Review Article

The Efficacy and Safety of Chinese Herbal Medicine in the Treatment of Knee Osteoarthritis: An Updated Systematic Review and Meta-Analysis of 56 Randomized Controlled Trials

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Objective. This systematic review and meta-analysis were performed to investigate the efficacy and safety of Chinese herbal medicine (CHM) in the treatment of knee osteoarthritis (KOA).

Methods. An electronic search was conducted in eight databases (PubMed, EMBASE, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, Chinese VIP Database, and Wanfang Database) from inception until December 2019. The risk of bias assessment of the included RCTs was evaluated by Cochrane collaboration’s tool. The inclusion criteria were RCTs that investigated the efficacy and safety of CHM in the treatment of KOA, with no restrictions on publication status or language. The exclusion criteria included nonrandomized or quasi-RCTs, no clear KOA diagnostic approach, combined Chinese medicinal herbs with other traditional Chinese medicine treatment modalities, and published using repeated data and missing data. We computed the relative risk (RR) and the standard mean difference (SMD) for dichotomous outcomes and continuous outcomes, respectively. When heterogeneity was detected or there was significant statistical heterogeneity (P < 0.05 or I² > 50%), a random-effects model was employed, followed by further subgroup analysis and metaregression estimations to ascertain the origins of heterogeneity. Otherwise, we used a fixed-effects model (P ≥ 0.05 or I² ≤ 50%). The primary outcome measures were visual analog score (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, and Lequesne index. Secondary outcome measures were the total clinical effective rate and adverse events. The meta-analysis was performed using the Stata 14.0 software.

Results. A total of 56 RCTs comprising 5350 patients met the inclusion criteria. This meta-analysis showed that application of CHM as adjuvant therapy or monotherapy for KOA can significantly decrease VAS, WOMAC, and the Lequesne index and improve the Lysholm score as well as the total effective rate. In addition, this treatment has fewer adverse effects, suggesting that CHM is generally safe and well tolerated among patients with KOA.

Conclusion. Our study offers supportive evidence that CHM, either adjuvant therapy or monotherapy, reduces the VAS, WOMAC, and Lequesne index and improves the Lysholm score as well as the total effective rate. In addition, this treatment has fewer adverse effects, suggesting that CHM is generally safe and well tolerated among patients with KOA. Additionally, CHM was well tolerated and safe in KOA patients. We found frequently used CHMs that might contribute to the formulation of a herbal formula that could be considered for further clinical use. However, given the heterogeneity and limited sample size in this study, larger multicenter and high-quality RCTs are needed to validate the benefits of CHM in the treatment of KOA.

1. Introduction

Knee osteoarthritis (KOA) is a multifactorial degenerative joint disorder characterized by changes in the structure of the joint tissues, including cartilage degeneration, subchondral bone restructuring, and synovial membrane inflammation in the elderly [1]. KOA is more prevalent in older adults [2]. A previous study reported that approximately 12% of the aging population in the West suffered from KOA, and 25% of the population above 55 years old had a persistent knee pain episode [3]. According to current data, 9.3 million adults in the US are affected by KOA [4]. As
As the population ages, it is projected that the number of persons with KOA will increase [5, 6]. Osteoarthritis was projected to become the fourth leading cause of disability by 2021 [7].

The primary management goals for KOA have been to alleviate pain, educate patients about the disease, rehabilitate, slow the progression of the disease, and maintain a healthy lifestyle [8]. However, effective therapeutic strategies for KOA disease modification are currently unavailable [9]. The current therapeutic options advanced in various evidence-based clinical guidelines include nonpharmacological therapies, weight loss, oral pharmacological medications, exercise, topical therapies, surgical treatments, and intra-articular therapies [10–12]. Notably, nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular hyaluronic acid or corticosteroids are the most frequently used in clinical practice [13–15]. Long-term use of NSAIDs and corticosteroids, on the other hand, has serious adverse effects [16]. Therefore, clinicians and patients are increasingly preferring to treat KOA using complementary as well as alternative medicine [17–19].

Chinese herbal medicine (CHM) has been used in various forms in the treatment of KOA, both in China and the rest of the world [20, 21]. The adoption of CHM for treating pain disorders, including KOA, has been steadily increasing in Asian countries as well as across the globe [22]. In comparison to other herbal medicines, CHM contains distinct medicinal components that target specific biological processes associated with disease, which are dependent on the differentiation of specific symptoms [23, 24]. According to a recent study, CHM actively reduces pain via analgesic, invigorating blood circulation, and anti-inflammatory effects [25]. CHM has long been regarded as a vital component in the treatment of KOA in China and is gaining popularity in other parts of the world. However, quantitative research evidence on its effects is currently limited. CHM’s biological effect and potential interactions with other prescription medications have not yet been elucidated [26]. Two systematic reviews found that CMH is both safe and effective in the treatment of KOA [27, 28]. However, due to the low quality of the methodology and the limited sample size in the included studies, there is a knowledge gap on the planned application of CHM in treating KOA. Recently, there has been an increase in the number of high-quality randomized controlled clinical trials (RCTs) on the safety and efficacy of CHM in the treatment of KOA. Therefore, we conducted a large sample size systematic review and meta-analysis of

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**Figure 1: Flowchart of study selection.**

| Identification | Screening | Eligibility | Included |
|---------------|-----------|-------------|----------|
| Records identified through database searching (n = 1532) | Records after duplicates removed (n = 1241) | Records excluded (n = 1114) | Studies included in qualitative synthesis (n = 56) |
| Additional records identified through other sources (n = 0) | | (i) Case report or review (n = 122) | (i) Not RCT or real RCT (n = 32) |
| | | (ii) Not clinical trial (n = 638) | (ii) Combining with other herbs (n = 20) |
| | | (iii) Not Chinese herb (n = 354) | (iii) Cochrane score<4 (n = 9) |
| | | | (iv) Lack of adequate information (n = 10) |

Records identified through database searching (n = 1532) Additional records identified through other sources (n = 0) Records after duplicates removed (n = 1241) Records excluded (n = 1114) (i) Case report or review (n = 122) (ii) Not clinical trial (n = 638) (iii) Not Chinese herb (n = 354) Records screened on title and abstract (n = 1241) Full-text articles assessed for eligibility (n = 127) Full-text articles excluded, with reasons (n = 71) (i) Not RCT or real RCT (n = 32) (ii) Combining with other herbs (n = 20) (iii) Cochrane score<4 (n = 9) (iv) Lack of adequate information (n = 10) Studies included in qualitative synthesis (n = 56) Studies included in quantitative synthesis (meta-analysis) (n = 56)
| Study        | Study design | Study design criteria | Sample size | Sample and characteristics (male/female; mean age, year) | Interventions | Interventions | Interventions | Disease duration | Course of treatment | Outcome index |
|-------------|--------------|-----------------------|-------------|----------------------------------------------------------|---------------|---------------|---------------|-------------------|-------------------|---------------|
| Chen 2017 [28] | RCT          | CRA criteria (2003)   | 92          | 46 (16/30); 51.2 ± 6.5                                   | Sanbi Xiao granule (0.3 g, tid, 4 w) | Glucosamine sulfate (628 mg, tid, 4 w) | TG: 6.3 ± 3.4 y | (1) VAS          | 4 w               | (1) VAS         |
| Chen 2018 [29] | RCT          | COA criteria (2007)   | 128         | 64 (26/38); 56.1                                        | (1) Danqi granule (12 g, bid, 24 w) | Glucosamine sulfate (500 mg, tid, 24 w) | TG: 0.6 ± 9 y | (2) WOMAC      | 24 w             | 24 w            |
| Cui 2017 [31]  | RCT          | ACR criteria (1986)   | 106         | 66 (30/36); 61.2 ± 8.60                                 | Chaihu Jiaju decoction (1 package, qod, 12 w) | Glucosamine hydrochloride (750 mg, bid, 12 w) | TG: 10.6 ± 5 y | (1) VAS          | 12 w             | 12 w            |
| Cui 2018 [30]  | RCT          | COA criteria (2007)   | 122         | 61 (30/31); 64.7 ± 6.92                                 | (1) Danqi granule (12 g, bid, 12 w) | Diclofenac sodium (75 mg, qd, 12 w) | TG: 3.12 ± 1.28 y | (2) ER           | 12 w             | 12 w            |
| Dou 2015 [32]  | RCT          | COA criteria (2007)   | 60          | 30 (14/16); 30 (17/13)                                  | Danzi Kangxi electuary (6 g, tid, 4 w) | Glucosamine sulfate (500 mg, tid, 4 w) | TG: 2 to 6 y | (1) VAS          | 4 w              | (1) VAS         |
| Fu 2018 [33]   | RCT          | ACR criteria (1995)   | 76          | 38 (13/25); 69 ± 4.96                                   | (1) Duhuo Jisheng decoction (1 package, bid, 4 w) | Celecoxib (200 mg, qd, 4 w) | TG: 3.1 ± 1.5 y | (1) ER           | 4 w              | (2) ADR         |
| Guo 2019 [34]  | RCT          | COA criteria (2007)   | 102         | 51 (31/20); 58.16 ± 5.24                                | (1) Duhuo Jisheng decoction (1 package, bid, 4 w) | Celecoxib (200 mg, bid, 4 w) | TG: 1.89 ± 0.74 y | (2) VAS          | 4 w              | (2) VAS         |
| He 2019 [35]   | RCT          | ACR criteria (1995)   | 70          | 35 (11/24); 52.2 ± 8.5                                  | (1) Shuanggu Sanzi capsule (0.9 g, tid, 4 w) | Celecoxib (200 mg, bid, 4 w) | TG: 5.9 ± 1.1 y | (3) ER           | 4 w              | 4 w             |
| Hong 2013 [36] | RCT          | ACR criteria (1995)   | 115         | 63 (25/38); 51.75 ± 7.84                                | (1) Qufeng Jiaju decoction (1 package, qd, 12 w) | Glucosamine hydrochloride (480 mg, tid, 12 w) | TG: 58 ± 34.7 y | (1) VAS          | 12 w             | (2) VAS         |
| Hu 2012 [37]   | RCT          | ACR criteria (1995)   | 90          | 45 (13/32); 58.73 ± 9.19                                | (1) Bushen Zhuang decoction (1 package, qd, 6 w) | Glucosamine hydrochloride (750 mg, bid, 6 w) | NR              | (3) ADR          | 6 w              | (3) ADR         |
| Study   | Study design | Diagnostic criteria | Sample size | Sample and characteristics | Interventions | Disease duration | Course of treatment | Outcome index |
|---------|--------------|---------------------|-------------|----------------------------|---------------|-----------------|--------------------|---------------|
| Huang 2015 [38] | RCT | ACR criteria (1986) | 80          | 40 (NR); 58.8 ± 4.4          | (1) Bushen Guangjie Huoluo Pulvis (1 package, bid, 4w) (2) Celecoxib (200 mg, bid, 4w) | Celecoxib (200 mg, bid, 4w) | TG: 4.5 ± 2.2 y  CG: 4.6 ± 2.1 y | 4w | (1) Lequesne (2) ER (3) ADR |
| Jiang 2009 [39] | RCT | ACR criteria (1995) | 60          | 30 (11/19); 52.1 ± 7.1       | Bushen Huoxue decoction (1 package, qd, 24w) | Glucosamine sulfate (628 mg, tid, 24w) | TG: 4.16 ± 2.11 y  CG: 3.89 ± 2.56 y | 24w | (1) VAS (2) WOMAC (3) Lequesne (4) ER |
| Li 2018 [40] | RCT | COA criteria (2007) | 100         | 50 (19/31); 59.72 ± 8.15     | (1) Duhuo Jisheng decoction (1 package, bid, 8 w) (2) Celecoxib (200 mg, qd, 8 w) | Glucosamine sulfate (628 mg, tid, 12 w) | TG: 3.93 ± 1.89 y  CG: 3.89 ± 1.63 y | 12w | (1) VAS (2) ER (3) Lysholm |
| Liu 2011 [43] | RCT | ACR criteria (1995) | 80          | 40 (19/21); 63 ± 8           | (1) Zhengqing Fengtongning tablet (60 mg, tid, 12 w) (2) Glucosamine hydrochloride (480 mg, tid, 12 w) | Celecoxib (200 mg, qd, 12 w) | TG: 32 ± 6 m  CG: 31 ± 5 m | 12w | (1) WOMAC (2) ER (3) ADR |
| Liu 2016 [41] | RCT | COA criteria (2007) | 90          | 45 (25/20); 55.22 ± 3.95     | (1) Lujiao Zhuanggu capsule (0.5 g, tid, 12 w) (2) Glucosamine hydrochloride (480 mg, tid, 12 w) | Glucosamine sulfate (628 mg, tid, 12 w) | TG: 3.93 ± 1.89 y  CG: 3.89 ± 1.63 y | 12w | (1) VAS (2) ER (3) Lysholm |
| Liu 2017 [42] | RCT | CRA criteria (2010) | 114         | 57 (35/22); 56.4 ± 5.2       | (1) Shujin decoction (1 package, qd, 4 w) (2) Celecoxib (200 mg, qd, 4 w) | Glucosamine sulfate (628 mg, tid, 12 w) | TG: 5.6 ± 1.7 y  CG: 5.2 ± 1.4 y | 4w | (1) VAS (2) WOMAC (3) Lysholm (4) ER |
| Lu 2016 [44] | RCT | CRA criteria (2010) | 100         | 50 (33/17); 64.53 ± 6.84     | (1) Lujiao Zhuanggu capsule (1.5 g, tid, 8 w) (2) Glucosamine hydrochloride (480 mg, tid, 8 w) | Glucosamine hydrochloride (480 mg, tid, 12 w) | TG: 9.86 ± 1.75 m  CG: 9.76 ± 1.63 m | 8w | (1) VAS (2) ER (3) ADR |
| Luo 2019 [45] | RCT | COA criteria (2007) | 98          | 49 (13/36); 57.49 ± 10.52    | (1) Zhengqing Fengtongning tablet (60 mg, bid, 12 w) (2) Glucosamine hydrochloride (750 mg, tid, 12 w) | Glucosamine hydrochloride (750 mg, tid, 12 w) | TG: 4.79 ± 0.88 y  CG: 4.99 ± 0.91 y | 12w | (1) WOMAC (2) ER (3) ADR |
| Ma 2009 [48] | RCT | CRA criteria (2003) | 118         | 59 (5/54); 52.07 ± 17.29     | Huoxue Tongluo decoction (1 package, qd, 12 w) | Celecoxib (200 mg, qd, 12 w) | TG: 7.03 ± 3.23 y  CG: 7.21 ± 3.13 y | 12w | (1) VAS (2) ER |
| Study       | Study design | Diagnostic criteria | Sample size | Sample and characteristics (male/female; mean age, year) | Interventions                          | Disease duration | Course of treatment | Outcome index |
|------------|--------------|---------------------|-------------|----------------------------------------------------------|----------------------------------------|------------------|---------------------|---------------|
| Ma 2018    | RCT          | COA criteria (2007) | 60          | 32 (22/10); 53.29 ± 3.11                                   | Duhuo Jisheng decoction (1 package, qd, 12 w) Celecoxib (200 mg, bid, 12 w) | TG: 50.87 ± 13.22 m | 12 w                | (1) Lysholm     |
| Ma 2019    | RCT          | COA criteria (2007) | 164         | 82 (38/44); 67.0 ± 4.0                                    | Bushen Yiqi Huayu Jiedu decoction (1 package, qd, 8 w) Glucosamine hydrochloride (480 mg, tid, 8 w) | TG: 7.4 ± 2.9 y   | 8 w                 | (1) VAS        |
| Mo 2018    | RCT          | COA criteria (2007) | 120         | 60 (26/34); 58.94 ± 12.1                                  | (1) Kangguzhi Zengsheng capsule (17.5 g, tid, 12 w) (2) Celecoxib (200 mg, bid, 12 w) | TG: 4.3 ± 1.6 w   | 12 w                | (1) VAS        |
| Pan 2017   | RCT          | CRA criteria (2010) | 80          | 40 (6/34); 64.53 ± 6.67                                   | Longbie capsule (1.2 g, tid, 4 w) Celecoxib (200 mg, qd, 4 w) | TG: 14.53 ± 5.88 m | 4 w                 | (1) Lequesne    |
| Qian 2019  | RCT          | COA criteria (2007) | 78          | 39 (17/22); 49.12 ± 1.23                                 | (1) Yishen Quyu decoction (1 package, bid, 2 w) (2) Celecoxib (200 mg, qd, 2 w) | TG: 2.12 ± 0.12 y | 2 w                 | (1) VAS        |
| Ren 2016   | RCT          | CRA criteria (2005) | 95          | 48 (34/14); 58.19 ± 7.16                                 | (1) Yishen Quyu decoction (1 package, bid, 4 w) (2) Celecoxib (200 mg, bid, 4 w) | TG: 3.68 ± 1.19 y | 4 w                 | (1) Lysholm     |
| Ren 2018   | RCT          | COA criteria (2007) | 80          | 40 (18/22); 47.9 ± 2.2                                    | Duhuo Jisheng decoction (1 package, qd, 5 w) Celecoxib (200 mg, qd, 5 w) | TG: 19.7 ± 3.2 m  | 5 w                 | (1) VAS        |
| Rong 2017  | RCT          | CRA criteria (2010) | 73          | 42 (19/23); 53.68 ± 8.49                                 | Duhuo Jisheng decoction (1 package, qd, 4 w) Glucosamine sulfate (500 mg, tid, 4 w) | TG: 2.73 ± 1.02 y | 4 w                 | (1) WOMAC      |
| Shi 2019   | RCT          | CRA criteria (2010) | 78          | 39 (22/17); 59.79 ± 4.54                                 | (1) Duhuo Jisheng decoction (1 package, qd, 4 w) (2) Glucosamine sulfate (500 mg, tid, 4 w) | TG: 2.62 ± 0.98 y | 4 w                 | (1) VAS        |
| Song 2017  | RCT          | COA criteria (2007) | 95          | 50 (28/22); 52.1 ± 3.8                                   | Duhuo Jisheng decoction (1 package, qd, 4 w) (2) Celecoxib (200 mg, qd, 4 w) | TG: 1.2 ± 0.5 y   | 4 w                 | (1) VAS        |
Table 1: Continued.

