: Forest plot of adverse events.

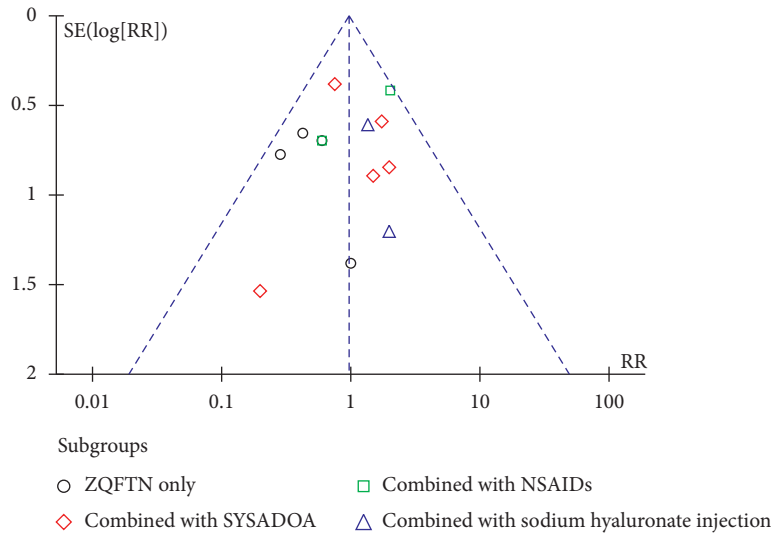

Figure 11: Publication bias of the funnel plot of adverse events.

5. Conclusion

This study demonstrated that ZQFTN has high clinical efficacy and safety in the treatment of KOA and thus has considerable potential as a CAM for KOA. However, due to the limitation of the quality of included studies, the strength of this conclusion is affected. In the next step, multicenter, large sample, high-quality randomized controlled studies are needed to further confirm the present conclusion.

Data Availability

The table data used to support the findings of this study are included within the article. The figure data used to support the findings of this study are included within the figure files.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

Authors' Contributions

HZL, MX, and CJM contributed equally to this work. HZL and HZQ contributed to the conception and design of the review. HZL and MX performed the search strategy. HZL and MX developed the search criteria and performed data extraction quality evaluation. HZL and CJM analyzed the data. HZL wrote the first draft of the manuscript. HJJ, SSN, GM and GHJ critically edited the manuscript. HZL and HZQ were responsible for the overall project. All authors read and approved the manuscript.

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Research Article

Jintiange Capsule May Have a Positive Effect on Pain Relief and Functional Activity in Patients with Knee Osteoarthritis: A Meta-Analysis of Randomized Trials

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Background. Knee osteoarthritis (KOA) occurs frequently in the elderly and causes pain, especially when they walk. Traditional Chinese medicine treatment is effective in releasing knee osteoarthritis. Jintiange (JTG) capsule is widely used in treating knee osteoarthritis, but its clinical effects such as pain relief are still unclear. This meta-analysis aims to evaluate the clinical results systematically and negative effects of JTG capsule in patients with knee osteoarthritis. *Methods*. A meta-analysis of clinical randomized controlled trials (RCTs) on JTG capsule treatment was carried out in KOA patients. The search time was from the establishment of the database to May 2021. The database included PubMed, Cochrane Library, EMBASE, Web of Science database, Chinese Biomedical database (CBM), Chinese VIP information, China National Knowledge Infrastructure (CNKI), and WanFang database. The outcome indicators were extracted from the included literature and analyzed, and the risk of bias was assessed through Cochrane Handbook 5.0.1. *Results*. Twenty-two articles analyzed in this study involved 1887 patients. JTG capsule used alone or used with other interventions affects total effective rate significantly (RR: 1.19; 95% Cl: 1.11, 1.29; $P = 0.045$), VAS score (SMD: −0.74; 95% Cl: −0.90, −0.59; $P \leq 0.001$), WOMAC score (SMD: −0.77; 95% Cl: −0.96, −0.59; $P \leq 0.001$), and Lequesne score (SMD: −0.82; 95% Cl: −1.02, −0.61; $P = 0.010$). *Conclusion*. Our current evidence indicated that JTG capsule may release the pain of KOA patients and improve their functional activity. However, considering the unsatisfactory quality of the included trials, more high-quality trials are needed to prove this issue.

1. Introduction

Osteoarthritis (OA) is a worldwide inflammatory joint disease, being one of the main causes of joint disability [1], and its incidence increases with age [2]. Knee osteoarthritis (KOA) accounts for 83% of OA. The prevalence rate of knee osteoarthritis is estimated to be 42.8% for women and 21.5% for men in China [3]. In the past, KOA was considered a cartilage degenerative disease, but now, the concept has changed to a complex condition that affects the entire joints. Cartilage, subchondral bone, synovium, and systemic inflammation are all involved in the onset of the disease [4]. Therefore, the treatment of KOA is quite complicated. Physical therapy and exercise cannot alleviate the process of KOA. In addition, the pharmacological treatment of KOA relies on analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular injections. However, gastrointestinal discomfort and dose

dependence are common problems with these drugs [5]. Patients with severe symptoms need to undergo knee arthroplasty, posing a significant economic burden to the patient and the family [6]. Therefore, to slow down the development process of KOA, reduce the side effects of treatment, and reduce the economic burden, as an inexpensive clinical method, Chinese herbal medicine is expected to become an alternative therapy for the prevention and treatment of KOA.

Chinese herbal medicine has been used in the healthcare system to prevent and treat various diseases in China's history. Jintiange (JTG) capsule, as a kind of herbal medicine, is composed of artificial tiger bone powder, which has anti-inflammatory, bone-formation, and antiosteoporosis effects. JTG capsule has been proven to contain high calcium levels, and the ratio of calcium to phosphorus in the capsule suits for human absorption [7]. Studies showed that tiger bones could increase an individual's pain threshold and relieve joint pain [8]. Despite its wide application, at present, the efficacy and potential adverse effects of JTG capsule on KOA are still controversial.

Therefore, here, we aim to conduct a meta-analysis of the effects of JTG capsule on KOA, focusing on clinical effectiveness and drug safety.

2. Materials and Methods

This work was conducted as claimed by the recommendations of the Cochrane and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9, 10].

2.1. Selection of Studies. All randomized controlled trials (RCTs) investigating JTG capsule combined with other drugs or therapies in the treatment of osteoarthritis were not limited by language or publication status. However, the nonrandomized controlled trials or animal trials were excluded.

2.2. Selection of Participants. Patients were diagnosed with KOA through validation criteria, such as the American Rheumatism Association (ARA), American College of Rheumatology (ACR), the Kellgren Lawrence classification (KL), and radio-graphic evidence [11]. However, secondary KOA caused by rheumatoid, bone tuberculosis, trauma, endocrine diseases, and the other reasons that affected bone metabolism were not analyzed by this research. Patients with previous knee joint infection, knee deformity before adulthood, unequal length of lower limbs, history of knee joint trauma surgery, and history of knee joint tumors were also not involved.

2.3. Types of Interventions. The experimental group was treated with JTG capsule alone or combined with conventional medication for intervention. The treatment dose was three times a day and three capsules each time, and the treatment duration was four to twelve weeks. The control group was treated with conventional Western medicine alone. Besides, the treatment of the two groups was carried out at the same time.

2.4. Types of Outcome Measures. According to the author's definition, the main result is the total effective rate. Effective: joint swelling and pain are significantly alleviated, joint activity improves, the patient feels better, and related inspection indicators are basically restored; invalid: joint swelling and pain, joint activity, patient self-feeling, and related inspection indicators are basically not significantly improved, or even worse. The second result includes VAS score, WOMAC score, Lequesne score, and the incidence of adverse events during treatment.

2.5. Search Strategy. Two researchers systematically conducted electronic searches in the following databases: PubMed, Cochrane Library, EMBASE, Web of Science database, Chinese Biomedical Database (CBM), Chinese VIP Information, China National Knowledge Infrastructure (CNKI), and WanFang, while the searches were accomplished from the inception of each database to 1 May 2021. During the process, if the two researchers disagree, the third researcher would make the decision. The search strategy of PubMed was as follows, and we adjusted it when searching other Chinese or English databases: (jintiange capsule OR jin tian ge capsule OR jintiange jiaonang OR jin tian ge jiaonang) AND (osteoarthritis, knee OR gonarthrosis OR osteoarthrosis OR osteoarthrit* OR osteoarthropathy OR arthralgia).

The two researchers also manually searched the reference lists of all identified articles for possible related studies to supplement the relevant literature. Integration and deletion of duplicate trials were performed on the EndNote software.

2.6. Data Extraction and Quality Assessment. The two researchers extracted relevant data and characteristics from the study, including the researcher, year of publication, sample size, male to female ratio, mean age of patients, intervention, control, duration of treatment, and outcome measures, and then investigated into it. The third author was responsible for resolving conflicts in the process. The quality of the study was independently evaluated by two researchers regarding the Cochrane Handbook for Systematic Reviews of Interventions [12]. The evaluation criteria were as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other bias. Meanwhile, the two reviewers routinely classify each study as low risk, high risk, or unclear. If there are disagreements, the result would refer to the third researcher's point of view.

2.7. Statistical Analysis. This meta-analysis was conducted by using Review Manager (RevMan) and Stata SE-64 (computer program). Regarding the research results, the relative risk with a 95% confidence interval was used for binary variables, and the weighted average difference and

95% confidence interval were utilized for continuous variables. I^2 were employed to test the heterogeneity of the study. Due to clinical and methodological factors, there was likely to be a high degree of heterogeneity. Thus, even if I^2 was small, this meta-analysis would use a random-effect model. The funnel chart and Begg's test were employed to test for potential publication bias. In addition, a sensitivity analysis was performed through sequential deletion tests to check the stability of the main results.

3. Result

3.1. Search Results. Acting by the search strategy, 144 references were identified. After excluding duplicate studies, 43 studies were scanned based on their abstracts and titles. Then, 33 articles were evaluated by full text. After the full manuscript was assessed, ten records were excluded with the following reasons: not RCT ($n = 8$), lack of outcomes ($n = 2$), and the control group was treated with acupuncture ($n = 1$). Eventually, 22 studies were included in this meta-analysis (Table 1). The PRISMA statement flow chart shows this process (Figure 1).

A total of 1887 participants were randomized into experimental groups ($n = 943$) and control groups ($n = 944$). The sample size ranged from 56 to 130. The ethnicity of all participants was Chinese. Moreover, all the studies enrolled KOA patients.

3.2. Risk of Bias Assessment. In general, the methodological quality of the included trials may not be high enough (Figures 2 and 3). All of the 22 included studies involved two-arm designs and were declared as random controlled trials, and 13 trials reported proper generation methods (random number table or coin toss) with a low risk of bias [13, 15, 16, 19–21, 23, 28, 30]. Nine trials did not describe the randomization procedure clearly [14, 17, 18, 22, 29, 31–34]. Only two trials reported the concealed allocation method of patients and investigators [13, 25]. In the incomplete outcome and the selective outcome reporting, a test was judged as high risk because the observation indicators in the test were not shown in the results [33]. None of the trials reported any blinding of patients and investigators.

3.3. Primary Outcomes

3.3.1. Total Effective Rate. Fourteen studies reported the total effective rate of the JTG capsule group and the Western medicine group. Meta-analysis showed that the total effective rate of the JTG capsule group was significantly higher (RR: 1.19; 95% Cl: 1.07, 1.33; $P \leq 0.001$, $I^2 = 83.4\%$) than that of the Western medicine group. The results of all these trials showed high heterogeneity, and thus, a sensitivity analysis was conducted (Figure 4), which showed that the included trail [14] had a more significant impact on the results. A careful review of the included article found that this article only included women with postmenopausal knee osteoarthritis, which may cause higher heterogeneity. The remaining 13 articles were used to analyze the total effective rate and get a new result (RR: 1.19; 95% Cl: 1.11, 1.29; $P = 0.045$, $I^2 = 43.9\%$, Figure 5).

3.3.2. VAS Score. Results on the VAS score were presented in eight trials involving 671 KOA patients. Meta-analysis showed that the VAS score of the JTG capsule group was significantly lower (SMD: −0.74; 95% Cl: −0.90, −0.59; $P \leq 0.001$, $I^2 = 80.5\%$, Figure 6) than that of the Western medicine group. Subgroup analysis (Supplementary Figure 1) was performed for the mean baseline of sample size ≥80 and <80. In 3 studies [13, 19, 34], sample size baseline levels were, respectively, 78, 60, and 70, which in the remaining 5 studies were all higher than 80. The heterogeneity analysis suggested that there was lower heterogeneity after subgroup analysis. The results suggested that the sample size may be a source of heterogeneity.

3.3.3. WOMAC Score. Compared with the Western medicine group, six studies reported the WOMAC score. Meta-analysis showed that the WOMAC score of the JTG capsule group was significantly lower (SMD: −0.77; 95% Cl: −0.96, −0.59; $P \leq 0.001$, $I^2 = 88.1\%$, Figure 7) than that of the Western medicine group. Subgroup analysis (Supplementary Figure 2) was performed for the mean baseline of age ≥60 and <60. In 2 studies [15, 24], age baseline levels were, respectively, 66.58 and 68.63, which in the remaining 4 studies were all lower than 60. The heterogeneity analysis suggested that there was lower heterogeneity after subgroup analysis. The results suggested that the age may be a source of heterogeneity.

3.3.4. Lequesne Score. Five studies reported the Lequesne score of the JTG capsule group and the Western medicine group. Meta-analysis showed that the Lequesne score of the JTG capsule group was significantly lower (SMD: −0.82; 95% Cl: −1.02, −0.61; $P = 0.010$, $I^2 = 69.8\%$, Figure 8) than that of the Western medicine group. The large heterogeneity may be due to the small number of trials reporting this indicator, which suggested that the results of the Lequesne score were unstable and need to be interpreted with caution.

3.3.5. Adverse Effect. Of the 24 trials, only three trials involved adverse events related to the treatment of KOA with JTG capsules. Few patients experienced some mild stomach discomfort, such as nausea and bloating.

3.3.6. Publication Bias. Although the funnel plot (Figure 9) of the total effective rate was asymmetrically distributed, Begg's test showed no potential publish bias ($P = 0.125$).

4. Discussion

Traditional herbal medicine has been used as a complementary and alternative treatment option for patients with osteoarthritis for a long time. JTG capsule may improve the function of the knee joint to a certain extent and has a particular analgesic effect [35]. However, its efficacy and side

Table 1: The basic characteristics of the included studies.

