

SYSTEMATIC REVIEW

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Efficacy and safety of traditional Chinese medicine in the treatment of osteonecrosis of the femoral head

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Abstract

Background Hip joint-preserving treatment options for osteonecrosis of the femoral head (ONFH) have been a research hotspot in recent years. The combination of Chinese and Western medicine has been used in clinical practice to treat early- and mid-stage ONFH. However, there is still a lack of high-quality evidence to verify the effectiveness and safety of this approach.

Objective To systematically evaluate the clinical efficacy and safety of the combination of traditional Chinese medicine (TCM) with Western medicine in the treatment of early- and mid-stage ONFH.

Methods Multiple electronic databases were searched to identify the randomized controlled trials (RCTs) examining the use of TCM in the treatment of ONFH. Based on the inclusion and exclusion criteria, eligible studies were selected, and the quality of the studies was evaluated using the risk of bias assessment tool recommended by the Cochrane system Evaluator manual 5.1.0. The meta-analysis of the included data was performed using Review Manager 5.4.1 software and Stata 17.0 software.

Results A total of 47 RCTs involving 3266 subjects were included in the meta-analysis. The results are observed: (1) Harris score: TCM + Western medicine versus Western medicine (SMD = 1.25, 95% CI: 1.02 to 1.48, $P < 0.00001$), TCM + physiotherapy versus physiotherapy (SMD = 2.26, 95% CI: 1.42 to 3.10, $P < 0.00001$), and TCM + hip preservation surgery versus hip preservation surgery (SMD = 1.28, 95% CI: 1.03 to 1.53, $P < 0.00001$); (2) Visual analogue scale score: TCM + Western medicine versus Western medicine (SMD = -3.99, 95% CI: -7.41 to -0.57, $P = 0.02$), TCM + physiotherapy versus physiotherapy (SMD = -0.99, 95% CI: -1.44 to -0.54, $P < 0.0001$), and TCM + hip preservation surgery versus hip preservation surgery (SMD = -1.08, 95% CI: -1.75 to -0.40, $P = 0.002$); (3) Imaging improvement: TCM + physiotherapy versus physiotherapy (RR = 1.42, 95% CI: 1.15 to 1.76, $P = 0.001$) and TCM + hip preservation surgery versus hip preservation surgery (RR = 1.21, 95% CI: 1.11 to 1.31, $P < 0.0001$); and (4) Occurrence of adverse reaction: TCM + Western medicine versus Western medicine (RR = 0.73, 95% CI: 0.28 to 1.92, $P = 0.53$), TCM + physiotherapy versus physiotherapy (RR = 0.46, 95% CI: 0.03 to 7.33, $P = 0.58$), and TCM + hip preservation surgery versus hip preservation surgery (RR = 1.11, 95% CI: 0.36 to 3.45, $P = 0.86$).

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Conclusion TCM combined with Western medicine is an effective and safe approach for the treatment of ONFH. However, due to the low quality and quantity of the included studies, additional large-scale, high-quality studies are required to verify the above conclusions.

Systematic review registration: <https://www.crd.york.ac.uk/prospero/#recordDetails>, CRD42023392030.

Keywords Traditional Chinese medicine, Osteonecrosis of the femoral head, Randomized controlled trial, Meta-analysis, Systematic review

Introduction

Osteonecrosis of the femoral head (ONFH) is a common and challenging disease in orthopedic practice [1]. Most cases are caused by localized ischaemic necrosis of bone tissue caused by glucocorticoid abuse, alcoholism, hip trauma, and other aetiologies, which can lead to microstructural destruction of the femoral head, collapse of the articular surface, hip pain, and functional impairment [2, 3]. At present, the main incidence of ONFH in China is in young and middle-aged people, and the number of new cases of ONFH diagnosed each year is up to approximately two hundred thousand [4, 5]. In addition, the number of new cases in the United States is increasing at a rate of 20,000 each year [6, 7]. This has placed a heavy burden on patients, families, and society. It has also become one of the most important public health issues threatening the health of society [8, 9].

The progression of ONFH often causes severe pain and degenerative changes in the joint. Studies show that more than 80% of untreated ONFH patients will develop femoral head collapse within 1–3 years and eventually have to undergo total hip joint arthroplasty [10–12]. However, patients may face multiple hip revision surgeries due to factors such as postoperative infection, loosening of instruments, and limitations on the life of the prosthesis [13, 14]. Therefore, early diagnosis and treatment of ONFH are particularly urgent and important. The treatment of ONFH is mainly based on the stage and type of the disease as well as the patient's state. In the early stage, medication, physiotherapy, core decompression, etc., are mainly used to reduce pain, delay the collapse of the femoral head and improve the function of the hip joint, thus achieving the goal of hip preservation [15–17].

A review of domestic and international literature revealed a variety of single Chinese medicines, Chinese medicine monomers, and Chinese medicine compounds can alleviate the main pathological changes in ONFH by regulating bone metabolism, lipid metabolism, and oxidative stress [18, 19]. Traditional Chinese medicine (TCM) has multiple components, targets, and pathways [20]. In recent years, numerous clinical trials have shown that combined TCM therapy can increase efficacy, reduce adverse effects, and delay the process of ONFH,

thus playing an active role in the early repair of the disease and improving immunity and quality of life for patients after hip preservation surgery [21, 22]. Therefore, this approach has become highly recommended in treatment guidelines and expert consensus. Nevertheless, there is a lack of high-quality evidence to support the clinical efficacy of TCM in the treatment of ONFH. Hence, this study aims to evaluate the efficacy and safety of TCM in the treatment of ONFH using an evidence-based approach and to seek a clinical basis for combining Chinese and Western medicine in the treatment of early- and mid-stage ONFH.

Methods and materials

Protocol Resiter

This systematic review and meta-analysis were conducted in accordance with the Cochrane Handbook of Systematic Reviews and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [23, 24]. This meta-analysis was registered with the PROSPERO platform (CRD42023392030).

Search strategy

The PubMed, Web of Science, Embase, Cochrane Central Register of Controlled Trials, Chinese National Knowledge Infrastructure, China Science and Technology Journal Database, WanFang, and Chinese Biological Medicine electronic databases were comprehensively searched from inception to February 28, 2023. The keywords included “traditional Chinese medicine”, “Chinese medicinal herbs”, “pill”, “decoction”, “capsule”, “osteonecrosis of the femoral head”, “femur head necrosis”, “ONFH”, “FHN”. Searches were conducted using a combination of theme and free words and adapted to the characteristics of each database. In addition, we reviewed the reference lists of included articles for other eligible studies. Only articles in English and Chinese were considered. The detailed search strategy for PubMed was as follows: (((traditional Chinese medicine [Title/Abstract]) OR (Chinese medicinal herbs [Title/Abstract]) OR (pill [Title/Abstract]) OR (decoction [Title/Abstract])) OR (capsule [Title/Abstract]) AND (“osteonecrosis of the femoral head” [Mesh]) OR ((femur head necrosis [Title/Abstract])) OR

(ONFH [Title/Abstract])) OR (FHN [Title/Abstract]). The detailed search strategy used is described in Additional file 1.

Inclusion criteria

1. Type of studies: Only randomized controlled trials (RCTs) related to the use of TCM for ONFH were included.
2. Type of participants: Patients who met the diagnostic criteria of ONFH. Patients were not limited by age, sex, or race. Diagnostic criteria and staging refer to the Association Research Circulation Osseous 0-III stage and Ficat 0-III stage [25, 26].
3. Type of interventions: The control group was treated with conventional Western medical treatment as prescribed in the guidelines, including anticoagulants, lipid-regulating drugs, osteoclast inhibition and increased osteogenesis, and hip preservation surgery. The treatment group was treated with traditional Chinese herbal medicine combined with the control group.
4. Type of outcomes measures: The primary outcomes included the Harris score, visual analogue scale score, and imaging improvement. The additional outcome was an occurrence of adverse reaction.

Exclusion criteria

1. RCTs with similar data and multiple publications.
2. Literature reviews, case reports, basic experimental studies, empirical summaries, etc.
3. Data recorded in the literature are unknown.
4. There were no primary or relevant outcome indicators in the RCTs.
5. A study of the use of Chinese medicine therapies other than oral Chinese medicine in interventions.

Data extraction

Two researchers independently screened the literature for inclusion criteria and exclusion criteria. Disagreements were resolved by discussion or consulting a third researcher. The following data were extracted: study title, publication year, first author, number of cases, interventions, duration of treatment, and outcome indicators.

Assessment of literature quality

Two reviewers independently evaluated the methodological quality of each included study using the Cochrane Risk of Bias tool, which assessed the following characteristics: random sequence generation, allocation

concealment, blinding, incomplete result data, selective reporting, and other biases [27].

Statistical analysis

Review Manager 5.4.1 software (Cochrane Collaboration, Oxford, UK) and Stata 17.0 software (StataCorp, College Station, USA) were used for statistical analysis. Risk ratio (RR) was used for binomial variables, and standardized mean difference (SMD) was used for continuous variables, both with 95% confidence interval (CI) to describe the effect value of the treatment groups and control groups comparison. Due to differences in the treatment duration and herbal compositions, there was significant clinical heterogeneity in the included studies. So, regardless of statistical heterogeneity, we would use a random effects model to analyze the data. To test the robustness of the outcome, a sensitivity analysis was performed by removing included studies one by one. If an article was excluded and the result was reversed, the article would be shown to be a source of heterogeneity and the article will be analyzed in depth. Otherwise, the results were robust. When the number of included articles was more than 10, the underlying publication bias was identified via an informal visual examination of a funnel plot. Publication bias was evaluated with Egger's test.