| Study   | Study design | Diagnostic criteria | Sample size | Sample and characteristics (male/female; mean age, year) | Interventions | Disease duration | Course of treatment | Outcome index |
|---------|--------------|---------------------|-------------|----------------------------------------------------------|---------------|-----------------|--------------------|---------------|
| Sun 2018 [57] | RCT | COA criteria (2007) | 50 | 25 (12/13); 54.46 ± 8.25 | Qinbi decoction (1 package, qd, 4 w) | Celecoxib (200 mg, qd, 4 w) | 9.40 ± 1.27 y | 4 w | (1) VAS (2) WOMAC (3) ER |
| Tan 2014 [58] | RCT | ACR criteria (1995) | 60 | 30 (8/22); 55.6 | Huangqi Biejia pill (15 g, tid, 6 w) | Glucosamine hydrochloride (480 mg, tid, 6 w) | 2.51 y | 6 w | (1) Lequesne (2) ER (3) ADR |
| Tang 2012 [59] | RCT | ACR criteria (1995) | 114 | 56 (20/36); 57.2 ± 5.43 | Jiedu Yishen pill (15 g, bid, 8 w) | Glucosamine sulfate (500 mg, tid, 8 w) | 5.1 ± 3.2 y | 8 w | (1) WOMAC (2) ER |
| Wang 2013 [60] | RCT | ACR criteria (1986) | 120 | 60 (35/25); 53.3 ± 5.1 | (1) Fufang Xiatian Wu pill (6 g, bid, 24 w) (2) Glucosamine hydrochloride (480 mg, bid, 24 w) | Glucosamine hydrochloride (480 mg, bid, 24 w) | 5.71 ± 2.19 y | 24 w | (1) Lequesne (2) ADR |
| Wang 2019 [61] | RCT | COA criteria (2007) | 96 | 48 (10/38); 56.9 | Duohuo Jisheng decoction (1 package, qd, 4 w) | Celecoxib (200 mg, bid, 4 w) | NR | 12 w | (1) VAS (2) WOMAC (3) ER (4) ADR |
| Wen 2016 [62] | RCT | ACR criteria (1995) | 142 | 72 (29/43); 48.7 ± 12.1 | Zhuanggu Tongbi pill (6 g, bid, 12 w) | Glucosamine hydrochloride (628 mg, tid, 12 w) | 73.0 ± 18.5 d | 4 w | (1) VAS (2) ER (3) ADR |
| Wu 2012 [65] | RCT | ACR criteria (1995) | 120 | 60 (22/38); 61.2 ± 4.22 | (1) Bushen Huoxue decoction (1 package, bid, 12 w) (2) Celecoxib (200 mg, qd, 12 w) | Glucosamine hydrochloride (628 mg, tid, 12 w) | NR | 12 w | (1) Lequesne (2) ER (3) ADR |
| Wu 2018 [63] | RCT | CRA criteria (2003) | 93 | 47 (20/27); 58.93 ± 3.56 | (1) Sanqi Xuejie capsule (4 capsules, tid, 4 w) (2) Celecoxib (200 mg, bid, 4 w) | Celecoxib (200 mg, bid, 12 w) | 7.69 ± 1.82 y | 12 w | (1) WOMAC (2) ER |
| Wu 2018 [64] | RCT | COA criteria (2007) | 64 | 32 (12/20); 57.36 ± 4.89 | (1) Jingu Tongning capsule (1.5 g, tid, 4 w) | Celecoxib (200 mg, bid, 4 w) | 3.56 ± 0.74 y | 4 w | (1) Lequesne (2) ER (3) ADR |
| Xia 2017 [66] | RCT | COA criteria (2007) | 92 | 46 (20/26); 46.02 ± 11.81 | Glucosamine hydrochloride (480 mg, tid, 4 w) | Glucosamine hydrochloride (480 mg, tid, 4 w) | 19.46 ± 4.89 m | 4 w | (1) WOMAC (2) ER |
| Study            | Study design | Diagnostic criteria | Sample size | Sample and characteristics (male/female; mean age, year) | Interventions                                                                 | Disease duration | Course of treatment | Outcome index |
|------------------|--------------|---------------------|-------------|----------------------------------------------------------|-------------------------------------------------------------------------------|-----------------|---------------------|---------------|
| Yang 2016 [67]   | RCT          | COA criteria (2007) | 96          | 48 (15/33); 55.4 ± 9.8                                   | Hydrochloride (480 mg, tid, 4 w)                                               |                 |                     |               |
|                  |              |                     |             | 48 (13/35); 56.6 ± 10.5                                  | Jiawei Simiao Pulvis (1 package, bid, 4 w)                                     |                 |                     |               |
|                  |              |                     |             |                                                          | Celecoxib (200 mg, bid, 4 w)                                                   |                 |                     |               |
| Yang 2019 [68]   | RCT          | COA criteria (2007) | 120         | 60 (32/28); 51.06 ± 9.01                                | Glucosamine sulfate (628 mg, tid, 4 w)                                        |                 |                     |               |
|                  |              |                     |             | 60 (27/33); 50.04 ± 11.04                                | (1) Dihuo Jisheng decoction (1 package, bid, 4 w)                               |                 |                     |               |
|                  |              |                     |             |                                                          | (2) Glucosamine sulfate (628 mg, tid, 4 w)                                     |                 |                     |               |
| Yao 2013 [69]    | RCT          | COA criteria (2007) | 81          | 41 (NR); 51 ± 06 ± 9.01                                 | Dihuo Jisheng decoction (1 package, bid, 4 w)                                  |                 |                     |               |
|                  |              |                     |             | 40 (NR); 50 ± 04 ± 11                                      | Celecoxib (200 mg, bid, 4 w)                                                   |                 |                     |               |
| Yi 2017 [70]     | RCT          | ACR criteria (1986) | 120         | 60 (21/39); 58                                          | Glucosamine sulfate (500 mg, tid, 4 w)                                        |                 |                     |               |
|                  |              |                     |             | 60 (23/37); 56                                          | (1) Qiangin Zhuanggu decoction (1 package, bid, 4 w)                           |                 |                     |               |
|                  |              |                     |             |                                                          | (2) Celecoxib (200 mg, bid, 4 w)                                               |                 |                     |               |
| Yu 2010 [72]     | RCT          | ACR criteria (1995) | 113         | 56 (21/35); 56                                          | Dihuo Jisheng decoction (1 package, bid, 4 w)                                  |                 |                     |               |
|                  |              |                     |             | 57 (18/38); 59 ± 18                                      | Celecoxib (200 mg, bid, 4 w)                                                   |                 |                     |               |
| Yuan 2017 [73]   | RCT          | COA criteria (2007) | 70          | 35 (18/17); 48.3 ± 5.6                                  | Bushen Huoxue decoction (1 package, bid, 12 w)                                 |                 |                     |               |
|                  |              |                     |             | 35 (15/20); 41.2 ± 4.8                                   | Glucosamine sulfate (500 mg, tid, 4 w)                                        |                 |                     |               |
| Zhang 2016 [74]  | RCT          | COA criteria (2007) | 156         | 80 (30/50); 53.1                                        | Jinhua Gutong capsule (0.3 g, tid, 12 w)                                       |                 |                     |               |
|                  |              |                     |             | 76 (24/52); 51.4                                        | (1) Jinwu Gutong capsule (0.3 g, tid, 12 w)                                    |                 |                     |               |
|                  |              |                     |             |                                                          | (2) Glucosamine hydrochloride (750 mg, bid, 12 w)                              |                 |                     |               |
| Zhang 2017 [77]  | RCT          | COA criteria (2007) | 63          | 32 (19/13); 65.86 ± 7.74                                | Fugui Gutong capsule (1.32 g, tid, 4 w)                                       |                 |                     |               |
|                  |              |                     |             | 31 (20/11); 65.70 ± 7.69                                 | (1) Qianggu capsule (0.25 g, tid, 12 w)                                       |                 |                     |               |
|                  |              |                     |             |                                                          | (2) Glucosamine sulfate (500 mg, tid, 12 w)                                   |                 |                     |               |
| Zhang 2018 [76]  | RCT          | COA criteria (2007) | 110         | 55 (21/34); 55.2                                       | Lequesne (200 mg, bid, 4 w)                                               |                 |                     |               |
|                  |              |                     |             | 55 (20/35); 54.5                                       | (1) Qianggu capsule (0.25 g, tid, 12 w)                                       |                 |                     |               |
|                  |              |                     |             |                                                          | (2) Glucosamine sulfate (500 mg, tid, 12 w)                                   |                 |                     |               |
| Zhang 2018 [76]  | RCT          | COA criteria (2007) | 110         | 55 (21/34); 55.2                                       | Lequesne (200 mg, bid, 4 w)                                               |                 |                     |               |
|                  |              |                     |             | 55 (20/35); 54.5                                       | (1) Qianggu capsule (0.25 g, tid, 12 w)                                       |                 |                     |               |
|                  |              |                     |             |                                                          | (2) Glucosamine sulfate (500 mg, tid, 12 w)                                   |                 |                     |               |
| Study     | Study design | Diagnostic criteria | Sample size | Sample and characteristics (male/female; mean age, year) | Interventions | Disease duration | Course of treatment | Outcome index |
|-----------|--------------|---------------------|-------------|--------------------------------------------------------|---------------|-----------------|-------------------|----------------|-----------|
| Zhang 2019 [75] | RCT           | ACR criteria (1995)  | 86          | 43 (17/26); 50.32 ± 6.65; 43 (15/28); 49.68 ± 6.12        | (1) Duhuo Jisheng decoction (1 package, tid, 8 w) (2) Meloxicam (7.5 mg, bid, 8 w) | TG: 70.52 ± 10.68 d CG: 68.20 ± 11.03 d | 8 w              | (1) WOMAC       | (2) ER          |
| Zheng 2014 [78] | RCT           | ACR criteria (1986)  | 80          | 40 (11/29); 60.8 ± 6.6; 40 (9/31); 61.2 ± 5.8           | (1) Zhengqing Fentongning tablet (60 mg, tid, 4 w) | Meloxicam (7.5 mg, bid, 8 w) | TG: 12.6 ± 2.6 y CG: 11.9 ± 3.7 y | 4 w             | (1) Lequesne (2) ER (3) ADR |
| Zheng 2019 [79] | RCT           | COA criteria (2007)  | 100         | 50 (27/23); 63.26 ± 7.42; 50 (24/26); 63.12 ± 4.19      | (1) Duhuo Jisheng decoction (1 package, tid, 4 w) | Celecoxib (200 mg, bid, 4 w) | TG: 32.37 ± 19.46 m CG: 33.24 ± 20.17 m | 4 w             | (1) VAS (2) WOMAC (3) ER (4) ADR |
| Zhong 2017 [80] | RCT           | ACR criteria (1995)  | 116         | 58 (26/32); 56.2 ± 8.3; 58 (28/30); 55.6 ± 8.5       | (1) Shentong Zhuyu decoction (1 package, qd, 4 w) | Glucosamine hydrochloride (750 mg, tid, 4 w) | TG: 3.3 ± 1.8 y CG: 3.3 ± 1.5 y | 4 w             | (1) VAS (2) ER |
| Zhou 2012 [81] | RCT           | ACR criteria (1986)  | 78          | 43 (17/26); 53.61 ± 6.37; 35 (14/21); 54.18 ± 6.13   | (1) Shufu Jiangu decoction (1 package, qd, 8 w) | Celecoxib (200 mg, qd, 8 w) | TG: 4.38 ± 1.52 y CG: 4.24 ± 1.49 y | 8 w             | (1) VAS (2) Lysholm (3) ER |
| Zhu 2013 [82]  | RCT           | ACR criteria (1995)  | 86          | 43 (8/22); 65.17 ± 8.73; 43 (12/18); 64.93 ± 9.12    | Zhengqing Fentongning tablet (60 mg, bid, 12 w) | Glucosamine hydrochloride (480 mg, tid, 12 w) | TG: 16.1 ± 3.73 m CG: 15.3 ± 3.86 m | 12 w            | (1) WOMAC (2) ER (3) ADR |
| Zhuo 2019 [83]  | RCT           | COA criteria (2007)  | 64          | 32 (13/19); 60.90 ± 3.05; 32 (14/18); 61.06 ± 2.86  | (1) Rendong Bixie decoction (1 package, bid, 4 w) (2) Celecoxib (200 mg, qd, 4 w) | Celecoxib (200 mg, qd, 4 w) | TG: 7.28 ± 2.45 y CG: 6.50 ± 1.68 y | 4 w             | (1) WOMAC (2) ER (3) ADR |