Trail	Sample size (T/C)	Man/ woman	Age (y), mean ± SD or median (range)	T	C	Duration (weeks)	Main outcomes
Jian and Sheng [13]	78 (39/39)	30/48	55.39 ± 8.38	JTG capsules	Alendronate	12	①②
Yi and Huan [14]	120 (60/60)	0/120	56 (48–60)	JTG capsules	Glucosamine hydrochloride	6	①②
Jianli [15]	102 (51/51)	NR	66.58 ± 6.23	JTG capsules	Glucosamine hydrochloride	6	②③
Jiewei et al. [16]	60 (30/30)	19/41	53.46 ± 5.74	JTG capsules	Etocoxib	12	①③
Fang and Qing [17]	80 (40/40)	NR	66.31 ± 5.67	JTG capsules	Glucosamine sulfate	12	②④
Cunzhu and Xiaodong [18]	120 (60/60)	61/59	61 (45–70)	JTG capsules + C	Sodium hyaluronate	5	①
Yuhong et al. [19]	60 (30/30)	27/33	54.96 ± 10.55	JTG capsules + C	Sodium hyaluronate	24	②
Yiebi et al. [20]	80 (40/40)	NR	52.0 ± 6.4	JTG capsules	Loxoprofen sodium	12	②
Zhilin [21]	120 (60/60)	NR	72.6 ± 10.2	JTG capsules	Voltaren	4	⑤
Fang et al. [22]	130 (65/65)	47/83	55.52 ± 5.43	JTG capsules	Diclofenac sodium	8	①③
Yun et al. [23]	83 (41/42)	31/52	44.9 ± 6.3	JTG capsules + C	Meloxicam	12	①②
Junlian and Pengcheng [24]	90 (45/45)	25/65	68.63 (50–75)	JTG capsules	Aceclofenac	12	①③
Dahua et al. [25]	90 (45/45)	42/48	59.8 ± 1.4	JTG capsules	Glucosamine sulfate	4	①
Dongwei [26]	90 (45/45)	41/49	60.8 ± 7.1	JTG capsules	Piroxicam	12	①④
Jinping at al. [27]	98 (49/49)	48/50	56.9 ± 13.0	JTG capsules + C	Naproxen	14	④
Guoyu [28]	72 (36/36)	38/34	66 (60–86)	JTG capsules	Ibuprofen	12	①
Jiangang et al. [29]	60 (30/30)	14/46	61.57 ± 6.68	JTG capsules	Aceclofenac	4	①④
Jian et al. [30]	60 (30/30)	16/44	56.85	JTG capsules	Voltaren	4	③
Yunzhao and Lin [31]	100 (50/50)	43/57	62.2 (40–80)	JTG capsules	Glucosamine hydrochloride	12	①
Dongliang et al. [32]	72 (36/36)	23/49	58.25 (44–75)	JTG capsules	Glucosamine hydrochloride	12	③④
Tao et al. [33]	61 (31/30)	26/35	51.3	JTG capsules	Glucosamine hydrochloride	12	①
Shuangli et al. [34]	70 (35/35)	27/43	62.12 (42–71)	JTG capsules	Glucosamine hydrochloride	12	①②

T: trial group; C: control group; NR: not reported; ①: the total effective rate; ②: the VAS score; ③: the WOMAC score; ④: the Lequesne score; ⑤: adverse events. Mean ± SD is mean, and median (range) is median.

effects in treating knee osteoarthritis are uncertain. To our knowledge, this is the first meta-analysis of the efficacy and side effects of JTG capsule on KOA.

Compared with the Western medicine group, the overall estimate showed that the symptoms of KOA were significantly relieved in 14 randomized controlled trials after four to twelve months. In terms of the VAS score, eight studies showed that the pain level of KOA patients was significantly reduced after four weeks of treatment. Similarly, in terms of the WOMAC score, six studies showed that, after four weeks of treatment, the WOMAC score of the JTG capsule group was lower than that of the Western medicine group, which indicated that it effectively reduced the patient's pain, stiffness, and the difficulty in activities in daily life. In terms of the Lequesne score, five studies showed that the pain level of KOA patients was significantly reduced, and the function of walk of patients was improved after treatment. However, the heterogeneity of some outcome indicators is high. The main reason may be that the number of trails investigated is limited. Therefore, more large-scale clinical trials are needed to prove our results better in the future. The side effect of JTG capsule may be mild stomach upset. In general, our research results showed that JTG capsule could reduce the pain of KOA patients, thereby improving the knee joint function of the patients, and there was no apparent liver and kidney damage except for mild gastrointestinal reactions. Part of the included trials also performed serological tests on patients, and the results showed that IL-1 and IL-6 in the JTG capsule group were lower than those in the Western medicine group. Therefore, it was supposed that the Jintiange capsule had a specific therapeutic effect on the inflammatory response of knee osteoarthritis. Because of the insufficient number of trials, we did not conduct a statistical analysis of inflammation-related indicators.

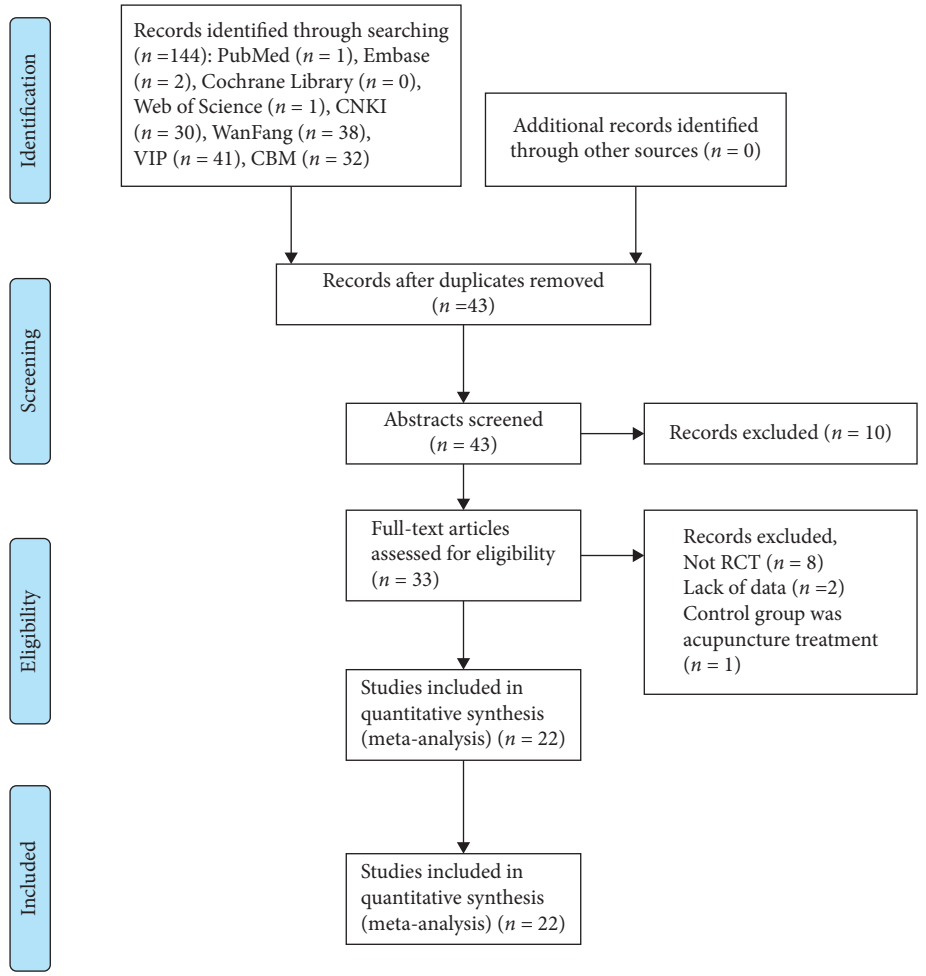

Figure 1: The inclusion process of the literature.

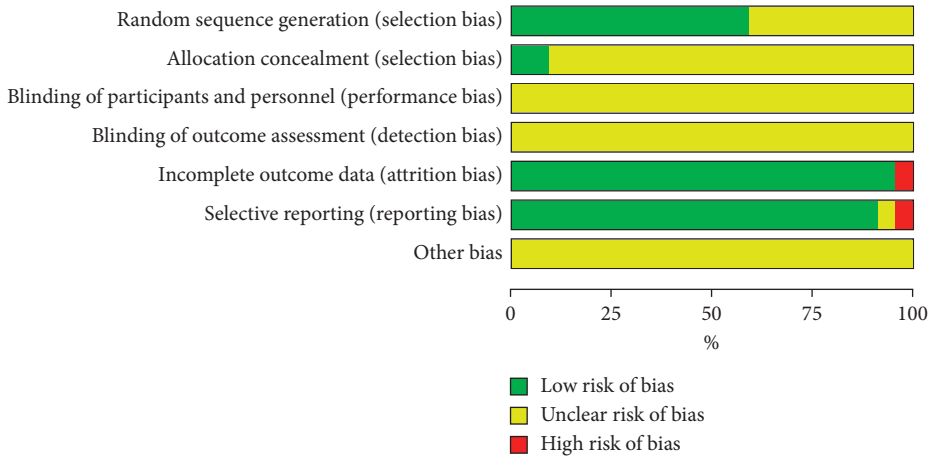

Figure 2: Risk of bias assessment in studies.

Clinically, JTG capsule is usually used to treat many common orthopaedic diseases such as osteoporosis, fractures, and rheumatoid arthritis. In 2017, it was listed as an effective treatment method in the treatment guidelines for osteoporotic fractures in China [36]. However, there is no large randomized controlled trial to prove that JTG capsule has an apparent effect on knee osteoarthritis. Ping [37] conducted acetic acid writhing and electric shock on mice tails to test the analgesic effect of tiger bone, one of the main ingredients of JTG capsule, and the results showed that it could effectively relieve pain. Se et al. [38] also demonstrated that tiger bone could enhance the pain threshold and

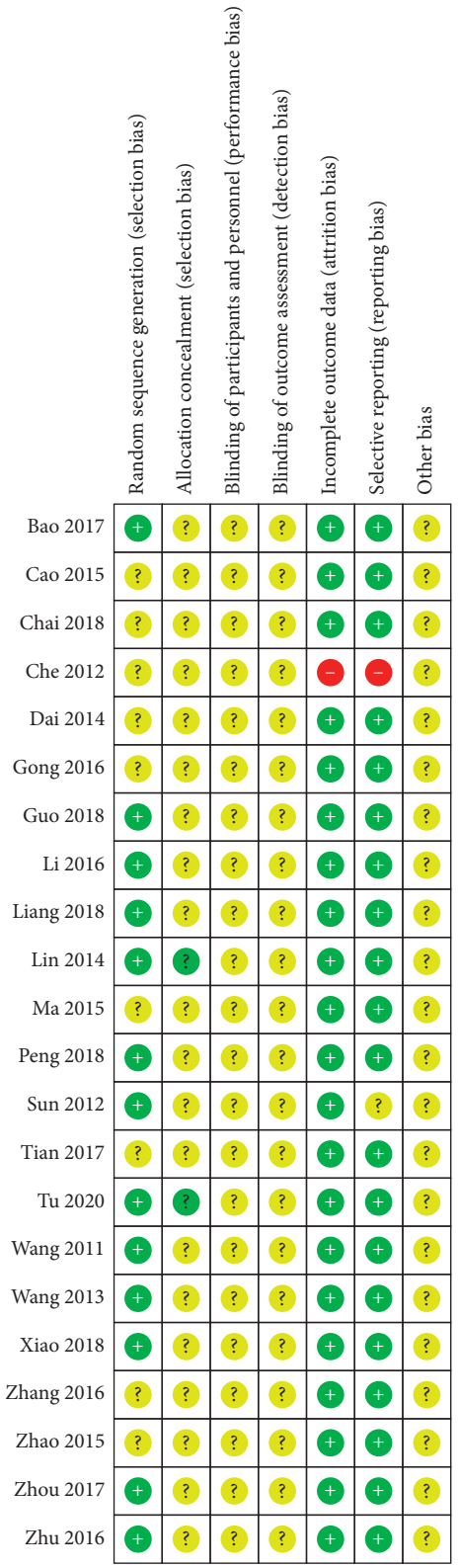

Figure 3: Risk of bias assessment for each included study in the review.

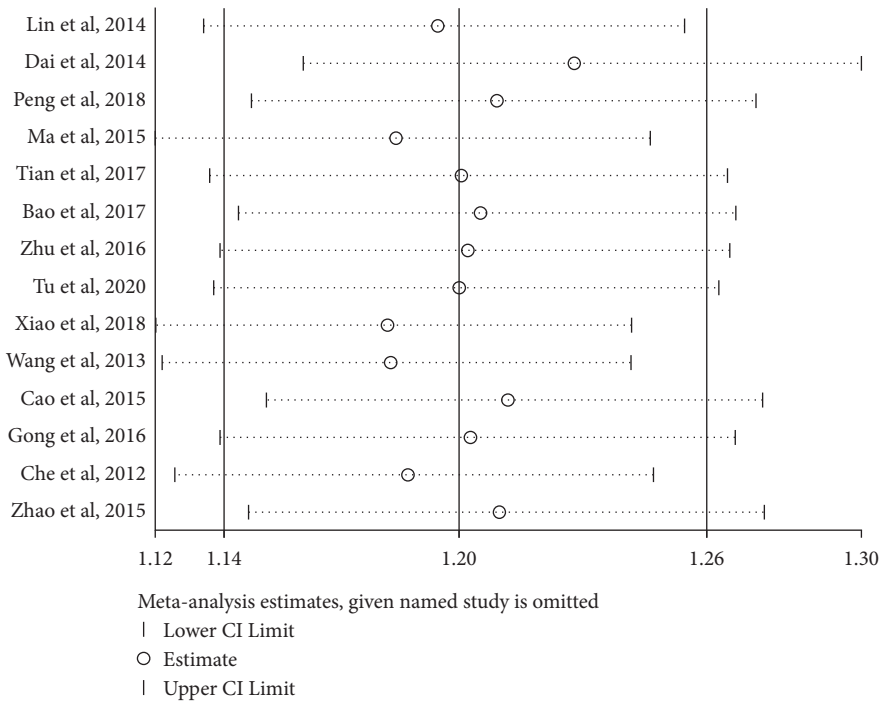

Figure 4: Sensitivity analysis of the total effective rate for each included study in the review.

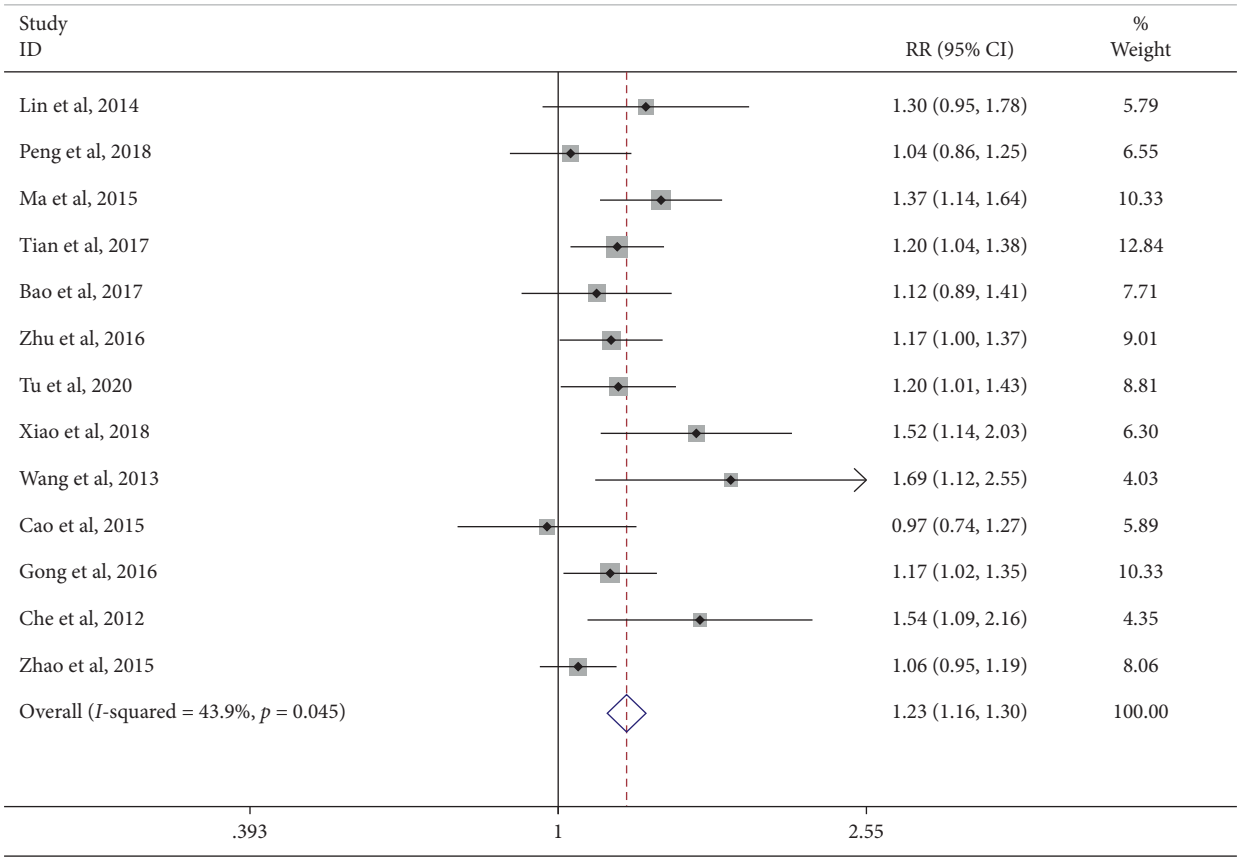

Figure 5: Forest plot of JTG capsule vs. conventional therapies on the total effective rate.