Results

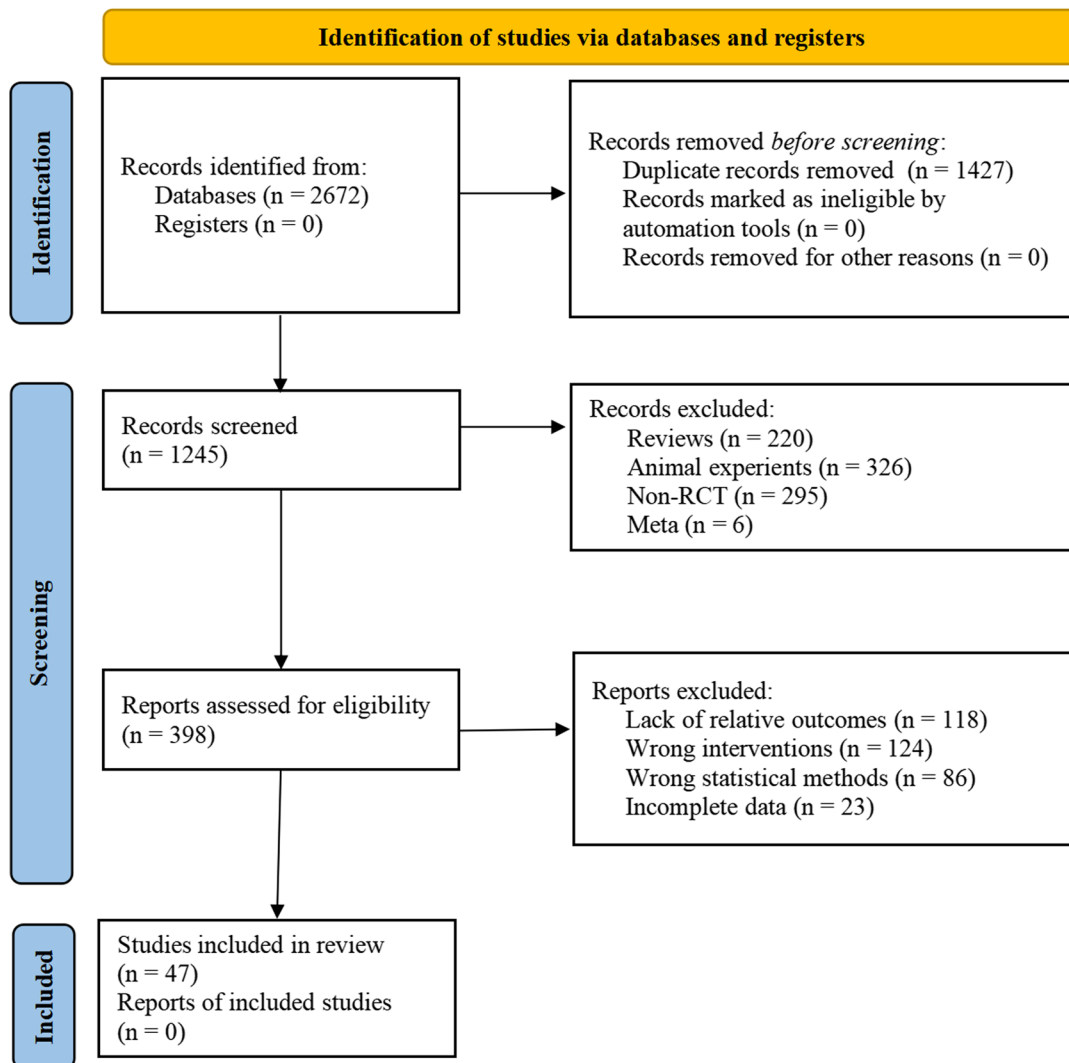
Study selection

A total of 2672 potentially relevant articles on the treatment of TCM by ONFH were preliminarily retrieved from the databases, and 1427 duplicate records were removed. A total of 847 articles were excluded by reviewing the titles and abstracts. A total of 351 articles were eliminated after reading the full texts and applying the inclusion and exclusion criteria. As a result, a total of 47 published articles [28–74] were ultimately included in the meta-analysis (Fig. 1).

Research characteristics

A total of 3266 adult participants with ONFH were included in the 47 eligible studies [28–74]. There were 1624 participants in the control group and 1642 participants in the treatment group. All studies had clear inclusion and exclusion criteria, and there were no significant differences in baseline information between the control groups and treatment groups. The control group intervention in all studies was Western medicine alone. The treatment group interventions in all studies were oral Chinese medicine combined with Western medicine (Tables 1, 2). The traditional Chinese herbal medicines commonly used in the treatment group were Danshen (*Radix Salviae Miltiorrhizae*), Niuxi (*Radix Achyranthis Bidentatae*), and Huangqi (*Radix Astragali*). The detailed

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

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Fig. 1 Literature screening process and results

physiotherapy protocols and traditional Chinese herbal medicine composition are presented in Additional file 1: Table S1. Nineteen studies [31, 32, 35, 38–40, 42–45, 49, 50, 54, 56, 58, 61, 68, 70, 74] were supported by the government or a professional organization, and twenty-eight studies [28–30, 33, 34, 36, 37, 41, 46–48, 51–53, 55, 57, 59, 60, 62–67, 69, 71–73] did not report the funding. Five studies [30, 45, 50, 53, 64] included treatment group interventions that involved TCM combined with

Western medicine. Eleven studies [29, 32–34, 36, 38–40, 44, 49, 51] included treatment group interventions that involved TCM combined with physiotherapy (Additional file 1: Table S2). Thirty-one studies [28, 31, 35, 37, 41–43, 46–48, 52, 54–63, 65–74] included a treatment group intervention that involved TCM combined with hip preservation surgery.

Table 1 Basic characteristics of the 47 studies included in the meta-analysis

Inclusion studies	Original place of patients	Sample (M/F)	Age (years)	Diagnostic standard	Disease stage
Zheng 2022 [28]	Zhejiang	T: 46 (28/18) C: 46 (26/20)	T: 36.03 ± 5.11 C: 35.58 ± 5.08	ARCO	II/III
Zhang 2022 [29]	Tianjin	T: 42 (17/25) C: 42 (16/26)	T: 41.21 ± 4.33 C: 41.25 ± 4.37	ARCO	I
Shen 2022 [30]	Heilongjiang	T: 46 (30/16) C: 46 (32/14)	T: 56.34 ± 5.29 C: 56.05 ± 5.11	ARCO	II
Sun 2022 [31]	Henan	T: 28 (15/13) C: 30 (17/13)	T: 40.64 ± 10.79 C: 38.10 ± 10.69	ARCO	II/III
Li 2022 [32]	Heilongjiang	T: 36 (20/16) C: 36 (22/14)	T: 43.6 ± 5.1 C: 42.7 ± 6.8	ARCO	I/II
Han 2021 [33]	Anhui	T: 30 (16/14) C: 30 (17/13)	T: 42.19 ± 3.58 C: 42.32 ± 3.92	ARCO	I/II
Liao 2021 [34]	Hunan	T: 22 (13/9) C: 21 (12/9)	T: 44.17 ± 6.97 C: 42.76 ± 5.03	ARCO	I/II
Han 2021 [35]	Hebei	T: 24 (16/14) C: 24 (12/12)	T: 42.19 ± 3.58 C: 42.32 ± 3.92	ARCO	I/II
Liao 2021 [36]	Hunan	T: 44 (27/17) C: 42 (24/18)	T: 43.7 ± 6.9 C: 42.3 ± 5.1	ARCO	I/II
Sun 2021 [37]	Guangxi	T: 16 (8/8) C: 16 (9/7)	T: 37.56 ± 9.85 C: 38.62 ± 8.10	ARCO	I/II
Liu 2020 [38]	Shanxi	T: 50 (28/22) C: 50 (27/23)	T: 65.13 ± 4.58 C: 65.25 ± 4.76	Ficat	I/II/III
Du 2020 [39]	Henan	T: 40 (28/12) C: 40 (31/9)	T: 43.12 ± 7.38 C: 44.73 ± 5.81	ARCO	I/II
Zhao 2020 [40]	Shandong	T: 17 (NA) C: 14 (NA)	T: 37 C: 35	ARCO	I/II/III
Yan 2020 [41]	Henan	T: 43 (33/10) C: 43 (31/12)	T: 38.2 ± 7.9 C: 39.4 ± 8.1	ARCO	I/II
Wei 2019 [42]	Nanjing	T: 16 (9/7) C: 14 (8/4)	T: 34.5 ± 6.5 C: 34.4 ± 6.4	ARCO	III
Sun 2019 [43]	Guangzhou	T: 29 (25/4) C: 31 (26/5)	T: 43.6 ± 4.8 C: 44.7 ± 5.3	ARCO	I/II
Zhou 2019 [44]	Henan	T: 30 (24/6) C: 30 (22/8)	T: 54.20 ± 5.68 C: 55.93 ± 6.92	ARCO	I/II
Zhan 2019 [45]	Zhejiang	T: 41 (NA) C: 41 (NA)	T: 43.52 ± 7.94 C: 42.81 ± 9.07	ARCO	I/II
Zhao 2019 [46]	Shandong	T: 21 (17/4) C: 21 (15/6)	T: 39.29 ± 7.99 C: 37.43 ± 7.14	ARCO	I/II/III
Cao 2018 [47]	Henan	T: 30 (16/14) C: 30 (15/15)	T: 40.53 ± 9.79 C: 41.13 ± 9.64	ARCO	I/II
Wang 2018 [48]	Shanxi	T: 46 (27/19) C: 46 (25/21)	T: 46.2 ± 6.53 C: 45.82 ± 6.37	Ficat	I/II
Song 2018 [49]	Henan	T: 30 (17/13) C: 30 (15/15)	T: 32.64 ± 8.65 C: 32.65 ± 8.76	ARCO	I/II
Du 2018 [50]	Henan	T: 36 (NA) C: 34 (NA)	T: 43.12 ± 7.38 C: 44.73 ± 5.81	ARCO	I/II
Yuan 2018 [51]	Guangzhou	T: 34 (NA) C: 34 (NA)	T: 30.9 ± 6.3 C: 31.5 ± 5.9	ARCO	I/II
Liu 2017 [52]	Shandong	T: 42 (NA) C: 40 (NA)	T: 39.8 C: 39.8	Ficat	I/II
Lu 2017 [53]	Zhejiang	T: 40 (NA) C: 40 (NA)	T: 48.6 ± 4.9 C: 48.6 ± 4.9	Ficat	I/II
Jiang 2017 [54]	Henan	T: 27 (21/6) C: 27 (19/8)	T: 41.66 ± 11.39 C: 40.55 ± 12.81	ARCO	I/II
Li 2017 [55]	Shanxi	T: 51 (38/13) C: 51 (37/14)	T: 45.12 ± 6.77 C: 45.71 ± 7.25	ARCO	I/II

Table 1 (continued)

Inclusion studies	Original place of patients	Sample (M/F)	Age (years)	Diagnostic standard	Disease stage
He 2017 [56]	Guangxi	T: 30 (NA) C: 30 (NA)	T: 38.9±9.21 C: 39.25±10.12	ARCO	0/I/II
Xu 2017 [57]	Shanxi	T: 41 (39/12) C: 42 (32/10)	T: 37.01±8.23 C: 36.92±7.51	ARCO	I/II
Zhang 2016 [58]	Jiangsu	T: 32 (24/8) C: 29 (22/7)	T: 36.30±9.65 C: 35.27±9.36	ARCO	II/III
Zhang 2016 [59]	Shanxi	T: 36 (NA) C: 36 (NA)	T: NA C: NA	ARCO	II/III
Nong 2016 [60]	Guangxi	T: 44 (NA) C: 43 (NA)	T: 40.7±10.5 C: 40.7±10.5	Ficat	I/II
Tian 2016 [61]	Henan	T: 25 (14/11) C: 25 (13/12)	T: 36±7 C: 36±6	ARCO	I/II/III
Zhu 2015 [62]	Zhejiang	T: 33 (NA) C: 33 (NA)	T: 38.27±4.06 C: 38.27±4.06	ARCO	II/III
Liu 2015 [63]	Sichuan	T: 39 (26/13) C: 39 (25/14)	T: 39.82±6.83 C: 39.90±6.74	Ficat	0/I/II
Zhou 2015 [64]	Hebei	T: 52 (18/34) C: 53 (17/36)	T: 51.45±5.41 C: 51.33±5.27	ARCO	I/II
Wang 2015 [65]	Liaoning	T: 47 (28/19) C: 47 (29/18)	T: 35.4±11.3 C: 34.5±10.6	Ficat	I/II
Li 2015 [66]	Hebei	T: 35 (24/11) C: 33 (23/10)	T: 42.6 C: 39.5	ARCO	I/II
Ang 2015 [67]	Hebei	T: 45 (28/17) C: 44 (30/14)	T: 43.6±7.4 C: 44.7±6.8	Ficat	II/III
Feng 2014 [68]	Shandong	T: 60 (NA) C: 60 (NA)	T: 35.3 C: 35.3	ARCO	II/III
Zhang 2014 [69]	Jiangsu	T: 52 (41/11) C: 51 (42/9)	T: 45.8±6.3 C: 44.9±5.9	ARCO	I/II
Cheng 2014 [70]	Jiangsu	T: 15 (9/6) C: 15 (8/7)	T: 37.11±5.61 C: 38.00±5.71	Ficat	I/II
Zhao 2012 [71]	Shandong	T: 25 (17/8) C: 23 (16/7)	T: 36.3 C: 35.2	ARCO	I/II
Lu 2012 [72]	Hunan	T: 12 (8/4) C: 12 (9/3)	T: 37.8±11.7 C: 38.6±12.3	Ficat	I/II
Su 2012 [73]	Fujian	T: 18 (15/3) C: 18 (14/4)	T: 37.91±12.14 C: 38.12±11.08	Ficat	I/II
Du 2011 [74]	Henan	T: 45 (39/6) C: 45 (28/7)	T: 36 C: 42	Ficat	I/II

Note: ARCO Association Research Circulation Osseous; C control group; NA not available; T treatment group

Assessment of the risk of bias

The Cochrane risk of bias tool was used to systematically evaluate the quality of the 47 RCTs [28–74]. Twenty-seven studies [28–33, 35, 37, 39–42, 44, 46, 47, 49–51, 56–60, 62, 64, 66, 74] clearly described correct random sequence generation methods (computerized random method or random number method, etc.), so they were rated as having a low risk of bias for that domain. Fifteen studies [34, 36, 45, 48, 52, 54, 55, 61, 65, 67, 68, 70–73] only referred to randomized groups but did not specify the specific method, so they were rated as having an unclear risk of bias for this domain. Five studies [38, 43,

53, 63, 69] did not mention randomization (admission order grouping or wishes, etc.), so they were rated as having a high risk of bias for this domain. Since allocation procedures and binding methods were not mentioned in any of the included RCTs, they were all rated as having an unclear risk of bias for this domain. The integrity of outcome data and selective reporting of all researchers were judged to be at low risk of bias, as no data deficiencies and specified indicators were completely reported. However, no details were found in all studies for other biases, and thus, they were rated as having an unclear risk of bias (Fig. 2).

