Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2014, Article ID 343176, 17 pages
http://dx.doi.org/10.1155/2014/343176

Review Article

Effectiveness, Medication Patterns, and Adverse Events of Traditional Chinese Herbal Patches for Osteoarthritis: A Systematic Review

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Received 5 June 2013; Revised 17 August 2013; Accepted 18 August 2013; Published 14 January 2014

Academic Editor: Byung-Cheul Shin

Objective. The aim of this study is to systematically evaluate the evidence whether traditional Chinese herbal patches (TCHPs) for osteoarthritis (OA) are effective and safe and analyze their medication patterns. *Methods*. A systematic literature search was performed using all the possible Medical Subject Headings (MeSH) and keywords from January 1979 to July 2013. Both randomized controlled trials (RCTs) and observational studies were included. Estimated effects were analyzed using mean difference (MD) or relative risk (RR) with 95% confidence intervals (CI) and meta-analysis. *Results*. 86 kinds of TCHPs were identified. RCTs and controlled clinical trials (CCTs) which were mostly of low quality favored TCHPs for local pain and dysfunction relief. TCHPs, compared with diclofenac ointment, had significant effects on global effectiveness rate (RR = 0.50; 95% CI (0.29, 0.87)). Components of formulae were mainly based on the compounds "Xiao Huo Luo Dan" (Minor collateral-freeing pill) and "Du Huo Ji Sheng Tang" (*Angelicae Pubescentis* and *Loranthi* decoction). Ten kinds of adverse events (AEs), mainly consisting of itching and/or local skin rashes, were identified after 3-4 weeks of follow-up. *Conclusions*. TCHPs have certain evidence in improving global effectiveness rate for OA; however, more rigorous studies are warranted to support their use.

1. Introduction

OA, which is manifested by joint pain, disability, stiffness, and/or swelling, is a common chronic disease in the elderly worldwide [1–3]. In Traditional Chinese Medicine (TCM), symptoms of OA are usually known as "*Bi*-arthralgia" or "flaccidity" [4].

Conventional therapies for the management of OA consist of exercises, weight loss, acetaminophen, and oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs), as well as intra-articular injection and several other treatments [3]. Such treatments may prove ineffective in some OA patients, and NSAIDs often have gastrointestinal (GI) and cardiovascular adverse events (AEs) [3, 5], so patients are turning increasingly to complementary and alternative medicine (CAM) as treatment options for OA [5].

Some reviews provide evidence for the effectiveness of herbal medicines for OA [5–8]. At the same time, external medications for the treatment of mild or moderate OA pain have been advocated by both the Chinese Orthopedic Association (COA) and the American College of Rheumatology (ACR), because it is deemed to have relatively less AEs and is more convenient for use [3, 9]. In many topical herbal medications, the patch or plaster is most frequently prescribed [10]. TCHPs are a class of transdermal plasters that dissolve or mix different herbs with the adhesive matrix, which could then be made into a thin patch. When affixed to the injured area or acupoints, it would have a therapeutic effect locally or even systemically [4, 11].

The biological mechanisms of TCHPs for OA are known to have the following characteristics. (1) Their herbs could reach the lesions with the help of the transdermal delivery

system, so they could continue to achieve an analgesic and anti-inflammatory effect [12, 13]. Some studies reveal that serum prostaglandin E2 (PGE2), interleukin-1 (IL-1), and interleukin-6 (IL-6) were decreased, while β-endorphin (β-EP) was increased in OA patients after using TCHPs [14, 15]. (2) They have a slight fixation effect and could help patients overcome fear of pain as taping [4, 16]. (3) The way of dispelling "cold evil," removing "dampness evil," and activating blood circulation might possibility have an impact on the immune and neurochemical systems to improve TCM syndrome [4].

At present, transdermal patches as TCHPs have been widely applied for patients with OA or chronic joint pain in China and worldwide and have accumulated abundant data in clinical practice [4, 10, 17]. To date, no comprehensive study has been documented for their effectiveness, medication patterns, and AEs, while such information would be of great value in guiding TCM practitioners or health care providers in the management of OA. Therefore, this systematic review is undertaken to investigate these important aspects of TCHPs for OA. RCTs and CCTs were chosen to evaluate the effectiveness, whereas both interventional and observational studies were included for analyzing medication patterns and AEs of TCHPs.

2. Methods

2.1. Selection Criteria. Given that chronic joint pain is the major symptom of OA and that a large number of TCHPs have listed chronic joint pain, rather than OA as their indications, it is necessary to index both OA and chronic joint pain during the search process.

Data has been pooled from the 2010 version of China Pharmacopoeia (one) and electronic databases from past decades, as they both provide clear evidence for TCHPs in the treatment of OA. When retrieving data from China Pharmacopoeia (one), TCHPs were required to show the indication of OA or chronic joint pain.

In the electronic searches, relevant articles published in English or Chinese were included if all the following criteria were met: treating OA or chronic joint pain, RCTs or observational studies; the case number enrolled into the treatment group of at least 15, and describing the main traditional Chinese herbs (commercially available or exclusively applied in the hospital). A study was excluded if, it was treating rheumatoid arthritis, gouty arthritis, or psoriatic arthritis; TCHPs were employed as one method in a combined therapy, and/or the unbalanced baseline before interventions, because it is not possible to identify the effect; it was a review or experimental articles or if there was no clinical data and/or details of herbs provided.

2.2. Search Strategy. The entire Academic Journals, Dissertations and Important Conference Papers Database in China National Knowledge Infrastructure (CNKI, 1989–2012), Sinomed (formerly as Chinese Biomedical Literature, CBM, 1979–2012), PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) were electronically performed up to February 2, 2012. We updated CENTRAL (Issue 7 of 12) and searched Ovid up to July 26, 2013. These databases were searched using all the possible MeSH and keywords of "osteoarthritis" and "Chinese herbal patch" (see supplementary Appendix 1 in Supplementry Material online at http://dx.doi.org/10.1155/2014/343176). Reference lists of relevant retrieved studies were extended to locate additional articles not identified in the electronic searches. Available TCHPs in the management of chronic joint pain or arthralgia in China Pharmacopoeia (one) were hand-searched.

2.3. Study Selection. Titles and abstracts of all records were initially checked to find relevant studies. If this information was insufficient, whole articles were retrieved to check whether the article had been missed in the initial search. Full text articles were retrieved for final analysis. The two reviewers (XZW and SPW) independently conducted study selection and assessed articles by the strategy of the established criteria.

2.4. Data Extraction. All articles were read and data was extracted, based on predefined standardized forms. This data mainly included first author, year of publication, title of study, simple size, types of trial, treatment and control group, methodological quality, eligibility criteria, outcome measures, name and components of TCHPs, descriptions of effectiveness, details of AEs, and follow-up period for each study.

A classical textbook was referred to, to standardize the herbal name involved in all TCHPs [18]. Synonyms of herbs were merged and different herbs were distinguished. Matrices such as honey, rosin, and licorice were excluded, because they act as processing materials, usually with no detailed dosage available.