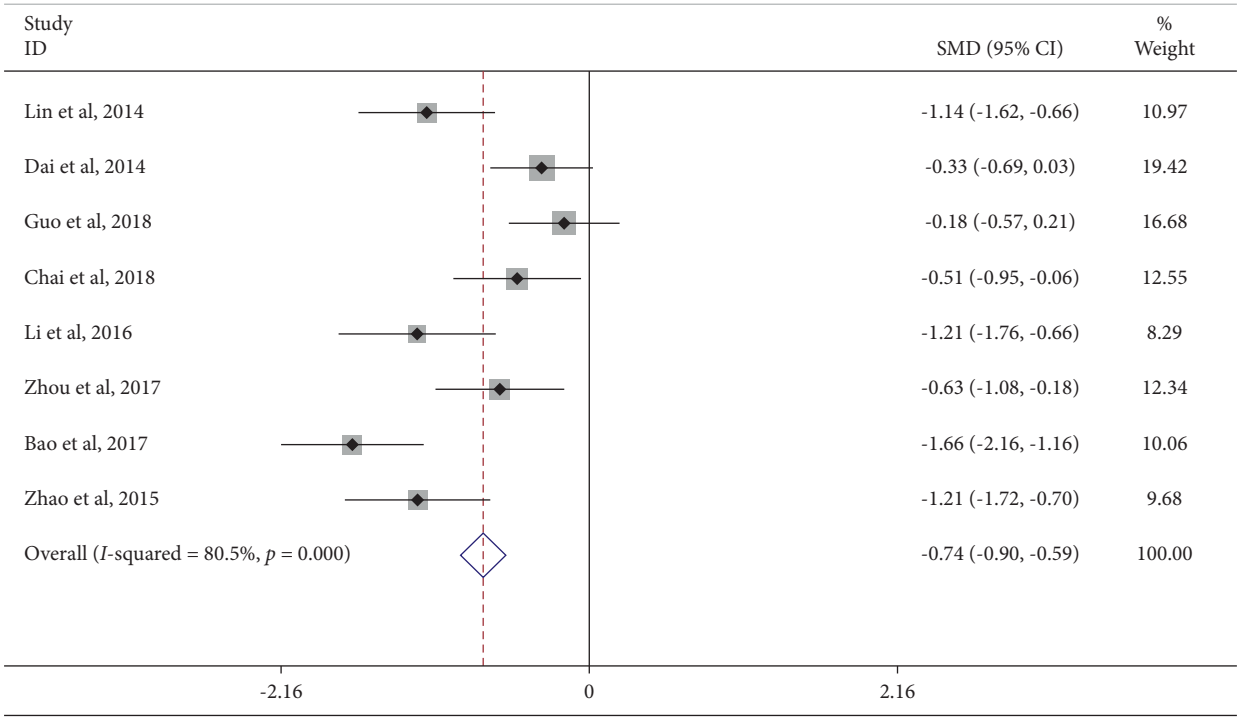

Figure 6: Forest plot of JTG capsule vs. conventional therapies on VAS score.

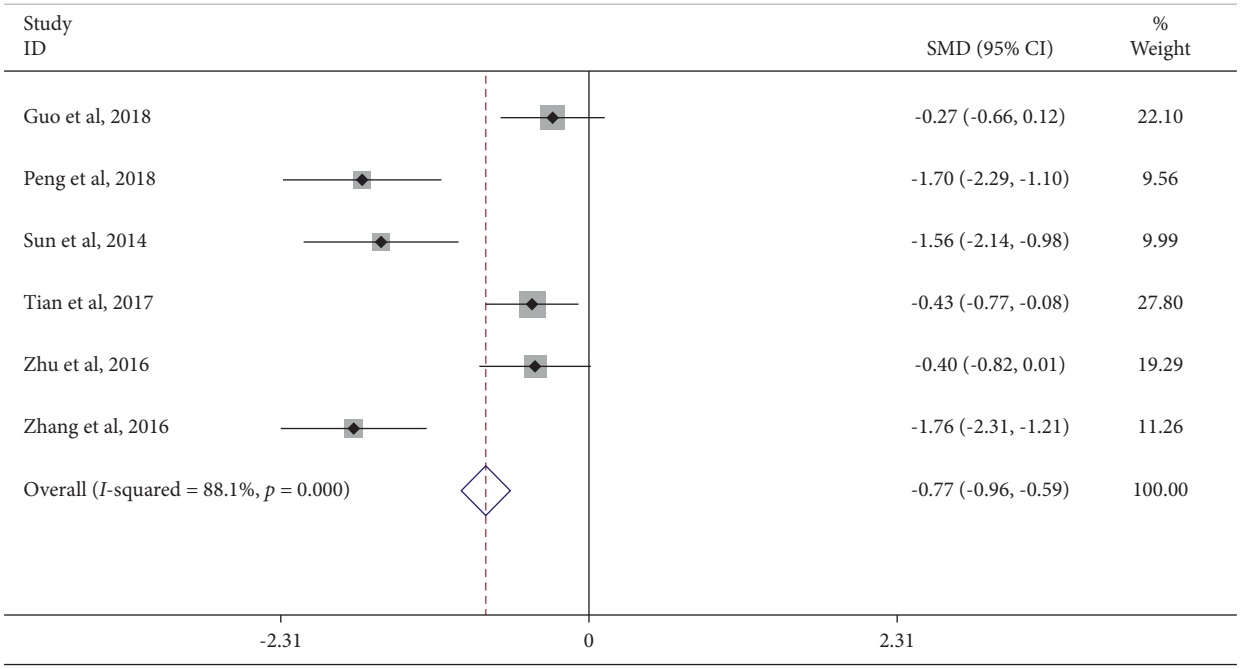

Figure 7: Forest plot of JTG capsule vs. conventional therapies on WOMAC score.

prolong the latent period of pain response by conducting the hot plate test and the acetic acid writhing test on mice. JTG capsule is an oral medication that has the advantage of good compliance and safety, with no apparent effect on hepatic and renal function [39]. Pharmacological studies have shown that JTG capsule can regulate the expression of osteopontin and matrix metalloproteinase 3, thereby affecting the metabolism of articular cartilage and subchondral bone, and can effectively improve the symptoms of postmenopausal osteoarthritis [40]. Modern pharmacological studies have shown that artificial tiger bone is rich in calcium, which can improve bone toughness and increase bone density. At the same time, the artificial tiger bone is rich in many factors required for bone growth, which can

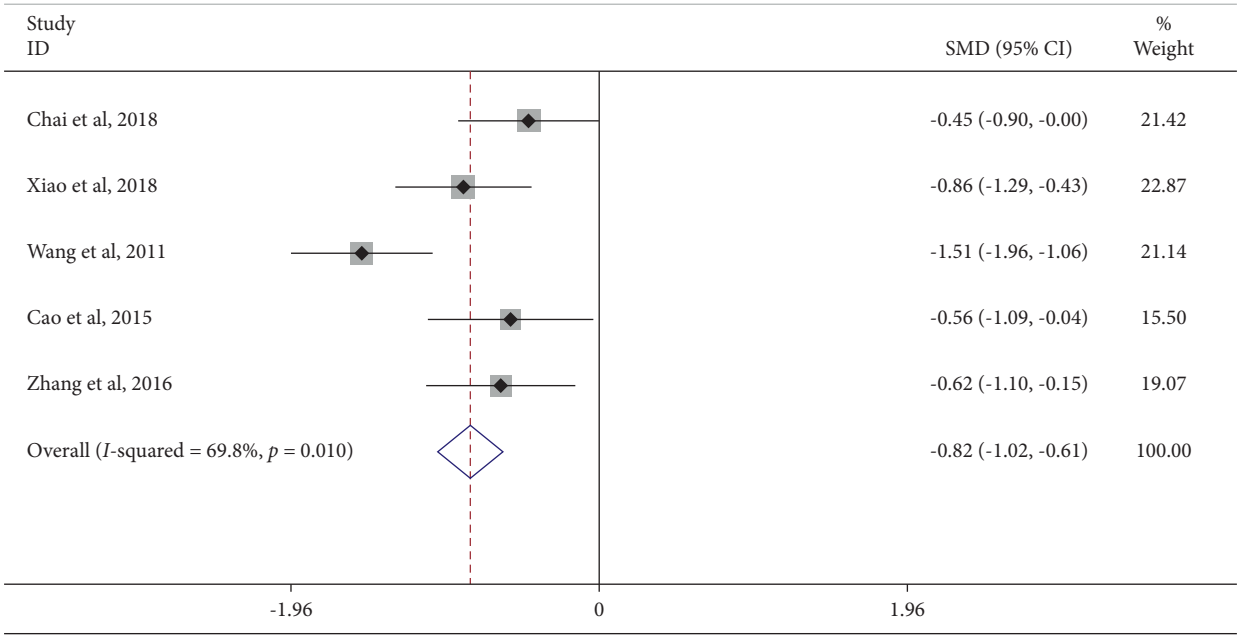

Figure 8: Forest plot of JTG capsule vs. conventional therapies on the Lequesne score.

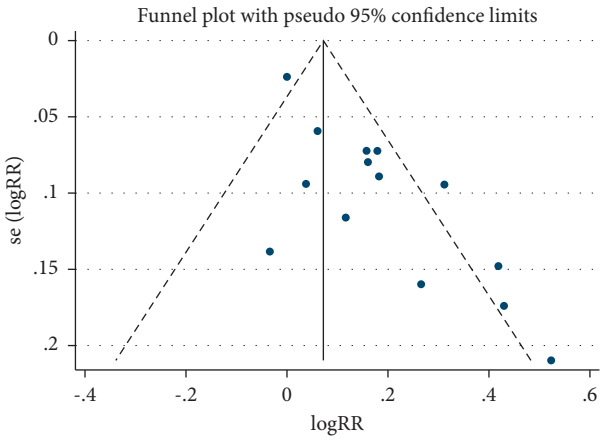

Figure 9: Funnel plot of the total effective rate.

provide adequate nutrition for chondrocytes, improve cartilage cell metabolism, and inhibit degenerative diseases of the human body. The pharmacology of the active ingredient of JTG capsule, artificial tiger bone, and natural tiger bone is basically the same, and the safety is higher. Therefore, the adverse reaction rate of the observation group is low [7].

To sum up, our research showed that the JTG capsule could reduce the pain of KOA patients, which is expected to become an optional treatment for KOA, and may be related to the inhibition of inflammatory factors IL-1 and IL-6. However, in order to verify this mechanism, more experiments are expected.

5. Limitations

Unavoidably, the comprehensive analysis of all studies in this research conducted had some limitations, which should be recognized. First, due to unclear allocation concealment, blinding of participants and personnel, and blinding of outcome assessments, some of the included studies may be of average quality. Second, although this research aimed to conduct an unbiased literature search without language restriction, all the experiments in this review were held in China and published in Chinese. There were no relevant foreign experiments, which may lead to potential prejudice, thus limiting the representativeness of this research. Third, few studies mentioned adverse reactions during or after treatment. Besides, no trials reported long-term follow-up, so the long-term safety of the intervention is still unknown.

6. Conclusions

This meta-analysis showed that the JTG capsule may have effects on KOA in the following aspects: relief of pain and improvement of functional activity. However, no conclusions about other indicators or safety issues could be drawn from the available evidence. Higher-quality and more rigorous research on larger samples are expected to confirm current results.

Data Availability

The datasets supporting the conclusions of this study are included within the article.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

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Supplementary Materials

Subgroup analysis of VAS score was performed for the mean baseline of sample size ≥80 and <80 (Supplemental Figure 1). Subgroup analysis of WOMAC score was performed for the mean baseline of age ≥60 and <60 (Supplemental Figure 2). (*Supplementary Materials*)

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Research Article

Distal Acupoints Outperform Proximal Acupoints in Treating Knee Osteoarthritis: A Randomized Controlled Trial

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Objectives. To determine the difference in efficacy between distal and proximal acupoints in treating knee osteoarthritis. *Design*. Ninety-two eligible participants were randomly assigned into three groups: distal acupoint treatment group (DG), proximal acupoint treatment group (PG), and sham acupuncture control group (SG). Primary and secondary outcomes were compared before and after the intervention. *Interventions*. A single acupuncture treatment was applied at *Quchi* (LI11), *Shaohai* (HT3), and *Tianjing* (TE10) in DG participants; *Yanglingquan* (GB34), *Yinlingquan* (SP9), and *Heding* (EX-LE2) in PG participants; and *Zhongwan* (CV12) and *Liangmen* (ST21) in SG participants. *Main outcome measures*. The visual analog scale (VAS) and active and passive knee range of motion (ROM) were used primarily to evaluate the treatment efficacy. The radial pulse diagnosis was used as a secondary outcome measure to determine the changes in the spectral energy of the radial pulses. *Results*. The three groups had significant pain reduction after acupuncture ($p < 0.05$). DG had the greatest difference in pre- and post-VAS scores. Compared with the control group, significant improvement was observed in DG active and passive ROM and in PG passive ROM ($p < 0.05$). The high-frequency spectral energy of the left *chi* pulse in PG was significantly decreased, while the low-frequency spectral energy of the left *cun* pulse in PG and the left *guan* pulse in DG were significantly increased after acupuncture. *Conclusions*. Distal acupoints provide better pain relief and improve ROM than proximal acupoints in treating knee osteoarthritis. Significant changes in spectral energy were observed in the left *cun*, *guan*, and *chi* pulses, indicating pain relief and blood flow improvement after acupuncture.

1. Introduction

Knee osteoarthritis (KOA) is a common chronic progressive joint disease in aging population. The main clinical manifestations include persistent knee pain, morning stiffness, swelling, and restricted mobility. The 2018 Taiwan National Health Insurance statistics showed that 857,979 patients were diagnosed with KOA (ICD-10-CM: M17). Most patients were middle-aged and elderly above 50 years old (89.7%) [1]. A 15-year retrospective Taiwanese study reported that OA is markedly prevalent among women and increases with age noticeably [2, 3]. Moreover, the total knee replacement incidence rate tripled among patients with KOA. Some other clinical solutions include pharmacological intervention such as the use of NSAIDs, lifestyle changes, and physical treatments [4].

Acupuncture is among the common non-pharmacological treatments of KOA in Taiwan. The 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee has included acupuncture among the conditional recommendations [5]. Some systematic reviews of randomized controlled trials (RCTs) related to acupuncture in KOA have concluded that acupuncture can

reduce pain and improve knee function compared with sham acupuncture [6]. To date, studies comparing the acupuncture effect between distal and proximal acupoints are lacking. Therefore, we investigated the differences in pain reduction and improvement in knee function primarily through the visual analog scale (VAS) and knee range of motion (ROM). Also, objective assessment of spectral energy (SE) in radial pulses through a pulse sphygmograph was performed as a secondary outcome measure.

Radial pulse diagnosis plays an important role in traditional Chinese medicine (TCM) in distinguishing the disease position, disease pathogenesis, and the disease prognosis. Also, it guides TCM physicians in clinical decision of treatment strategy and evaluation of the treatment efficacy [7]. Traditionally, TCM physicians palpate radial pulses on both wrists of the patient using the index, middle, and ring fingers concurrently or individually [8]. Three regions corresponding to these fingers are named *cun*, *guan*, and *chi* (Chun, Guan, and Chy pulses were used in some studies), respectively [7]. Figure 1 shows the respective visceral organs corresponding to these pulses. In the modernization of pulse diagnosis, researchers have actively developed modern pulse diagnostic tools to quantify and digitalize pulse profiles since 1950 [8]. The radial pulse wave dynamics are often analyzed using time- and frequency-domain analyses. Frequency-domain analyses measure changes in SE. Wei et al. concluded that patients under metabolic stress or acute illnesses show large variations beyond 10 Hz of SE [9]. Several studies using frequency-domain analyses include observations of rhinitis, dyspepsia, atopic dermatitis, hypertension, colorectal cancer, and heat- and cold-stress patients [10–15].

There is a general perception that proximal acupoints near the diseased location are usually more effective. This study provides a novel understanding that distal acupoints outperform proximal acupoints in treating KOA using objective and subjective outcome measures.