RCT: randomized controlled trial; TG: trial group; CG: control group; COA: Chinese Orthopedic Association; CRA: Chinese Rheumatology Association; ACR: American College of Rheumatology; VAS: visual analog score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; ER: effective rate; ADR: adverse drug reaction; NR: not reported.
high-quality RCTs focusing on CHM for treating KOA, excluding low-quality studies, in accordance with Cochrane’s group guidelines for clinical reviews [29].

2. Methods

We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement to perform a systematic review and meta-analysis [30]. This study has been registered at http://www.researchregistry.com, and the study’s unique identifying number (UIN) from the Research Registry is reviewregistry971. There are no protocols preregistered for this review. We did not collect any primary personal data; hence, we did not require ethical approval.

2.1. Database and Search Strategies. We performed electronic searches in eight repositories from their inception to December 2019: PubMed, Web of Science, EMBASE, Cochrane Library, Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, Wanfang Database, and Chinese VIP Database. Additionally, we performed manual searches in the references section of previously published systematic reviews for additional relevant literature. Moreover, the literature search was not limited to any language of publishing. The search criteria used for PubMed were provided as a supplementary material (available here) and were appropriately modified for the other databases.

2.2. Eligibility Criteria

2.2.1. Types of Studies. We included RCTs that investigated the efficacy and safety of CHM in the treatment of KOA, with no restrictions on publication status or language. If we discovered a relevant study with three treatment arms, we only retrieved data for the CHM arm(s) and the control arm(s). We excluded quasirandomized trials, such as studies in which subjects were allocated based on their date of birth, as well as the order in which they were admitted.

2.2.2. Participant Types. We included subjects diagnosed with KOA based on the Chinese Orthopedic Association (COA) criteria (2007), American College of Rheumatology (ACR) criteria (1986 or 1995), and Chinese Rheumatology Association (CRA) criteria (2003, 2005, or 2010) regardless of disease course and severity, age, and gender.

2.2.3. Types of Interventions. Regardless of the dosage, duration, administration route, administration techniques, or duration of therapy, the evaluated therapeutic intervention constituted CHM as monotherapy or a complement to western conventional medicine (WCM). The control group received WCM either alone or in combination with placebo. We excluded trials in which multiple types of CHM therapies were compared.

2.2.4. Outcome Measure Types. The primary outcome parameters included the following: (1) visual analog score (VAS), (2) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), (3) Lysholm score, and (4) Lequesne index. The secondary outcome parameters included the following: (1) the overall clinical effectiveness rate and (2) adverse events.

2.3. Literature Selection. The PRISMA flow diagram was used to select the trials that were included. We imported the literature results into the Endnote X7 software. Two independent authors initially screened the titles and abstracts of potentially eligible articles to remove duplications as well as RCTs that did not meet the inclusion criteria. Following that, we downloaded and reviewed the full texts of the remaining prospective studies. Any disagreements between the two authors were resolved through discussion with a third independent author.

2.4. Data Extraction. Two independent reviewers extracted the data, while a third independent reviewer checked for consistency. A standard form was used to collect the retrieved items, which included the following basic research information: the name(s) of the author(s), publication date, study design, diagnostic criteria, sample size, age, CHM and WCM intervention methods, gender, disease duration, and course of treatment. We retrieved the mean, standard deviation (SD), and the number of participants in each study for continuous outcomes. For dichotomous outcomes, we retrieved the total number of CHM and WCM events as well as the number of occurrences in each group. Where possible, we recomputed the data in other formats to allow for pooled analysis. Any disagreements that arose between these two reviewers were resolved through dialogue. We contacted the relevant authors of the included studies to provide us with any missing data and additional information.

2.5. Quality Assessment of Included Studies. Two independent authors used the Cochrane collaboration tool to assess the quality of methodology and risk of bias of the included RCT studies [31]. This Cochrane tool assesses the following parameters: randomization, subject blinding, allocation concealment, outcome evaluation blinding, selective outcome reporting, incomplete outcome data, and other bias, and categorizes studies as unclear, low, or high risk of bias for each item.

2.6. CHM Composition. We compiled a list of the major components of the CHM formulae. We determined the frequency of use of all Chinese medicinal herbs and estimated and discussed in detail those that were frequently used.

2.7. Statistical Analysis. The Stata software (version 12.0; StataCorp, College Station, TX) was used to evaluate all of the data retrieved in this study for meta-analysis. When heterogeneity was detected or there was significant statistical heterogeneity ($I^2 > 50\%$), a random-effects model was employed, followed by further subgroup analysis and metaregression estimations to ascertain the origins of heterogeneity. Otherwise, we used a fixed-effects model ($I^2 \leq 50\%$). We conducted a sensitivity analysis by excluding individual studies one by one to determine the strength and stability of the pooled data. Besides, the effect of publication bias was examined using Begg’s and Egger’s tests. We computed the relative risk (RR) and the standard mean difference (SMD) for dichotomous outcomes and continuous outcomes, respectively.
3. Results

3.1. Description of Studies. We identified 1532 potentially relevant hits from the repositories. After eliminating duplicated RCTs, we were left with 1241 peer-reviewed articles. Subsequently, we applied the inclusion and exclusion criteria to the titles and abstracts and eliminated 1114 irrelevant studies. Additionally, after reviewing the full text of the 127 remaining studies, we eliminated 71 studies for failing to meet at least one of the following criteria:

1. Nonrandomized or quasi-RCTs
2. No clear KOA diagnostic approach
3. Combined Chinese medicinal herbs with other TCM treatment modalities
4. Published using repeated data
5. Missing data.

Finally, 56 articles [32–87] were included for analysis (Figure 1).

3.2. Characteristics and Quality Assessment of the Eligible Studies. Table 1 summarizes the characteristics of the 56 included RCTs. All the included RCTs were published between 2009 and 2019. All studies enrolled 5350 patients, with 2710 in the treatment arm vs. 2640 in the control arm. Table 2 summarizes the risk of bias analysis conducted on RCTs. Table 3 summarizes the ingredients of CHM used in the included studies.