2.5. Quality Assurance. All authors worked together to develop relevant MeSH, keywords of each database, and screening methods of citations. All works were applied independently by two authors to screen the full texts of articles. In case of disagreement, the two reviewers tried to discuss and achieve a consensus. When a consensus could not be reached, a third reviewer (YLC) was consulted to make the final decision.

2.6. Analysis Plan. According to the unique philosophical and methodological characteristics of TCM [19], evidence of effectiveness, medication patterns, and related AEs of TCHPs have been synthesized, respectively.

The qualities of the reports of RCTs and CCTs were assessed by the Cochrane Collaboration's tool for assessing risk of bias to address the following domains: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. Judgments were categorized as low risk of bias, high risk of bias, or unclear risk of bias. If insufficient information was prevented to make judgment, trials were categorized into high risk of bias; if adequate reporting was provided, trials

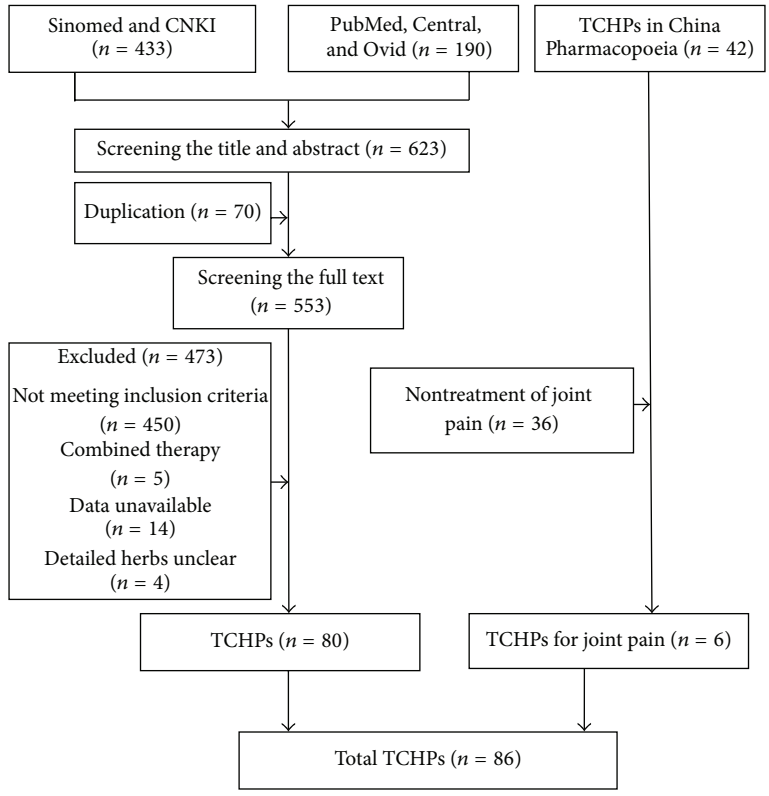

Figure 1: Flow diagram of search of TCHPs for OA.

were categorized to low risk of bias, and the rest were recorded unclear risk of bias.

The effectiveness of TCHPs for OA was defined as a significant improvement compared to the placebo, NSAIDs, or other therapeutic interventions (e.g., infrared therapy) in outcomes of OA pain, dysfunction, or global effectiveness rate (TCM syndrome). Statistically, the difference between the intervention group and the control group was considered to be an improvement ($P < 0.05$ or $P < 0.01$); noninferiority results of TCHPs group compared to NSAIDs were also included.

Data was pooled using MD with 95% CI for continuous outcomes or RR with 95% CI for binary outcomes through Revman 5.2 software. Meta-analysis would be done if RCTs had a good homogeneity and the funnel plot would explore publication bias if enough trials were identified. When the I^2 was greater than 50%, higher levels of statistical heterogeneity were existed and random effects model was used. When I^2 was less than 50%, a fixed effects model would be more appropriate. RCTs and observational studies were included for analyzing the medication patterns and AEs in all included TCHPs.

3. Results

3.1. Description of Included TCHPs. 623 citations were initially screened (433 in Sinomed and CNKI and 190 in PubMed and CENTRAL). Among them, 70 citations were duplicated and 473 citations were excluded, mainly due to not meeting inclusion criteria. The 2010 version of China Pharmacopoeia (one) recorded 42 kinds of topical TCHPs, but only 6 documented the indication of chronic joint pain. Hence, a final library of 80 articles from electronic database and 6 records from China Pharmacopoeia (one) remained for evidence synthesis (supplementary Appendix 2). In other words, 86 kinds of TCHPs were involved in our final analysis (Figure 1). Of the 86 TCHPs, 22 were commercially available, whereas the remainders were exclusively applied in the hospital. Six kinds of TCHPs were recorded in China Pharmacopoeia (one), with the indication of chronic joint pain rather than OA name. On the contrary, varieties of new TCHPs have been reported in the treatment of OA in our literature search but were not recorded by China Pharmacopoeia (one).

3.2. Description of Included RCTs and CCTs. 80 articles included 44 RCTs, 35 observational studies, and 1 study protocol for an RCT [10]. The number enrolled into TCHPs group was 9723 patients.

3.2.1. Description of Included RCTs. 36 studies declared a greater effect compared with the control group, of which 5 studies used diclofenac ointment [20–24] and 7 studies reached noninferiority effect [25–31], including 3 studies using diclofenac ointment and 1 using diclofenac [25–28]. The characteristics of TCHPs compared with diclofenac ointment or placebo were listed in Table 1 and 686 participants were involved. The duration of treatment ranged from 7 to 42 days

Table 1: Characteristics of TCHPs versus diclofenac ointment or placebo for OA in included RCTs.