2. Materials and Methods

2.1. Study Setting and Design. This study was conducted in the Acupuncture Department of the China Medical University Hospital (CMUH), Taichung, and Yiyuantang Chinese Medicine Clinic, Hsinchu, Taiwan, from April 2019 through March 2020. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklists were used to guide this three-arm, single-blinded, randomized study. Figures 2 and 3 illustrate the study flow and procedure.

2.2. Inclusion and Exclusion Criteria of Study Participants. We recruited eligible participants aged 20 or above with acute or chronic knee pain. Also, these participants must meet three out of six symptoms recommended by the ACR: (i) any gender aged 50 years or above; (ii) having less than 30 min of morning stiffness; (iii) crepitus on active motion; (iv) bony tenderness; (v) bony enlargement; and (vi) no palpable warmth. The following are the conditions that were

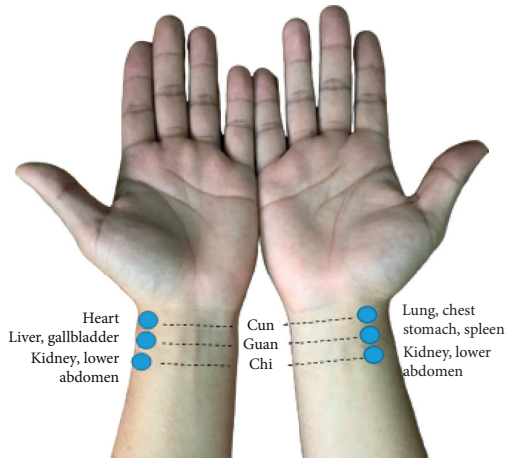


Figure 1: Pulse diagnosis in TCM illustrating the relationship between radial pulses and the corresponding visceral organs. Right *cun* (lung, chest); right *guan* (stomach, spleen); right *chi* (kidney, lower abdomen); left *cun* (heart); left *guan* (liver, gallbladder); and left *chi* (kidney, lower abdomen).

excluded in this study: (a) participants with malignancy, any acute medical condition, poorly controlled diabetes or hypertension, a motor or sensory nerve defect, blood clotting disease, mental illness, dementia, mental retardation, or other abnormal person on the organic mind; (b) participants with intra-articular solid or hyaluronic acid injection in the past three months; (c) participants who had undergone knee surgery, knee trauma, congenital knee deformation, severe knee varus or valgus deformation, or endocrine, metabolic, infectious, inflammatory, secondary degenerative knee arthritis caused by problems with rheumatic immune diseases; (d) participants unable to walk; (e) participants who were hypersensitive to needles; and (f) participants who were unwilling to provide written informed consent.

2.3. Randomization. The enrolled participants were randomly assigned to three groups: distal acupoint treatment group (DG), proximal acupoint treatment group (PG), and sham acupuncture control group (SG). We used a sealed envelope system for randomization. Randomly generated treatment allocations were written on each slip and inserted into sealed opaque envelopes. The envelope was randomly picked by the patient after written informed consent was received.

2.4. Intervention. A single 20-minute acupuncture treatment was provided to each participant. The participants were asked to complete the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire in addition to the collected demographical information, including age, gender, height, weight, body mass index, and TCM meridian-related area of knee pain at baseline. Table 1 and Figure 4 describe and illustrate the acupoints used in this study. In a meta-analysis of 18 RCTs involving KOA, GB34, SP9, and EX-LE2 were one of the common local acupoints used [17]. The distal acupoints on the upper arm, LI11, HT3,

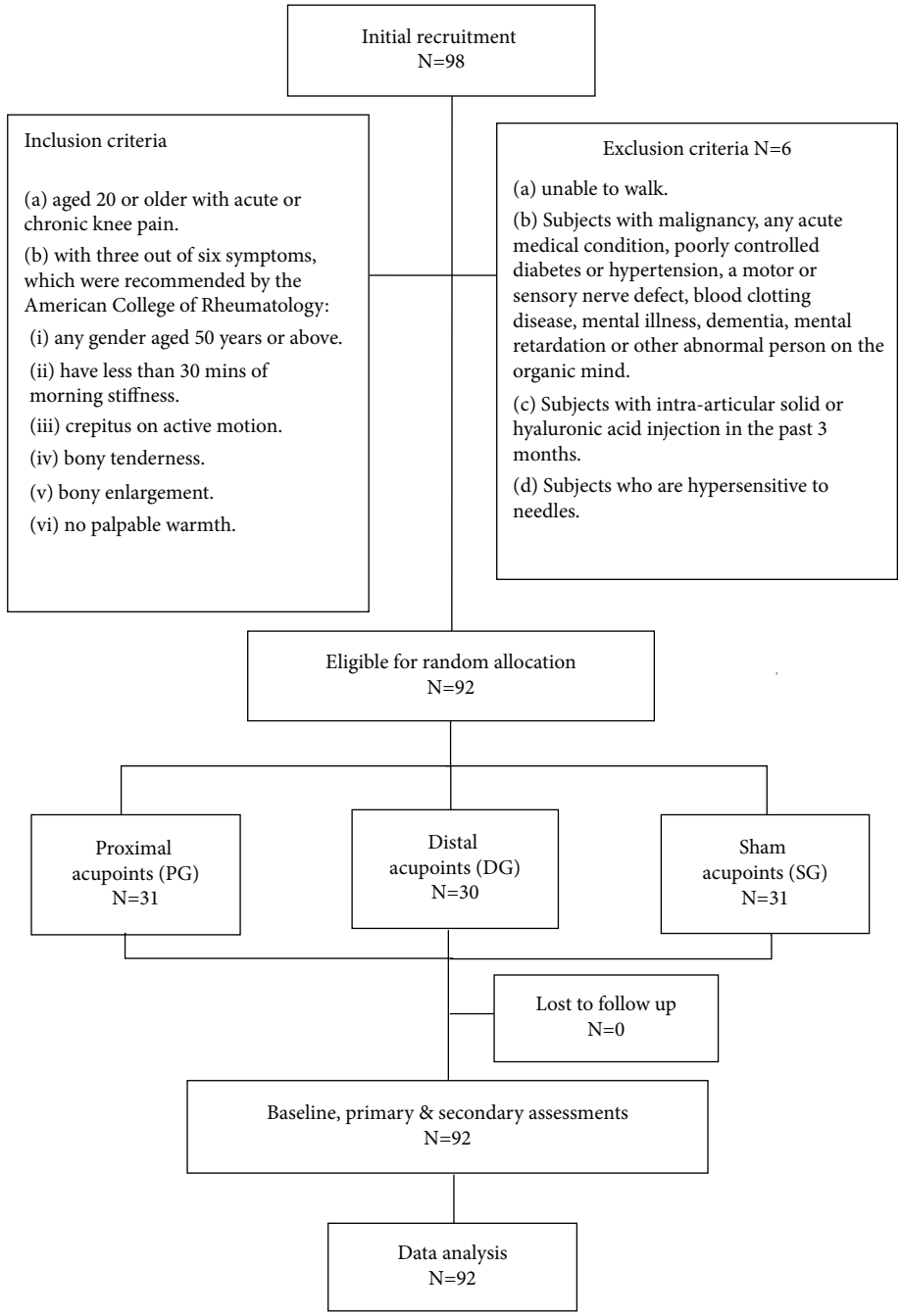


Figure 2: The study flow diagram.

and TE10, were selected based on the holographic counterpoint theory in acupuncture. The sham acupoints at the upper abdominal region, CV12 and ST21, were selected, as there were no existing clinical studies reporting the relationship between these points and KOA treatment.

All participants were blinded in this single-blinded RCT. The acupuncture treatment was performed by a qualified TCM physician with over ten years' clinical experience. Each acupoint was located, and a circular intermediate ring adhered to the skin. Disposable, stainless steel acupuncture needles (0.25×40 mm; Asoon Acupuncture Needles, Taiwan) were inserted through the center of the ring for each acupoint in both DG and PG participants at the safe needling depth, and the recommended angle is described in Table 1. Moderate lift and thrust stimulations were applied while inserting and repeated after 10 min. The needles were inserted superficially without penetrating the skin through the ring for the sham acupoints. The needles were retained for 20 min.

During the acupuncture treatment, the response of the subjects was closely monitored by the qualified TCM physician. No adverse events such as acupuncture syncope, extreme pain, and hematoma were reported in all groups.

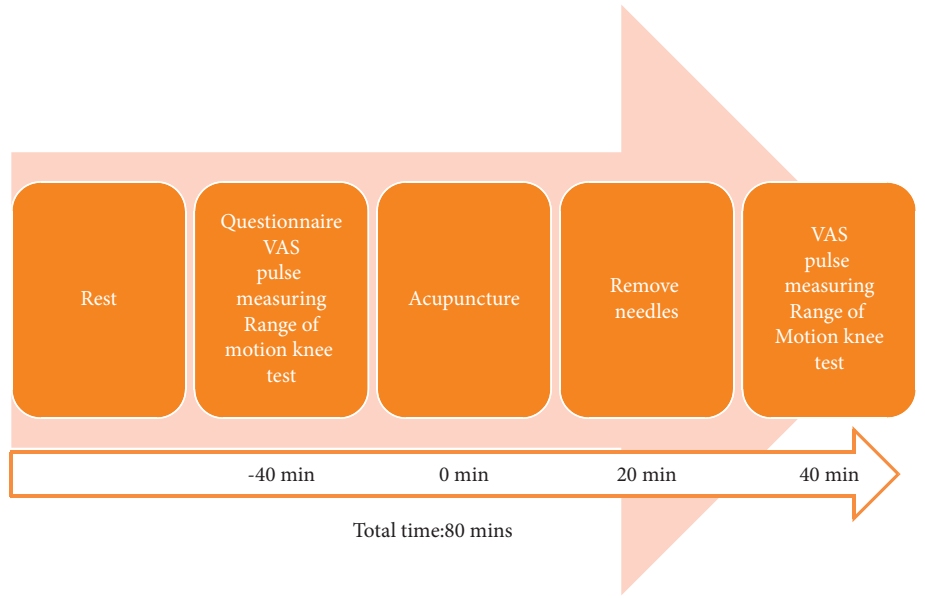


Figure 3: The study procedure and timeline. Each participant underwent a baseline assessment through a questionnaire. VAS, pulse assessment, and knee ROM tests were performed before and after acupuncture.

Table 1: Distal acupoints, proximal acupoints, and sham acupoints were used in this study.

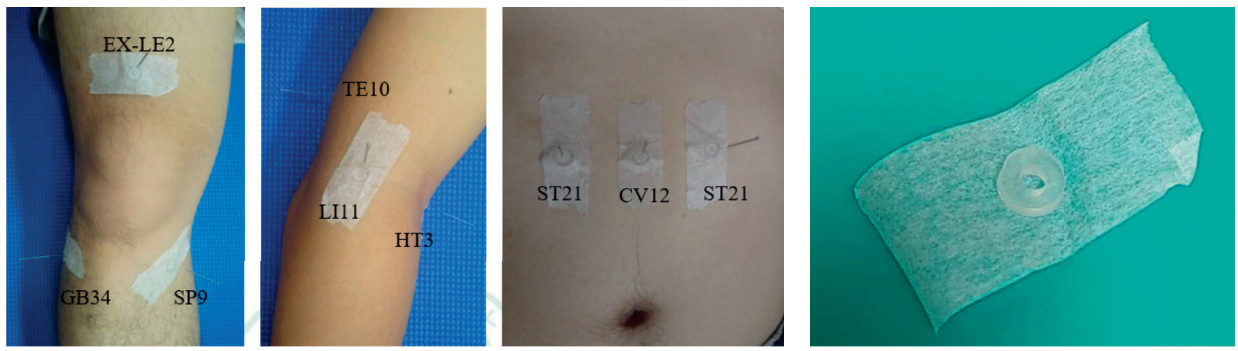
Group	Acupoints	Location [16]	Application
Distal (DG)	*Quchi* (LI11)	On the lateral aspect of the elbow, at the midpoint of the line connecting LU5 with the lateral epicondyle of the humerus.	Bilateral, perpendicular insertion, 15–30 mm depth
	Shaohai (HT3)	On the anteromedial aspect of the elbow, just anterior to the medial epicondyle of the humerus, at the same level as the cubital crease.	Bilateral, perpendicular insertion, 15–30 mm depth
	Tianjing (TE10)	On the posterior aspect of the elbow, in the depression 1 B-cun proximal to the prominence of the olecranon.	Bilateral, oblique insertion (30°), 15–30 mm depth
Proximal (PG)	*Yanglingquan* (GB34)	On the fibular aspect of the leg, in the depression anterior and distal to the head of the fibula.	Bilateral, perpendicular insertion, 15–30 mm depth
	Yinlingquan (SP9)	On the tibial aspect of the leg, in the depression between the inferior border of the medial condyle of the tibia and the medial border of the tibia.	Bilateral, perpendicular insertion, 15–30 mm depth
	Heding (EX-LE2)	Above the knee, in the depression of the midpoint of the superior patellar border.	Bilateral, oblique insertion (30°), 15–30 mm depth
Sham (SG)	*Zhongwan* (CV12)	On the upper abdomen, 4 B-cun superior to the center of the umbilicus, on the anterior median line.	Unilateral, perpendicular nonpenetrating insertion.
	Liangmen (ST21)	On the upper abdomen, 4 B-cun superior to the center of the umbilicus, 2 B-cun lateral to the anterior median line.	Bilateral, perpendicular nonpenetrating insertion.

2.5. Study Objective and Hypothesis. This study primarily compared the immediate therapeutic effects of proximal and distal acupoints in treating KOA, including reduction of pain intensity and improvement of the knee flexibility. We hypothesized that (a) the distal and proximal acupoints may be differentially effective in relieving knee pain and improving knee flexibility and (b) the *chi* pulse will be an effective indicator for evaluating the treatment effectiveness of KOA.

2.6. Outcome Measures. All the assessments were performed within 40 min before and after the acupuncture (Figure 3).

2.6.1. Baseline Assessments. Demographical information including age, gender, height, weight, body mass index, and affected TCM meridians distribution in addition to the WOMAC questionnaire was collected at the baseline 40 min before the acupuncture.

(1) Western Ontario and McMaster Universities Arthritis Index. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire is widely used to assess the symptoms and physical ability of patients with KOA or hip osteoarthritis [18]. This self-reporting questionnaire evaluates three dimensions, including pain (five questions), stiffness (two questions), and physical



(a) (b)

Figure 4: Acupoints used in this study (a) and a circular intermediate ring used (b) for all acupoints.

functions (17 questions), which can be completed within 5–10 min. An ordinal scale of zero to four was rated for each question.

(2) Affected TCM Meridian Distribution. Each participant was asked to identify the area of knee pain following TCM meridians and collaterals. Six options were given: lateral (Gallbladder Meridian of Foot—Shaoyang), anteromedial (Spleen Meridian of Foot—Taiyin), medial (Liver Meridian of Foot—Jueyin), posteromedial (Kidney Meridian of Foot—Shaoyin), posterior (Bladder Meridian of Foot—Taiyang), and anterolateral (Stomach Meridian of Foot—Yangming).

Figure 5: Knee ROM measured with a goniometer.

2.6.2. Primary Outcome Measures

(1) VAS. The VAS is a 0-to-10 line on the left "0" (it means no pain) and on the right "10" (it means extreme pain). The patients were asked to mark their current pain levels on the line before and after the acupuncture. A 10-min rest was given before the second assessment was performed at postintervention.

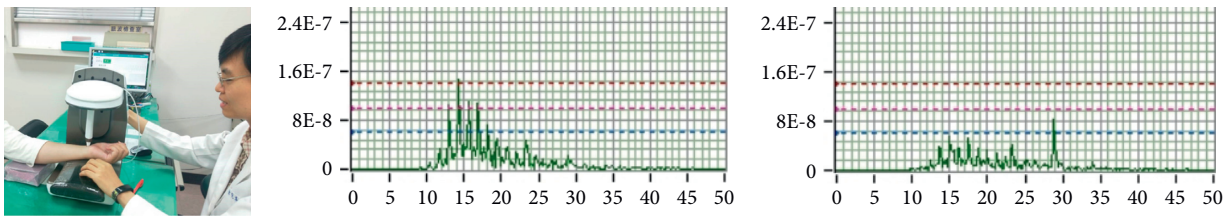
(2) ROM. ROM is used to determine knee joint flexibility. Active ROM and passive ROM were assessed. The active ROM is the extent of motion when the subject moves the joint voluntarily, while the passive ROM is the extent of motion when external force is applied by the investigator to move the knee. A goniometer was used to measure the angle ROM of the knee joint before and after the acupuncture (Figure 5). A 10-min rest was given before the second assessment was performed at postintervention.