3.3. Results of Meta-Analysis

3.3.1. VAS. On the basis of regarding the VAS, nine studies compared CHM plus NSAIDS with NSAIDS alone [38, 46, 53, 55, 60, 65, 75, 81]. The pooled results revealed that CHM plus NSAIDS significantly decreased VAS when compared to NSAIDS alone (SMD = −1.990; 95% CI = −2.698 to −1.282; P ≤ 0.001; heterogeneity $\chi^2 = 155.33, df = 8, I^2 = 94.8\%$, $P \leq 0.001$) (Figure 2(a)). Ten studies compared the VAS of CHM and NSAIDS [50, 52, 54, 56, 61, 71, 73, 77, 83, 85].

### Table 2: Assessment of study quality and risk of bias.

| Study       | A | B | C | D | E | F | G | Total |
|-------------|---|---|---|---|---|---|---|-------|
| Chen 2017 [28] | ? | – | ? | + | + | + | + | 4    |
| Chen 2018 [29] | + | ? | + | + | + | + | + | 6    |
| Cui 2017 [31] | + | ? | + | + | + | + | + | 5    |
| Cui 2018 [30] | ? | ? | + | + | + | + | + | 5    |
| Dou 2015 [32] | + | – | + | + | + | + | + | 7    |
| Fu 2018 [33]  | + | – | + | + | + | + | 5    |
| Guo 2019 [34] | + | + | – | + | + | + | 5    |
| He 2019 [35]  | ? | ? | + | + | + | – | 4    |
| Hong 2013 [36]| ? | ? | + | + | + | + | + | 5    |
| Hu 2012 [37]  | ? | ? | + | + | + | + | + | 5    |
| Huang 2015 [38]| ? | – | + | + | + | + | + | 4    |
| Jiang 2009 [39]| ? | ? | + | + | + | + | ? | 4    |
| Li 2018 [40]  | ? | – | + | + | + | + | + | 4    |
| Liu 2016 [41] | ? | ? | + | + | + | + | + | 5    |
| Liu 2017 [42] | ? | ? | + | + | + | + | + | 5    |
| Lu 2016 [44]  | ? | ? | + | + | + | + | + | 4    |
| Luo 2014 [45] | ? | ? | + | + | + | + | + | 4    |
| Ma 2009 [48]  | ? | ? | + | + | + | + | + | 4    |
| Ma 2013 [46]  | + | – | + | + | + | + | + | 5    |
| Ma 2014 [47]  | + | – | + | + | + | + | + | 5    |
| Mo 2018 [48]  | ? | ? | + | + | + | + | + | 4    |
| Pan 2017 [42] | – | – | + | + | + | + | 4    |
| Qian 2019 [51]| + | – | + | + | + | + | 6    |
| Ren 2016 [53] | ? | + | + | + | + | + | 5    |
| Ren 2018 [52] | + | – | + | + | + | + | 4    |
| Rong 2017 [54]| ? | + | – | + | + | + | 4    |
| Shi 2019 [55]| + | – | + | + | + | + | + | 6    |
| Song 2017 [56]| + | – | + | + | + | + | 6    |
| Sun 2018 [57]| + | – | + | + | + | + | 6    |
| Tan 2014 [58]| ? | ? | + | + | + | + | 4    |
| Tang 2012 [59]| + | + | – | + | + | + | 5    |
| Wang 2013 [60]| + | – | + | + | + | + | 5    |
| Wang 2019 [61]| + | – | ? | + | + | + | + | 5    |
| Wen 2016 [62]| + | – | + | + | + | + | 5    |
| Wu 2012 [63]| + | – | + | + | + | + | 7    |
| Wu 2018 [64]| + | – | + | + | + | + | 5    |
| Xia 2017 [66]| + | – | + | + | + | + | 4    |
| Yang 2016 [67]| ? | – | + | + | + | + | 4    |
| Yang 2019 [68]| + | – | + | + | + | + | 5    |
| Yao 2013 [69]| + | – | + | + | + | + | 6    |
| Yi 2017 [70]| + | – | + | + | + | + | 6    |
| Yi 2017 [71]| + | – | + | + | + | + | 6    |
| Yu 2010 [72]| + | – | + | + | + | + | 4    |
| Yuan 2017 [73]| + | – | + | + | + | + | 5    |
| Zhang 2016 [74]| ? | ? | + | + | + | + | 4    |
| Zhang 2017 [77]| ? | – | + | + | + | + | 5    |

A to G, the 7-item criteria. A: random sequence generation; B: allocation concealment; C: blinding of participants and personnel; D: blinding of outcome assessment; E: incomplete outcome data; F: selective reporting; G: other bias; +: low risk of bias; –: high risk of bias; ?: uncertain risk of bias.

### Table 2: Continued.

| Study       | A | B | C | D | E | F | G | Total |
|-------------|---|---|---|---|---|---|---|-------|
| Zhang 2018 [76]| + | – | ? | – | + | + | + | 5    |
| Zheng 2019 [75]| + | + | – | – | – | – | 4    |
| Zheng 2014 [78]| ? | ? | + | + | – | + | 4    |
| Zheng 2017 [79]| + | + | + | + | + | + | 7    |
| Zhong 2017 [80]| + | ? | + | + | + | + | 6    |
| Zhu 2012 [81]| – | – | + | + | + | + | 5    |
| Zhu 2013 [82]| + | – | + | + | + | + | 6    |
| Zhuo 2019 [83]| ? | – | + | + | + | + | 4    |

A to G, the 7-item criteria. A: random sequence generation; B: allocation concealment; C: blinding of participants and personnel; D: blinding of outcome assessment; E: incomplete outcome data; F: selective reporting; G: other bias; +: low risk of bias; –: high risk of bias; ?: uncertain risk of bias.
Table 3: Ingredients of CHM in the included studies.

| Study     | Prescription name | Ingredients of herb prescription                                                                 | Preparations          | Quality control                        |
|-----------|------------------|---------------------------------------------------------------------------------------------------|-----------------------|----------------------------------------|
| Chen 2017 | Sanbi Xiao       | Angelica sinensis, Radix Paeoniae Alba, Radix Rehmanniae Recens, Ginseng, Atragalnus, Achyranthes root, Eucommia ulmoides | Granule               | Guangdong FDA approval number: ZB20060530 |
| Chen 2018 | Danqi granule    | Radix Rehmanniae Praeparata, Corvus officinalis, Rhizoma alismatis, Chinese yam, Epimedium, Paeonia suffruticosa, Tuckahoe, Barberry wolfberry fruit, Semen Cuscutae, herba Cistanches, Concha osteaera | Granule               | SFDA approval number: Z20050537         |
| Cui 2017  | Chaihu Jiangu    | Radix Bupleuri, Scutellaria baicalensis, Rhizoma Pinelliae Praeparata, Codonopsis pilosula, Cassia twig, Radix Paeoniae Alba, Rhizoma Chuanxiong, Achyranthes root, Arisaema cum bile, liquorice | Decoction             | Hospital preparation                    |
| Cui 2018  | Bushen Huoxue    | Radix Rehmanniae Praeparata 15 g, Epimedium 15 g, Semen Cuscutae 15 g, Angelica sinensis 10 g, Salviae miltiorrhiza 10 g, Achyranthes root 10 g, Eucommia ulmoides 10 g, Radix Dipsaci 10 g, Radix Codonopsis 15 g, Rhizoma Atractylodis macrocephalae 15 g, liquorice 6 g | Decoction             | Hospital preparation                    |
| Dou 2015  | Danzi Kangxi     | Human placenta, Salviae miltiorrhiza, Radix Rehmanniae Praeparata, Achyranthes root, Fructus psoraleae, Morinda officinalis, parasitic Loranthus, woodlouse, Radix Angelicae Pubescens, Radix Paeoniae Alba | Electuary             | Hospital preparation                    |
| Fu 2018   | Duhuo Jisheng    | Radix Angelicae Pubescens 15 g, parasitic Loranthus 15 g, glossy privet fruit 15 g, Semen Cuscutae 15 g, Angelica sinensis 15 g, Eucommia ulmoides 15 g, Barberry wolfberry fruit 15 g, Radix Sileris 15 g, Semen Psoraleae 15 g, Achyranthes root 15 g, peach seed 10 g, flowers carthami 10 g, Rhizoma Chuanxiong 10 g, herba Lycosi 10 g, liquorice 6 g, Asarum 3 g | Decoction             | Hospital preparation                    |
| Guo 2019  | Duhuo Jisheng    | Radix Angelicae Pubescens 15 g, parasitic Loranthus 15 g, glossy privet fruit 15 g, Semen Cuscutae 15 g, Angelica sinensis 15 g, Eucommia ulmoides 15 g, Barberry wolfberry fruit 15 g, Radix Sileris 15 g, Semen Psoraleae 15 g, Achyranthes root 15 g, peach seed 10 g, flowers carthami 10 g, Rhizoma Chuanxiong 10 g, herba Lycosi 10 g, liquorice 6 g, Asarum 3 g | Decoction             | Hospital preparation                    |
| He 2019   | Shuanggu Sanzi   | Woodlouse, Rhizoma Drynariae, Pyritum, Atragalnus, Angelica sinensis, Resina Draconis, Rheum officinale, olibanum, myrrh, Rhizoma Cibotii, Semen Allii Tuberosi, muskmelon seed, cucumber seed | Capsule               | SFDA approval number: B20020788        |
| Hong 2013 | Qufeng Jiangu     | Rhizoma seu Radix Notopterygii 30 g, Caulis Spatholobi 30 g, Radix Cynanchi Paniculati 30 g, Rhizoma Chuanxiong 15 g, Rhizoma Curcuma 15 g, Rhizoma Drynariae 15 g, obscured homalomena rhizome 15 g, Berberis aristolochiae mollissimae 15 g, liquorice 6 g, Pericarpium citri Reticulatae 6 g | Decoction             | Hospital preparation                    |
| Hu 2012   | Bushen Zhuangu   | Radix Rehmanniae Praeparata 15 g, Epimedium 15 g, Semen Cuscutae 15 g, Angelica sinensis 10 g, Salviae miltiorrhiza 10 g, Achyranthes root 10 g, Eucommia ulmoides 10 g, Radix Dipsaci 10 g, Radix Codonopsis 15 g, Rhizoma Atractylodis macrocephalae 15 g, liquorice 6 g | Decoction             | Hospital preparation                    |
| Huang 2015 | Bushen Guangjie  | Semen Cuscutae 10 g, Rhizoma Atractylodis macrocephalae 20 g, Morinda officinalis 20 g, Notoginseng Radix 15 g, Radix Curcumae Longae 15 g, Achyranthes root 30 g, Radix Arnebiae seu Lithospermi 15 g, Rhizoma Alismatis 20 g, desert Cistanches 20 g, Radix Sileris 20 g, liquorice 5 g, Rhizoma Chuanxiong 20 g, Radix Arnebiae seu Lithospermi 15 g, cowherb seed 15 g | Pulvis                | Hospital preparation                    |
| Jiang 2009 | Bushen Huoxue    | Radix Rehmanniae Praeparata 15 g, Epimedium 15 g, Semen Cuscutae 15 g, Angelica sinensis 10 g, Salviae miltiorrhiza 10 g, Achyranthes root 10 g, Eucommia ulmoides 10 g, Radix Dipsaci | Decoction             | Hospital preparation                    |
| Study     | Prescription name | Ingredients of herb prescription                                                                 | Preparations                  | Quality control     |
|-----------|-------------------|---------------------------------------------------------------------------------------------------|-------------------------------|---------------------|
| Li 2018 [40] | Duhuo Jisheng decoction | 10 g, Radix Codonopsis 15 g, Rhizoma Atractylodis macrocephalae 15 g, liquorice 6 g  
Radix Angelicae Pubescentis 15 g, parasitic Loranthus 15 g, glossy privet fruit 15 g, Semen Cuscutae 15 g, Angelica sinensis 15 g, Eucommia ulmoides 15 g, Barbary wolfberry fruit 15 g, Radix Sileris 15 g, Semen Psoraleae 15 g, Achyranthes root 15 g, peach seed 10 g, flowers carthami 10 g, Rhizoma Chuanxiong 10 g, herba Lycopii 10 g, liquorice 6 g, Asarum 3 g | Decoction                     | Hospital preparation     |
| Liu 2011 [43] | Zhengqing Fengtongning tablet | Sinomenine 60 mg                                                                                     | Tablet                        | SFDA approval number: Z20010174 |
| Liu 2016 [41] | Jingu Tongning capsule | Rheum officinale, woodlouse, obilanium, myrrh, Angelica sinensis, flowers carthami, Radix Paoniae Alba, Fructus forsythiae, Fructus gardeniae, borneol  
Astragalus 15 g, Epimedium 15 g, cornu Cervi degelatinatum 15 g, Rhizoma Chuanxiong 15 g, Radix Rehmanniae Praeparata 15 g, Radix Angelicae Pubescentis 15 g, Radix Aconiti Lateralis Preparata 10 g, Lycopodium clavatum 10 g, Rhizoma seu Radix Nototerygii 10 g, Barbary wolfberry fruit 10 g, Angelica sinensis 10 g, Radix Sileris 10 g, Kadsura pepper stem 8 g, Radix Paeoniae Alba 30 g, Fructus criniti 12 g, Caulis Spatholobi 20 g, Elecampane 8 g, liquorice 8 g | Capsule                       | Henan FDA approval number: Z204090031 |
| Liu 2017 [42] | Shujin decoction | Cornu Cervi Degelatinatum, Fructus psoraleae, Astragalus, wolfberry, Rhizoma Chuanxiong, Rheum officinale, Radix Dipsaci  
Lycocodium 15 g, Astragalus 15 g, Eucommia ulmoides 15 g, Angelica sinensis 10 g, Radix Sileris 10 g, Kadsura pepper stem 8 g, Radix Paeoniae Alba 30 g, Fructus criniti 12 g, Caulis Spatholobi 20 g, Elecampane 8 g, liquorice 8 g | Capsule                       | Guizhou EDA approval number: Z20120003 |
| Luo 2019 [45] | Zhengqing Fengtongning tablet | Sinomenine 60 mg                                                                                     | Tablet                        | SFDA approval number: Z20010174 |
| Ma 2009 [48] | Huoxue Tongluo decoction | Peach seed 10 g, flowers carthami 12 g, Rhizoma Chuanxiong 10 g, Angelica sinensis 12 g, root of common peony 10 g,  
Achyranthes root 12 g, parasitic Loranthus 15 g, Eucommia ulmoides 12 g, Radix Clematidis 12 g | Decoction                     | Hospital preparation     |
| Ma 2018 [46] | Duhuo Jisheng decoction | Radix Angelicae pubescentis 15 g, Parasitic loranthus 15 g, glossy privet fruit 15 g, Semen cuscutae 15 g, Angelica sinensis 15 g, Eucommia ulmoides 15 g, Barbary Wolfberry fruit 15 g, Radix Sileris 15 g, Semen psoraleae 15 g, Achyranthes root 15 g, peach seed 10 g, flowers carthami 10 g, Rhizoma Chuanxiong 10 g, Herba Lycopii 10 g, liquorice 6 g, Asarum 3 g | Decoction                     | Hospital preparation     |
| Ma 2019 [47] | Bushen Yiqi decoction | Astragalus 15 g, Fructus psoraleae 15 g, herba Cistanche 15 g,  
Radix Codonopsis 12 g, Rhizoma Chuanxiong 9 g, Salviae millitorrhizae 9 g, synthetic musk 0.03 g | Decoction                     | Hospital preparation     |
| Mo 2018 [49] | Kangzuzhi Zengsheng capsule | Radix Rehmanniae Praeparata, desert Cistanche, Rhizoma Cibotii, glossy privet fruit, Epimedium, Caulis Spatholobi, Radish seed, Rhizoma Drynariae, Achyranthes root | Capsule                       | SFDA approval number: Z10980006 |
| Pan 2017 [22] | Longbie capsule | Morinda officinalis, Rhizoma Curculiginis, Semen Cuscutae, Scorpio, centipepe, Agkistrodon, woodlouse, Salviae millitorrhizae, Radix Aconiti Preparata | Capsule                       | Guangdong FDA approval number: Z20071030 |
| Qian 2019 [51] | Yishen Quyu decoction | Rhizoma Chuanxiong 18 g, Chinese angelica 18 g, root of  
Achyranthes bidentata 18 g, Rhizoma Drynariae 18 g, Rhizoma Cibotii 15 g, Epimedium 15 g, pubescent angelica root 12 g,  
Eucommia ulmoides 12 g, Radix Dipsaci 12 g | Decoction                     | Hospital preparation     |
| Ren 2016 [53] | Yishen Quyu decoction | Rhizoma Chuanxiong 18 g, Angelica sinensis 18 g, Achyranthes root 18 g, Rhizoma Drynariae 18 g, Rhizoma Cibotii 15 g, Epimedium 15 g, Radix Angelicae Pubescentis 12 g, Morinda officinalis 12 g, Eucommia ulmoides 12 g, Radix Dipsaci 12 g | Decoction                     | Hospital preparation     |
### Table 3: Continued.