Meta-analysis results

Harris score

A total of 45 studies [28–44, 46–72, 74] with 3148 participants compared the Harris score between the treatment groups and control groups. Three studies [32, 62, 72] had a treatment duration of 1 month, 2 studies [44, 52] had a treatment duration of 2 months, 23 studies [29, 30, 33, 34, 36–41, 48–50, 53, 55, 57, 59, 60, 67, 69–71, 74] had a treatment duration of 3 months, 1 study [65] had a treatment duration of 4 months, 11 studies [31, 35, 42, 43, 46, 51, 54, 58, 61, 63, 64] had a treatment duration of 6 months, 1 study [47] had a treatment duration of 9 months, and 4 studies [28, 56, 66, 68] had a treatment duration of 12 months. Due to differences in the durations of treatment and herbal compositions, a more rigorous random effects model was used. The results showed that the TCM + Western medicine versus Western medicine groups [30, 50, 53, 64] (SMD = 1.25, 95% CI: 1.02 to 1.48, $P < 0.00001$) (Fig. 3a). The TCM + physiotherapy versus physiotherapy group [29, 32–34, 36, 38–40, 44, 49, 51] (SMD = 2.26, 95% CI: 1.42 to 3.10, $P < 0.00001$) (Fig. 3b). The TCM + hip preservation surgery versus hip preservation surgery group [28, 31, 35, 37, 41–43, 46–48, 52, 54–63, 65–72, 74] (SMD = 1.28, 95% CI: 1.03 to 1.53, $P < 0.00001$) (Fig. 3c). The results indicating that TCM combined with Western medicine was superior to Western medicine alone in improving the Harris score.

Visual analogue scale score

A total of 16 studies [30–33, 35, 39, 42, 44–46, 49, 51, 55, 59, 62, 64] with 1097 participants compared the visual analogue scale score between the treatment groups and control groups. Two studies [32, 62] had a treatment duration of 1 month, 1 study [44] had a treatment duration of 2 months, 6 studies [30, 33, 39, 49, 55, 59] had a treatment duration of 3 months, and 7 studies [31, 35, 42, 45, 46, 51, 64] had a treatment duration of 6 months. Due to differences in the durations of treatment and herbal compositions, a more rigorous random effects model was used. The results showed that the TCM + Western medicine versus Western medicine groups [30, 45, 64] (SMD = -3.99, 95% CI: -7.41 to -0.57, $P = 0.02$) (Fig. 4a). The TCM + physiotherapy versus physiotherapy group [32, 33, 39, 44, 49, 51] (SMD = -0.99, 95% CI: -1.44 to -0.54, $P < 0.0001$) (Fig. 4b). The TCM + hip preservation surgery versus hip preservation surgery group [31, 35, 42, 46, 55, 59, 62] (SMD = -1.08, 95% CI: -1.75 to -0.40, $P = 0.002$) (Fig. 4c). The results indicating that TCM combined with Western medicine was superior to Western medicine alone in relieving joint pain.

Imaging improvement

A total of 23 studies [31, 34, 36, 39, 41, 43, 46, 47, 54–57, 60, 62, 63, 65–67, 69, 70, 72–74] with 1579 participants compared improvements in imaging results between the treatment groups and control groups. Ten studies described the number of cases that showed improvement, 1 study [65] described changes in ONFH volume, 3 studies [41, 55, 72] reported scores on the hip imaging scale, 5 studies [43, 54, 60, 66, 69] evaluated the collapse of the femoral head, and 4 studies [39, 47, 56, 63] examined the Association Research Circulation Osseous or Ficat stage criteria. A total of 10 studies [31, 34, 36, 46, 57, 62, 67, 70, 73, 74] were included for analysis, of which 1 study [62] had a treatment duration of 1 month, 7 studies [34, 36, 57, 67, 70, 74] had a treatment duration of 3 months, 2 studies [31, 46] had a treatment duration of 6 months, and 1 study [73] had a treatment duration of 12 months. Due to differences in the durations of treatment and herbal compositions, a more rigorous random effects model was used. The results showed that the TCM + physiotherapy versus physiotherapy group [34, 36] (RR = 1.42, 95% CI: 1.15 to 1.76, $P = 0.001$) (Fig. 5a). The TCM + hip preservation surgery versus hip preservation surgery group [31, 46, 57, 62, 67, 70, 73, 74] (RR = 1.21, 95% CI: 1.11 to 1.31, $P < 0.0001$) (Fig. 5b). The comprehensive analysis showed that both the number of cases that showed improvements and the description of the change in volume and score of femoral head necrosis indicated that TCM combined with Western medicine was superior to Western medicine alone in terms of imaging improvement.

Occurrence of adverse reaction

A total of 9 studies [28, 30, 33, 40, 41, 50, 53, 54, 61] with 611 participants reported the occurrence of adverse reaction, including abdominal pain, nausea, and constipation, and no life-threatening events were reported in the treatment group or control group (Additional file 1: Table S3). Six studies [30, 33, 40, 41, 50, 53] had a treatment duration of 3 months, 2 studies [54, 61] had a treatment duration of 6 months, and 1 study [28] had a treatment duration of 12 months. Due to differences in the durations of treatment and herbal compositions, a more rigorous random effects model was used. The results showed that the TCM + Western medicine versus Western medicine groups [30, 50, 53] (RR = 0.73, 95% CI: 0.28 to 1.92, $P = 0.53$) (Fig. 6a). The TCM + physiotherapy versus physiotherapy group [33, 40] (RR = 0.46, 95% CI: 0.03 to 7.33, $P = 0.58$) (Fig. 6b). The TCM + hip preservation

Table 2 Intervention characteristics of included studies

Inclusion Studies	Treatment group	Control group	Duration (month)	Follow-up (month)	Outcome
Zheng 2022 [28]	Oral Xianling Gubao capsule (3 capsules, bid)+C	CD+BG	12	12	HHS Occurrence of adverse reaction
Zhang 2022 [29]	Oral Duzhongjiangu granule (12 g, tid)+C	ESWT (2–3 sessions/1 week)	3	3	HHS
Shen 2022 [30]	Oral Taoren decoction (300 mL, bid)+C	Oral Alendronate sodium (70 mg, qw)	3	NA	HHS VAS Occurrence of adverse reaction
Sun 2022 [31]	Oral Guguton Huaisiyu Capsule (5 capsules, tid)+C	CD+BG	6	NA	HHS VAS Imaging improvement
Li 2022 [32]	Oral Sanqi Huogu Pill (6 g, bid)+C	ESWT (1 session/2 days)	1	NA	HHS VAS
Han 2021 [33]	Oral Xianling Gubao Capsule (1.5 g, bid)+C	ESWT (1 session/2 days)	3	NA	HHS VAS Occurrence of adverse reaction
Liao 2021 [34]	Oral Huanggu Bone Healing Compound (25 mL, q2d)+C	ESWT (1 session/2 days)	3	3	HHS Imaging improvement
Han 2021 [35]	Oral Gubi tongxiao granule (5 g, tid)+C	CD+BG	6	12	HHS VAS
Liao 2021 [36]	Oral Fuyang Revitalizing Bone Pill (1 dose, bid)+C	ESWT (1 session/2 days)	3	3	HHS Imaging improvement
Sun 2021 [37]	Oral Self-made prescription (1 dose, bid)+C	CD+BG	3	NA	HHS
Liu 2020 [38]	Oral Self-made prescription (300 mL, bid)+C	ESWT (20 min/1 session, 1 session/1 day)	3	NA	HHS
Du 2020 [39]	Oral Tiansui capsule (6 capsules, tid)+C	ESWT (25 min/1 session, 2 sessions/1 week)	3	12	HHS VAS Imaging improvement
Zhao 2020 [40]	Oral Bushen huogu capsule (5 capsules, tid)+C	ESWT (2 sessions/1 week)	3	NA	HHS Occurrence of adverse reaction
Yan 2020 [41]	Oral Supplemented No.1 Zhuli Decoction (300 mL, bid)+C	CD+BG	3	6	HHS Imaging improvement Occurrence of adverse reaction
Wei 2019 [42]	Oral Bushen Huoxue Decoction (1 dose, NA)+C	Osteotomy	6	12	HHS VAS
Sun 2019 [43]	Oral Huoxue Shenggu Decoction (1 dose, bid)+C	CD+BG	6	24	HHS Imaging improvement
Zhou 2019 [44]	Oral Sanjiao paste (10 mL, bid)+C	ESWT (1 session/1 week)	2	NA	HHS VAS
Zhan 2019 [45]	Oral Self-made Bu Gu Decoction (2 doses, bid)+C	Oral Alendronate sodium (70 mg, qw)	6	NA	VAS
Zhao 2019 [46]	Oral Guningwan (5 g, tid)+C	CD+BG	6	6	HHS VAS Imaging improvement
Cao 2018 [47]	Oral Modified Shentong Zhuyutang (1 dose, bid)+C	CD+BG	9	9	HHS Imaging improvement
Wang 2018 [48]	Oral Wenyang Bushen Decoction (1 dose, bid)+C	CD+BG	3	3	HHS
Song 2018 [49]	Oral Gugutou Huaisiyu Capsule (6 capsules, tid)+C	ESWT (2 sessions/1 week)	3	24	HHS VAS
Du 2018 [50]	Oral Shenqi Decoction (400 mL, bid)+C	Oral Alendronate sodium (10 mg)	3	6	HHS Occurrence of adverse reaction
Yuan 2018 [51]	Oral Yuanshi ShengmaiChenggu Tablet (3 tablets, tid)+C	ESWT (5 sessions/1 week)	6	12	HHS VAS
Liu 2017 [52]	Oral Shenggu II Decoction (200 mL, bid)+C	CD+BG	2	NA	HHS

Table 2 (continued)