2.6.3. Secondary Outcome Measures

(1) Pulse Assessment. The acupuncture effects on the high-frequency SE ($SE_{13-50Hz}$) in the bilateral radial pulses were assessed using a noninvasive pulse sphygmograph (Pen Pulse Analysis System Model PPAS-96; Asia Plus Biotech Co., Taiwan) before and after the intervention. This objective diagnostic tool comprised a highly precise, detachable pulse detection sensor pen with a stable Y-axial movable frame. A pulse signal analyzer containing a filter, an amplifier, and a signal-recording card was connected to collect the information for analysis. A frequency response of 0.1–50 Hz and a sampling rate of 3,000 Hz were designed in this device. The input voltage of USB_DC5V was used. The fast Fourier transform processed and digitalized the physiological signals of the radial pulses. A real-time display of the pulse spectrogram and time- and frequency-domain analyses were available as the digital output.

Each participant was seated in front of the device. *Cun*, *guan*, and *chi* pulse positions on each wrist were located and marked to ensure that same positions were subsequently repeatedly assessed at postintervention. The *guan* pulse was first identified at the prominence distal to the radial styloid process [7]. Then, the *cun* and *chi* pulses were located at the distal and proximal aspects, respectively. The assessments were performed before and after acupuncture. A 10-min rest was given before the second assessment was performed at postintervention. Figure 6 illustrates the vertical movement of the pulse detection sensor pen at each individual pulse. The design and mechanism of PPAS-96 were described in previous studies [7, 8].

2.7. Sample Size. With reference to various studies related to pulse sphygmograph, a sample size of 30 participants was applied in this study. Huang et al. reported a significant



(a) (b) (c)

Figure 6: (a) Assessing each pulse on the wrist of the participants using the pulse detection sensor pen attached to the pulse sphygmograph; (b) graphical presentation of $SE_{13-50Hz}$ of left *chi pulses* before acupuncture; and (c) graphical presentation of $SE_{13-50Hz}$ of left *chi pulses* after acupuncture.

difference of 0.0029 in $SE_{13-50Hz}$ between the pre- and postintervention to compare the effects of acupuncture on radial pulse in healthy subjects and patients with dyspepsia [7, 14]. Based on the mean change and standard deviation in Huang et al.'s study, Kim et al. and Shin et al. had calculated a sample size of 25 subjects based on a 5% type 1 error, 80% power, and 5% dropout rates in their single-arm studies [19, 20].

2.8. Statistical Analysis. IBM SPSS Statistics V21.0 package software was used for statistical analyses. The descriptive statistics, including height, weight, WOMAC Index, VAS, and active and passive knee ROM data were analyzed. Paired *t*-tests were used to examine the spectral energy changes in the six pulses before and after acupuncture. Furthermore, one-way analysis of variance (ANOVA) was used to first investigate the preintervention results in BMI, VAS, and active and passive knee ROM between the three groups. The Scheffe method was used to identify group differences when a statistically significant difference was found. ANOVA was subsequently adopted to examine the postintervention differences in VAS and active and passive knee ROM between the three groups if no difference was found. Also, the difference in the pre-post interventions of the three groups regarding VAS, active ROM, and passive ROM was compared using ANOVA. The Scheffe method was further used to determine group differences.

2.9. Ethical Approval and Consent to Participate. This study was approved by the China Medical University Hospital Research Ethical Committee, Taichung, Taiwan, under protocol nos. CMUH108-REC2–033 on 10 April 2019. This study was also registered at http://www.clinicaltrials.gov under identifier: NCT03925467. We obtained written informed consent from each participant before commencing the study.

3. Results

Ninety-eight individuals were enrolled, but six were excluded because they were ineligible or insensitive to needles. We included 92 eligible participants who were randomly allocated to DG (30 participants), PG (31 participants), and SG (31 participants).

3.1. Demographic Characteristics of the Patients. The demographic characteristics, including gender, age, height, weight, and BMI, are presented in Table 2. There were 71 female and 21 male participants with an average age of 65 years. There was no significant difference in BMI, VAS, WOMAC, or active and passive knee ROM ($p > 0.05$) before the intervention when compared between the three groups using ANOVA (Table 3).

3.2. Affected TCM Meridian Distribution. As shown in Table 4, 76.1% of the participants suffered pain at the anteromedial aspect, while 63% suffered pain at the medial aspect of the knees, corresponding to the pathway of the spleen and liver meridians at the knee, respectively. There were often multiple meridians being affected concurrently.

3.3. VAS. Figure 7 compares the pain scores before and after the intervention. All three groups had significant differences ($p < 0.05$) in the VAS, although the pain reduction in SG is the least. Table 5 provides the VAS differences between the three groups and post-VAS comparison. A post hoc comparison test revealed no significant difference between the PG and DG pain scores. However, significant pain reduction was found when comparing PG and SG, and DG and SG ($p < 0.05$). The greatest decrease in pain scores was observed in DG, indicating that this group of participants had the most significant improvement in pain.

Moreover, both PG-SG VAS and DG-SG VAS reached statistical significance of $p < 0.005$ and $p < 0.001$, respectively. A further step was taken to explore their Cohen's *d* effect sizes, and it was found that PG-SG VAS and DG-SG VAS differences were 0.80 and 1.05, respectively. This demonstrated that the size of difference between DG and SG VAS difference was larger than that between PG and SG VAS difference.

3.4. ROM. Figure 8 illustrates that DG showed a significant increase in knee flexibility when active and passive ROM were performed ($p < 0.05$). In contrast, PG showed the most significant increase in knee flexibility when passive ROM was performed after acupuncture.

Table 6 provides the active and passive ROM differences between the three groups, postintervention comparisons, and post hoc analysis. There were insignificant changes in

Table 2: Demographic characteristics of the study participants.

	All	PG	DG	SG
Male	21	10	6	5
Female	71	21	24	26
Age (years)	65.32 ± 10.02	64.84 ± 10.14	64.73 ± 9.57	66.35 ± 10.56
Height (m)	1.59 ± .08	1.60 ± .08	1.58 ± .07	1.58 ± .08
Weight (kg)	63.00 ± 12.66	62.55 ± 11.86	63.18 ± 13.50	63.26 ± 13.01
BMI (kg/m^2)	24.91 ± 4.30	24.41 ± 4.69	25.09 ± 4.12	25.25 ± 4.15

Values are presented as mean ± SD. PG = proximal acupoints group; DG = distal acupoints group; SG = sham acupoints group; BMI = body mass index.

Table 3: Comparing the differences in BMI, WOMAC, VAS, and active and passive knee ROM in the three groups before the intervention using ANOVA.

	PG	DG	SG	p value
BMI (kg/m^2)	24.41 ± 4.69	25.09 ± 4.12	25.25 ± 4.15	0.72
WOMAC (%)	27.39 ± 16.99	28.4 ± 16.97	32.58 ± 18.58	0.47
VAS	3.74 ± 1.44	3.67 ± 1.67	3.81 ± 1.82	0.95
Active ROM (°)	122.84 ± 11.89	121.27 ± 10.41	119.42 ± 13.01	0.53
Passive ROM (°)	126 ± 10.71	125.87 ± 8.65	124.71 ± 11.53	0.87

Values are presented as mean ± SD. PG = proximal acupoints group; DG = distal acupoints group; SG = sham acupoints group; BMI = body mass index.

Table 4: Affected TCM meridian distribution in the participants.

Group	Gallbladder (%)	Spleen (%)	Liver (%)	Kidney (%)	Bladder (%)	Stomach (%)
All	29.3	76.1	63.0	18.5	16.3	47.8
PG	19.4	77.4	64.5	29.0	19.4	54.8
DG	23.3	86.7	60.0	6.7	6.7	50.0
SG	45.2	64.5	64.5	19.4	22.6	38.7

PG = proximal acupoints group; DG = distal acupoints group; SG = sham acupoints group.

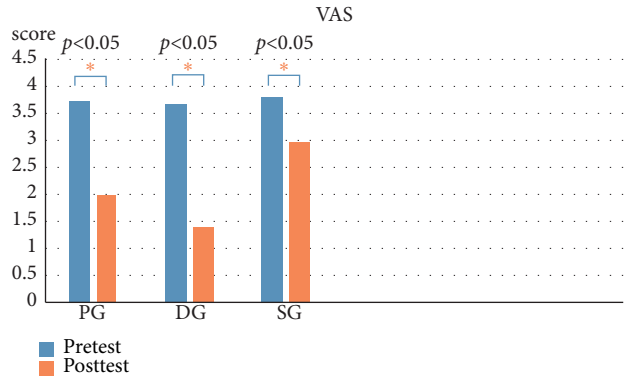


Figure 7: Pain scores compared before and after intervention.

Table 5: VAS differences between the three groups, post-VAS comparisons, and post hoc analysis.

	PG	DG	SG	p value (PG vs DG vs SG)	Post hoc tests
Post-VAS	2.00 ± 1.63	1.40 ± 1.67	2.97 ± 2.06	0.001	SG > DG
VAS difference	−1.74 ± 1.12	−2.27 ± 1.55	−0.84 ± 1.13	0.001	PG > SG; DG > SG

Values are presented as mean ± SD. PG = proximal acupoints group; DG = distal acupoints group; SG = sham acupoints group.

the active and passive ROM differences in SG. A post hoc comparison test showed no significant difference between PG and DG passive ROM. However, marked improvement in passive knee flexibility was observed when comparing PG and SG, and DG and SG ($p < 0.05$).

3.5. Radial Pulse Spectral Energy. The low-frequency SE ($SE_{0–10Hz}$) and high-frequency SE ($SE_{13–50Hz}$) were determined in each pulse on both wrists of participants in each group. $SE_{13–50Hz}$ significantly decreased in the left *chi* pulse, while $SE_{0–10Hz}$ significantly increased in the left *cun* pulse

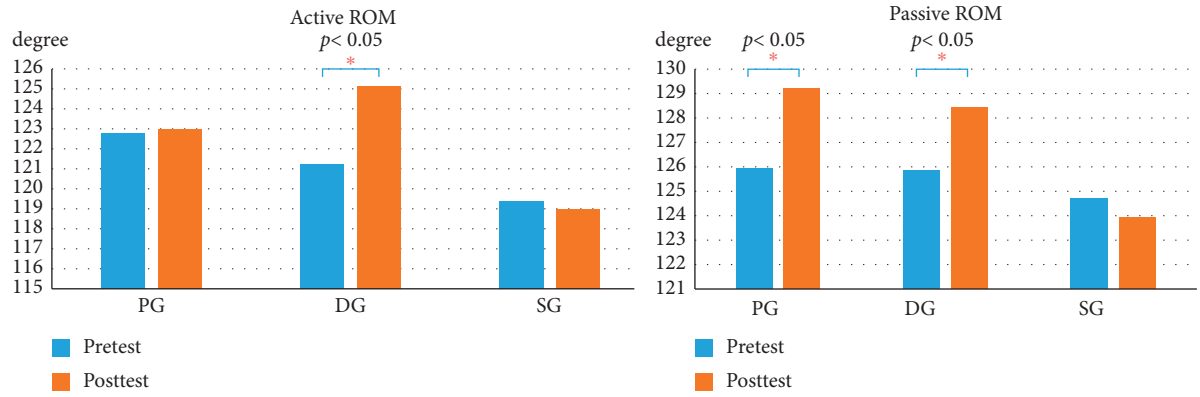


Figure 8: Active and passive knee ROM before and after intervention.

Table 6: Active and passive ROM differences between the three groups, postintervention comparisons, and post hoc analysis.

	PG	DG	SG	p value (PG vs DG vs SG)	Post hoc tests
Postintervention active ROM	122.97 ± 23.29	125.20 ± 6.96	119.03 ± 12.56	0.31	Not applied
Active ROM difference	0.13 ± 16.38	3.93 ± 5.64	−0.39 ± 3.40	0.21	Not applied
Postintervention passive ROM	129.23 ± 11.67	128.43 ± 7.53	123.94 ± 11.03	0.10	Not applied
Passive ROM difference	3.23 ± 5.21	2.57 ± 4.08	−0.77 ± 3.53	0.001	DG > SG; PG > SG

Values are presented as mean ± SD. PG = proximal acupoints group; DG = distal acupoints group; SG = sham acupoints group.

after acupuncture in PG ($p < 0.05$; Table 7). In contrast, SE_{0-10Hz} significantly increased in the left *guan* pulse in DG ($p < 0.05$; Table 8). An increasing trend was observed in the SE_{0-10Hz} of right *cun* in PG and the left *cun* in DG ($p = 0.07$). Table 9 shows that no significant difference was observed in the six pulses of participants in the SG.

4. Discussion

4.1. Prevalence and Demographic Factors. Our study contained a higher proportion of female participants (77.2%) with an average age of 65 years. This agrees with the 2019 Taiwan's National Health Insurance statistics that reported that females have a higher prevalence rate, and the majority were middle-aged and elderly above 50 years old. [1] According to the recommendations from the Taiwan National Health Agency, the normal adult BMI should be maintained between 18.5 and 23.9 (kg/m^2) [21]. We observed that all the participants were considered overweight with an average BMI above 24 kg/m^2. A meta-analysis reported that overweight and obesity had been associated with a significantly high risk of KOA [22]. A higher score of WOMAC Osteoarthritis Index represents worse health status with noticeable joint pain, stiffness, functional limitations, and impact on quality of life [23]. An index score of ≤70% indicates mild disability (low risk), while that of >70% is noted as severe disability (high risk) [24]. The average score in each group was 28–34%, representing that all participants had mild disability.

4.2. Effects of Acupuncture on Pain Reduction and Knee Flexibility. The findings in pain reduction and knee flexibility suggest that our primary hypothesis is true; that is, the distal and proximal acupoints are differentially effective in relieving knee pain and improving knee flexibility.

A decrease in the VAS score is generally correlated with the effectiveness of acupuncture at proximal and distal acupoints. Marked pain reduction was observed in PG and DG patients after acupuncture in this study. Studies have revealed the immediate analgesic effect within 30 min of acupuncture treatment [25]. Some animal studies have concluded that acupuncture reduces visceral pain and induces distinct changes in neuronal activity, including the concentration level of cytokines and neurotransmitters that are related to pain or inflammation in the brain-gut axis [26]. Interestingly, the VAS score most significantly decreased in the DG, indicating the most distinct improvement in pain compared with the PG. We speculated that the concept of biohologrаphic acupuncture had played a part in this phenomenon. Biohologrаphic acupuncture uses the concept of "Embryo Containing Information of the Whole Organism (ECIWO)" developed during the 1980s. The principle involves the hypothesis that the whole organism is projected in a circumscribed part of body [27]. This principle has been used in auricular acupuncture, foot reflexology, Yamamoto's new scalp acupuncture, and others. According to the concept, the elbow corresponds to the knees. Acupuncturing the acupoints LI11, HT3, and TE10 around the elbow reduced pain in the knees. Moreover, *Quchi* (LI11) belongs to the Large Intestine Meridian of the Hand—*Yangming*, which has an abundant supply of *qi* and blood according to the meridian theory [28]. The Large Intestine Meridian of the Hand—*Yangming* is connected to the Stomach Meridian of the Foot—*Yangming*, which passes through the knees. We also observed a lesser significant pain reduction in the SG

Table 7: Spectral energy parameters of the radial pulse wave in PG.