| Study   | Prescription name | Ingredients of herb prescription | Preparations         | Quality control                     |
|---------|-------------------|-----------------------------------|----------------------|-------------------------------------|
| Ren 2018 [52] | Duhuo Jisheng decoction | *Radix Angelicae Pubescentsis* 15 g, parasitic *Loranthus* 15 g, glossy privet fruit 15 g, *Semem Cuscutae* 15 g, *Angelica sinensis* 15 g, *Eucommia ulmoides* 15 g, Barbary wolfberry fruit 15 g, *Radix Sileris* 15 g, *Semem Psoraleae* 15 g, *Achyranthes* root 15 g, peach seed 10 g, flowers carthami 10 g, *Rhizoma Chuanxiong* 10 g, herba *Lycopi* 10 g, liquorice 6 g, *Asarum* 3 g | Decoction | Hospital preparation |
| Rong 2017 [54] | Duhuo Jisheng decoction | *Radix Angelicae Pubescentsis* 15 g, parasitic *Loranthus* 15 g, glossy privet fruit 15 g, *Semem Cuscutae* 15 g, *Angelica sinensis* 15 g, *Eucommia ulmoides* 15 g, Barbary wolfberry fruit 15 g, *Radix Sileris* 15 g, *Semem Psoraleae* 15 g, *Achyranthes* root 15 g, peach seed 10 g, flowers carthami 10 g, *Rhizoma Chuanxiong* 10 g, herba *Lycopi* 10 g, liquorice 6 g, *Asarum* 3 g | Decoction | Hospital preparation |
| Shi 2019 [55] | Duhuo Jisheng decoction | *Radix Angelicae Pubescentsis* 15 g, parasitic *Loranthus* 15 g, glossy privet fruit 15 g, *Semem Cuscutae* 15 g, *Angelica sinensis* 15 g, *Eucommia ulmoides* 15 g, Barbary wolfberry fruit 15 g, *Radix Sileris* 15 g, *Semem Psoraleae* 15 g, *Achyranthes* root 15 g, peach seed 10 g, flowers carthami 10 g, *Rhizoma Chuanxiong* 10 g, herba *Lycopi* 10 g, liquorice 6 g, *Asarum* 3 g | Decoction | Hospital preparation |
| Song 2017 [56] | Duhuo Jisheng decoction | *Radix Angelicae Pubescentsis* 15 g, parasitic *Loranthus* 15 g, glossy privet fruit 15 g, *Semem Cuscutae* 15 g, *Angelica sinensis* 15 g, *Eucommia ulmoides* 15 g, Barbary wolfberry fruit 15 g, *Radix Sileris* 15 g, *Semem Psoraleae* 15 g, *Achyranthes* root 15 g, peach seed 10 g, flowers carthami 10 g, *Rhizoma Chuanxiong* 10 g, herba *Lycopi* 10 g, liquorice 6 g, *Asarum* 3 g | Decoction | Hospital preparation |
| Sun 2018 [57] | Qinbi decoction | Ginseng, *Cortex Cinnamomi*, *Radix Rehmanniae Recens*, *Pinellia ternata*, *Radix Asteris*, *Rhizoma Anemarrhena*, *Astragalus*, liquorice, *Radix Asparagi*, *Carapax Trionycis*, *Gentiana macrophylla*, white poria, *Cortex Lycii Radicis*, *Radix Bupleuri* | Pill | Hospital preparation |
| Tan 2014 [58] | Huangqi Bieja pill | *Corydalis amabilis*, *Radix Aconiti Kusnezoffi Preparata*, herba *Siegesbeckiae*, *Cissus assamica*, *Caulis Spatholobi*, *Paederia scandens*, *Radix Clematidis*, *Aristolochia fangchi*, *Cortex Acanthopanacis*, *Rhizoma seu Radix Notopyretygii*, *Gentiana macrophylla*, Agkistrodon, herba ephedra | Pill | Hospital preparation |
| Tang 2012 [59] | Jiedu Yishen pill | *Eucommia ulmoides* 80 g, *Rhizoma Chuanxiong* 80 g, woodlouse 40 g, *Cortex Phellodendri* 40 g | Pill | Hospital preparation |
| Wang 2013 [60] | Fufang Xiathan Wu pill | *Corydalis amabilis*, *Radix Aconiti Kusnezoffi Preparata*, herba *Siegesbeckiae*, *Cissus assamica*, *Caulis Spatholobi*, *Paederia scandens*, *Radix Clematidis*, *Aristolochia fangchi*, *Cortex Acanthopanacis*, *Rhizoma seu Radix Notopyretygii*, *Gentiana macrophylla*, Agkistrodon, herba ephedra | Pill | SFDA approval number: Z20003105 |
| Wang 2019 [61] | Taoren Xikang pill | *Radix Rehmanniae Praeparata*, *Rhizoma Chuanxiong*, *Radix Paonae Alba*, *Radix Angelicae Pubescentsis*, *Radix Sileris*, parasitic *Loranthus*, *Achyranthes* root, *Asarum*, olibanum, myrrh | Pill | Henan FDA approval number: Z20120243 |
| Wen 2016 [62] | Duhuo Jisheng decoction | *Radix Angelicae Pubescentsis* 15 g, parasitic *Loranthus* 15 g, glossy privet fruit 15 g, *Semem Cuscutae* 15 g, *Angelica sinensis* 15 g, *Eucommia ulmoides* 15 g, Barbary wolfberry fruit 15 g, *Radix Sileris* 15 g, *Semem Psoraleae* 15 g, *Achyranthes* root 15 g, peach seed 10 g, flowers carthami 10 g, *Rhizoma Chuanxiong* 10 g, herba *Lycopi* 10 g, liquorice 6 g, *Asarum* 3 g | Decoction | Hospital preparation |
| Wu 2012 [65] | Zhuanggu Tongbi pill | *Radix Rehmanniae Praeparata* 12 g, *Eucommia ulmoides* 15 g, herba *Pyroloae* 30 g, pulp of dogwood fruit 15 g, *Rhizoma Drynariae* 15 g, *Radix Clematidis* 30 g, *Radix Dipsaci* 15 g, *Achyranthes* root 15 g, garden balsam stem 15 g, Chinese | Pill | Hospital preparation |
| Study       | Prescription name              | Ingredients of herb prescription                                                                 | Preparations          | Quality control                  |
|------------|--------------------------------|--------------------------------------------------------------------------------------------------|-----------------------|----------------------------------|
| Wu 2018    | Bushen Huoxue decoction        | Polypha 9 g, Tuckahoe 12 g, Radix Aconiti Preparata 9 g, Fructus psoraleae 15 g, parasitic Loranthus 15 g Radix Rehmanniae Praeparata 15 g, Epimedium 15 g, Semen Cuscutae 15 g, Angelica sinensis 10 g, Salviae miltiorrhizae 10 g, Achiyranthes root 10 g, Eucommia ulmoides 10 g, Radix Dipsaci 10 g, Radix Codonopsis 15 g, Rhizoma Atractylodis macrocephala 15 g, liquorice 6 g | Decoction             | Hospital preparation             |
| Wu 2018    | Sanqi Xuejie capsule           | Rhizoma Cibotii, Epimedium, Radix Clematidis, Zaocys dhumnade, Achyranthes root, Chinese quince, root of kudzu vine, Radix Curcumae Longae, Fructus psoraleae, Radix Campanumoeae | Capsule               | Hospital preparation             |
| Xia 2017   | Jinwu Gutong capsule           | Cortex Phellodendri 5 g, Rhizoma Atractylodis 10 g, Semen Coicis 10 g, Achiyranthes root 10 g, Radix Stephaniae Tetrandrae 10 g, Fructus forsythiae 10 g, Radix Sophorae Flavescentis 10 g, Chinese quince 10 g, Gentiana macrophylla 10 g, Radix Rehmanniae Recenc 15 g, honeysuckle stem 15 g | Capsule               | Hospital preparation             |
| Yang 2016  | Jiawei Simiao Pulvis          | Radix Angelicae Pubescents 15 g, parasitic Loranthus 15 g, glossy privet fruit 15 g, Semen Cuscutae 15 g, Angelica sinensis 15 g, Eucommia ulmoides 15 g, Barberry wolfberry fruit 15 g, Radix Sileris 15 g, Semen Psoraleae 15 g, Achiyranthes root 15 g, peach seed 10 g, flowers carthami 10 g, Rhizoma Chuanxiong 10 g, herba Lycopi 10 g, liquorice 6 g, Asarum 3 g | Pulvis                | Hospital preparation             |
| Yang 2019  | Duhuo Jisheng decoction       | Radix Angelicae Pubescents 15 g, parasitic Loranthus 15 g, glossy privet fruit 15 g, Semen Cuscutae 15 g, Angelica sinensis 15 g, Eucommia ulmoides 15 g, Barberry wolfberry fruit 15 g, Radix Sileris 15 g, Semen Psoraleae 15 g, Achiyranthes root 15 g, peach seed 10 g, flowers carthami 10 g, Rhizoma Chuanxiong 10 g, herba Lycopi 10 g, liquorice 6 g, Asarum 3 g | Decoction             | Hospital preparation             |
| Yao 2013   | Duhuo Jisheng decoction       | Radix Rehmanniae Praeparata 15 g, Epimedium 15 g, Semen Cuscutae 15 g, Angelica sinensis 10 g, Salviae miltiorrhizae 10 g, Achiyranthes root 10 g, Eucommia ulmoides 10 g, Radix Dipsaci 10 g, Radix Codonopsis 15 g, Rhizoma Atractylodis macrocephala 15 g, liquorice 6 g | Decoction             | Hospital preparation             |
| Yi 2017    | Bushen Huoxue decoction        | Semen Cuscutae 15 g, Rhizoma Curculiginis 20 g, Morinda officinalis 10 g, Radix Rehmanniae Praeparata 15 g, parasitic Loranthus 10 g, Radix Aconiti Preparata 9 g, Scorpio 4 g, centipede 4 g, Radix Clematidis 15 g, Lycopodium clavatum 15 g, Caulis Spatolobi 15 g, Rhizoma Chuanxiong 15 g, Ramulus mori 10 g, Radix Sileris 10 g, Tribulus terrestris 15 g, liquorice 10 g | Decoction             | Hospital preparation             |
| Yi 2017    | Qiangjin Zhuanggu decoction    | Radix Angelicae Pubescents 15 g, parasitic Loranthus 15 g, glossy privet fruit 15 g, Semen Cuscutae 15 g, Angelica sinensis 15 g, Eucommia ulmoides 15 g, Barberry wolfberry fruit 15 g, Radix Sileris 15 g, Semen Psoraleae 15 g, Achiyranthes root 15 g, peach seed 10 g, flowers carthami 10 g, Rhizoma Chuanxiong 10 g, herba Lycopi 10 g, liquorice 6 g, Asarum 3 g | Decoction             | Hospital preparation             |
| Yu 2010    | Duhuo Jisheng decoction       | Radix Rehmanniae Praeparata 15 g, Epimedium 15 g, Semen Cuscutae 15 g, Angelica sinensis 10 g, Salviae miltiorrhizae 10 g, Achiyranthes root 10 g, Eucommia ulmoides 10 g, Radix Dipsaci 10 g, Radix Codonopsis 15 g, Rhizoma Atractylodis macrocephala 15 g, liquorice 6 g | Decoction             | Hospital preparation             |
| Yuan 2017  | Bushen Huoxue decoction       | Radix Rehmanniae Praeparata 15 g, Epimedium 15 g, Semen Cuscutae 15 g, Angelica sinensis 10 g, Salviae miltiorrhizae 10 g, Achiyranthes root 10 g, Eucommia ulmoides 10 g, Radix Dipsaci 10 g, Radix Codonopsis 15 g, Rhizoma Atractylodis macrocephala 15 g, liquorice 6 g | Decoction             | Hospital preparation             |
| Zhang 2016 | Jinwu Gutong capsule           | Rhizoma Cibotii, Epimedium, Radix Clematidis, Zaocys dhumnade, Achyranthes root, Chinese quince, root of kudzu vine, Radix Curcumae Longae, Fructus psoraleae, Radix Campanumoeae | Capsule               | Hospital preparation             |
Table 3: Continued.