Inclusion Studies	Treatment group	Control group	Duration (month)	Follow-up (month)	Outcome
Lu 2017 [53]	Oral Syndrome differentiation (300 mL, bid)+C	Oral Alendronate sodium (70 mg, qw)	3	NA	HHS Occurrence of adverse reaction
Jiang 2017 [54]	Oral Gugutou Huaisiy Capsule (5 capsules, bid)+C	Porous tantalum rod	6	12	HHS Imaging improvement Occurrence of adverse reaction
Li 2017 [55]	Oral Busui Huoxue Jiangu Decoction (1 dose, bid)+C	CD+BG	3	NA	HHS VAS Imaging improvement
He 2017 [56]	Oral Shenggu Decoction (200 mL, bid)+C	CD+BG	12	12	HHS Imaging improvement
Xu 2017 [57]	Oral Bushen Huoxue Decoction (1 dose, bid)+C	CD+BG	3	3	HHS Imaging improvement
Zhang 2016 [58]	Oral Bushen Huoxue Decoction (1 dose, NA)+C	CD+BG	6	12	HHS
Zhang 2016 [59]	Oral Tongluo Shenggu Decoction (1 dose, bid)+C	CD+BG	3	24	HHS VAS
Nong 2016 [60]	Oral Huoxue Jiangu Decoction (1 dose, bid)+C	CD+BG	3	12	HHS Imaging improvement
Tian 2016 [61]	Oral Gugutou Huaisiyu Capsule (5 capsules, tid)+C	Porous tantalum rod	6	NA	HHS Occurrence of adverse reaction
Zhu 2015 [62]	Oral Self-made prescription (200 mL, bid)+C	CD+BG	1	6	HHS VAS Imaging improvement
Liu 2015 [63]	Oral Huogu Decoction (1 dose, bid)+C	CD+BG	6	NA	HHS Imaging improvement
Zhou 2015 [64]	Oral Jiawei Qing E Pill (1 dose, bid)+C	Oral Western medicine (600 mg, qd)	6	6	HHS VAS
Wang 2015 [65]	Oral Jianbu Huqian Pill (1 dose, bid)+C	CD+BG	4	12	HHS Imaging improvement
Li 2015 [66]	Oral Lugui Shenggu Pill (10 g, bid)+C	CD	12	12	HHS Imaging improvement
Ang 2015 [67]	Oral Busui Huoxue Jiangu Decoction (300 mL, bid)+C	CD+BG	3	12	HHS Imaging improvement
Feng 2014 [68]	Oral Xianling Gubao Capsule (3 capsules, bid)+C	CD+BG	12	NA	HHS
Zhang 2014 [69]	Oral Huoxue Busui Decoction (150 mL, tid)+C	CD+BG	3	3	HHS Imaging improvement
Cheng 2014 [70]	Oral Syndrome differentiation (1 dose, bid)+C	CD+BG	3	12	HHS Imaging improvement
Zhao 2012 [71]	Oral Bushen Huoxue Decoction (1 dose, bid)+C	Porous tantalum rod	3	13	HHS
Lu 2012 [72]	Oral Bushen Huoxue Decoction (300 mL, bid)+C	CD+BG	1	NA	HHS Imaging improvement
Su 2012 [73]	Oral Syndrome differentiation (1 dose, bid)+C	CD+BG	12	NA	Imaging improvement
Du 2011 [74]	Oral Syndrome differentiation (1 dose, bid)+C	CD+BG	3	12	HHS Imaging improvement

BG bone-grafting; C control group; CD core decompression; ESWT extracorporeal shock wave; HHS Harris hip score therapy; NA not available; T treatment group; VAS visual analogue scale

surgery versus hip preservation surgery group [28, 41, 54, 61] (RR=1.11, 95% CI: 0.36 to 3.45, $P=0.86$) (Fig. 6c). It is suggested that TCM combined with Western medicine does not increase the incidence of adverse effects.

Sensitivity analysis

To determine the effect of each individual clinical trial on the pooled effect size, we excluded each study from the analysis. In the test for the overall effect P -value

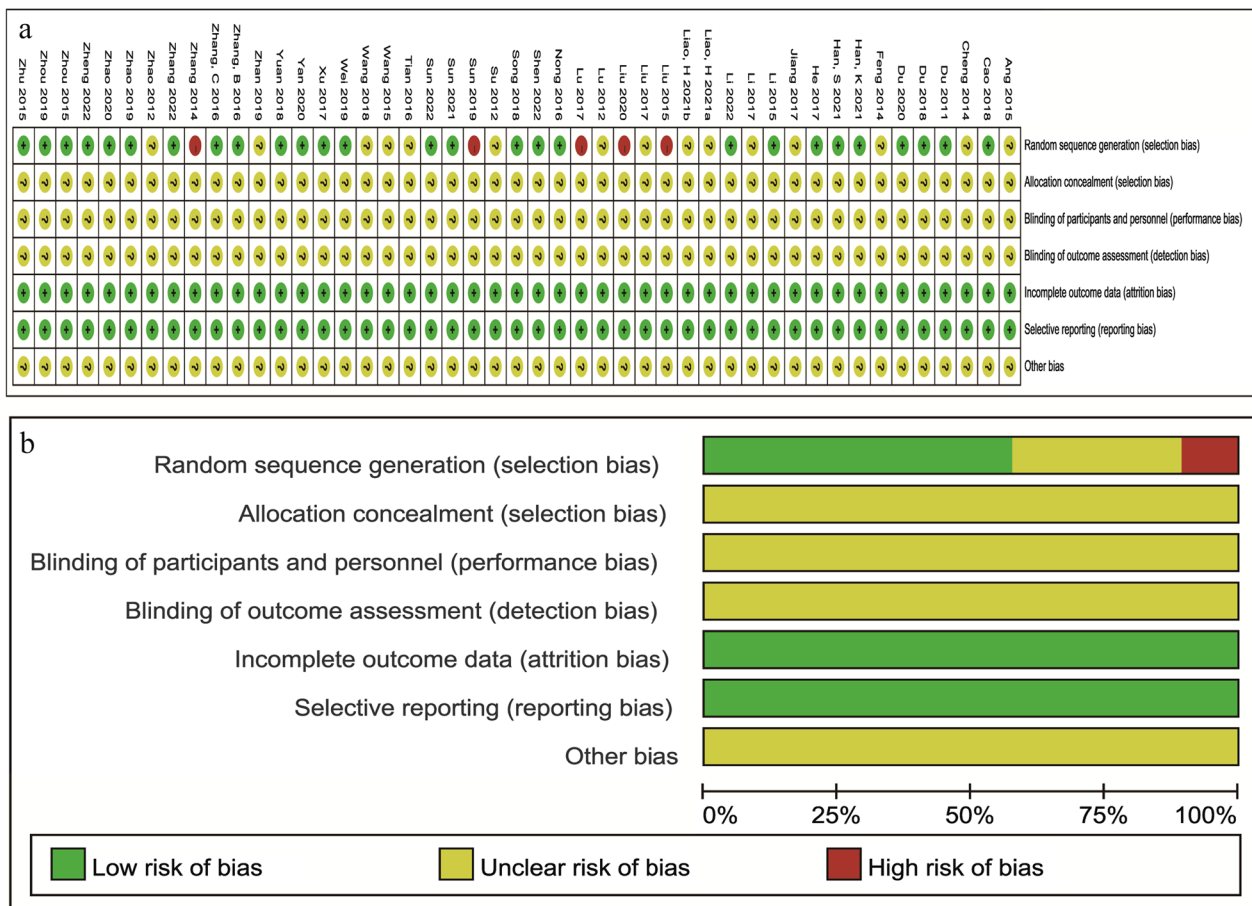


Fig. 2 Risk of bias graph in the included studies. **a** Risk of bias summary **b** Risk of bias graph

of visual analogue scale score in the TCM+Western medicine versus Western medicine group, there were changes in the outputs after excluding each study. After removing the study conducted by Shen’s study [30], Zhan’s study [45], and Zhou’s study [64], the result showed no significance. Results also showed that in Du’s study [50], and Lu’s study [53], the I^2 of occurrence of adverse reaction in the TCM+Western medicine versus Western medicine group dropped to 0%. The I^2 of occurrence of adverse reaction in the TCM+hip preservation surgery versus hip preservation surgery group decreased to 0% after the elimination of study [61]. After removing any study from other outcome indicators, no other important changes were found, reflecting that the results of the meta-analysis were robust. The details of sensitivity analysis are presented in Additional file 1: Table S4-S7.

Publication bias

The funnel plotting for the Harris score in the TCM+physiotherapy versus physiotherapy group and TCM+hip preservation surgery versus hip preservation surgery group showed asymmetry, thus indicating potential publication bias (Additional file 1: Fig. S1-S2). Therefore, Egger’s test was used to analyze the publication bias. The results of Egger’s test showed possible publication bias in the analysis results of the Harris score in the TCM+physiotherapy versus physiotherapy group and TCM+hip preservation surgery versus hip preservation surgery group ($P < 0.05$) (Additional file 1: Table S8). This bias may be related to the fact that articles with negative results are not easily published, the small sample size of some studies, and the fact that the literature included in this study was all in Chinese, so there was language bias. We did not perform a publication bias test for the other observational indicators. Due to the small number of studies (< 10).

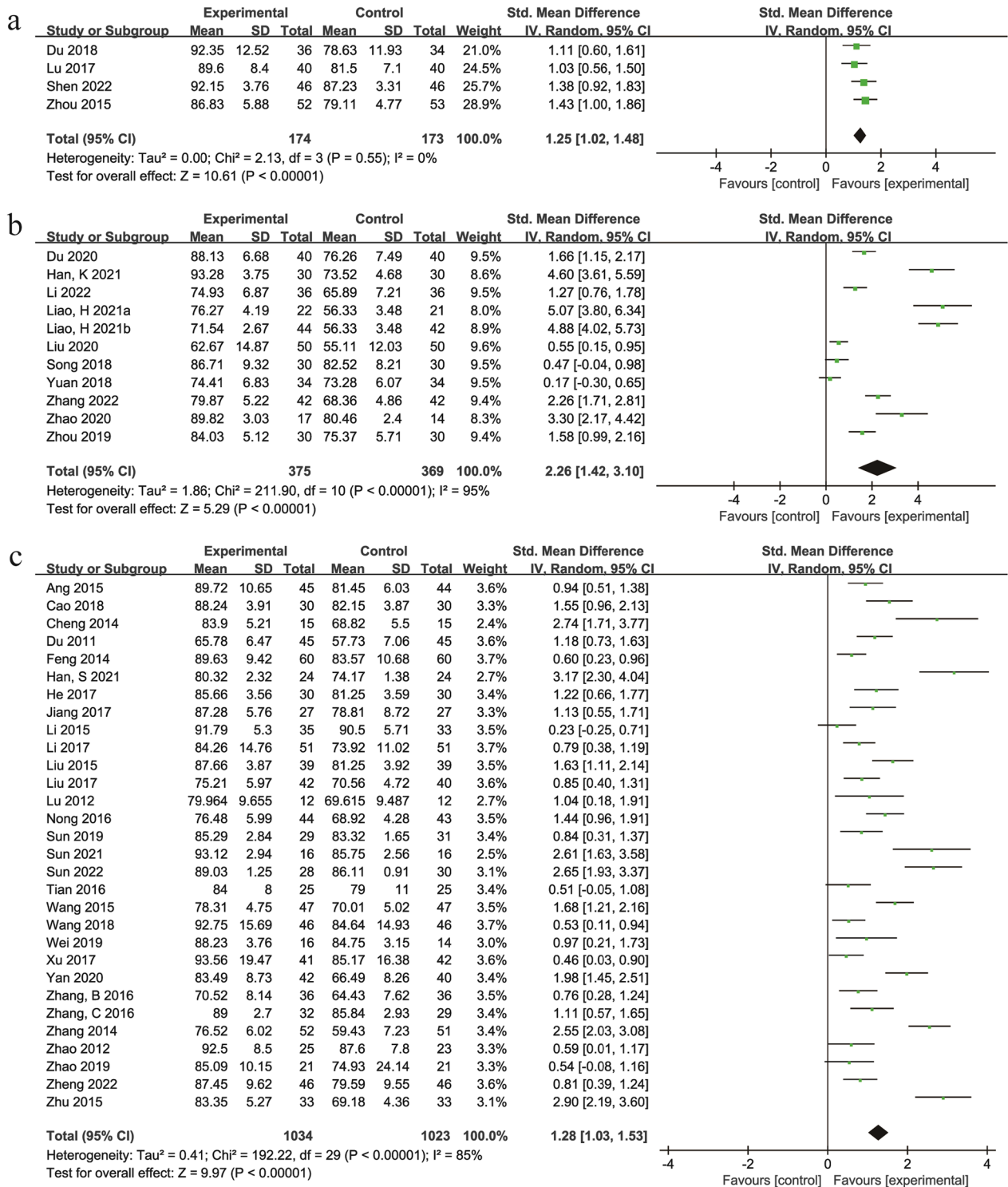


Fig. 3 Forest plot of the meta-analysis of the Harris score: **a** traditional Chinese medicine + Western medicine versus Western medicine **b** traditional Chinese medicine + physiotherapy versus physiotherapy **c** traditional Chinese medicine + hip preservation surgery versus hip preservation surgery