First author (year)	No. (M/F)	Age (yrs)	Disease duration	Comparisons	Outcome measures	AEs
Guan, 2010 [22]	*T*: 9/24; *C*: 6/23	*T*: 53.15 ± 12.76; *C*: 54.28 ± 11.12	*T*: 18.3 ± 9.36; *C*: 17.5 ± 10.22	Zhuang Gu Tong Bi patch versus diclofenac ointment for the treatment of 28 days	Global effectiveness rate	No AEs were identified
Liu, 2004 [28]	*T*: 12/18; *C*: 10/20	*T*: 46.8; *C*: 48.7	*T*: 8.2; *C*: 9.2	Self-prescribed herbal patch versus diclofenac ointment for the treatment of 42 days	Global effectiveness rate and function	One case exited because of lack of effect in treatment group (1/30; 3.33%); three cases of skin allergic reactions exited in control group (3/30; 10.00%)
Lin, 2006 [25]	*T*: 7/11; *C*: 5/13	*T*: 42~85; *C*: 46~81	Not reported	Shang Ke Xiao Yan patch versus diclofenac for the treatment of 28 days	Global effectiveness rate	Two patients exited in the medium term of treatment in diclofenac group due to AEs (2/18, 11.11%)
Long, 2006 [26]	*T*: 15/31; *C*: 16/27	42~67 (mean = 57.7) (for all)	Not reported.	Shang Ke Hei Yao patch versus diclofenac ointment for the treatment of 28 days	Global effectiveness rate	No AEs were identified
Wang, 2010 [21]	*T*: 4/26; *C*: 5/25	*T*: 57.20 ± 8.10; *C*: 58.60 ± 8.00	5 d~3 yrs (for all)	Huo Xue Hua Yu patch versus diclofenac ointment for the treatment of 14 days	Pain, range of motion (ROM), and flexion deformity	Not reported
Wang, 2012 [4]	*T*1: 7/53; *T*2: 4/56; *C*: 3/27	*T*1:58.5 ± 7.7; *T*2: 59.6 ± 6.1; *C*: 60.4 ± 8.0	*T*1: 5.1 ± 4.1; *T*2: 3.5 ± 3.0; *C*: 4.6 ± 3.0 (yrs)	Fu Fang Nan Xing Zhi Tong patch versus placebo; Shang Shi Zhi Tong patch versus placebo for the treatment of 7 days	Pain, stiffness, and physical function; TCM syndrome	Fu Fang Nan Xing Zhi Tong patch leading to one withdrawal; 4 cases of rash, itching, slightly damaged skin, or erythema in two patches, respectively; no AEs were identified in placebo
Wang, 2006 [58]	42/40 (for all)	45~70 (for all)	1~18 (median = 7) (for all)	Xiao Tong patch versus diclofenac ointment for the treatment of 7 days	Global effectiveness rate	One case of mild local inflammation in treatment group (1/41; 2.44%); three cases of local allergic dermatitis found in control group (3/41; 7.32%)
Zhang, 2008 [20]	80 (for all)	Not reported	Not reported	Zhi Tong Tou Gu patch versus diclofenac ointment for the treatment of 28 days	Global effectiveness rate	Six cases exited the trial because of local allergy (not reported in which group)
Zheng, 2006 [23]	*T*: 12/24; *C*: 9/27	*T*: 51.06 ± 6.6; *C*: 52.78 ± 7.1	6 m~7 yrs (for all)	Qing Peng patch versus diclofenac ointment for the treatment of 21 days	Global effectiveness rate and pain	No AEs were identified

Values are the number (frequency or percentage). *T*: intervention group; *C*: control group.

[4, 28]. 18 studies provided information on patients' syndrome differentiations (TCM-Zheng) as the basis of effectiveness for using TCHPs [4, 12, 21, 22, 25–27, 29, 32–41]. For example, when applied for knee OA with syndrome of kidney deficiency and blood stasis, the "Huo Xue Hua Yu" patch (Gao) significantly improved total scores of TCM syndrome and OA symptoms compared with diclofenac ointment [21].

3.2.2. Description of Included CCTs. According to the study design checklist and guidance about collecting the information of the studies (Chapters 13.2 and 13.4), apart from 23 case series, 10 nonrandomized controlled trials (NRCT) [33, 34, 42–49] and 2 interrupted-time-series (ITS) studies [12, 50] were identified among 35 observational studies. A summary of the included CCTs were listed in Table 2. In total,

Table 2: Characteristics of TCHPs for OA in included CCTs.

First author (year)	No. (M/F)	Age (yrs)	Disease duration	Eligibility criteria	Comparisons	AEs	Comparability at baseline
Liu, 2004 [42]	*T*: 40/50; *C*: 39/47	*T*: 68.5; *C*: 64.5	1 m~20 yrs (for all)	Unclear	Self-prescribed herbal patch versus sodium hyaluronate for the treatment of 5 weeks	No AEs were identified.	Unclear
Cheng, 2009 [44]	238/122 (for all)	54.8 (for all)	2 m~20 yrs (for all)	The standard of TCM syndrome diagnostic and efficacy	San Huang patch versus Gu Tong patch for the treatment of 12 days	Unclear	Yes
Dong, 2007 [46]	*T*: 17/25; *C*: 14/22	*T*: 65.3; *C*: 68.2	*T*: 3.2; *C*: 3.4	ACR	Shu Jin patch versus Zhi Tong Xiao Yan patch for the treatment of 12 days	No AEs were identified	Yes
Feng*, 2006 [43]	*T*: 13/23; *C*: 15/18	Not reported	*T*: 50 ± 10; *C*: 50 ± 9	Hemigou	Gu Ci patch versus one control patch for the treatment of 9 days	No AEs were identified	Unclear
Kuang, 2010 [12]	*T*: 17/31; *C*: 18/28	*T*: 50.4 ± 8.53; *C*: 49.42 ± 9.47	*T*: 1.83 ± 0.35; *C*: 1.92 ± 0.47	ACR and clinical research guidelines of traditional Chinese patent drug	Zhong Tong Xiao Babu patch versus Zhong Tong Xiao patch for the treatment of 10 days	Unclear	Yes
Liu, 2008 [49]	122/238 (*T*: 260; *C*: 100; for all)	54.8 (for all)	2 m~50 yrs (for all)	ACR	Hei Hu patch versus Qian Shan Huo Xue patch for the treatment of 5 weeks	*T*: redness, oozing, purulent or itching, rash mentioned; *C*: fewer people of itching	Yes
Wang, 2005 [45]	*T*: 48; *C*: 16 (for all)	16~72 yrs (for all)	1~20 yrs (for all)	ACR	Zhen Tong Xiao Yan patch versus Fu Fang Nan Xing Zhi Tong patch for the treatment of 28 days	Unclear	Unclear
Wen, 2008 [34]	*T*: 13/39; *C*:14/40	*T*: 48~75 yrs; *C*: 47~72 yrs	*T*: 3 m~5 yrs; *C*: 47~74 yrs	ACR and clinical research guidelines of traditional Chinese patent drug	Xi Tong Kang patch versus Tong Luo Qu Tong pacth for the treatment of 28 days	Unclear	Yes
Xu, 2000 [48]	*T*: 31/65 (105); *C*: 20 (25)	*T*: 62.3; *C*: not reported	6 cases less than 1 year; 32 cases between 1 and 3 yrs; 28 cases more than 3 yrs	ACR	Fu Fang San sheng patch versus Zhuang Gu Guan Jie pill	2 cases showed local skin itching within 48 h after patching, which disappeared after a day by the discontinuation, but not affecting patching	Unclear

Table 2: Continued.

First author (year)	No. (M/F)	Age (yrs)	Disease duration	Eligibility criteria	Comparisons	AEs	Comparability at baseline
Zhang, 2010 [50]	*T*: 10/26; *C*: 13/23	*T*: 48.6; *C*: 51	*T*: 1 m~3 yrs; *C*: 1.5 m~3 yrs	ACR and clinical research guidelines of traditional Chinese patent drug	Gu Ci patch versus She Xiang Zhuang Gu patch for the treatment of 10 days	No AEs were identified	Unclear
Zhang, 2010 [33]	*T*: 18/36; *C*: 13/23	*T* : 45~85; *C* : 45~80	T: 3 m~5 yrs; C: 3 m~5 yrs	COA and the standard of TCM syndrome diagnostic and efficacy	Wen Tong patch versus Tong Luo Qu Tong patch for the treatment of 28 days	Unclear	Yes
Zhao, 2007 [47]	52/60 (for all)	10 cases (15 m~30 yrs); 20 cases (31~45 yrs); 35 cases (45 m~60 yrs); 47 cases more than 61 yrs	30 cases (6 m~3 yrs); 37 cases more than 10 yrs	The standard of TCM syndrome diagnostic and efficacy	Gu Bi Tong patch versus Fu Fang Nan Xing zhi Tong patch with 1-year follow-ups	Unclear	Unclear

*Three-arm study; Gu Ci patch versus control patch was selected.