| Study            | Prescription name                  | Ingredients of herb prescription                                                                 | Preparations          | Quality control                  |
|------------------|-----------------------------------|---------------------------------------------------------------------------------------------------|----------------------|----------------------------------|
| Zhang 2017 [77]  | Fugui Gutong capsule              | Radix Aconiti Lateralis Preparata, Radix Aconiti Preparata, Cortex Cinnamomi, Codonopsis pilosula, Angelica sinesis, Radix Paeoniae Alba, Epimedium, olibanum | Capsule              | SFDA approval number: Z19990026  |
| Zhang 2018 [76]  | Qianggu capsule                   | Rhizoma Drynariae 0.25 g                                                                          | Capsule              | SFDA approval number: Z20030007  |
| Zhang 2019 [75]  | Duhuo Jisheng decoction           | Radix Angelicae Pubescentsis 15 g, parasitic Loranthus 15 g, glossy privet fruit 15 g, Semen Cuscutae 15 g, Angelica sinesis 15 g, Eucommia ulmoides 15 g, Barbary wolfberry fruit 15 g, Radix Sileris 15 g, Semen Psoraleae 15 g, Achyranthes root 15 g, peach seed 10 g, flowers carthami 10 g, Rhizoma Chuanxiong 10 g, herba Lycopi 10 g, liquorice 6 g, Asarum 3 g | Decoction             | Hospital preparation             |
| Zheng 2014 [78]  | Zhengqing Fengtongming tablet     | Sinomenine 60 mg                                                                                   | Tablet               | SFDA approval number: Z20010174  |
| Zheng 2019 [79]  | Bushen Huoxue decoction           |                                                                                                   | Decoction             | Hospital preparation             |
| Zheng 2017 [80]  | Shentong Zhuyu decoction          |                                                                                                   | Decoction             | Hospital preparation             |
| Zhou 2012 [81]   | Shufu Jiangu decoction            |                                                                                                   | Decoction             | Hospital preparation             |
| Zhu 2013 [82]    | Zhengqing Fengtongming tablet     |                                                                                                   | Tablet               | SFDA approval number: Z20010174  |
| Zhuo 2019 [83]   | Rendong Bixie decoction           |                                                                                                   | Decoction             | Hospital preparation             |

SFDA: State Food and Drug Administration; FDA: Food and Drug Administration.

The pooled results indicated that CHM monotherapy significantly reduced VAS when compared to NSAIDS alone (SMD = −0.803; 95%CI = −1.158 to −0.449; P < 0.001; heterogeneity χ² = 53.68, df = 9, I² = 83.2%, P < 0.001, Figure 2(b)). We identified five studies that compared CHM plus Glu to Glu alone in terms of the VAS [33, 45, 48, 72, 80]. CHM plus Glu significantly decreased the VAS in comparison to Glu alone (SMD = −1.204; 95%CI = −1.593 to −0.815; P < 0.001; heterogeneity χ² = 17.89, df = 4, I² = 77.6%, P = 0.001, Figure 2(c)). Eight studies compared CHM and Glu on the basis of their VAS scores [32, 35, 36, 43, 51, 58, 66, 84]. The pooled results indicated that CHM monotherapy significantly decreased VAS compared with Glu alone (SMD = −1.533; 95%CI = −1.688 to −1.076; P < 0.001; heterogeneity χ² = 123.94, df = 7, I² = 94.4%, P < 0.001, Figure 2(d)). Metaregression was used to investigate the sources of heterogeneity in the findings. To ascertain the potential sources of interstudy heterogeneity, we conducted a metaregression analysis on the year of publication, course of treatment, and sample size (Figure 3). In general, the year of publication (β = −0.103; P = 0.120; R² = 5.20%), the duration of treatment (β = 0.037; P = 0.231; R² = 1.33%), and the sample size (β = −0.011; P = 0.100; R² = 6.37%), were not significant sources of heterogeneity for the VAS.

3.3.2. WOMAC. Seven studies compared CHM plus NSAIDS to NSAIDS alone in terms of the WOMAC score [38, 44, 46, 68, 75, 79, 87]. The pooled data revealed that CHM plus NSAIDS was significantly more effective at reducing WOMAC than NSAIDS alone (SMD = −2.131; 95%CI = −3.082 to −1.180; P < 0.001; heterogeneity χ² = 150.92, df = 6, I² = 96.0%, P ≤ 0.001, Figure 4(a)). There were three studies comparing CHM and NSAIDS in terms of the WOMAC [61, 73, 83]. The pooled data showed that...
CHM monotherapy significantly decreased WOMAC when compared to NSAIDs alone (SMD = −0.672; 95%CI = −1.226 to −0.119; \( P = 0.017 \); heterogeneity \( \chi^2 = 8.19, df = 2, I^2 = 75.6\% \), \( P = 0.017 \), Figure 4(b)). Six studies compared CHM plus Glu with Glu alone in terms of WOMAC [33, 40, 47, 49, 59, 72]. The findings indicated that CHM plus Glu significantly decreased WOMAC score when compared to Glu alone (SMD = −1.315; 95%CI = −2.162 to −0.468; \( P = 0.002 \); heterogeneity \( \chi^2 = 112.54, df = 5, I^2 = 95.6\% \), \( P \leq 0.001 \), Figure 4(c)). Six studies examined the efficacy of CHM and Glu in terms of WOMAC. The pooled data indicated that CHM monotherapy was significantly more effective than Glu in reducing WOMAC (SMD = −1.095; 95%CI = −1.607 to −0.583; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 36.84, df = 5, I^2 = 86.4\% \), \( P \leq 0.001 \), Figure 4(d)). We used metaregression to determine the sources of heterogeneity in the findings. We also conducted metaregression to examine the year of publication, duration of treatment, and the sample size to ascertain the potential reasons of interstudy heterogeneity (Figure 5). Altogether, the year of publication (\( \beta = 0.112; P = 0.171; R^2 = 4.83\% \)), duration of treatment (\( \beta = 0.007; P = 0.861; R^2 = 5.18\% \)), and the sample size (\( \beta = 0.012; P = 0.303; R^2 = 0.24\% \)) were not significant predictors of heterogeneity for WOMAC.
3.3.3. Lysholm Score. Five studies compared the Lysholm score between CHM plus NSAIDS and NSAIDS alone [44, 46, 53, 57, 75]. The pooled data indicated that CHM plus NSAIDS was significantly more effective at improving Lysholm score than NSAIDS alone (SMD = 2.503; 95% CI = 1.424 to 3.583; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 99.72, \ df = 4, I^2 = 96.0\% , \ P \leq 0.001 \), Figure 6(a)). There were three studies comparing the Lysholm score of CHM to that of NSAIDS [56, 77, 85]. The pooled data revealed that CHM monotherapy significantly increased the Lysholm score more than NSAIDS alone (SMD = 1.071; 95% CI = 0.459 to 1.683; \( P = 0.001 \); heterogeneity \( \chi^2 = 9.47, \ df = 2, I^2 = 78.9\% , \ P = 0.009 \), Figure 6(b)).

3.3.4. Lequesne Index. Five studies compared the effect of CHM plus NSAIDS to that of NSAIDS alone on the Lequesne index [42, 55, 60, 68, 81]. The pooled data revealed that CHM plus NSAIDS treatment significantly decreased the Lequesne index when compared to NSAIDS alone (SMD = -0.883; 95% CI = -1.095 to -0.672; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 3.63, \ df = 4, I^2 = 0\% , \ P = 0.458 \), Figure 7(a)). There was only one study comparing the Lequesne index between CHM and NSAIDS [54]. The results indicated that CHM monotherapy significantly decreased the Lequesne index when compared to NSAIDS alone (SMD = -0.804; 95% CI = -1.239 to -0.369; \( P \leq 0.001 \), no heterogeneity, Figure 7(b)). Six studies compared the Lequesne index of CHM plus Glu to Glu alone [33, 41, 64, 78, 80, 82]. The available data demonstrated that CHM plus Glu significantly reduced the Lequesne index when compared to Glu alone (SMD = -0.734; 95% CI = -0.890 to -0.579; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 11.74, \ df = 5, I^2 = 57.4\% , \ P = 0.038 \), Figure 7(c)). Based on the Lequesne index, four studies compared CHM versus Glu [35, 62, 69, 76]. The pooled results indicated that CHM monotherapy significantly reduced the Lequesne index when compared to Glu alone (SMD = -1.071; 95% CI = -1.283 to -0.859; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 3.61, \ df = 3, I^2 = 17.0\% , \ P = 0.306 \), Figure 7(d)).