Parameter	Position	Preintervention	Postintervention	p value
SE_{0-10Hz}	Left *cun*	$2.898E-10 \pm 2.133E-10$	$3.559E-10 \pm 2.479E-10$	**0.03**
	Left *guan*	$2.629E-10 \pm 1.768E-10$	$2.562E-10 \pm 1.638E-10$	0.82
	Left *chi*	$2.046E-10 \pm 1.031E-10$	$2.337E-10 \pm 2.349E-10$	0.43
	Right *cun*	$3.041E-10 \pm 2.502E-10$	$3.679E-10 \pm 2.304E-10$	0.07
	Right *guan*	$2.691E-10 \pm 1.805E-10$	$3.324E-10 \pm 2.576E-10$	0.08
	Right *chi*	$1.947E-10 \pm 1.260E-10$	$2.124E-10 \pm 1.775E-10$	0.52
$SE_{13-50Hz}$	Left *cun*	$9.688E-14 \pm 2.108E-13$	$9.788E-14 \pm 1.395E-13$	0.97
	Left *guan*	$1.101E-13 \pm 2.313E-13$	$8.375E-14 \pm 1.322E-13$	0.24
	Left *chi*	$1.017E-13 \pm 1.781E-13$	$5.891E-14 \pm 9.056E-14$	**0.047**
	Right *cun*	$1.288E-13 \pm 2.502E-13$	$1.455E-13 \pm 3.827E-13$	0.63
	Right *guan*	$1.967E-13 \pm 4.383E-13$	$1.881E-13 \pm 3.536E-13$	0.74
	Right *chi*	$8.860E-14 \pm 1.228E-13$	$1.551E-13 \pm 4.413E-13$	0.40

Values are presented as mean ± SD. SE = spectral energy; E = exponential notation.

Table 8: Spectral energy parameters of the radial pulse wave in DG.

Parameter	Position	Preintervention	Postintervention	p value
SE_{0-10Hz}	Left *cun*	$3.144E-10 \pm 2.521E-10$	$3.871E-10 \pm 2.777E-10$	0.07
	Left *guan*	$2.449E-10 \pm 1.598E-10$	$3.243E-10 \pm 2.697E-10$	**0.02**
	Left *chi*	$2.738E-10 \pm 2.062E-10$	$2.405E-10 \pm 1.775E-10$	0.37
	Right *cun*	$2.884E-10 \pm 1.872E-10$	$3.643E-10 \pm 3.021$e-10	0.11
	Right *guan*	$3.441E-10 \pm 3.694E-10$	$3.547E-10 \pm 2.799E-10$	0.86
	Right *chi*	$3.025E-10 \pm 2.416E-10$	$2.756E-10 \pm 2.091E-10$	0.43
$SE_{13-50Hz}$	Left *cun*	$1.313E-13 \pm 1.894E-13$	$1.196E-13 \pm 1.468E-13$	0.74
	Left *guan*	$9.398E-14 \pm 1.216E-13$	$1.279E-13 \pm 1.732E-13$	0.10
	Left *chi*	$1.515E-13 \pm 2.734E-13$	$1.181E-13 \pm 2.057E-13$	0.12
	Right *cun*	$1.865E-13 \pm 2.833E-13$	$1.500E-13 \pm 2.714E-13$	0.17
	Right *guan*	$2.307E-13 \pm 3.367E-13$	$2.000E-13 \pm 3.660E-13$	0.68
	Right *chi*	$1.391E-13 \pm 1.936E-13$	$1.009E-13 \pm 1.317E-13$	0.24

Values are presented as mean ± SD. SE = spectral energy; E = exponential notation.

Table 9: Spectral energy parameters of the radial pulse wave in SG.

Parameter	Position	Preintervention	Postintervention	p value
SE_{0-10Hz}	Left *cun*	$3.405E-10 \pm 2.691E-10$	$3.219E-10 \pm 2.017E-10$	0.67
	Left *guan*	$2.927E-10 \pm 2.351E-10$	$3.126E-10 \pm 2.462E-10$	0.57
	Left *chi*	$2.606E-10 \pm 2.213E-10$	$2.647E-10 \pm 2.006E-10$	0.84
	Right *cun*	$3.633E-10 \pm 2.096E-10$	$3.451E-10 \pm 2.162E-10$	0.63
	Right *guan*	$3.178E-10 \pm 2.007E-10$	$3.187E-10 \pm 2.770E-10$	1.00
	Right *chi*	$2.545E-10 \pm 1.651E-10$	$2.378E-10 \pm 1.827E-10$	0.56
$SE_{13-50Hz}$	Left *cun*	$1.291E-13 \pm 1.663E-13$	$1.030E-13 \pm 1.543E-13$	0.24
	Left *guan*	$1.463E-13 \pm 1.670E-13$	$1.188E-13 \pm 1.323E-13$	0.30
	Left *chi*	$1.191E-13 \pm 1.454E-13$	$1.157E-13 \pm 1.834E-13$	0.87
	Right *cun*	$2.377E-13 \pm 4.028E-13$	$1.720E-13 \pm 2.490E-13$	0.14
	Right *guan*	$2.725E-13 \pm 3.287E-13$	$2.503E-13 \pm 3.823E-13$	0.42
	Right *chi*	$1.425E-13 \pm 1.464E-13$	$1.209E-13 \pm 1.262E-13$	0.43

Values are presented as mean ± SD. SE = spectral energy; E = exponential notation.

compared with the other two treatment groups. We suspected that a placebo effect could have contributed to this phenomenon.

The active knee ROM refers to the maximum extent of knee flexion-extension movement performed by the participants, while the passive knee ROM refers to that performed by an assessor. We observed that both proximal and distal acupoints improved joint flexibility. The distal acupoints significantly increased knee flexibility when active and passive ROM were performed, attributed to the result of greater pain reduction using the distal acupoints. In contrast, the proximal acupoints provided the most significant increase in knee flexibility when passive ROM was applied.

4.3. Effects of Acupuncture on Radial Pulses. Although we hypothesized that the *chi* pulse is an effective indicator for evaluating the treatment effectiveness of KOA, our findings

showed that the high-frequency SE was significantly reduced in the left *chi* pulse, while the low-frequency SE was significantly increased in the left *cun* pulse when proximal acupoints were used. In contrast, the low-frequency SE was significantly increased in the left *guan* pulse when distal points were used. An increasing trend was observed in the low-frequency SE of the right *cun* and left *cun* when proximal acupoints and distal acupoints were applied, respectively.

We attempt to explain these observations using TCM theory and modern research. The ancient text, *Huang Di Nei Jing*, has documented that "Diagnose the pulses before acupuncture, treat the disease condition upon distinguishing the severity or ease of the *Qi*" [29]. This observation was evidenced by several modern studies that concluded that acupuncture can significantly affect radial pulses [10–15]. A hemodynamic study on healthy volunteers reported that acupuncture at ST36 (*Zusanli*) resulted in increased low-frequency SE, which corresponded to the increased blood flow velocity [19]. According to the pulse diagnosis theory, the left *cun* pulse represents the heart, which governs the blood, while the left *guan* pulse represents the liver, which stores blood. We therefore speculated that the significant increase in the low-frequency SE of the left *cun* and left *guan* pulses after acupuncture corresponded to improved blood flow in the heart and liver, respectively.

A significant reduction of high-frequency SE of the left *chi* pulse when local acupoints were used inferred that pain and inflammation were reduced after acupuncture. We speculated that the higher density and intensity of high-frequency SE generally occurred before acupuncture due to the increased vasomotion triggered by pain. A study on the effect of pain on the autonomic nervous system reported that vasomotion generally increased when sympathetic nervous activity was stimulated by pain [30]. This observation coincides with the study by Huang et al. in which elevated high-frequency SE was reported in heat-stress patients due to expanded peripheral arterioles and reduced peripheral resistance [15]. We speculated that GB34, SP9, and EX-LE2 could have attenuated sympathetic nerve activity, decreased affected muscle contraction, and decreased peripheral vasomotion. This agrees with the observation in the acupuncture treatment in the low back pain study conducted previously [7]. As the left *chi* pulse corresponds to the kidneys and lower extremities, a direct response was reflected when the local acupoints were acupunctured. This phenomenon was unobserved in the distal acupoints' treatment.

Interestingly, we found that the distal and proximal acupoints differentially affected the *chi* radial pulses on each wrist. For instance, the high-frequency SE decreased significantly in the left *chi* pulse but increased in the right *chi* pulse in PG. In contrast, a decreasing trend was observed in the high-frequency SE of both *chi* pulses in DG. Chuang et al. reported that the increase in high frequency is inferred to the increase of peripheral vascular movement. The high-frequency SE of the right *chi* pulse was significantly increased after the colectomy [13]. We speculated that acupuncture at local acupoints around the knees increased the local circulation. This observation agreed with Tsuchiya et al.'s study, which concluded that acupuncture increases the nitric oxide level in the treated regions, which may have contributed to the pain relief by acupuncture [31]. In contrast, the distal acupoints did not immediately affect the local blood flow of the knees. Therefore, only the high-frequency SE of the right *chi* pulses *in* the PG showed an upward trend.

According to TCM syndrome differentiation, symptoms of *yin* and blood deficiency increase with age [32]. The etiology of KOA is related to *qi* and blood insufficiency in the liver and kidney, which resulted in pain. The observed significant SE changes in the left *cun*, *guan*, and *chi* pulses coincided with the TCM theory that the left body is associated with blood disorders, while the right body is associated with *qi* disorders [33]. The *Huang Di Nei Jing* advised that "the kidneys dominated bones." Therefore, this joint disorder was observed with significant changes in the *chi* pulses.

The sham acupoints CV12 and ST21 were on the abdomen. Although the acupuncture needles did not puncture the skin, the participants could still feel light stimuli. We observed a decreasing trend in the low-frequency SE of the right *guan* pulse corresponding to the stomach meridian.

The interval of assessing VAS, ROM, and pulse analysis was estimated 50–60 min. The participants were asked to rest for 10 min before the pre- and postintervention assessments. The immediate effect of acupuncture on the pain intensity, knee flexibility, and radial pulse waves were determined with minimal bias.

4.4. Speculated Underlying Mechanism for Distal Acupoints Outperforming Proximal Acupoints. Our study showed that the distal acupoints outperformed proximal acupoints in treating KOA. This result coincided with the conclusion in some studies investigating the effect of distal acupuncture. For instance, Irnich et al. concluded that acupuncture at distal acupoints could improve the flexibility and pain intensity in patients with chronic neck pain more than dry needling [34]. We speculated that the mechanism underlying the better results of distal points may also be due to the major role of nonsegmental antinociceptive systems in acupuncture analgesia as reported in previous studies. Various research studies have concluded that acupuncture stimulates the secretion of endorphin in the brain and it may influence the level of other neurotransmitters in the limbic system such as dopamine and serotonin. In addition, acupuncture may influence the concentration of pain-modulating neurotransmitters including substance P and met-enkephalin at the trigeminal nucleus in the brain and the spinal dorsal horn. This may be the basis for acupuncture treatment for pain including headache [35]. Further investigation on the mechanism is warranted.

4.5. Limitations. Several limitations of our study are as follows: First, this single-treatment study design could not observe a long-term maintenance effect of the proximal and distal acupoints. A design of multiple sessions of acupuncture can be considered in future studies to compare short- and long-term effects. Second, the VAS and ROM of the

distal acupuncture had both significantly improved. In contrast, we observed a downward trend of high-frequency SE in the *chi* pulse of the DG participants. We speculated that the insignificant difference in SE was due to the low sample size. Future studies with larger sample size are warranted. Third, all participants had mild KOA, according to the WOMAC Osteoarthritis Index. The treatment outcomes may differ from those with severe KOA. Fourth, pulse wave measurement could be affected when the pressure and angle of the pulse detection sensor pen were inaccurately applied due to the sensitivity of the device. To address the issue of deviations that might be caused by the operational process, all measurements were performed by the same research staff with over a year operating experience. Fifth, the interference factors on the pulse sphygmograph, including hunger, fullness, sleep, exercise, even gender, weight, and age, have not been fully established. Further research is required to investigate the effect of these factors on the SE of pulses.

4.6. Implications for Future Practice and Research. This single-treatment study provides a good foundation for comparing the acupuncture effects of proximal and distal acupoints, which can be maintained during treatment. It would be interesting to add proteomic analysis to understand the mechanism of the curative effect of both treatment groups and the differences in the specific protein expression corresponding to the SE changes in the radial pulses.

5. Conclusion

Both distal and proximal acupoints are effective in treating KOA. However, distal acupoints provide better pain relief and improve ROM compared with proximal acupoints. Following TCM theory, significant changes in spectral energy were observed in the left *cun*, *guan*, and *chi* pulses, indicating pain relief and blood flow improvement after acupuncture.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Additional Points

Acupuncture provides immediate pain relief and improves knee ROM in treating knee osteoarthritis. Distal acupoints provide better treatment efficacy than proximal acupoints. Radial pulse diagnoses can provide an objective assessment of the acupuncture effect using a pulse sphygmograph.

Conflicts of Interest

The authors claim no conflicts of financial interest.

Authors' Contributions

All the authors participated in the study design, reviewed the manuscript, and approved the final version. Wan-Zhen Yu and Chin-Ming Huang equally contributed to this study as co-first authors. Wan-Zhen Yu acquired clinical trial data, performed statistical analyses, and drafted the manuscript. Hui-Ping Ng critically reviewed the manuscript. Yu-Chen Lee provided supervision in the study.

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Research Article

Wang-Bi Tablet Ameliorates DMM-Induced Knee Osteoarthritis through Suppressing the Activation of p38-MAPK and NF-κB Signaling Pathways in Mice

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Background. Traditional Chinese medicine (TCM) exhibits outstanding therapeutic effects on the treatment of osteoarthritis (OA). Wang-Bi tablets (WBTs) have been used in clinics to treat knee osteoarthritis (KOA) by alleviating joint swelling and paining, and thus, the quality of life in patients with KOA was improved. However, its underlying molecular mechanism of anti-inflammatory response remains unclear. Therefore, further investigation is required. *Purpose*. This study aimed to explore the function of WBT in KOA mice and uncover the possible molecular mechanisms. *Study Design*. A KOA model was constructed by destabilizing the medial meniscus (DMM). IL-1β-treated chondrocytes were used to investigate the precise mechanism in vitro. *Methods*. (1) C57BL/6 male mice (8-week-old) were divided into Model, Sham, WBT-L, WBT-M, and WBT-H groups. After intragastric administration of 0.5% CMC-Na or WBT for 4 weeks, inflammation and pathological change were analyzed by ELISA, RT-qPCR, hematoxylin and eosin (H & E) and safranine O staining. (2) Isolated chondrocytes were stimulated with IL-1β followed by WBT-containing serum treatment, and then, the expression of inflammatory cytokines was analyzed by ELISA and RT-qPCR. (3) The effects of WBT on inflammatory signaling cascades in mice knee joint and chondrocytes were detected by WB. *Results*. The results indicated that WBT could alleviate inflammation and prevent cartilage injury in KOA mice. Compared with 0.5% CMC-Na-treated mice, the serum glycosaminoglycans (GAG) level in WBT-treated mice was notably increased, while the proinflammatory cytokine interleukin- (IL-) 6 level was decreased. In addition, WBT treatment suppressed the activation of NF-κB and p38 signaling pathways both in vivo and in vitro. *Conclusion*. WBT can effectively inhibit articular cartilage injury and inflammatory response in KOA mice. The protective role of WBT in mice KOA was a result of the downregulation of NF-κB and p38-MAPK signal pathways.

1. Introduction

Osteoarthritis (OA) is a common health problem that is characterized by articular cartilage loss and joint tissue remodeling [1]. It is estimated that more than 350 million people are currently suffering from OA in the world according to the Global Burden of Disease Study 2019 [2]. Knee osteoarthritis (KOA) is the most common type of OA. As reported, the high incidence of KOA among the elderly contributes to the poor quality of life by letting them bear the pain of physical disability [3, 4]. Although the pathogenesis of OA is not yet fully distinct and has much controversies, lots of studies have confirmed that the essential inflammatory factors including TNF-α, IL-1β, and IL-6 are upregulated in the early stage of OA [5].

p38 and NF-κB pathways are essential in the pathogenesis and progression of considerable human diseases, especially in OA [6, 7]. As reported, the blockage of p38-MAPK with p38 inhibitor could alleviate the degradation of bone and cartilage by suppressing chondrocyte apoptosis,

downstream inflammatory cytokine secretion, and inflammatory cell recruitment [8]. Similarly, nuclear factor-κB (NF-κB) is an essential regulator for inflammatory factors such as IL-6, which could increase the secretion of cartilage catabolic enzymes including matrix metalloproteinases (MMPs), thus causing extracellular matrix (ECM) degradation [9, 10]. Therefore, it is meaningful to explore appropriate drugs to alleviate the inflammatory injury of chondrocytes when treating OA clinically.