1607 participants were included. The duration of treatment ranged from 9 days to 5 weeks, even with 1-year follow-ups [47]. A three-arm study concerning knee pain and range of motion (ROM) about "Gu Ci" patch versus control patch was obtained [43]. One reported using "Gu Bi" patch for the chronic joint pain of knee, ankle, and shoulder [47]. In these studies, the outcome measure was unclear and stated rare in 4 trials [42, 43, 48, 49].

3.3. Methodological Assessments

3.3.1. Assessments of Risk of Bias of Included RCTs. RCTs were generally of poor methodological quality or were poorly reported (supplementary Appendix 3). The randomized allocation of participants was declared in all included RCTs. However, only 12 trials mentioned methods for sequence generation, such as random number table [21, 22, 30, 35, 36, 41, 51, 52] or computer software [4, 10, 23, 25]. Three trials were of single-blind design [40, 51, 53] and 2 were of double [4, 31]. Two trials were assessed as having concealment and obtained research ethics approval [4, 36]. Nearly, all the trials provided baseline data for the comparability among groups. Four trials reported information on withdrawal/dropout [20, 25, 28, 35]. Majority of studies lacked the information for dropouts and outcome measures were quite varied. Most studies have conducted follow-ups of 3 to 4 weeks. Risk of bias summary of TCHPs versus diclofenac ointment or placebo was shown in Figure 2.

3.3.2. Quality Assessments of CCTs. Ten NRCT [33, 34, 42–49] and 2 ITS studies [12, 50] were assessed (supplementary Appendix 3). As reported, 1 mentioned randomization; actually it was an NRCT mainly for within group comparison [12]. Only 6 reported comparability at baseline [12, 33, 34, 44, 46, 49]. Biases were found at statistical methods [46], unreasonable formulations compared with TCHPs, such as using tablet [43], pill [44], and sodium hyaluronate [42]. Four used eligibility criteria with diagnosis/grade of OA and TCM syndrome differentiations [12, 33, 34, 50]. No studies reported information on withdrawal/dropout and described precisely how confounding factors were measured or fitted as covariates to control.

3.4. Effect Estimates of RCTs. All the RCTs demonstrated a positive effect, favoring TCHPs for OA, except one study protocol [10]. Pain relief was the most frequently reported positive benefit of TCHPs [21, 24, 31, 35, 36, 38, 40, 41, 53–56]. The onset time of reducing pain was from 4.02 hours to 15.40 hours [56, 57], and the effect could be maintained from 2.30 days to 6.77 days [53]. The reported outcome measures included local pain relief, dysfunction relief, and overall effectiveness rate. According to the analysis plan and established outcome measures, firstly, TCHPs were compared with diclofenac ointment or placebo. Effect estimates of TCHPs compared with diclofenac ointment or placebo for OA were shown in Table 3.

For the global effectiveness rate, as most studies have used diclofenac ointment as the control group, the meta-analysis has been applied. Concerning specific outcomes of local pain or dysfunction relief, there was high heterogeneity in the aspects of control group and methodology design, so data was only synthesized using MD or RR with 95% CI rather than the meta-approach.

3.4.1. Local Pain Relief. Four trials with 5 comparisons including 342 participants reported the favorable effect of TCHPs individually versus diclofenac ointment or placebo [4, 8, 21, 23]. Among them, local pain was reduced by Lequesne's

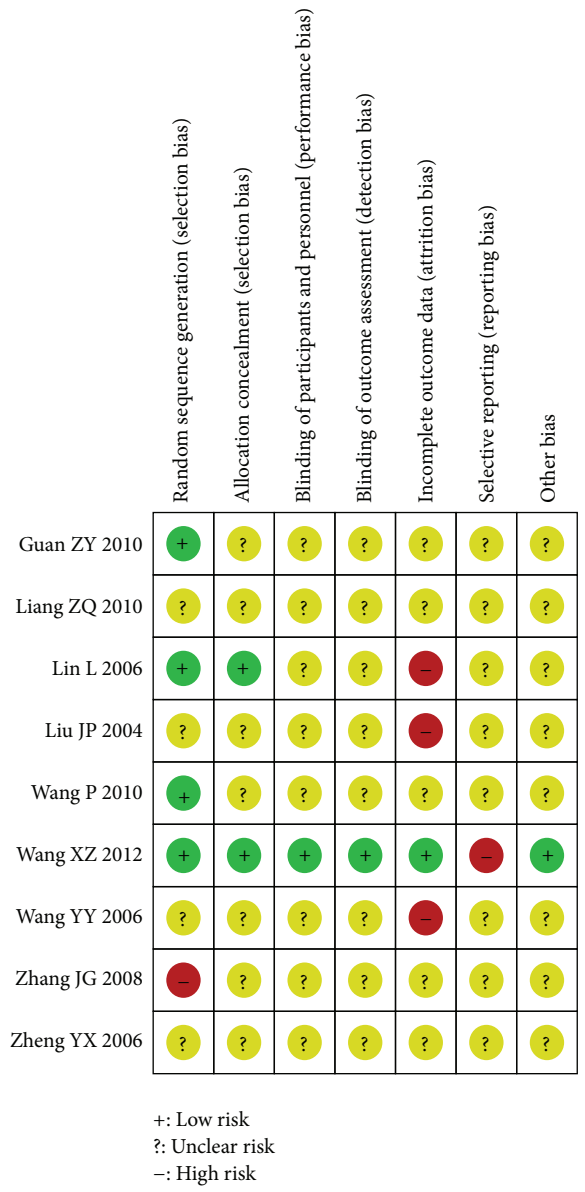

Figure 2: Risk of bias summary of TCHPs versus diclofenac ointment or placebo.

Index, clinical research guidelines of traditional Chinese patent drug by the 21st day [RR 0.50, 95% CI 0.10 to 2.56; $n = 91$] [23], and the Hospital for Special Surgery (HSS) by the 14th day [MD 0.00, 95% CI −1.09 to 1.09; $n = 60$] [21]. One study demonstrated a similar effect by the Western Ontario and McMaster Universities Arthritis Index (WOMAC), compared with diclofenac by the 42nd day [MD −1.14, 95% CI −3.56 to 1.28; $n = 60$] [28]; however, 1 three-arm study showed no significant improvement in the aspect of pain compared with placebo in the visit of the 6th day [MD −1.44, 95% CI −1.69 to −1.19; MD 1.08, 95% CI 0.83 to 1.33; 1 trial; $n = 150$] [4].

3.4.2. Local Dysfunction Relief. Three studies with 7 comparisons involving 270 participants have identified TCHPs compared with diclofenac ointment [8, 21] or placebo [4] in the aspect of improving dysfunction of knee OA. The "Huo Xue Hua Yu" patch was documented as giving an improved effect on ROM and flexion deformity over a 14-day treatment as compared to diclofenac ointment [MD 0.06, 95% CI −0.29 to 0.41; MD 0.06, 95% CI −0.40 to 0.55; 1 trial; $n = 60$] [21]. One demonstrated similar effect compared with diclofenac ointment for the treatment over 42 days [MD −1.30, 95% CI −6.46 to 3.86; $n = 60$] [28], but one showed no significant improvement in the aspect of stiffness and physical function compared with placebo in the visit of the 6th day [4].