3.3.5. Effective Rate. Eighteen studies examined the effectiveness of CHM plus NSAIDS to NSAIDS alone [34, 37, 38, 42, 44, 46, 53, 55, 57, 60, 65, 67, 68, 75, 79, 81, 87]. The pooled data demonstrated that CHM plus NSAIDS significantly increased the effective rate when compared to NSAIDS alone (RR = 1.247; 95% CI = 1.192 to 1.303; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 16.86, \ df = 17, I^2 = 0\% , \ P = 0.464 \), Figure 8(a)). There were ten studies comparing the effective rate between CHM and NSAIDS [50, 52, 54, 56, 61, 71, 73, 77, 83, 85]. The pooled data indicated that CHM monotherapy significantly improved the effective rate when compared to NSAIDS alone (RR = 1.154; 95% CI = 1.084 to 1.229; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 9.20, \ df = 9, I^2 = 2.2\% , \ P = 0.419 \), Figure 8(b)). Ten studies compared the effective rate between CHM plus Glu with Glu [33, 40, 45, 47–49, 59, 72, 80, 82]. The pooled data demonstrated that CHM plus Glu significantly increased the effective rate when compared to Glu alone (RR = 1.223; 95% CI = 1.156 to 1.295; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 4.21, \ df = 9, I^2 = 0\% , \ P = 0.897 \), Figure 8(c)). Ten studies compared the effective rate of CHM and Glu treatment [35, 43, 51, 62, 63, 69, 70, 76, 84, 86]. The pooled data demonstrated that CHM monotherapy significantly increased the effective rate when compared to Glu alone (RR = 1.208; 95% CI = 1.148 to 1.272; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 12.03, \ df = 9, I^2 = 25.2\% , \ P = 0.212 \), Figure 8(d)).
3.3.6. Adverse Events. We identified adverse events in thirty-two studies. The trial group experienced 108/1489 adverse events, whereas the control group experienced 172/1472. The risk of adverse events was significantly lower in the CHM group than that in the control group (RR = 0.625; 95% CI = 0.500 to 0.783; \( P \leq 0.001 \); heterogeneity \( \chi^2 = 40.94, \text{df} = 31, I^2 = 24.3\% \), \( P = 0.109 \), Figure 9). Our findings indicated that the most often occurring adverse effects included gastrointestinal discomfort (nausea, diarrhea, thirst, poor appetite, stomach pain, and constipation), abnormal liver function, and rash. Significant adverse impacts that were mild, no severe adverse impacts, and death were reported in the included RCTs.

3.3.7. Publication Bias and Sensitivity Analysis. We examined the possibility of publication bias of the adverse effects in this meta-analysis using Begg’s funnel plot and Egger’s test (Figure 10). As a result of the symmetrical shape of the funnel plots and the \( P \) values from Begg’s and Egger’s tests, there was evidence of notable publication bias for adverse events (\( P = 0.661 \) and \( P = 0.847 \), respectively).

To establish the influence of each included study on the pooled RRs for the effective rate and adverse effects and to validate the robustness of our findings, we performed a sensitivity analysis by excluding one study at a time and computing the pooled RRs for the rest of the RCTs. The results of the sensitivity analysis indicated that excluding each study individually had no discernible influence on the pooled RRs showing that the findings of this meta-analysis are comparatively robust (Figure 11).

3.3.8. Description of the CHMs. The most commonly used herbs across all formulae included Niu Xi (Radix Achyranthis Bidentatae, Twotooth Achyranthes root), Di Huang (Radix Rehmanniae, Rehmannia root), Dang Gui (Radix Angelicae Sinensis, Chinese angelica), Chuan Xiong (Radix Ligustici Wallichii, Sichuan lovage rhizome), Du Zhong (Cortex Eucommiae Ulmoidis, Epimedium), Gan Cao (Radix Glycyrrhizae,
Figure 5: Metaregression analysis of WOMAC for (a) publication year, (b) course of treatment, (c) and sample size.

| Study ID | SMD (95% CI) | Weight % |
|----------|--------------|----------|
| Mo 2018  | 3.80 (3.19, 4.40) | 12.23 |
| Li 2018  | 4.43 (3.70, 5.16) | 11.79 |
| Liu 2017 | 1.19 (0.79, 1.59) | 12.79 |
| Yi 2017  | 1.84 (1.44, 2.24) | 12.78 |
| Ren 2016 | 1.43 (0.99, 1.86) | 12.71 |
| Subtotal (I-squared = 96.0%, \( p = 0.000 \)) | 2.50 (1.42, 3.58) | 62.30 |

(a) CHM plus NSAIDS versus NSAIDS

(b) CHM versus NSAIDS

Ren 2018            | 1.69 (1.18, 2.20) | 12.50 |
Yuan 2017           | 0.91 (0.42, 1.41) | 12.55 |
Zhou 2012           | 0.63 (0.18, 1.09) | 12.65 |
Subtotal (I-squared = 78.9%, \( p = 0.009 \)) | 1.07 (0.46, 1.68) | 37.70 |

Overall (I-squared = 94.9%, \( p = 0.000 \)) | 1.96 (1.20, 2.72) | 100.00 |

Note: weights are from random effects analysis

Figure 6: Forest plot of Lysholm score: (a) CHM plus NSAIDS versus NSAIDS and (b) CHM versus NSAIDS.
liquorice), Du Huo (*Radix Angelicae Pubescentis*, Pubescent angelica root), Sang Ji Sheng (*Radix Loranthi Seu visci*, Chinese taxillus twig), Bai Shao (*Radix Paeoniae Alba*, White peony root), Fang Feng (*Radix Ledebouriellae Divaricatae*, Divaricate saposhnikovia root), Qin Jiao (*Radix Gentianae Macrophyllae*, Largeleaf gentian root), Fu Ling (*Poria Cocos Wolff*, Tuckahoe), Xi Xin (*Asarum*), Yin Yang Huo (*Epimedium brevicornu Maxim*, Icariin), Huang Qi (*Radix Astragali Membranacei*, Astragalus), Wei Ling Xian (*Radix Clematidis Chinensis*, Chinese clematis root), and Bu Gu Zhi (*Psoralea corylifolia Linn*, *Fructus psoraleae*) (Table 4).

### 4. Discussion

#### 4.1. Summary of Evidence

Herein, we updated a systematic review and meta-analysis on the efficacy and safety of CHM treatment in patients with KOA. A total of fifty-six high-quality RCTs, including 5350 patients with KOA, were included in the analysis. Our primary findings indicated that using CHM as adjuvant therapy or monotherapy for KOA treatment reduced the VAS, WOMAC, and Lequesne index while improving the Lysholm score and overall effective rate. Additionally, we discovered that CHM adjuvant or monotherapy had fewer adverse effects than the controls, indicating that CHM was safe and effective in treating KOA. Therefore, we provide supporting evidence that, to a significant extent, CHM can potentially be recommended for use in KOA patients.

#### 4.2. Comparison with Previous Studies

Significant research demonstrates that the oral and topical use of CHM is both safe and effective in the treatment of KOA. A meta-analysis of 23 RCTs including 2362 patients demonstrated that CHM is both safe and effective in alleviating pain, restoring function, and promoting health in patients with KOA [28]. Another systematic review found that Du Huo Jisheng decoction (DJD) combined with Western medicine or sodium hyaluronate injection was effective in treating KOA [88]. However, the effectiveness and safety of DJD remain debatable due to a scarcity of clinical trials and a lack of methodological rigor. Additionally, a Cochrane review of two RCTs including 327 patients found that orally bioavailable avocado soybean unsaponifiables (ASU) significantly relieved the pain symptoms in hip-OA patients when compared to a placebo. Additionally, this review established that the use of ASU helped patients in reducing their use of NSAIDs [89]. However, a primary concern in these earlier investigations has been the limited sample size and low quality. Therefore, in the current systematic review, we included 56

| Study ID | SMD (95% CI) | % Weight |
|----------|--------------|----------|
| (a) CHM plus NSAIDS versus NSAIDS | -0.75 (-1.21, -0.29) | 5.19 |
| (b) CHM versus NSAIDS | -0.80 (-1.24, -0.37) | 5.80 |
| (c) CHM plus Glu versus Glu | -0.73 (-0.89, -0.58) | 45.27 |
| (d) CHM versus Glu | -0.86 (-0.96, -0.75) | 100.00 |

**Figure 7:** Forest plot of Lequesne index: (a) CHM plus NSAIDS versus NSAIDS, (b) CHM versus NSAIDS, (c) CHM plus Glu versus Glu, and (d) CHM versus Glu.
| Study ID | RR (95% CI) | Weight |
|---------|-------------|--------|
| CHM plus NSAIDS versus NSAIDS | | |
| Qian 2019 | 1.31 (1.02, 1.68) | 1.52 |
| Wang 2019 | 1.18 (0.94, 1.47) | 1.91 |
| Zhuo 2019 | 1.25 (1.00, 1.56) | 1.40 |
| Guo 2019 | 1.28 (1.05, 1.56) | 2.10 |
| Zhang 2019 | 1.21 (1.02, 1.43) | 1.99 |
| Wu 2018 | 1.25 (1.02, 1.53) | 1.38 |
| Mo 2018 | 1.18 (1.05, 1.33) | 2.92 |
| Li 2018 | 1.81 (1.37, 2.38) | 1.52 |
| Wu 2018 | 1.30 (1.07, 1.59) | 1.95 |
| Fu 2018 | 1.12 (0.98, 1.28) | 1.93 |
| Cui 2018 | 1.10 (0.96, 1.26) | 2.98 |
| Liu 2017 | 1.21 (1.02, 1.43) | 2.51 |
| Yi 2017 | 1.22 (1.04, 1.42) | 2.98 |
| Zhang 2017 | 1.25 (1.02, 1.53) | 1.43 |
| Song 2017 | 1.26 (0.99, 1.60) | 1.85 |
| Ren 2016 | 1.30 (1.07, 1.57) | 2.01 |
| Yi 2017 | 1.15 (0.97, 1.36) | 2.69 |
| Huang 2015 | 1.42 (1.12, 1.82) | 1.52 |
| Subtotal (I-squared = 0.0%, p = 0.464) | 1.25 (1.19, 1.30) | 36.59 |
| CHM versus NSAIDS | | |
| Zheng 2019 | 1.03 (0.84, 1.26) | 2.28 |
| Ma 2018 | 1.29 (1.03, 1.61) | 1.31 |
| Ren 2018 | 1.28 (1.03, 1.57) | 1.70 |
| Yuan 2017 | 1.19 (0.96, 1.46) | 1.58 |
| Sun 2018 | 1.05 (0.84, 1.31) | 1.23 |
| Pan 2017 | 1.03 (0.90, 1.18) | 2.10 |
| Yang 2016 | 1.16 (0.97, 1.39) | 2.16 |
| Yao 2013 | 1.16 (0.97, 1.38) | 1.89 |
| Zhou 2012 | 1.08 (0.94, 1.23) | 2.00 |
| Ma 2009 | 1.34 (1.05, 1.72) | 2.05 |
| Subtotal (I-squared = 2.2%, p = 0.419) | 1.15 (1.08, 1.23) | 18.29 |
| CHM plus Glu versus Glu | | |
| Luo 2019 | 1.26 (1.08, 1.54) | 2.05 |
| Shi 2019 | 1.23 (1.02, 1.49) | 1.75 |
| Yang 2019 | 1.17 (1.01, 1.35) | 2.81 |
| Zhang 2018 | 1.22 (1.02, 1.45) | 2.40 |
| Chen 2018 | 1.23 (1.05, 1.44) | 2.81 |
| Lu 2016 | 1.22 (1.01, 1.47) | 2.16 |
| Liu 2016 | 1.27 (0.99, 1.61) | 1.75 |
| Zheng 2014 | 1.31 (1.07, 1.61) | 1.70 |
| Hong 2013 | 1.28 (1.07, 1.53) | 2.43 |
| Liu 2011 | 1.09 (0.95, 1.25) | 2.05 |
| Subtotal (I-squared = 0.0%, p = 0.897) | 1.22 (1.16, 1.30) | 21.90 |
| CHM versus Glu | | |
| Xia 2017 | 1.26 (1.05, 1.53) | 1.99 |
| Ma 2019 | 1.10 (1.00, 1.20) | 4.21 |
| Zhong 2017 | 1.22 (1.05, 1.42) | 2.63 |
| Cui 2017 | 1.25 (1.04, 1.51) | 2.18 |
| Tan 2014 | 1.45 (1.12, 1.88) | 1.17 |
| Zhu 2013 | 1.17 (1.00, 1.37) | 2.05 |
| Wu 2012 | 1.09 (0.99, 1.21) | 3.10 |
| Tang 2012 | 1.36 (1.07, 1.73) | 2.01 |
| Yu 2010 | 1.17 (1.03, 1.33) | 2.72 |
| Jiang 2009 | 1.35 (1.02, 1.79) | 1.17 |
| Subtotal (I-squared = 25.2%, p = 0.212) | 1.21 (1.15, 1.27) | 23.22 |
| Overall (I-squared = 1.3%, p = 0.448) | 1.22 (1.18, 1.25) | 100.00 |