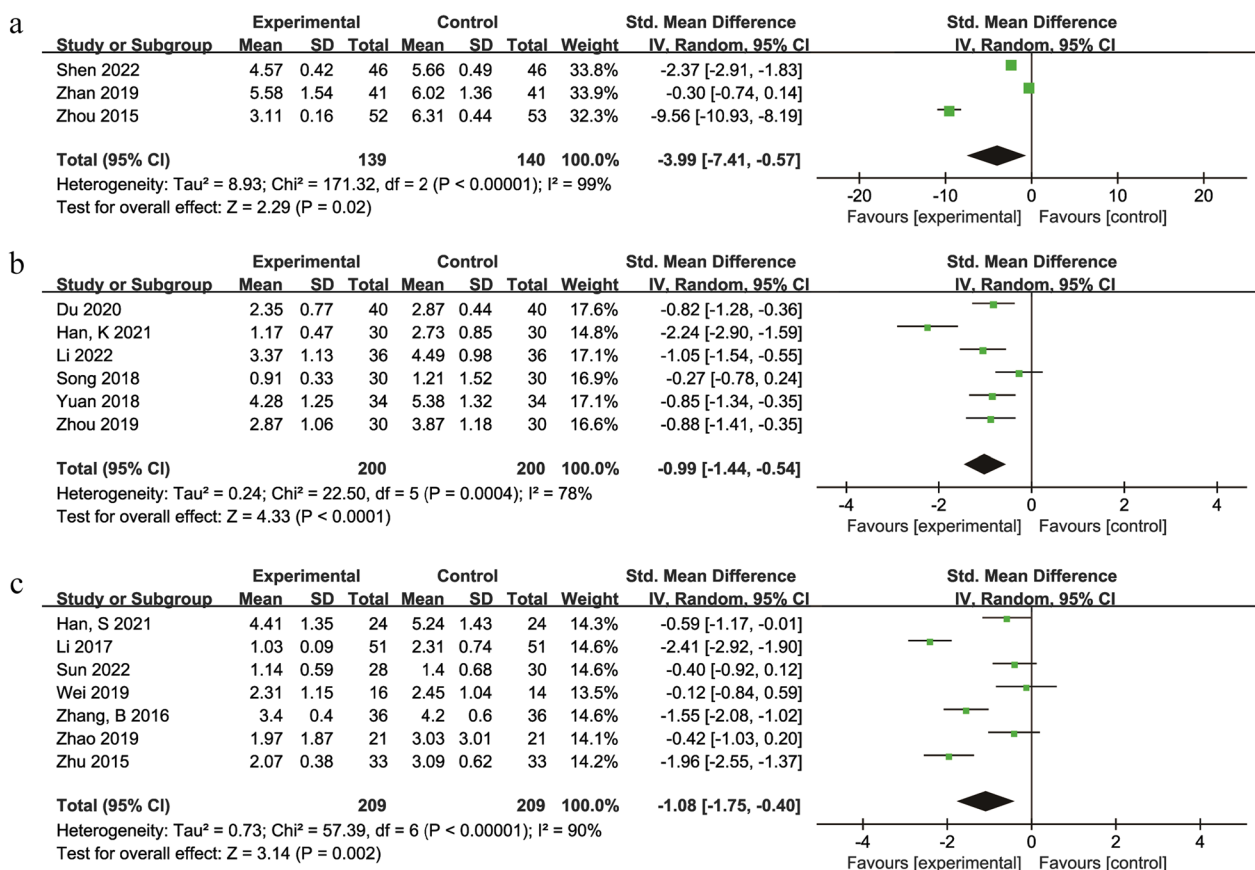


Fig. 4 Forest plot of the meta-analysis of the visual analogue scale score: **a** traditional Chinese medicine + Western medicine versus Western medicine **b** traditional Chinese medicine + physiotherapy versus physiotherapy **c** traditional Chinese medicine + hip preservation surgery versus hip preservation surgery

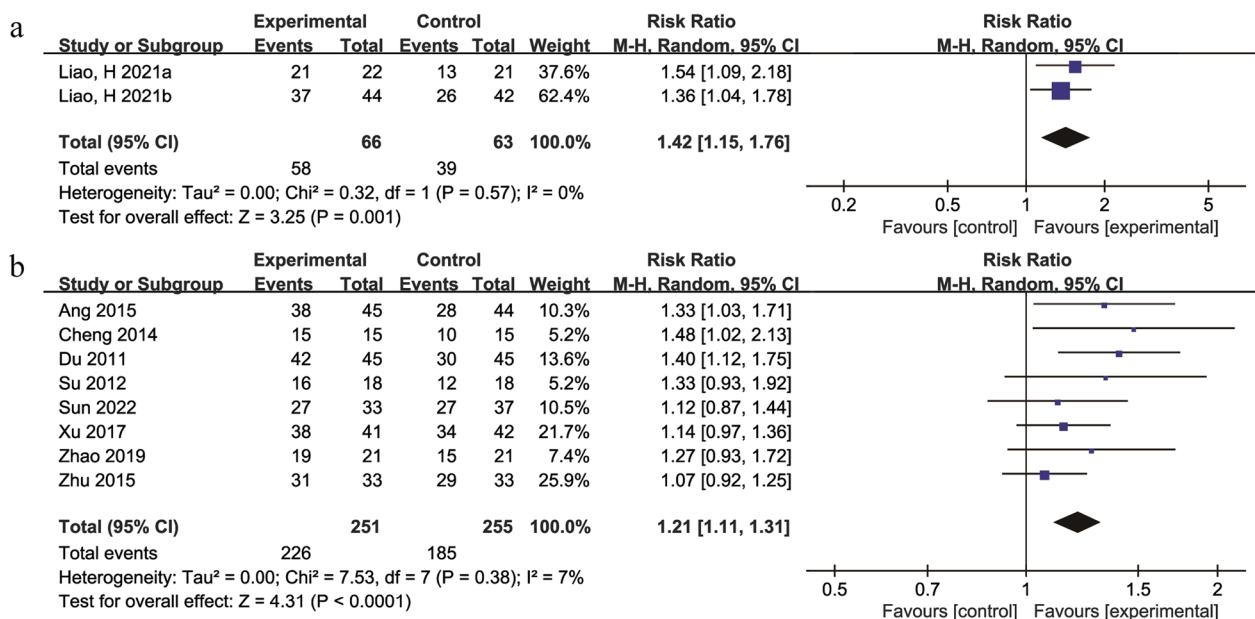


Fig. 5 Forest plot of the meta-analysis of the imaging improvement: **a** traditional Chinese medicine + physiotherapy versus physiotherapy **b** traditional Chinese medicine + hip preservation surgery versus hip preservation surgery

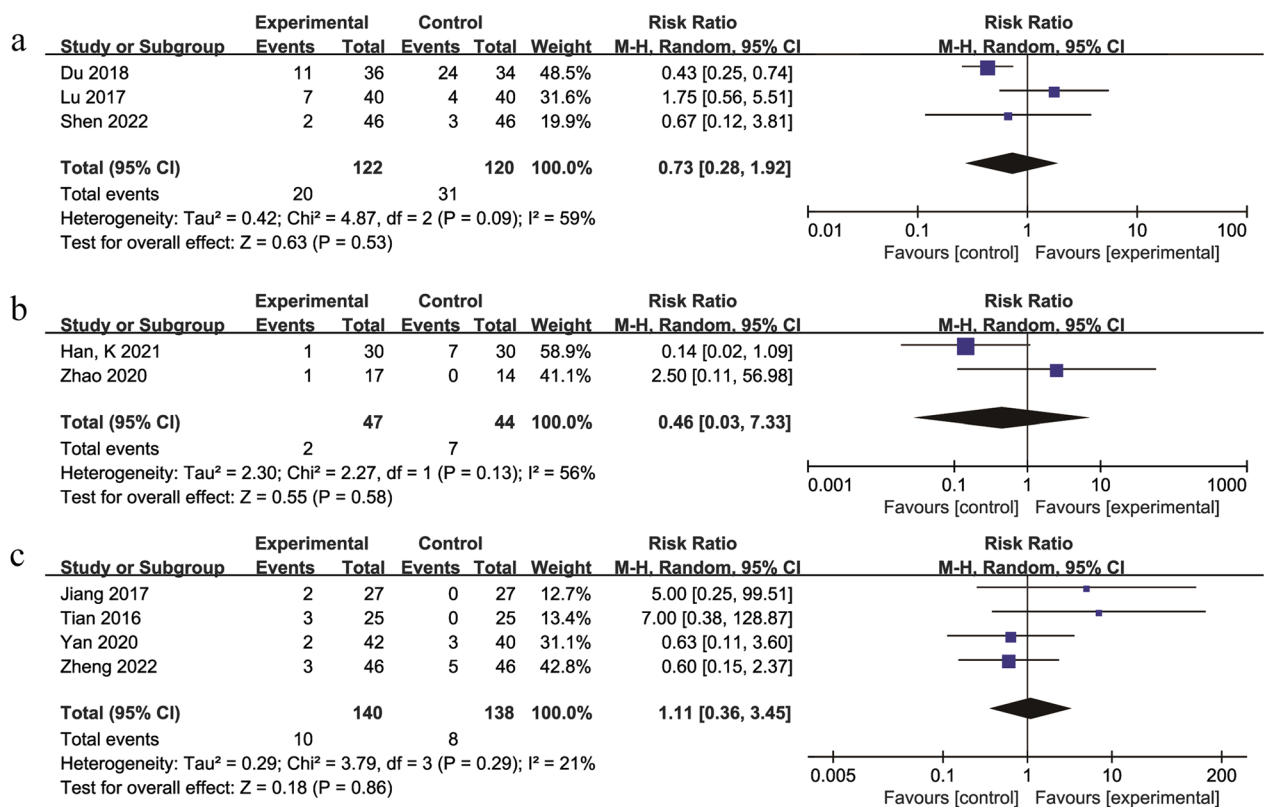


Fig. 6 Forest plot of the meta-analysis of the occurrence of adverse reaction: **a** traditional Chinese medicine + Western medicine versus Western medicine **b** traditional Chinese medicine + physiotherapy versus physiotherapy **c** traditional Chinese medicine + hip preservation surgery versus hip preservation surgery

Discussion

In patients with ONFH, the effectiveness of TCM combined with Western medicine remains controversial [75]. Previous systematic reviews [76, 77] reported that compared with controls, TCM treatment had a consistent treatment effect in patients. Recently, TCM has attracted considerable attention, and considerable research has been conducted on the effects of oral traditional Chinese herbal medicine on ONFH. Consequently, this meta-analysis of studies updates the literature and further evaluates the impact of TCM combined with Western medicine on patients with ONFH. A total of 47 articles with a total of 3266 patients were included in this meta-analysis. The overall posttreatment Harris score, visual analogue scale score, and imaging improvement were better in the TCM combined with the Western medicine group than in the Western medicine group. There was no significant difference between the two groups in the occurrence of adverse reaction. Additionally, funnel plots and Egger’s test were constructed for the Harris score in the TCM+physiotherapy versus physiotherapy group and TCM+hip preservation surgery versus hip

preservation surgery group included in the study and indicated potential publication bias.