Wang-Bi tablet (WBT), a Chinese herbal formula, is used to treat rheumatoid arthritis, joint swelling, and stiffness in clinics for several years, which contains 16 herbal medicines, including Radix Rehmanniae, Radix Rehmanniae Preparata, Radix aconiti lateralis preparata, Rhizoma Drynariae, Cassia Twig, Radix Dipsaci, Epimedium brevicornu Maxim, Rhizoma Cibotii Preparata, Carthami Flos, Radix Clematidis, Spina Gleditsiae, Radix Angelicae Pubescentis, Radix Saposhnikoviae, Radix Paeoniae Alba, Rhizoma Anemarrhenae, and goat bone [11]. Due to its prominent therapeutic effect with few side effects, WBT has become more and more popular in clinical practice. However, few studies have been carried out on its mechanisms [12, 13]. As a result, the pharmacological mechanism of WBT in KOA is largely unclear. Our research aimed to explore the anti-inflammatory influence and underlying mechanism of WBT in mice KOA.

2. Materials and Methods

2.1. Reagents. WBTs (SFDA approval number Z20044066) were provided by Shanghai Pharmaceuticals Holding Co., Ltd. To prepare oral suspension, WBTs were dissolved in sterilized 0.5% CMC-Na. Mouse IL-6 and GAG ELISA kits were obtained from BioLegend. Antibodies against p65, p-p65, p-IkB kinase (IkK) α/β, IkBα, p38, and p-p38 were purchased from Epitomics. Anti-β-actin antibody was obtained from Sigma-Aldrich.

2.2. Preparation and Quantity Control of WBT. WBT containing sixteen kinds of herbal medicines was prepared as described in our previous works. WBT used for the present experiments was from the same batch as in the previous report, and the quality of WBT was also determined by high-performance liquid chromatography fingerprinting analysis [14].

2.3. Animal Experiments. All mice were fed in a $25 \pm 1^{\circ}$C temperature and $50 \pm 5\%$ humidity SPF environment with a 12 h light/dark cyclic schedule and free access to standard diet. All animal procedures were authorized by the ethics committee of Experimental Research, Fudan University.

The KOA model was constructed by DMM. In short, the medial collateral ligament and the medial meniscus of knee joints were cut off. Then, the patella was reduced and the wound was cleaned with normal saline. The capsule of knees was opened as a sham operation (Sham group, $n = 8$) and lavaged with 0.5% CMC-Na solvent. After DMM surgery, mice were administered intragastrically with 0.5% CMC-Na solvent (Mod, $n = 8$), low dose of WBT (0.20 g/kg/d, WBT-L, $n = 8$), medium dose of WBT (0.40 g/kg/d, WBT-M, $n = 8$), and high dose of WBT (0.60 g/kg/d, WBT-H, $n = 8$) for 4 weeks, respectively.

2.4. Preparation of Medicated Sera. Rats were administered with WBT solvent at a dose of 2.8 g/kg/day or 0.5% CMC-Na solution for 7 days. On day 8, the serum from overnight fasting mice was isolated. WBT-containing serum was mixed with normal rat serum at the ratios of 1 : 4, 4 : 6, and 6 : 4 and then added to a basic medium to prepare 10% serum-containing culture medium.

2.5. Primary Mice Chondrocyte Isolation and Treatment. The knee cartilages were isolated from new-born mice and digested with 0.1% collagenase II for 2 h, followed by 0.05% collagenase II for another 10 h. Chondrocytes then were collected and cultured in 10% FBS-containing medium. When 80% to 90% confluency was reached, chondrocytes were harvested and passaged. The chondrocytes used in the current study were the second passage. For IL-1β-treated groups, chondrocytes were treated with 10 ng/ml IL-1β for 6 h and further cultured in a medium containing 10% normal serum or medicated sera for 48 h [14].

2.6. Histological Analysis. The knee joint of mice was isolated and embedded in paraffin. After slicing, these paraffin sections were submitted to H&E staining and safranin O staining [15, 16]. The quantification of cartilage damages was then evaluated according to the Osteoarthritis Research Society International (OARSI) cartilage OA histology grading system [16, 17].

2.7. ELISA. ELISA was applied to analyze the levels of IL-6 and GAG in the serum. All procedures were performed as per our previously published research [15].

2.8. RT-qPCR. Total RNA was extracted from the knee cartilages and managed according to our previous research. The cDNA was prepared by reverse transcription and submitted to quantitative PCR (Q-PCR) analysis as per previous research [18]. Primers used in this study were synthesized by Huagene, and primer sequences are listed in Table S1.

2.9. Western Blot. Total proteins from the knee cartilages were prepared according to our previous study. After quantification, the samples were submitted to western blotting analysis referring to the standard protocol [15].

2.10. Statistics. All the numerical data were expressed as mean ± standard error of mean (SEM), and the experiment was repeated for no less than 3 times. The independent-samples t test and one-way ANOVA were performed by Statistical Program for Social Sciences 13 (SPSS 13). In detail,

the independent-samples t test was used for observing the difference between two groups, while one-way ANOVA was applied for multiple comparisons. $P < 0.05$ was considered as the significance level.

3. Results

3.1. WBT Alleviated the Inflammation and Cartilage Injury in KOA Mice. To evaluate the influence of WBT in osteoarthritis, we constructed a DMM-induced KOA model in mice and analyzed the degree of injury. As shown in Figure 1(a), WBT treatment significantly reversed the reduction of body weight compared with the Mod group. Inflammatory factors are important evaluation indexes for KOA, so the levels of various inflammatory factors in the serum were analyzed (Figure 1(b)). The level of proinflammatory cytokine IL-6 was significantly increased after DMM. However, high-dose WBT treatment notably reduced the production of IL-6 (Figure 1(b)). GAG, another key evaluation index for KOA, can stimulate the formation, repairment, and enhancement of the cartilage and promote the secretion of proteoglycan to lubricate the joint, thus improving joint pain and stiffness. As shown in Figure 1(c), the content of GAG in the Mod group was notably lower than that in the Sham group. Compared with the Mod group, GAG levels in WBT groups were notably increased in a dose-dependent manner. Together, these results suggested that WBT poses a repressive effect on the articular cartilage injury and inflammatory response in KOA mice.

3.2. WBT Improved the Injury of Joint Cartilage in KOA Mice. To further explore the possible role of WBT in the joint cartilage damages of KOA mice, the histological changes and inflammatory cytokine expression in the knee cartilages were measured. DMM could induce inflammatory cell infiltration and synoviocyte proliferation, which together contributed to the extensive pannus formation and serious cartilage destruction. However, after WBT administration, these phenomena were notably alleviated. The WBT-M and WBT-H groups only showed mild hyperplasia and few inflammatory cell infiltration (Figures 2(a) and 2(b)). In addition, the articular cartilage surface was smooth and the joint morphology was intact in these two groups.

Furthermore, safranin O and fast green examinations were performed by using mice knee joint sections. The knee joints of the Mod group exhibited tidal line damage and cartilage calcification, which was more serious than those in Sham group (Figures 3(a) and 3(b)). However, the cartilage injury and calcification were alleviated in all WBT groups. These results suggest that WBT can improve the cartilage injury KOA mice.

The relative cytokine mRNA levels from the knee cartilages were consistent with the histology. As seen, the anti-inflammatory cytokine IL-10 and collagen-II were notably increased in both WBT-M and WBT-H groups (Figures 4(a) and 4(b)). In contrast, IL-6, IL-18, MMP9, and TNF-α mRNA levels were obviously upregulated in the model group when compared with the Sham group. WBT treatment, to some extent, abolished DMM-induced proinflammatory cytokine expression (Figures 4(c)–4(f)). In summary, these findings indicate that WBT inhibited joint inflammation and cartilage injury in KOA mice.

3.3. WBT Attenuated the Phosphorylation of NF-κB p65 and p38. As known, the production of proinflammatory cytokines is associated with KOA progression. NF-κB and p38 pathways are considered to induce excessive expression of proinflammatory cytokines. Therefore, we detected the activation of p38 and NF-κB pathways in KOA mice (Figures 5(a) and 5(b)). As seen, WBT treatment reduced the phosphorylation of p65 and p38 in DMM-induced arthritis. These results suggested that WBT might suppress the inflammatory response in KOA via regulating the activation of these two signaling pathways mentioned above.

3.4. WBT Inhibits NF-κB and p38 Signaling Pathways and Inflammation in IL-1β-Stimulated Chondrocytes. To further explore the role of WBT in NF-κB and p38 signaling pathways in vitro, proteins from mice chondrocytes were isolated and the levels of IκB, p-IκKα/β, and p-p38 were detected. Figures 6(a) and 6(b) indicate that WBT-containing serum treatment could restrain the degradation of IκB protein and reduce the level of p-IκKα/β and p-p38. In addition, the increase of IL-6, MMP9, and TNF-α mRNA levels induced by IL-1β were notably suppressed by WBT-containing serum treatment in a dose-dependent manner (Figure 6(c)). All the above findings made it clear that the antiarthritic and anti-inflammatory effects of WBT are involved in the regulation of NF-κB and p38-MAPK signaling pathways.

4. Discussion

Osteoarthritis (OA) is characterized by structural alterations in the whole joint including hyaline articular cartilage, subchondral bone, ligaments, capsule, synovium, and periarticular muscles [19, 20]. The high incidence of OA has become a major public health problem and attracted increasing attention. The pathogenesis of OA is unclear according to the present research. Moreover, the majority of patients with OA do not receive appropriate therapy [21]. As reported, education, self-management, and exercise are widely considered as first-line treatment. The most recommended pharmacological treatments are paracetamol and NSAID [22]. Unfortunately, these pharmacological treatments neither slow nor prevent OA progression. Therefore, it is of great interest to explore new effective therapeutic candidates that can strongly prevent cartilage injury along with less adverse effects. WBT is a traditional Chinese medicine that is widely used in herbal remedies in Asian countries [11, 23]. However, WBT's protective role in articular cartilage and related mechanisms in KOA chondrocytes have not been reported yet. In this study, we found that WBT could suppress KOA progression in the mice DMM model through inhibiting the p38 and NF-κB

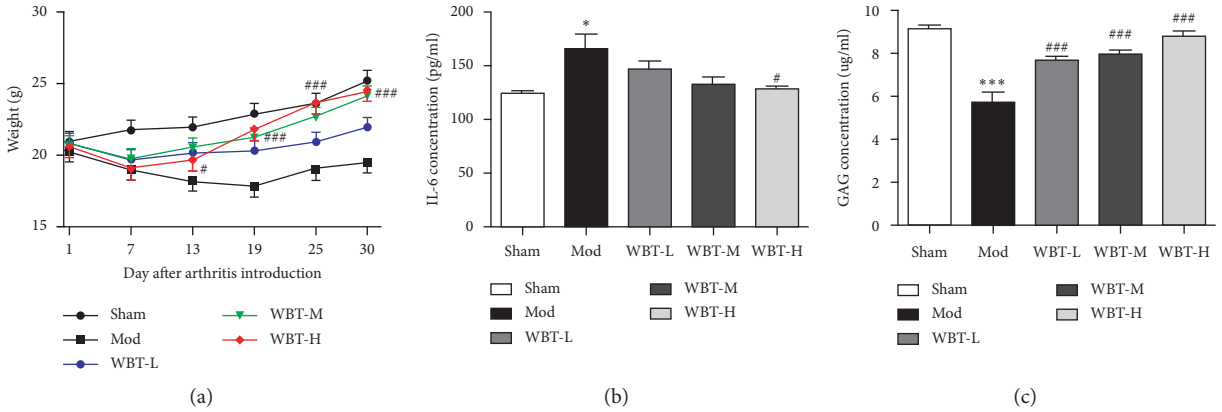


FIGURE 1: Therapeutic effect of WBT on KOA mice. Sham and Mod groups' mice administered by gavage with 0.5% CMC-Na solvent (Sham, Mod, $n = 8$), low dose of WBT (0.20 g/kg/d, WBT-L, $n = 8$), medium dose of WBT (0.40 g/kg/d, WBT-L, $n = 8$), and high dose of WBT (0.60 g/kg/d, WBT-H, $n = 8$) for 4 weeks, respectively. The body weight of each group was recorded. Effects of WBT on the IL-6 and GAG in KOA mice are given. The concentration of proinflammatory cytokine IL-6 (a) and GAG (b) in the serum was measured by ELISA. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ vs Mod group. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ vs Sham group.

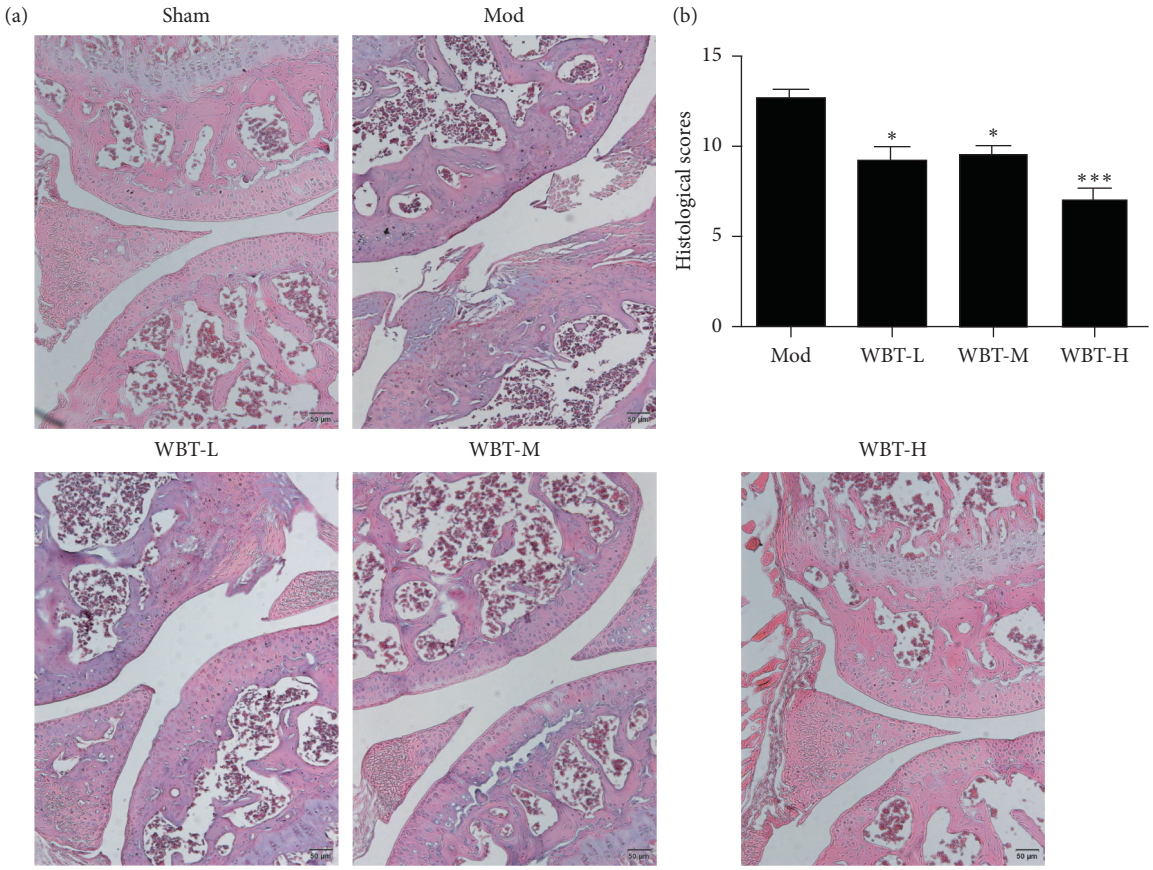


FIGURE 2: Effects of WBT on pathological changes of KOA mice. (a) The representative images of HE staining of the knee joint sections in each group. (b) The histological changes were scored and analyzed. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ vs Mod group.

pathways. Consistently, WBT attenuated the inflammatory response in chondrocytes via the same pathways.