Figure 8: Forest plot of effective rate: (a) CHM plus NSAIDS versus NSAIDS, (b) CHM versus NSAIDS, (c) CHM plus Glu versus Glu, and (d) CHM versus Glu.
| Study ID | RR (95% CI) | Weight |
|---------|-------------|--------|
| Qian 2019 | 1.67 (0.43, 6.50) | 1.72 |
| Wang 2019 | 0.51 (0.05, 5.44) | 1.13 |
| Zhuo 2019 | 2.50 (0.52, 11.96) | 1.14 |
| He 2019 | 1.20 (0.40, 3.57) | 2.86 |
| Wu 2018 | 1.03 (0.07, 15.78) | 0.56 |
| Mo 2018 | 2.00 (0.038, 10.51) | 1.14 |
| Fu 2018 | 0.75 (0.18, 3.13) | 2.29 |
| Cui 2018 | 0.67 (0.20, 2.25) | 3.43 |
| Zhang 2017 | 0.24 (0.06, 1.05) | 4.65 |
| Huang 2015 | 0.19 (0.07, 0.51) | 12.02 |
| Zheng 2019 | 0.14 (0.02, 1.12) | 4.01 |
| Ma 2018 | 0.47 (0.24, 0.93) | 9.45 |
| Ren 2018 | 0.38 (0.11, 1.31) | 4.58 |
| Pan 2017 | 1.33 (0.32, 5.58) | 1.72 |
| Yang 2016 | 0.14 (0.01, 2.69) | 2.00 |
| Luo 2019 | 1.50 (0.26, 8.59) | 1.14 |
| Shi 2019 | 1.67 (0.43, 6.50) | 1.72 |
| Yang 2019 | 0.20 (0.05, 0.87) | 5.72 |
| Zhang 2018 | 1.50 (0.45, 5.02) | 2.29 |
| Zhang 2016 | 4.75 (0.23, 97.43) | 0.29 |
| Lu 2016 | 1.20 (0.39, 3.68) | 2.86 |
| Zheng 2014 | 0.75 (0.36, 1.58) | 6.87 |
| Wang 2013 | 1.20 (0.39, 3.72) | 2.86 |
| Hu 2012 | 0.67 (0.12, 3.80) | 1.72 |
| Liu 2011 | 0.67 (0.12, 3.78) | 1.72 |
| Chen 2017 | 1.00 (0.06, 15.51) | 0.57 |
| Rong 2017 | 3.72 (0.18, 74.86) | 0.33 |
| Wen 2016 | 0.78 (0.22, 2.78) | 2.90 |
| Tan 2014 | 0.13 (0.02, 0.94) | 4.58 |
| Zhu 2013 | 0.25 (0.06, 1.11) | 4.58 |
| Wu 2012 | 0.80 (0.23, 2.83) | 2.86 |
| Yu 2010 | 0.07 (0.00, 1.16) | 4.26 |
| Overall (I-squared = 24.3%, p = 0.109) | 0.63 (0.50, 0.78) | 100.00 |

Figure 9: Forest plot of adverse events.

Figure 10: Begg’s funnel plot (a) and Egger’s test (b) of adverse events.
high-quality RCTs involving 5350 patients with KOA, which provides strong evidence that CHM is safe and effective for patients with KOA, consistent with the previous studies.

4.3. Strengths. The strengths of this meta-analysis study included a clearly defined research question, which minimized the bias in the selection of RCTs and improved the fidelity and consistency due to a precise research approach that we designed before the meta-analysis, an in-depth search of the literature, agreement between the two researchers on the entry data components, and quality control appraisal of all data. All of the studies included were RCTs with a significant proportion being of high quality. This assisted in overcoming the drawbacks associated with recall or selection bias in nonrandomized studies. Additionally, the total number of trials and the overall sample size were comparatively large (56 trials with 5350 patients). To ascertain the source of heterogeneity, we performed subgroup and metaregression analyses. Consequently, we found no evidence of publication bias in this meta-analysis, and sensitivity analysis revealed that the findings of this meta-analysis are comparatively robust.

4.4. Limitations. This study has several limitations. First, although RCTs were included, the primary studies included

Figure 11: Sensitivity analysis for effective rate (a) and adverse events (b).
had certain inherent and methodological limitations; specifically, only 42 of the trials supplied sufficient information on the randomization process. The remaining RCTs, on the other hand, reported the allocation concealment. KOA is a chronic condition requiring lifelong treatment. Long-term efficacy and safety studies are critical for determining a drug’s therapeutic usefulness. However, the duration of therapy, in this case, was between two and twelve weeks. Therefore, we were unable to assess the long-term safety of CHM for treating KOA since the duration of treatment in the included studies was short, and no dropouts were revealed in a significant percentage of the included studies. Thirdly, the formula composition, dosage, administration approaches, and duration of CHM treatments varied significantly in the primary RCTs. This clinical heterogeneity has the potential to jeopardize the validity of our findings. Fourthly, a significant proportion of the included RCTs did not involve a formal pretrial sample size calculation. Inadequate sample size in RCTs appears to be one risk factor for overestimating intervention benefit. Finally, we limited our search to studies published in English or Chinese repositories; therefore, studies published in other languages may have been overlooked. Additionally, because all RCTs included in the study were conducted in China, our findings may not be generalizable. Therefore, more multicenter RCTs of CHM for treating KOA are required to allow for global data generalization.

4.6. Implications for Research. Here, we provide key concepts that are likely to stimulate further research in this field. Initiatives to increase the methodological quality of RCTs are urgently needed. We urge that in the future, recommendations such as the CONSORT Extension for Chinese Herbal Medicine Formulas 2017 [90], the CONSORT 2010 statement [91], and the protocols for designing RCTs to investigate CHM [92] be used to establish and report RCTs on CHM. Despite the finding that CHM therapy was reasonably safe for patients with KOA in the evaluated studies, further research is needed to corroborate the safety of CHM for KOA. Bian et al. [93] established a standard format for reporting adverse drug reactions (ADR) in CHM, which is likely to enhance ADR reporting. Clinical trials and studies with a longer follow-up time are recommended to provide a complete understanding of the long-term safety profile of CHM in patients with KOA. Recent advances in integrative medicine have enabled research to be conducted on disease-syndrome combinations. The effectiveness of TCM practice is contingent upon accurate syndrome differentiation. Therefore, an excellent distinction of disease symptoms is required for drug prescriptions [94]. Accurate syndrome differentiation of KOA should be performed during the evaluation of the safety and efficacy of CHM treatment. Individualized TCM prescriptions will give satisfactory treatment.

Table 4: Frequently used herbs in included studies.

| Chinese name | Latin name | English name | Family | Number of studies (%) |
|--------------|------------|--------------|--------|-----------------------|
| Niu xi       | Radix Achyranthis Bidentatae | Twotooth Achyranthes root | Amaranthaceae | 33 (58.93%) |
| Di Huang     | Radix Rehmanniae | Rehmannia root | Scrophulariaceae | 30 (53.57%) |
| Tang Gui     | Radix Angelicae Sinensis | Chinese angelica | Apiaceae | 29 (51.79%) |
| Chuan Xiong  | Radix Ligustici Wallichii | Sichuan lovage rhizome | Apiaceae | 29 (51.79%) |
| Du Zhong     | Cortex Eucommiae Ulmoidis | Epimedium | Eucommiaceae | 26 (46.43%) |
| Gan Cao      | Radix Glycyrrhiza | Liquorice | Papilionaceae | 25 (44.64%) |
| Du Huo       | Radix Angelicae Pubescentis | Pubescent angelica root | Apiaceae | 21 (37.50%) |
| Sang li sheng | Radix Loranthi Seu visci | Chinese taxillus twig | Loranthaceae | 21 (37.50%) |
| Bai shao     | Radix Paoniae Alba | White paony root | Asclepiadaceae | 19 (33.93%) |
| Fang Feng    | Radix Ledebouriellae Divaricatae | Divaricate sapooshnikovia root | Apiaceae | 18 (32.14%) |
| Qin Jiao     | Radix Gentianae Macrophylla | Largeleaf gentian root | Gentianaceae | 18 (32.14%) |
| Fu Ling      | Poria Cocos Wolff | Tuckahoe | Polyoporaceae | 17 (30.36%) |
| Xi Xin       | Asari Radix et Rhizoma | Asarum | Aristolochiaceae | 16 (28.57%) |
| Yin Yang Huo | Epimedium brevicornu Maxim | Icariin | Berberidaceae | 11 (19.64%) |
| Huang qi     | Radix Astragali Membranacei | Astragalus | Leguminosae | 11 (19.64%) |
| Wei Ling Xian | Radix Clematidis Chinensis | Chinese clematis root | Ranunculaceae | 11 (19.64%) |
| Bu Gu Zhi    | Psoralea corylifolia Linn | Fructus psoraleae | Leguminosae | 11 (19.64%) |
for specific diseases. For example, a study by Bensoussan et al. [95] published in JAMA showed that using personalized CHM to treat irritable bowel syndrome was superior to common hypnotic prescriptions. Thus, in future clinic practice, a suitable selection of medications among the 17 most often used herbs is recommended based on syndrome-specific characteristics. This will improve the efficacy of CHM in the treatment of KOA.

5. Conclusion

Our systematic and meta-analysis study offers supportive evidence that CHM, either adjuvant therapy or monotherapy, reduces the VAS, WOMAC, and Lequesne index and improves the Lysholm score and overall effective rate in patients with KOA. Additionally, CHM was well tolerated and safe in KOA patients. We found frequently used CHMs that might contribute to the formulation of a herbal formula that could be considered for further clinical use. However, given the heterogeneity and limited sample size in this study, larger multicenter and high-quality RCTs are needed to validate the benefits of CHM in the treatment of KOA.

Abbreviations

ADR: Adverse drug reactions
RCT: Randomized controlled trial
TG: Trial group
CG: Control group
COA: Chinese Orthopedic Association
CRA: Chinese Rheumatology Association
ACR: American College of Rheumatology
VAS: Visual analog score
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
ER: Effective rate
NR: Not reported
CHM: Chinese herbal medicine
KOA: Knee osteoarthritis
NSAIDS: Nonsteroidal anti-inflammatory drugs
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WCM: Western conventional medication
TCM: Traditional Chinese medicine
SMD: Standard mean difference
RR: Relative risk
DJD: Duhuo Jisheng decoction
ASU: Avocado soybean unsaponifiables.

Data Availability

Previously reported data were used to support this study. These prior studies and datasets are cited at relevant places within the text as references [28–83].

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this study.

Authors’ Contributions

J.J.L. is responsible for conceptualization, methodology, and software. J.J.Z. is responsible for data curation and writing of the initial draft. J.R.C. is responsible for visualization and investigation. M.M.C. is responsible for supervision. Z.L. is responsible for writing—reviewing and editing.

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Supplementary Materials

PubMed search strategies and graphical abstract were provided as supplementary material. (Supplementary Materials)

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