3.4.3. Meta-Analysis for Global Effectiveness Rate. Six trials with 6 comparisons including 417 participants demonstrated the effectiveness rate of TCHPs versus diclofenac ointment [20, 22, 23, 25, 26, 58] (Figure 3). As reported, 4 trials showed that TCHPs had better effect on the global effectiveness rate [20, 22, 23, 58]. Two trials demonstrated noninferiority results favoring TCHPs [25, 26]. As I^2 was less than 50%, lower levels of statistical heterogeneity were denoted and the fixed effects model was used for meta-analysis. Collectively, the results showed that TCHPs had significant effects on the global effectiveness rate [RR = 0.50, 95% CI 0.29 to 0.87; 6 trials; $n = 417$]. However, the funnel plot of comparison of TCHPs versus diclofenac ointment for OA demonstrated asymmetry, suggesting the possibility of publication bias (Figure 4).

Compared to other RCTs interventions, TCHPs could reduce local pain by the 10th day [36], local pain, joint swelling, and locomotor disability by the 14th day [31], local pain by the 21st day [55], locomotor disability by the 14th/28th day [27, 41], local pain, stiffness, and dysfunction by the 28th day [35], local pain, locomotor disability, and burning sensation [24], local pain by the 60th day. They could also improve walking distance and ROM by the 60th day [54].

3.5. Effect Estimates of TCHPs for OA about CCTs. Results of favored TCHPs for OA about CCTs were shown in Table 4. Global effectiveness rate from 75% to 97.91% was the main outcome [46, 50]. Kuang studied 48 cases of "Zhong Tong Xiao Babu" patch compared with 46 cases of its old dosage form in the treatment of knee OA; it had a better global effectiveness rate of TCM than the old one [RR 0.43, 95% CI 0.14 to 1.29] at 10 days and could improve pain [MD −0.96, 95% CI −1.65 to −0.27], [MD −0.90, 95% CI −1.56 to −0.24] and function [MD −0.90, 95% CI −1.18 to −0.62], [MD −1.00, 95% CI −1.27 to −0.73] at 5 and 10 days, but no statistically significant difference of the swelling were showed [MD −0.10, 95% CI −0.32 to 0.12; MD −0.01, 95% CI −0.21 to 0.19] [12], respectively. Compared with "She Xiang Zhuang Gu" patch on the basis of visual analog scale, "Gu Ci" bapu patch also showed an improvement of global effectiveness rate in the treatment of knee OA [RR 0.67, 95% CI 0.26 to 1.68; $n = 72$] and [RR 0.57, 95% CI 0.18 to 1.78; $n = 72$] and could improve pain [MD 0.21, 95% CI −0.02 to 0.44], [MD −1.20, 95% CI −1.34 to −1.06] at 5 and 10 days, respectively [50]. One patch showed significant difference compared with sodium hyaluronate 20 mg per week with a course of treatment of 5 weeks [RR 0.48, 95% CI 0.26 to 0.89; $n = 176$] [42]. The intensity of pain of knee about "Gu Ci" patch compared with

Table 3: Effect estimates of TCHPs compared with diclofenac ointment or placebo for OA.

First author (year)	Effect estimate (95% CI)	Comparisons
	Local pain relief	
Liu, 2004 [28][#]	MD −1.14 (−3.56, 1.28)	Self-prescribed herbal patch versus diclofenac ointment
Wang, 2010 [21]	MD 0.00 (−1.09, 1.09)	Huo Xue Hua Yu patch versus diclofenac ointment
Wang, 2012 [4][*]	MD −1.44 (−1.69, −1.19)	Fu Fang Nan Xing Zhi Tong patch versus placebo
Wang, 2012 [4][*]	MD 1.08 (0.83, 1.33)	Shang Shi Zhi Tong patch versus placebo
Zheng, 2006 [23]	RR 0.50 (0.10, 2.56)	Qing Peng patch versus diclofenac ointment
	Function of knee OA	
Liu, 2004 [28][#]	MD −1.30 (−6.46, 3.86)	Self-prescribed herbal patch versus diclofenac ointment (function)
Wang, 2010 [21]	MD 0.06 (−0.29, 0.41)	Huo Xue Hua Yu patch versus diclofenac ointment (ROM)
Wang, 2010 [21]	MD 0.06 (−0.40, 0.52)	Huo Xue Hua Yu patch versus diclofenac ointment (flexion deformity)
Wang, 2012 [4][*]	MD −0.42 (−0.47, −0.37)	Fu Fang Nan Xing Zhi Tong patch versus placebo (stiffness)
Wang, 2012 [4][*]	MD −0.37 (−0.42, −0.32)	Shang Shi Zhi Tong patch versus placebo (stiffness)
Wang, 2012 [4][*]	MD −2.61 (−3.01, −2.21)	Fu Fang Nan Xing Zhi Tong patch versus placebo (physical function)
Wang, 2012 [4][*]	MD −2.97 (−3.38, −2.56)	Shang Shi Zhi Tong patch versus placebo (physical function)
	Global effectiveness rate	
Lin, 2006 [25][#]	RR 0.67 (0.13, 3.53)	Shang Ke Xiao Yan versus diclofenac
Long, 2006 [26][#]	RR 1.87 (0.50, 7.01)	Shang Ke Hei Yao patch versus diclofenac ointment
Guan, 2010 [22]	RR 0.43 (0.12, 1.51)	Zhuang Gu Tong Bi patch versus diclofenac ointment
Zheng, 2006 [23]	RR 0.25 (0.03, 2.13)	Qing Peng patch versus diclofenac ointment
Zhang, 2008 [20]	RR 0.43 (0.14, 1.26)	Zhi Tong Tou Gu patch versus diclofenac ointment
Wang, 2006 [58]	RR 0.22 (0.05, 0.97)	Xiao Tong patch versus diclofenac ointment

Data was synthesized using MD with 95% CI for continuous outcomes or RR with 95% CI for binary outcomes; [*] there was no statistically significant difference between the intervention and control group in score reduction or global effectiveness rate ($P > 0.05$); [#] noninferiority results.

Table 4: Effect estimates of TCHPs for OA about CCTs.