Increasing expression of proteolytic enzymes such as MMPs is one of the important factors for OA development, which is crucial for the degradation of various ECM components of articular cartilage [24]. As reported, GAG can facilitate proteoglycan synthesis, alleviate the loss of cartilage matrix, and inhibit MMP9 expression, thus contributing to the repairment of the cartilage [25]. Due to its essential role in maintaining ECM homeostasis, GAG has

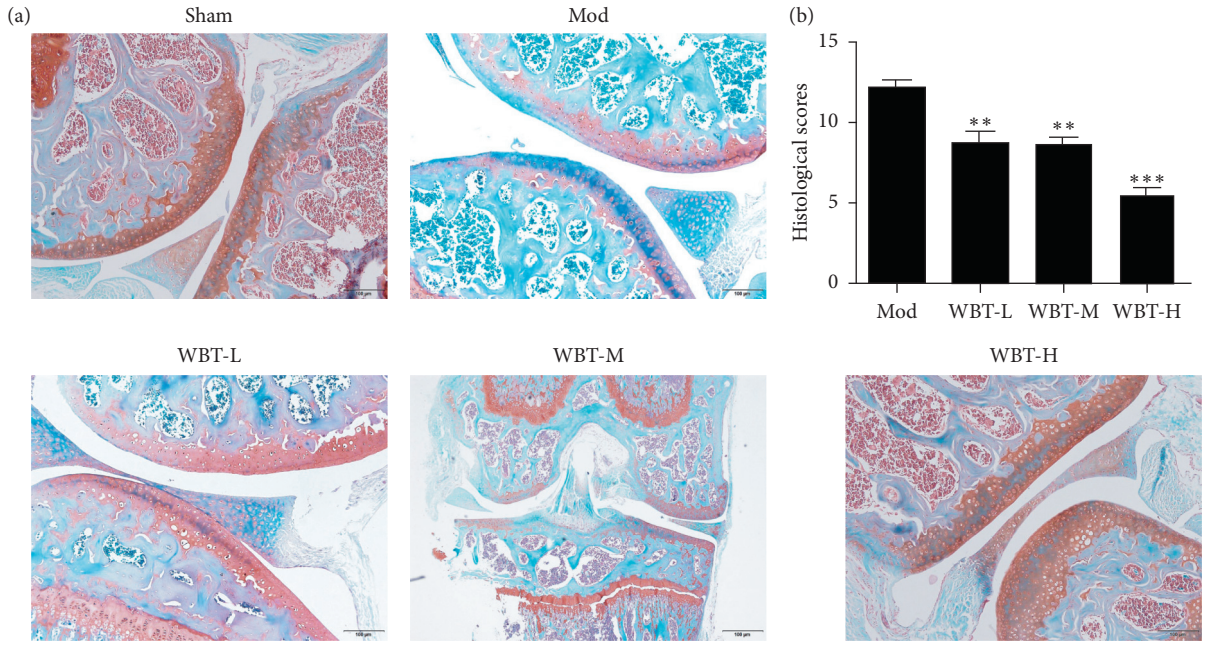


FIGURE 3: Effects of WBT on cartilage injury of KOA mice. (a) The representative images of safranin O and fast green staining of the knee joint section in each group. (b) The cartilage calcification changes were scored and analyzed. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ vs Mod group.

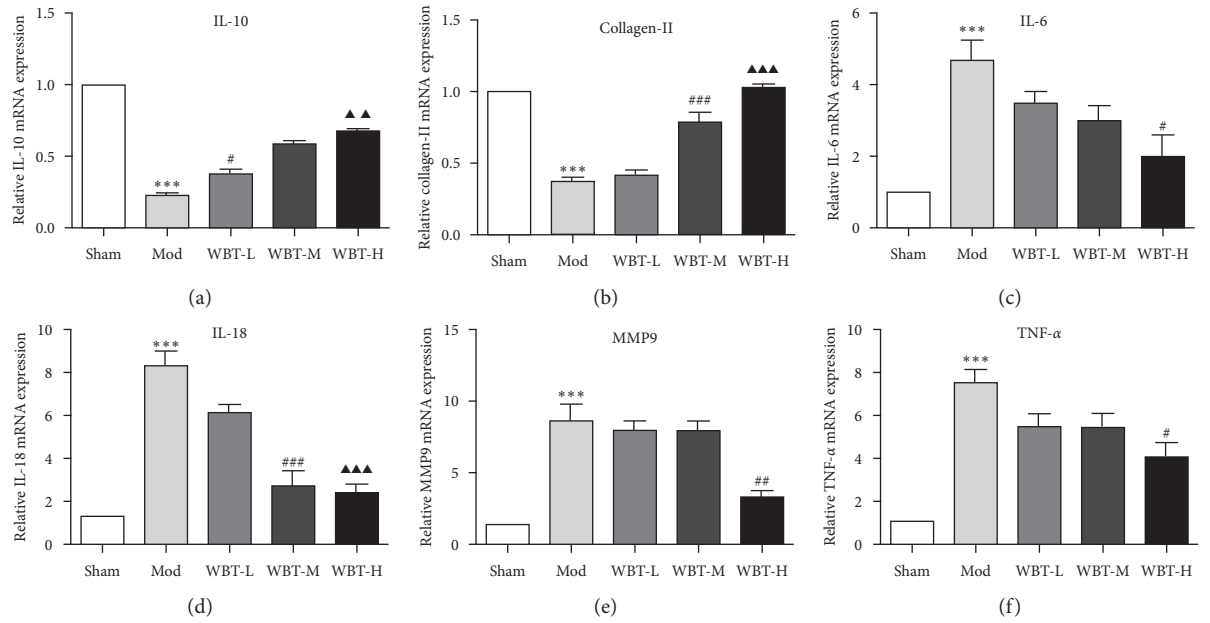


FIGURE 4: Effects of WBT on the expression of cytokine in the joints of KOA mice. (a–f) The mRNA levels of TNF-α, MMP9, IL-6, IL-18, IL-10, and collagen-II in the knee joints were analyzed by RT-qPCR. $^{***}P < 0.001$ vs Sham group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ vs Mod group; $^{\blacktriangle\blacktriangle}P < 0.01$ and $^{\blacktriangle\blacktriangle\blacktriangle}P < 0.001$ vs WBT-L.

been considered as an important indicator of cartilage injury in OA [26]. Here, we also found that WBT can increase the serum level of GAG in the mice KOA model, indicating that WBT probably alleviates articular cartilage injury by inhibiting the loss of GAG.

Previous studies indicated that NF-κB signal pathway plays significant influence in OA pathogenesis and changing process [27]. The development of OA is accompanied by the excessive secretion of proinflammatory factors and the loss of collagen-II. Proinflammatory cytokines and other factors could activate NF-κB pathway to attenuate the expression of large amount of cytokines and chemokines, such as IL-6 and TNF-α [28]. NF-κB blockage can suppress IL-1β-induced inflammatory response, apoptosis, and collagen-II

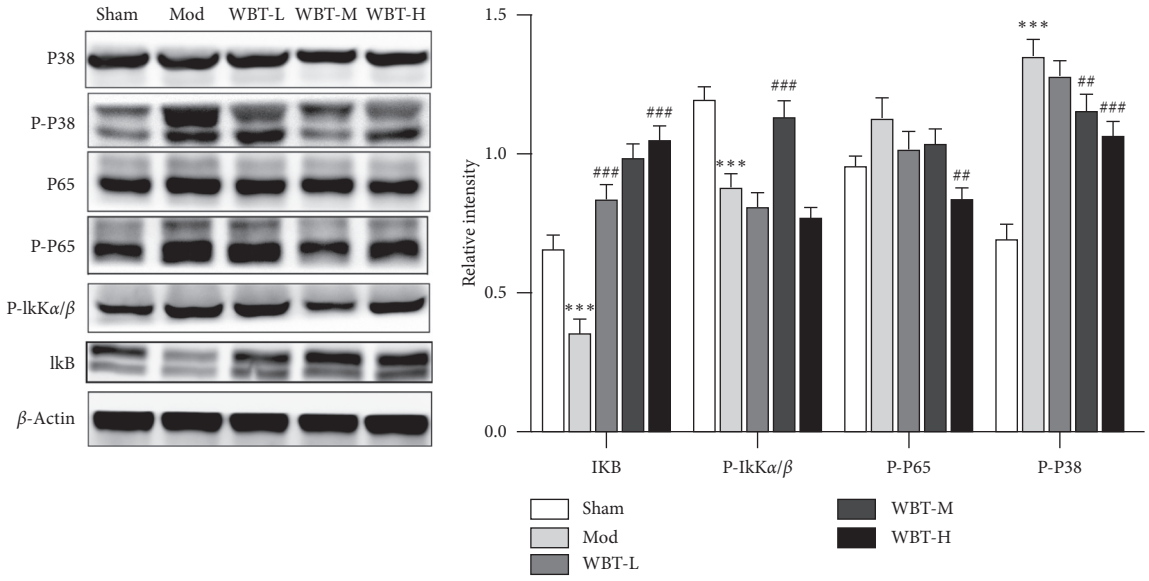


Figure 5: Effect of WBT on the phosphorylation of NF-κB p65 and P38. In drug treatment groups, KOA mice were treated daily by gavage with WBT from the first day of arthritis onset for 4 weeks. Mice in Sham and Mod groups were given 0.5% CMC-Na solvent during the same period. (a) Total proteins from the knee joints of mice were isolated and subjected to immunoblotting with indicated antibodies. (b) Densitometry quantification in (a) was analyzed by ImageJ software. Data are expressed as means ± SEM. All experiments are repeated for three times at least. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ vs Sham group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ vs Mod group.

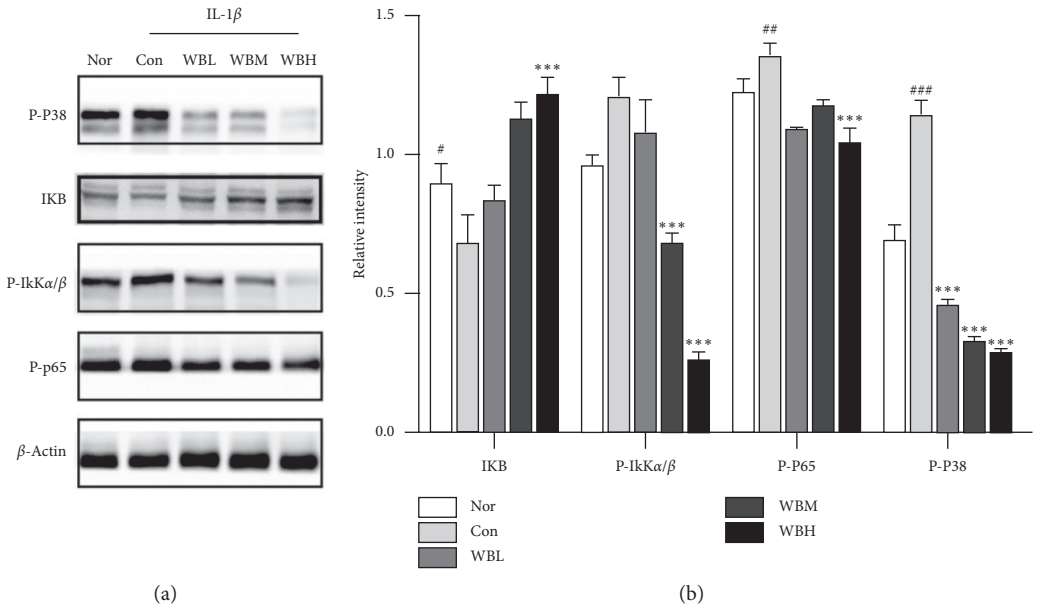
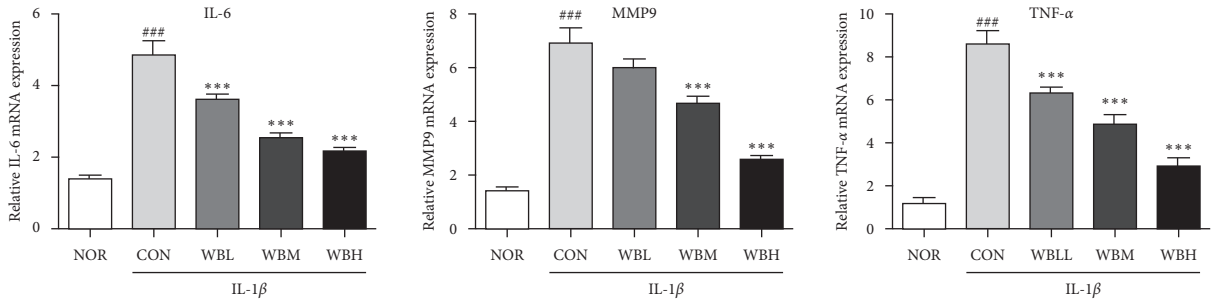


Figure 6: Continued.



(c)

Figure 6: Effect of WBT on the phosphorylation of NF-κB p65, p38 signaling pathways, and inflammation. Chondrocytes were treated with normal serum medium, WBT serum medium, WBL (low dose of WBT) serum medium, WBM (medium dose of WBT) serum medium, and WBH (high dose of WBT), followed by IL-1β stimulation. (a) Equal amount of proteins from the chondrocytes in each group were merged, and samples (30 μg) were subjected to immunoblotting with indicated antibodies. (b) Densitometry quantification in (a) was analyzed by ImageJ software. Data are means ± SEM. All experiments are repeated for three times at least. (c) The mRNA levels of TNF-α, MMP9, and IL-6 were analyzed by RT-qPCR (a, b, c). $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, and $^{\#\#\#}P < 0.001$ vs Nor group; $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ vs Con group.

degradation in chondrocytes [29, 30]. WBT treatment significantly decreases the activity of NF-kB signaling pathway finally. Consistently, the levels of TNF-α mRNA and IL-6 mRNA in WBT-treated KOA mice were notably lower when compared to the model group, suggesting that WBT might inhibit inflammatory response and OA cartilage injury in the DMM mice model.

Mitogen-activated protein kinase (MAPK) signaling pathway-p38/JNK/ERK involves in the progression of OA, and p38-MAPK signaling pathway inhibition could alleviate the inflammation in KOA [8]. As shown, WBT treatment inhibited the phosphorylation of p38 and reduced the occurrence and development of inflammation. The inhibition of p38 and NF-kB pathways induced by WBT treatment might synergistically downregulate the proinflammatory factor expression and promote cartilage repair and regeneration, thereby achieving protective effect in KOA.

5. Conclusion

In this study, we proved that oral medication of WBT possesses antiarthritic effect on the KOA mice model. WBT treatment not only ameliorated cartilage injury and calcification but also inhibited inflammation response to improve poor functional outcome. Mechanically, WBT inhibits p38 and NF-κB signaling pathways, thus suppressing the expression of proinflammatory cytokines. Altogether, the data acquired in the present study extend our understanding that WBT is a promising candidate for treating KOA.

Abbreviations

KOA: Knee osteoarthritis
OA: Osteoarthritis
WBT: Wang-Bi tablet
DMM: Destabilization of the medial meniscus
GAG: Glycosaminoglycans.

Data Availability

The data used to support the findings of this study are included within the article.

Additional Points

Highlights. (i) Degenerative arthritis has a higher incidence than rheumatoid arthritis and significantly decreases patients' quality of life. (ii) Wang-Bi tablets possess prominent therapeutic effects on degenerative knee osteoarthritis in a dose-dependent manner. (iii) The outbreak of inflammation in degenerative knee osteoarthritis involves the activation of p38-MAPK and NF-κB pathways, which can be suppressed by Wang-Bi tablet treatment.

Conflicts of Interest

All authors declare no conflicts of interest.

Authors' Contributions

HL, BJ, XL, HDL, WW, and HC participated in experiments; HL analyzed the states and wrote the draft; XS and JZ designed and supervised the work; XS provided the facilities for the study. YY reviewed and edited the work; Hui Li and Yan You contributed equally to this work.

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Supplementary Materials

Table S1: the primer sequences for RT-qPCR. (*Supplementary Materials*)

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