The Harris score has been widely used to evaluate the efficacy of hip preservation therapy by comprehensively evaluating pain, hip function, and daily activities. The results showed that TCM combined with Western medicine is positively effective in improving joint function. According to a study by Zheng’s study [28], hip preservation surgery combined with TCM therapy resulted in a significant increase in the Harris score after 12 months, which aligns with findings from relevant literature [35], further confirming the clinical efficacy of the combination of Chinese and Western medicine therapy. Similarly, du’s study [39] observes higher Harris score in the treatment group. On the one hand, physical therapy can loosen the tissues around the hip joint and remodel the necrotic femoral head’s bone structure [78, 79]. On the other hand, TCM can enhance the blood supply to the femoral head and promote the repair of osteonecrosis [80]. These complementary effects mutually improve joint function.

We identified the visual analogue scale score as the primary outcome. The results demonstrated that TCM

combined with Western medicine contributes to a reduction in pain intensity. Han's study [35] showed a significant decrease in visual analogue scale score for 24 subjects who received postoperative oral Chinese medicine treatment. Core decompression by reducing pressure within the femoral head and increasing blood flow to the necrotic area. Additionally, oral Chinese medicine promotes local blood flow and inhibits platelet agglutination, further mitigating hip pain in patients [46]. Zheng's study [81] suggested that TCM may achieve pain relief by decreasing levels of serum TNF- α and CRP.

On the contrary, our study found the combination of TCM and Western medicine can delay femoral head collapse. Yan's study [41] discovered that TCM may effectively delay femoral head collapse by improving intraosseous microcirculation, inhibiting osteoclast proliferation, and promoting bone tissue regeneration. Similarly, animal experiments by Zhou's study [18] demonstrated that TCM may reduce the occurrence of empty bone lacunae and stimulate bone formation by modulating the Wnt/ β -catenin signaling pathway.

Our review has produced consistent findings with another two reviews [76, 77] published in the English language on TCM combined with Western medicine for ONFH. The primary outcome from one of their reviews used total effective rate to estimate the efficacy [77]. However, the total effective rate to ONFH was rarely used in the RCTs. The series of scales, such as the Harris score scale and visual analogue scale are widely used worldwide. Hence, symptom severity measured by Harris score scale and pain relief measured by visual analogue scale are necessary to be assessed. In this review, we also focused on the use of imaging improvement to assess efficacy. Compared to the previous systematic reviews [76, 77], our review provides a variety of new perspectives. First, more rigorous inclusion and exclusion criteria could increase the quality of evidence and reduce the risk of bias. Additionally, we indicated the most commonly used traditional Chinese herbal medicines in our analysis and listed them in Additional file 1: Table S1. There are three main sources of heterogeneity: (1) differences in measures of the same outcome indicators between studies; (2) the period of the treatment course was inconsistent across the included studies; (3) different levels of experience and competence among clinicians. The safety of oral traditional Chinese herbal medicine is a key concern of the article due to the specific nature of traditional Chinese herbal medicine. Only 9 RCTs in this study reported adverse effects, including abdominal pain, nausea, and constipation. The reasons for this may include the following: (1) the researchers did not consider observing safety when developing the protocol; or (2) the investigators guided the medication promptly to detect

adverse reactions and actively intervened in the treatment; thus, they did not cause serious adverse reactions.

Nevertheless, this meta-analysis has many shortcomings. (1) Only 27 of the included studies mentioned scientific allocation, and most studies did not report allocation concealment, blinding, and other circumstances with the potential risk of measurement bias and implementation bias. (2) Since TCM adopts holistic dialectical thinking, it is necessary to add or subtract medication to address individual patient differences, making it difficult to measure the impact of drug addition or subtraction on efficacy, and confounding factors are difficult to control, thus increasing heterogeneity. (3) Most studies did not follow up with patients, and there is a lack of data on the long-term effects of TCM on improving function and relieving pain. (4) There was inconsistency between the protocol and the manuscript, which can lead to bias. Thus, it should be gradually improved and enhanced in future studies.

ONFH belongs to the category of bone erosion in Chinese medicine, and its cause is mostly due to deficiency of the liver and kidney, lack of qi and blood, resulting in the development of phlegm, and stagnation of blood vessels. The herbs Danshen (*Radix Salviae Miltiorrhizae*), Niuxi (*Radix Achyranthis Bidentatae*), and Huangqi (*Radix Astragali*) are commonly used in clinical treatment and have the effect of tonifying the liver, benefiting the kidneys and activating blood circulation to remove blood stasis [82, 83]. Modern research has shown that *Radix Salviae Miltiorrhizae* has mainly anti-inflammatory, immunomodulatory, and glucolipid metabolic effects, which can effectively improve the hematopoietic function of patients [84]. The active ingredients of *Radix Achyranthis Bidentatae* can achieve osteoprotective effects by inhibiting adipogenesis, the inflammatory response, and osteoblast apoptosis in a series of ways [85]. *Astragalus polysaccharide* has the ability to promote the proliferation and differentiation of osteoblasts and inhibit inflammatory factors [86].

A number of common problems in the included articles were identified in this study. First, for any intervention, safety evaluation is as important as efficacy evaluation. In particular, the current clinical studies of TCM for the treatment of ONFH are dominated by self-prepared formulas, the adverse effects of which are less clear than those of listed proprietary Chinese medicines, and a standardized safety evaluation would help to improve acceptance [41, 50]. Second, the implementation of blinding is difficult due to the specificity of herbal therapy, but it is still recommended that this step be implemented where possible; if not, then it should be detailed in the limitations of the study section. Finally, in clinical trials of TCM for ONFH, the diagnostic criteria for TCM

evidence should be clarified to help better exploit the value of the study and guide practice [39, 47, 73].

Conclusion

TCM combined with Western medicine may be a superior treatment approach for ONFH compared with the use of Western medicine alone. However, the included studies in this meta-analysis had a low overall level of evidence. Therefore, large-scale and high-quality RCTs are needed for further evaluation to provide a rational and effective treatment plan for the clinical management of early- and mid-stage ONFH.

Abbreviations

CI	Confidence interval
ONFH	Osteonecrosis of the femoral head
RCTs	Randomized controlled trials
RR	Risk ratio
SMD	Standardized mean difference
TCM	Traditional Chinese medicine

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13018-023-04086-9>.

Additional file 1. Search strategies. **Table S1.** Composition of TCM in the study. **Table S2.** Characteristics of physiotherapy. **Table S3.** Details of reported adverse events from included studies. **Table S4.** Sensitivity analysis for Harris score. **Table S5.** Sensitivity analysis for visual analogue scale score. **Table S6.** Sensitivity analysis for imaging improvement. **Table S7.** Sensitivity analysis for occurrence of adverse reaction. **Fig. S1.** Funnel plot for publication bias of the literature reporting the Harris score: traditional Chinese medicine + physiotherapy vs. physiotherapy. **Fig. S2.** Funnel plot for publication bias of the literature reporting the Harris score: traditional Chinese medicine + hip preservation surgery vs. hip preservation surgery. **Table S8.** Publication bias of the included studies.

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Author contributions

All authors contributed to the writing of the manuscript. WO: First author, designed the study, article writing, and data collation. YM: Second author, article review, literature quality assessment, and language editing. GG: Third author, article selection, literature quality evaluation, article modification, investigation, and statistical analysis. CZ: Correspondent author, article revision, and article review. XZ: Second correspondent author, article guide, and article review. All authors read and approved the final manuscript.

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Declarations

Competing interests

The authors declare that there is no competing interests.

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References

- Cui Q, Jo WL, Koo KH, Cheng EY, Drescher W, Goodman SB, et al. ARCO consensus on the pathogenesis of non-traumatic osteonecrosis of the femoral head. *J Korean Med Sci.* 2021;36(10):e65. <https://doi.org/10.3346/jkms.2021.36.e65>.
- Konarski W, Poboży T, Śliwarczyński A, Kotela I, Krakowiak J, Hordowicz M, et al. Avascular necrosis of femoral head-overview and current state of the art. *Int J Environ Res Public Health.* 2022;19(12):7348. <https://doi.org/10.3390/ijerph19127348>.
- Mont MA, Salem HS, Piuizzi NS, Goodman SB, Jones LC. Nontraumatic osteonecrosis of the femoral head: where do we stand today?: A 5-year update. *J Bone Joint Surg Am.* 2020;102(12):1084–99. <https://doi.org/10.2106/JBJS.19.01271>.
- Tan B, Li W, Zeng P, Guo H, Huang Z, Fu F, Gao H, et al. Epidemiological study based on China osteonecrosis of the femoral head database. *Orthop Surg.* 2021;13(1):153–60. <https://doi.org/10.1111/os.12857>.
- Mont MA, Cherian JJ, Sierra RJ, Jones LC, Lieberman JR. Nontraumatic osteonecrosis of the femoral head: where do we stand today? A ten-year update. *J Bone Joint Surg Am.* 2015;97(19):1604–27. <https://doi.org/10.2106/JBJS.O.00071>.
- Migliorini F, Maffulli N, Baroncini A, Eschweiler J, Tingart M, Betsch M. Prognostic factors in the management of osteonecrosis of the femoral head: a systematic review. *Surgeon.* 2023;21(2):85–98. <https://doi.org/10.1016/j.surge.2021.12.004>.
- Hungerford DS. Osteonecrosis: avoiding total hip arthroplasty. *J Arthroplasty.* 2002;17(4 Suppl 1):121–4. <https://doi.org/10.1054/arth.2002.33300>.
- Migliorini F, La Padula G, Oliva F, Torsiello E, Hildebrand F, Maffulli N. Operative management of avascular necrosis of the femoral head in skeletally immature patients: a systematic review. *Life.* 2022;12(2):179. <https://doi.org/10.3390/life12020179>.
- Quaranta M, Miranda L, Oliva F, Aletto C, Maffulli N. Osteotomies for avascular necrosis of the femoral head. *Br Med Bull.* 2021;137(1):98–111. <https://doi.org/10.1093/bmb/ldaa044>.
- Hou YY, Yan C, Wu JJ, Lei Z. Clinical efficacy and mechanism of action of autologous bone marrow mesenchymal stem cell transplantation combined with medullary decompression in ischemic femoral head necrosis in the elderly. *Chin J Gerontol.* 2021;41(17):3686–90. <https://doi.org/10.3969/j.issn.1005-9202.2021.17.017>.
- Petek D, Hannouche D, Suva D. Osteonecrosis of the femoral head: pathophysiology and current concepts of treatment. *EFORT Open Rev.* 2019;4(3):85–97. <https://doi.org/10.1302/2058-5241.4.180036>.
- Sadile F, Bernasconi A, Russo S, Maffulli N. Core decompression versus other joint preserving treatments for osteonecrosis of the femoral head: a meta-analysis. *Br Med Bull.* 2016;118(1):33–49. <https://doi.org/10.1093/bmb/ldw010>.
- Kim HS, Park JW, Ha JH, Lee YK, Ha YC, Koo KH. Third-generation ceramic-on-ceramic total hip arthroplasty in patients with osteonecrosis of the femoral head: a 10- to 16-year follow-up study. *J Bone Joint Surg Am.* 2022;104(Suppl 2):68–75. <https://doi.org/10.2106/JBJS.20.00720>.
- Kobayashi S, Kubo T, Iwamoto Y, Fukushima W, Sugano N. Nationwide multicenter follow-up cohort study of hip arthroplasties performed for osteonecrosis of the femoral head. *Int Orthop.* 2018;42(7):1661–8. <https://doi.org/10.1007/s00264-018-3980-1>.
- Migliorini F, Maffulli N, Eschweiler J, Tingart M, Baroncini A. Core decompression isolated or combined with bone marrow-derived cell therapies for femoral head osteonecrosis. *Expert Opin Biol Ther.* 2021;21(3):423–30. <https://doi.org/10.1080/14712598.2021.1862790>.