First author (year)	Treatment group (n/N)	Control group (n/N)	Effect estimate (95% CI)	Comparisons
		Global effectiveness rate		
Liu, 2004 [42]	12/90	24/86	RR 0.48 (0.26, 0.89)	Self-prescribed herbal patch versus sodium hyaluronate
Cheng, 2009 [44]	3/42	3/21	RR 0.50 (0.11, 2.27)	San Huang patch versus Gu Tong patch
Dong, 2007 [46]	3/42	5/36	RR 0.51 (0.13, 2.00)	Shu Jin patch versus Zhi Tong Xiao Yan patch
Feng, 2006 [43][*]	5/36 6/36	8/33 12/33	RR 0.48 (0.26, 0.89)[#] RR 0.46 (0.19, 1.08)[§]	Gu Ci patch versus one control patch
Kuang, 2010 [12]	4/48	9/46	RR 0.43 (0.14, 1.29)	Zhong Tong Xiao Babu patch versus Zhong Tong Xiao patch
Liu, 2008 [49]	4/260	4/100	RR 0.38 (0.10, 1.51)	Hei Hu patch versus Qian Shan Huo Xue patch
Wang, 2005 [45]	1/48	4/18	RR 0.09 (0.01, 0.78)	Zhen Tong Xiao Yan patch versus Fu Fang Nan Xing Zhi Tong patch
Wen, 2008 [34]	5/52	11/54	RR 0.47 (0.18, 1.27)	Xi Tong Kang patch versus Tong Luo Qu Tong patch
Xu, 2000 [48]	7/105	5/20	RR 0.27 (0.09, 0.76)	Fu Fang San sheng patch versus Zhuang Gu Guan Jie pill
Zhang, 2010 [50]	6/36 (5d) 4/36 (10d)	9/36 (5d) 7/36 (10d)	RR 0.67 (0.26, 1.68) RR 0.57 (0.18, 1.78)	Gu Ci pacth versus She Xiang Zhuang Gu patch
Zhang, 2010 [33]	6/54	12/54	RR 0.50 (0.20, 1.24)	Wen Tong patch versus Tong Luo Qu Tong patch
Zhao, 2007 [47]	7/62	15/50	RR 0.38 (0.17, 0.85)	Gu Bi Tong patch versus Fu Fang Nan Xing Zhi Tong patch

Data was synthesized using RR with 95% CI; [*] three-arm study, knee pain, and ROM about "Gu Ci" patch versus control patch were obtained; [#] for knee pain; [§] for ROM.

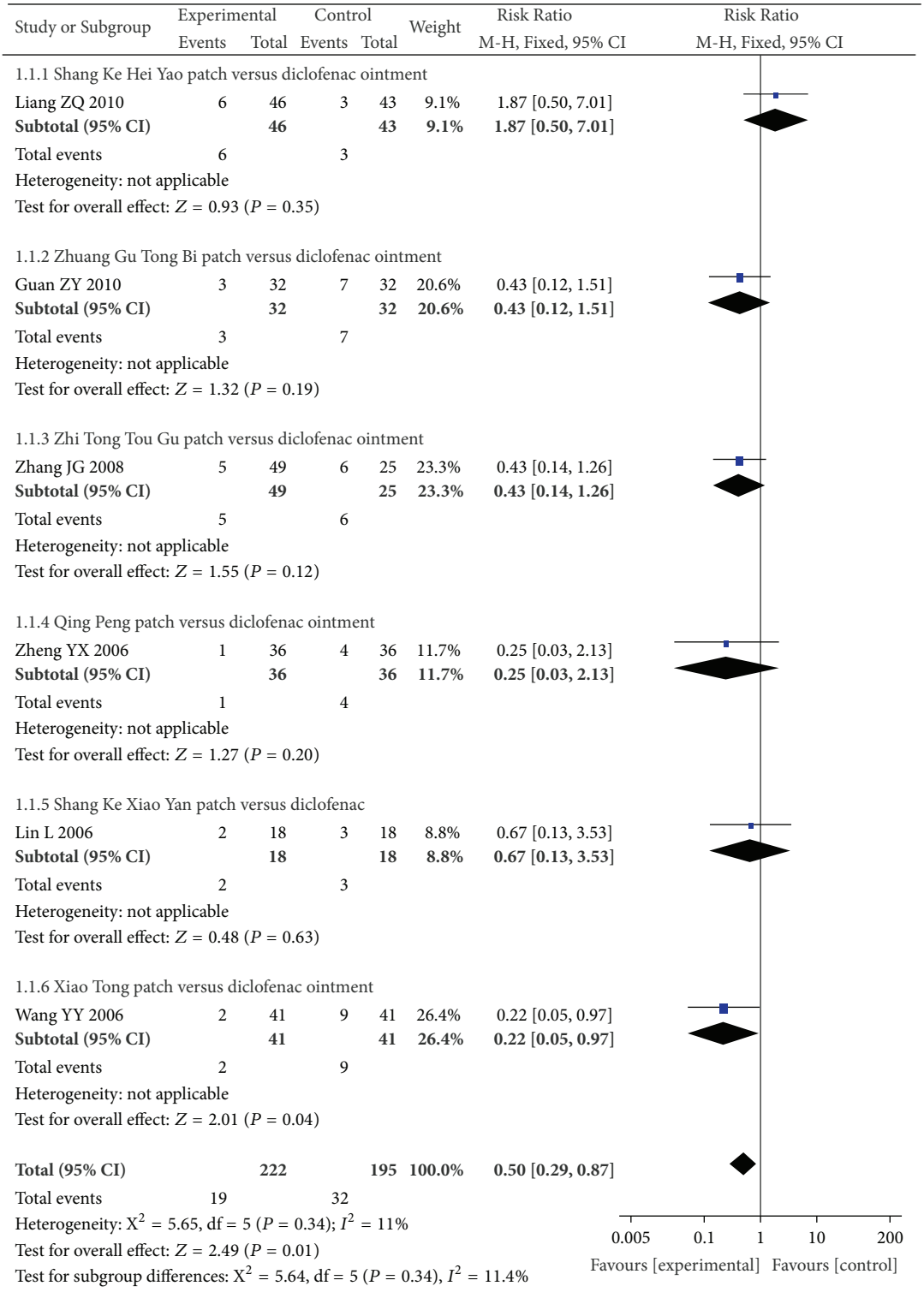

Figure 3: Forest plot of comparison of TCHPs versus diclofenac ointment for OA in global effectiveness rate.

control patch was obtained at a three-arm study [RR 0.48, 95% CI 0.26 to 0.89; $n = 69$] and also showed significant difference on ROM [RR 0.46, 95% CI 0.19 to 1.08; $n = 69$] [43]. "Xi Tong Kang" patch compared with "Tong Luo Qu Tong" patch on global effectiveness rate was [RR 0.47, 95% CI 0.18 to 1.27; $n = 108$] at 28 days [34]; similarly, there were statistically significant differences in 7 trials with the course of treatment from 14 days to 5 weeks [33, 44–49].

3.6. Medication Patterns. Based on TCM clinical pathways and the textbook [17, 59], there are mainly two types of therapeutic principles for the treatment of OA.

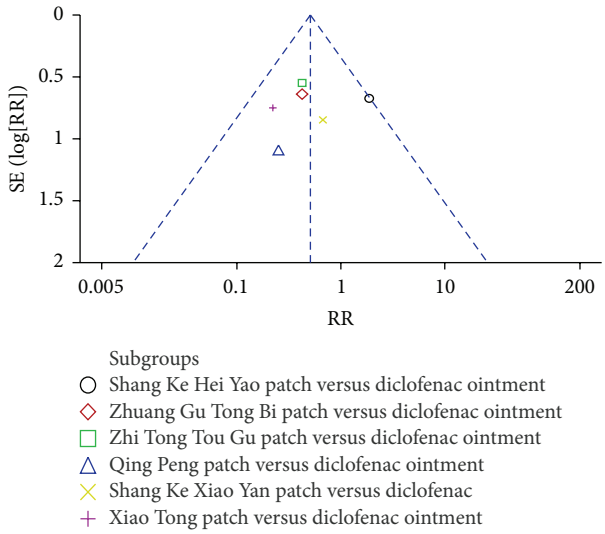

Figure 4: Funnel plot of comparison of TCHPs versus diclofenac ointment for OA in global effectiveness rate.

One was a class of dispelling cold-damp, promoting blood circulation and strengthening analgesic efficacy to treat syndrome of cold-damp stasis blockage (wind-cold-damp *Bi*-arthralgia or tendons-muscular stasis) with local joint pain, swelling or effusion, feeling of heaviness, and functional impairment. All these symptoms are most likely to become worse on cloudy and rainy days, as well as a preference for warmth and pressing, unchangeable skin color, thick tongue, thin or greasy tongue coating, thin or string pulse condition, and so forth. Such targeted TCHPs were the "Gou Pi" patch, the "Fu Fang Nan Xing Zhi Tong" patch, and the "Hei Yao" patch [4, 26, 60].

Another small portion was a class for clearing heat and damp, cooling blood, and relieving pain to treat syndrome of wind-damp-heat *Bi*-arthralgia with pain or tingling, increased skin temperature, effusion or swelling, functional impairment, associated with local burning, thirst or lack of thirst, bitter mouth, dry stool and yellow urine, red tongue, thin yellow or yellow greasy tongue coating, slippery-quick or string pulse condition, and so forth. Targeted TCHPs were the "San Huang" patch, the "Huang Bo Wu Wei" patch, and the "Xi Tong Ning" patch [24, 44, 61].

All TCHPs included in the survey involved 179 herbs with 981 frequencies. On average, 12 kinds of herbs were included (ranging from 2 to 31) [62, 63] and every patch contained 7 g–15 g of herbs [64, 65], but no detailed dosage of each herb was available. Frequency of each herb was added and the top 20 were listed based on the accumulated frequency (Table 5). Among them, the top 7 above 30 percent were "Chuan Wu" (*Radix Aconiti*), "Cao Wu" (*Radix Aconiti Kusnezoffii*),"Mo Yao" (*Myrrha*), "Ru Xiang" (*Olibanum*), "Dang Gui" (*Radix Angelicae*), "Bing Pian" (*Borneolum Syntheticum*), and "Chuan Xiong" (*Rhizoma Ligusticum chuan xiong*).

It is clear that the top 7 herbs are suited for the syndrome of cold-damp stasis blockage: Chuan Wu and Cao Wu are used to dispel the evil of wind, damp, and cold as well as relieve pain; Mo Yao and Ru Xiang promote blood circulation

Table 5: Top 20 most frequently used herbs from 86 kinds of TCHPs.

Herbs	Freq. (*n*)	Percentage (%)
Chuan Wu (*Radix Aconiti*)	37	43.02
Cao Wu (*Radix Aconiti Kusnezoffii*)	34	39.53
Mo Yao (*Myrrha*)	33	38.37
Ru Xiang (*Olibanum*)	32	37.21
Dang Gui (*Radix Angelicae*)	29	33.72
Bing Pian (*Borneolum Syntheticum*)	29	33.72
Chuan Xiong (*Rhizoma Ligusticum chuanxiong*)	28	33.56
Bai Zhi (*Dahuricae*)	25	29.07
Wei Ling Xian (*Radix Clematisdis*)	24	27.91
Tian Nan Xing (*Rhizoma Arisaematis*)	22	25.58
Xi Xin (*Herba Asari*)	21	24.42
Ma Qian Zi (*Semen Strychni*)	21	24.42
Hong Hua (*Flos Carthami*)	20	23.25
Niu Xi (*Radix Achyranthis Bidentatae*)	19	22.09
She Xiang (*Moschus*)	18	20.93
Zhang Nao (*Camphora*)	18	20.93
Du Huo (*Angelicae Pubescentis*)	17	19.77
Da Huang (*Radix et Rhizoma Rhei*)	17	19.77
Rou Gui (*Cortex Cinnamomi*, 15)	15	17.44
Xu Duan (*Radix Dipsaci*)	15	17.44

Values are the number (frequency or percentage).

to achieve analgesic effect; Chuan Xiong accelerates blood circulation and qi and relieves pain; the effects of Dang Gui enrich the blood and promote blood circulation; and the emitting of Bing Pian stimulates drug absorption, so they have the effect of promoting blood circulation and dredging meridians, eliminating swelling and pain with the help of a transdermal delivery system [12, 13, 50].

After categorizing the different herbs according to their actions, the most used ones are those which have the effect of dispelling cold-damp and promoting blood circulation [18] (Table 6). If we investigated the formula, it is clear that they are mainly based on "Xiao Huo Luo Dan" (minor collateral-freeing pill) and "Du Huo Ji Sheng Tang" (*Angelicae Pubescentis* and *Loranthi* decoction).

3.7. Adverse Events. For AEs of patches in 80 literature sources, 38.75% studies (31 of 80) did not mention whether they had monitored AEs or not, 32.50% studies described AEs, whereas the remaining 28.25% reported no incidence of AEs. Among all the reports, detailed information of AEs was identified (Tables 1 and 7). Apart from a special therapy of blistering [41], the incidence of AEs ranged from 0.66% to 12.24% [20, 36]. When we compared the incidence of withdrawal and AEs of TCHPs with diclofenac ointment or placebo, it was found that the TCHPs group was more than the placebo [7.56% (9/119) versus 0.00% (0/30)] [4] and less than diclofenac ointment [2.82% (2/71) versus 8.99% (8/89)] [25, 28, 58].

Table 6: Herbs and actions of TCHPs.