16. Zhao D, Zhang F, Wang B, Liu B, Li L, Kim SY, et al. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). *J Orthop Translat*. 2020;21:100–10. <https://doi.org/10.1016/j.jot.2019.12.004>.
17. Sodhi N, Acuna A, Etcheson J, Mohamed N, Davila I, Ehiorobo JO, et al. Management of osteonecrosis of the femoral head. *Bone Joint J*. 2020;102-B(7_Supple_B):122–8. <https://doi.org/10.1302/0301-620X.102B7.BJJ-2019-1611.R1>.
18. Zhou ZX, Zhu L, Li WH, Li L, Liu T, Kang JP, et al. Experimental study on Gubi Tongxiao granules treating steroid-induced necrosis of femoral head regulating Wnt/ β -catenin pathway. *Chin Arch Tradit Chin Med*. 2023;41(01):21–4. <https://doi.org/10.13193/j.issn.1673-7717.2023.01.006>.
19. Fang B, Li Y, Chen C, Wei Q, Zheng J, Liu Y, et al. Huo Xue Tong Luo capsule ameliorates osteonecrosis of femoral head through inhibiting lncRNA-Miat. *J Ethnopharmacol*. 2019;238:11862. <https://doi.org/10.1016/j.jep.2019.11.1862>.
20. Zhang XY, Li HN, Chen F, Chen YP, Chai Y, Liao JZ, et al. Icaritin regulates miR-23a-3p-mediated osteogenic differentiation of BMSCs via BMP-2/Smad5/Runx2 and WNT/ β -catenin pathways in osteonecrosis of the femoral head. *Saudi Pharm J*. 2021;29(12):1405–15. <https://doi.org/10.1016/j.sps.2021.10.009>.
21. Zhang J, Wang F, Wu D, Zhao D. Revealing the mechanisms of Weishi Huogu 1 capsules used for treating osteonecrosis of the femoral head based on systems pharmacology with one mechanism validated with in vitro experiments. *J Ethnopharmacol*. 2022;295:115354. <https://doi.org/10.1016/j.jep.2022.11.5354>.
22. Yeh YA, Chiang JH, Wu MY, Tsai CH, Hsu HC, Hsu HC, et al. Association of traditional Chinese medicine therapy with risk of total hip replacement in patients with nontraumatic osteonecrosis of the femoral head: a population-based cohort study. *Evid Based Complement Alternat Med*. 2019. <https://doi.org/10.1155/2019/5870179>.
23. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Intervention*. Chichester: Wiley; 2022. p. 2019.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Int J Surg*. 2021;88:105906. <https://doi.org/10.1016/j.ijsu.2021.105906>.
25. Yoon BH, Mont MA, Koo KH, Chen CH, Cheng EY, Cui Q, et al. The 2019 revised version of association research circulation osseous staging system of osteonecrosis of the femoral head. *J Arthroplasty*. 2020;35(4):933–40. <https://doi.org/10.1016/j.arth.2019.11.029>.
26. Ficat RP. Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment. *J Bone Joint Surg Br*. 1985;67(1):3–9. <https://doi.org/10.1302/0301-620X.67B1.3155745>.
27. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. <https://doi.org/10.1136/bmj.d5928>.
28. Zheng YH. Clinical Study on Xianling Gubao capsules assisted surgery for non-traumatic femoral head necrosis. *New Chin Med*. 2022;54(08):104–7. <https://doi.org/10.13457/j.cnki.jncm.2022.08.024>.
29. Zhang WR. Clinical effect of compound Duzhongjiangu granules combined with extracorporeal shock wave in the treatment of early femoral head necrosis. *Chin J Clin Ration Drug Use*. 2022;15(24):40–3. <https://doi.org/10.15887/j.cnki.13-1389/r.2022.24.012>.
30. Shen P, Ding JG, He L, Li JX. Effects of Taoren decoction combined with Alendronate sodium in treatment of patients with mid-term avascular necrosis of femoral head. *Med J Chin People's Health*. 2022;34(16):124–6. <https://doi.org/10.3969/j.issn.1672-0369.2022.16.037>.
31. Sun MY, Yang GY, Zhang LL, Jia YD, Yue C, Wang HC, et al. Clinical observation on the treatment of non-traumatic femoral head necrosis with Gugutou Huaisiyu capsules combined with femoral head neck fenestration and bone grafting. *Chin J Trad Med Traum Orthop*. 2022;30(06):42–7.
32. Li JC, Li ZG, Liu XZ, Liu Z, Zhang J, Bao R, et al. Clinical efficacy of Sanqi Huogu Pill combined with shock wave on the treatment of early osteonecrosis of femoral head. *Chin J Trad Med Traum Orthop*. 2022;30(06):25–9.
33. Han K, Yu J, Zhu YF, Tian YF. Clinical observation of Xianling Gubao capsule combined with shock wave in the treatment of femoral head necrosis. *Smart Healthc*. 2021;7(29):88–90. <https://doi.org/10.19335/j.cnki.2096-1219.2021.29.029>.
34. Liao HW, Tian HL, Li XD. Clinical efficacy of Henggu bone healing agent combined with extracorporeal shock wave in the treatment of early femoral head necrosis. *Gansu Med J*. 2021;40(08):710–1. <https://doi.org/10.15975/j.cnki.gsyj.2021.08.013>.
35. Han SD, Zhu L, Zhou ZX, Gu YF, Xu H. Clinical observation on the treatment of ARCO-II femoral head necrosis by Gubi Tongxiao granule combined with bone marrow core decompression and bone grafting. *Clin J Tradit Chin Med*. 2021;33(08):1559–62. <https://doi.org/10.16448/j.cjctcm.2021.08.38>.
36. Liao HW, Liu YM, Li XD. 44 cases of early osteonecrosis of femoral head treated with extracorporeal shock wave combined with Fuyang Revitalizing Bone Pill formula. *TCM Res*. 2021;34(08):28–31. <https://doi.org/10.3969/j.issn.1001-6910.2021.08.09>.
37. Sun B. Clinical observation on the treatment of early phlegm-stasis obstructed femoral head necrosis by combination of self-developed bone etching formula and coarse channel medullary core decompression implant fibula support. *Guangxi Chin Med*. 2021;44(05):12–5.
38. Liu HC. Clinical observation on early ischemic necrosis of the femoral head treated with the combination of tonifying the kidney, benefiting the liver and activating blood circulation formula and medium frequency pulsed electricity. *Chin Folk Therapy*. 2020;28(19):76–8. <https://doi.org/10.19621/j.cnki.11-3555/r.2020.1933>.
39. Du CF, Zhang YJ, Wang SZ, Zheng FZ. Clinical observation on treating 40 cases of osteonecrosis of the femoral head of kidney deficiency and blood stasis type with Tiansui Jiaonang combined with focused extracorporeal shock wave. *Rheumat Arthritis*. 2020;9(08):22–4. <https://doi.org/10.3969/j.issn.2095-4174.2020.08.005>.
40. Zhao JX, Zhuo CF, Sun LW, Zhao J, Zhao XD. Observation of Bushen huogu capsule combined with extracorporeal shock wave in the treatment of femoral head necrosis. *Acta Acad Med Weifang*. 2020;42(03):228–30. <https://doi.org/10.16846/j.issn.1004-3101.2020.03.021>.
41. Yan C, Wu JJ, Lu XJ, Wang JJ, Xing H. Clinical effects of Supplemented No. 1 Zhuli Decoction combined with core decompression and internal support bone grafting on patients with early and middle stage osteonecrosis of femoral head due to Cold-dampness Obstruction. *Chin Tradit Patent Med*. 2020;42(1):2913–8. <https://doi.org/10.3969/j.issn.1001-1528.2020.11.016>.
42. Wei W, Shen JR, Yao C, Zhang C. Short-term clinical curative effects of rotational osteotomy combined with oral application of Bushen Huoxue decoction in the treatment of ARCO phase III osteonecrosis of femoral head (ONFH) in young and middle-aged patients. *World Chin Med*. 2019;14(04):936–40. <https://doi.org/10.3969/j.issn.1673.7202.2019.04.031>.
43. Sun HZ, Wei BF. Study on the treatment of pre-collapse osteonecrosis of the femoral head by combining blood and bone generating soup with compression support bone grafting. *Lishizhen Med Materia Medica Res*. 2019;30(08):1911–3. <https://doi.org/10.3969/j.issn.1008-0805.2019.08.040>.
44. Zhou SB, Tian SY, Zheng YZ, Li MF, Tian YZ. Clinical observation of Sanjiao paste combined with extracorporeal shock wave in the treatment of femoral head necrosis. *Clin J Tradit Chin Med*. 2019;32(11):51–4. <https://doi.org/10.16448/j.cjctcm.2019.0280>.
45. Zhan XY. Clinical observation of self-made Bu Gu decoction combined with alendronate in the treatment of nontraumatic femoral head necrosis. *Clinical J Tradit Chin Med*. 2019;31(08):1568–71. <https://doi.org/10.16448/j.cjctcm.2019.0462>.
46. Zhao J, Sun RW, Zhao JX, Zhao XD, Ren ZF, Feng XT, et al. Clinical efficacy of Guningwan cooperated with bone grafting through a window at the femoral head neck junction surgery in the treatment of osteonecrosis of the femoral head. *J Weifang Med Coll*. 2019;41(04):251–4. <https://doi.org/10.16846/j.issn.1004-3101.2019.04.004>.
47. Cao JW, Zhai MY. 30 cases of early stage femoral head necrosis with Qi stagnation and blood stasis treated with the combination of Body Pain and Blood Stasis Tang and Marrow Core Decompression Osteotomy. *J Shaanxi Univ Chin Med*. 2018;41(05):88–91. <https://doi.org/10.13424/j.cnki.jsctcm.2018.05.028>.
48. Wang X. Efficacy of warming Yang and tonifying the kidney formula in the treatment of early stage femoral head necrosis and its effect on serum calcium, phosphorus and bone metabolism with the aid of medullary core decompression osteotomy. *Mod J Integr Tradit Chin Western Med*. 2018;27(28):3156–9. <https://doi.org/10.3969/j.issn.1008-8849.2018.28.024>.

49. Song SP, Yan L, Li FL, Sun YQ, Zhang QQ. Clinical observation on 30 cases of early osteonecrosis of the femoral head treated by extracorporeal shock wave combined with Gugutou Huaisiyu Jiaonang. *Rheumat Arthritis*. 2018;8:12–4.
50. Du SG, Gu ZH, Kong QQ, Wang XC. Clinical observation of modified Shenqi Decoction in the treatment for patients with early-to-middle stage nontraumatic osteonecrosis of femoral head. *Chin Tradit Patent Med*. 2018;40(01):55–60. <https://doi.org/10.3969/j.issn.1001-1528.208.01.010>.
51. Yuan LJ, Chen HC, Chen C. Treatment of early osteonecrosis of the femoral head by high energy extracorporeal shock wave combined with Yuanshi Shengmai Chenggu Tablets: a report of 34 cases. *Hainan Med J*. 2018;29(08):1088–90. <https://doi.org/10.3969/j.issn.1003-6350.2018.08.015>.
52. Liu MY, Zhao ZY, Wu YD. Clinical study on the treatment of early femoral head necrosis with Chinese medicine and surgery. *Orthop J China*. 2017;25(03):274–7. <https://doi.org/10.3977/j.issn.1005-8478.2017.03.18>.
53. Lu JQ. Observation on the effect of Chinese medicine dialectic combined with sodium alenophosphate in the treatment of non-traumatic necrosis of femoral head. *Chin Rural Med*. 2017;24(04):61–2. <https://doi.org/10.19542/j.cnki.1006-5180.000128>.
54. Jiang QL, Shen JT, Guo HL. Clinical observation on treatment of early osteonecrosis of the femoral head with Gugutou Huaisiyu Jiaonang combined with porous tantalum rod insertion. *Rheumat Arthritis*. 2017;6(10):22–6. <https://doi.org/10.3969/j.issn.2095-4174.2017.10.004>.
55. Li Q, Dang JJ. Treatment of ischaemic necrosis of the femoral head by combining marrow tonifying, blood activating and bone strengthening soup with intramedullary decompression osteotomy. *Mod J Integr Tradit Chin Western Med*. 2017;26(22):2435–7. <https://doi.org/10.3969/j.issn.1008-8849.2017.22.013>.
56. He KY, Yi SH, Qin G, Du MD, Chen J, Huang XH, et al. Clinical effect of Shenggu Decoction combined with modified core decompression and osteotomy on early treatment of femoral head necrosis. *China Med Herald*. 2017;14(27):97–100.
57. Xu XH. Clinical effect of Bushen Huoxue Prescription cooperated with core decompression and internal support bone grafting in the treatment of early necrosis of the femoral head. *China Med Herald*. 2017;14(16):98–101.
58. Zhang C, Yao C, Shen JR. Observation on the short-term clinical curative effect of minimally invasive core decompression combined with impaction bone grafting and oral application of Bushen Huoxue Tang in the treatment of ARCO phase II and III osteonecrosis of the femoral head. *J Trad Chin Orthop Trauma*. 2016;28(03):20–3.
59. Zhang BG, Hao YQ, Liu ZY, Liu J, Wang YG. Clinical study on the treatment of early stage femoral head necrosis by combining Tongluo Bone Generating Tang with marrow core decompression. *J Shaanxi Univ Chin Med*. 2016;37(03):297–9. <https://doi.org/10.3969/j.issn.1000-7369.2016.03.017>.
60. Nong HS. Efficacy of medullary core decompression and compression-supported bone grafting in combination with blood-strengthening bone broth in the treatment of pre-collapse non-traumatic femoral head necrosis. *Mod J Integr Tradit Chin Western Med*. 2016;25(13):1456–8. <https://doi.org/10.3969/j.issn.1008-8849.2016.13.032>.
61. Tian XY, Gao FF, Gao ST, Liu YW, Chen XT, Liu LY. Treatment of steroid-induced osteonecrosis of femoral head by porous tantalum rod and Gugutou Huaisiyu capsule. *Chin J Integr Chin Western Med*. 2016;36(01):40–3. <https://doi.org/10.7661/CJIM.2016.01.0040>.
62. Zhu XF, Feng XD, Chen YD. Clinical efficacy of integrated traditional chinese medicine combined with core decompression treatment of osteonecrosis of femoral head. *Chin Arch Tradit Chin Med*. 2015;33(10):2523–6. <https://doi.org/10.13193/j.issn.1673-7717.2015.10.068>.
63. Liu ZQ, Li GS, Hu M, You HL. Clinical analysis of applying traditional Chinese medicine combined with core decompression and bone graft to treat early femoral head necrosis. *J Sichuan Tradit Chin Med*. 2015;33(02):91–2.
64. Zhou ZL. Clinical effect of Jiawei Qing E Pills on early ischemic necrosis of femoral head. *Pharmacol Clin Chin Materia Med*. 2015;31(03):131–2. <https://doi.org/10.13412/j.cnki.zyyj.2015.03.040>.
65. Wang YD, Liu Y, Wang JX, Sun DT. Analysis of the efficacy of Jian Bu Hu Qian Pill with medullary core decompression osteotomy in the treatment of early ischemic necrosis of the femoral head. *Guiding J Tradit Chin Med Pharm*. 2015;21(13):59–61. <https://doi.org/10.13862/j.cnki.cn43-1446/r.2015.13.021>.
66. Li XM, Guo DH, Shi GJ, Gao HY, Xiao L, Ma SQ, et al. Analysis of the recent efficacy of medullary core decompression with Deer Turtle Bone Building Pill in the treatment of early femoral head necrosis. *Chinese J Integr Chin Western Med Surg*. 2015;21(02):173–5. <https://doi.org/10.3969/j.issn.1007-6948.2015.02.022>.
67. Ang HK. Clinical observation of Busui-Huoxue-Jiangu decoction combined with bone grafting pith decompression on the treatment of nontraumatic avascular necrosis of the femoral head. *Hebei J TCM*. 2015;37(10):1466–9. <https://doi.org/10.3969/j.issn.1002-2619.2015.10.008>.
68. Feng Z, Zhao BX, Sun BY. Clinical observation of opening bone grafting in head and neck combined with Xianling Gubao capsule in treating nontraumatic osteonecrosis of the femoral head. *Chin J Trad Feb Traum Orthop*. 2014;22(07):24–5.
69. Zhang YW. Clinical study on the treatment of hormonal osteonecrosis of the femoral head by combining blood and marrow tonifying soup with marrow core decompression. *Liaoning J Tradit Chin Med*. 2014;41(10):2177–9. <https://doi.org/10.13192/j.issn.1000-1719.2014.10.062>.
70. Cheng ZM. Clinical studies of traditional chinese medicine syndrome differentiation combined bone grafting pith decompression treatment of early femoral head necrosis. *China J Chin Med*. 2014;29(12):1751–2. <https://doi.org/10.16368/j.issn.1674-8999.2014.12.022>.
71. Zhao BX. Clinical study on the treatment of pre-collapse osteonecrosis of the femoral head by traditional Chinese medicine and tantalum rod implantation. *China J Chin Med*. 2012;27(10):1273–4. <https://doi.org/10.16368/j.issn.1674-8999.2012.10.008>.
72. Lu XL, Xiao QM, Xiao SW. Clinical observation on early necrosis of the femoral head treated with method of core decompression and internal support bone grafting combined with Traditional Chinese Medicine. *J TCM Univ Hunan*. 2012;32(09):63–6. <https://doi.org/10.3969/j.issn.1674-070X.2012.09.017.063.04>.
73. Su CH. Treatment of early osteonecrosis of the femoral head with oral Chinese medicine and medullary core decompression implantation. *Asia-Pac Tradit Med*. 2012;8(12):57–8.
74. Du WS, Han FW, Xie YL, Jiang SQ. 45 cases of early osteonecrosis of the femoral head treated with Chinese medicine and medullary core decompression implantation. *Chin J Exp Tradit Med Formulae*. 2011;17(21):271–2. <https://doi.org/10.13422/j.cnki.syfx.2011.21.009>.
75. Tian KW. Clinical observation of combined Chinese and Western medicine in the treatment of non-traumatic femoral head necrosis. *Guangming Chin Med*. 2018;33(4):555–7.
76. He P, Chen J, Yue C, Ma M, Hong Z, Liu Y, et al. Effectiveness and safety of traditional Chinese medicine in the treatment of steroid-osteonecrosis of femoral head: a protocol for systematic review and meta-analysis. *Medicine*. 2021;100(30):e26811. <https://doi.org/10.1097/MD.00000000000026811>.
77. Zhang QW, Yang F, Chen Y, Wang H, Chen D, He W, et al. Chinese herbal medicine formulas as adjuvant therapy for osteonecrosis of the femoral head: a systematic review and meta-analysis of randomized controlled trials. *Medicine*. 2018;97(36):e12196. <https://doi.org/10.1097/MD.00000000000012196>.
78. Yang X, Shi L, Zhang T, Gao F, Sun W, Wang P, et al. High-energy focused extracorporeal shock wave prevents the occurrence of glucocorticoid-induced osteonecrosis of the femoral head: a prospective randomized controlled trial. *J Orthop Translat*. 2022;36:145–51.
79. Wang QW, Zhang QY, Gao FQ, Sun W. Focused extra-corporeal shockwave treatment during early stage of osteonecrosis of femoral head. *Chin Med J*. 2019;132(15):1867–9.
80. Huang RL, Hu WB, Zhan QH. Research advances of traditional Chinese medicine in treating osteonecrosis of femoral head by regulating bone metabolism related signaling pathways. *Chin J Exp Tradit Med Formulae*. 2021;27(08):241–50. <https://doi.org/10.13422/j.cnki.syfx.20210622>.
81. Zheng YZ, Tian YZ, Li MF, Wang SZ. Clinical observation of TCM three glue paste in treating femoral head necrosis and its influence on serum inflammatory factors, erythrocyte sedimentation rate and bone metabolism index. *Chin Arch Tradit Chin Med*. 2018;36(11):2747–9.
82. He L, Gao S, Li ZG, Gao YH, Sun ZJ, Zhang N, et al. The feasibility of treating SANFH based on “phlegm, deficiency and stasis” is explored

based on three major histologists. *Lishizhen Med Materia Med Res.*

2022;33(08):1947–9. <https://doi.org/10.3969/j.issn.1008-0805.2022.08.44>.

83. Zhi LF, Wu QJ. Discussion on the treatment of avascular necrosis of femoral head by cultivating the yu and clearing blockage. *China J Tradit Chin Med Pharm.* 2022;37(06):3315–8.
84. Su YJ, Xi JY, Shi Q, Huang YF, Zhao KP, Yang FD. Research progress on *Codonopsis Radix* as medicinal and edible traditional Chinese medicine. *Chin Tradit Herbal Drugs.* 2023;54(08):2607–17. <https://doi.org/10.7501/j.issn.0253-2670.2023.08.028>.
85. Zhang JZ, Yang YJ, Guang XF. Research progress on physical medical effectiveness and functional mechanism of *Niuxi* (*Radix Achyranthis Bidentatae*) towards prevention and treatment of osteoarthritis by regulating chondrocyte metabolism. *Chin Arch Tradit Chin Med.* 2022;40(01):147–53. <https://doi.org/10.13193/j.issn.1673-7717.2022.01.035>.
86. Li L, Li K, Hu Y, Li JY, Song M. Research progress on anti-osteoporosis mechanism of active components in *Astragali Radix*. *Chin Tradit Herbal Drugs.* 2023;54(04):1321–8. <https://doi.org/10.7501/j.issn.0253-2670.2023.04.033>.

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