Categories of effectiveness
Expelling wind-cold and eliminating dampness medicinal (accumulated no.: 37; accumulated freq.: 286)
Chuan Wu (*Radix Aconiti*, 37), Cao Wu (*Radix Aconiti Kusnezoffii*, 34), Bai Zhi (*Radix Angelicae Dahuricae*, 25), Wei Ling Xian (*Radix Clematidis*, 24), Xi Xin (*Herba Asari*, 21), Du Huo (*Angelicae Pubescentis*, 17), Ma Huang (*Herba Ephedra*, 15), Mu Gua (*Fructus Chaenomelis*, 14), Tou Gu Cao (*Herba Speranskiae Tuberculatae*, 14), Gui Zhi (*Ramulus Cinnamomie, Cassia Twig*, 12), Qiang Huo (*Rhizoma seu Radix Notopterygii*, 12), Fang Feng (*Radix Saposhnikoviae*, 9), Shen Jin Cao (*Herba Lycopodir*, 5), Qing Feng Teng (*Caulis Sinomenii seu Diploclisiae*, 4), Sang Ji Sheng (*Loranthi*, 3), Song Jie (*Lignum Pini Nodi*, 3), Hai Feng Teng (*Caulis Piperis Futokadsuae*, 3), Ge Gen (*Radix Puerariae*, 3), Wu Shao She (*Zaocys dhumnades*, 3), Xue Shang Yi Zhi Hao (*Radix Aconiti brachypodi*, 3), Xu Chang Qing (*Radix Cynaachi Paniculati*, 3), Du Yi Wei (*Radix Lamiophlomidis rotatae*, 3), Man Jing Zi (*Fructus viticis*, 2), Mu Bie Zi (*Semen Momordicae*, 2), Hai Tong Pi (*Cortex Erythrinae*, 2), Xi Qian Cao (*Herba Siegesbeckiae*, 2), others (11).
Blood-activating and stasis-resolving medicinal (accumulated no.: 27; accumulated freq.: 268)
Mo Yao (*Myrrha*, 33), Ru Xiang (*Olibanum*, 32), Chuan Xiong (*Rhizoma Ligusticum chuan xiong*, 28), Ma Qian Zi (*Semen Strychni*, 21), Hong Hua (*Flos Carthami*, 20), Niu Xi (*Radix Achyranthis Bidentatae*, 19), She Xiang (*Moschus*, 18), Xue Jie (*Sanguis Draconis*, 14), Tu Bie Chong (*Eupolyphaga seu Steleophaga*, 11), San Qi (*Radix Notoginseng*, 11), Chuan Shan Jia (*Squama Manitis*, 11), Jiang Huang (*Rhizoma Curcumame Longae*, 10), Tao Ren (*Semen Persicae*, 6), E. Zhu (*Rhizoma Curcumae*, 5), San Ling (*Rhizoma Sparaganii*, 5), Yan Hu Suo (*Rhizoma Corydalis*, 5), Pu Huang (*Pollen Typhae*, 4), Ji Xue Teng (*Caulis Spatholobi*, 3), Wu Ling Zhi (*Faeces Trogopterori*, 2), Su Mu (*Lignum Sappan*, 2), Ban Mao (*Radix Saccharri arundinacei*, 2), and others (6).
Tonic medicinal (accumulated no.: 24; accumulated freq.: 107)
Dang Gui (*Radix Angelicae*, 29), Xu Duan (*Radix Dipsaci*, 15), Gu Sui Bu (*Rhizoma Drynariae*, 11), Wu Jia Pi (*Cortex Acanthopanacis*, 10), Du Zhong (*Cortex Eucommiae*, 7), Bu Gu Zhi (*Fructus Psoraleae*, 5), Huang Qi (*Radix Astragali*, 4), Gou Ji (*Rhizoma Cibotii*, 4), Shu Di Huang (*Radix Rehmanniae Preparata*, 3), Bai Shao (*Radix Paeoniae*, 3), Yin Yang Huo (*Herba Epimedii*, 3), and others (13).
Heat-clearing medicinal (accumulated no.: 22; accumulated freq.: 92)
Da Huang (*Radix et Rhizoma Rhei*, 17), Chi Shao (*Radix Paeoniae Rubra*, 10), Zhi Zi (*Fructus Gardeniae*, 7), Dan Shen (*Radix Salviae Miltiorrhizae*, 7), Qin Jiao (*Radix Gentianae Macrophyllae*, 7), Huang Bo (*Cortex Phellodendri*, 6), Huang Qin (*Radix Scutellariae*, 5), Fang Ji (*Radix Stephaniae Tetrandrae*, 5), Hua Shi (*Talcum*, 4), Ling Qiao (*Fructus Forsythiae*, 4), Di Long (*Pheretima*, 3), Mang Xiao (*Natrii Sulfas*, 3), Shi Gao (*Gypsum Fibrosum*, 2), Tian Hua Feng (*Radix Trichosanthis*, 2), Pu Gong Ying (*Herba Taraxaci*, 2), Chuan Shan Long (*Dioscorea nipponica Makino*, 2), and others (6).
Phlegm-eliminating and damp-draining medicinal (accumulated no.: 19; accumulated freq.: 63)
Tian Nan Xing (*Rhizoma Arisaematis*, 22), Bai Jie Zi (*Semen Sinapis*, 13), Zao Jiao (*Fructus Gleditsiae*, 4), Cang Zhu (*Rhizoma Atractylodis*, 3), Yi Yi Ren (*Semen Coicis*, 3), Jiang Can (*Bombyx Batryticatus*, 3), Huo Xiang (H*erba Pogostemonis*, 2), Hai Zao (*Sargassum, Seaweed*, 2), and others (11).
Interior-waring medicinal (accumulated no.: 7; accumulated freq.: 40)
Rou Gui (*Cortex Cinnamomi*, 15), Ding Xiang (*Flos Caryophylli*, 8), Gan Jiang (*Rhizoma Zingiberis*, 6), Xiao Hui Xiang (*Fructus Foeniculi*, 4), Gao Liang Jiang (*Rhizoma Alpiniae Officinarum*, 3), Hua Jiao (*Pericarpium*, 3), and others (1).
Qi-regulating medicinal (accumulated no.: 5; accumulated freq.: 8)
Xiang Fu (*Rhizoma Cyperi*, 3), Mu Xiang (*Radix Aucklandiae*, 2), and others (3).
Others (accumulated no.: 38; accumulated freq.: 117)
Bing Pian (*Borneolum Syntheticum*, 29), Zhang Nao (*Camphora*, 18), Qian Dan (*Componere Hydrargyrum*, 9), Quan Xie (*Scorpio*, 8), Xiong Huang (*Realgar*, 6), Bo He (*Herba Menthae*, 4), Zi Jin Pi (*Cortex Cercis Chinensis*, 3), Teng Huang (*Garcinia morella Desv*, 3), A. Wei (*Resina Ferulae*, 3), Ji Dou (*Herba Oxytropis chiliophyllae*, 2), Chan Su (*Venenum Bufonis*, 2), Yang Jin Hua (*Flos Daturae*, 2), Ma Ren (*Semen Cannabis*, 2), Sha Jiang (*Rhizoma Kaempferiae*, 2), and others (24).

Values are the number (frequency). Herbal name presented only when the value is above 1.

Ten kinds of AEs were identified in 49 articles (Figure 5). The most common were local itching in 28.57% (14 of 49) articles and rashes or papules (20.41%). The following were blister (8.41%) [66–69], erythema (6.12%) [4, 20, 53], contact dermatitis (6.12%) [4, 64, 70], burning sensation (4.08%) [71, 72], GI discomfort (4.08%) [73, 74], nausea (2.04%) [74], and/or pain (2.04%) [41], respectively. Infection was reported for redness, oozing, and purulent [49]. Withdrawal or drop-out occurred for blister and contact dermatitis [4, 28, 35, 64, 66, 70] and even for unsatisfied efficacy [28, 73].

4. Discussion

This is the first study to systematically investigate the evidence of effectiveness and AEs and analyze medication patterns of

Table 7: Detailed AEs of TCHPs for OA after 3-4-week follow-ups.

First author (year)	Intervention group			Control group		
	Patches	Incidence	AEs	Patches	Incidence	AEs
Cao*, 2002 [84]	Qu Tong	11.49% (10/87)	Skin allergy	Gu Tong	Not stated	Not stated
Du, 1997 [53]	Ji Li Huo Xue	10.00% (6/60)	Erythema after 4-5 days; itching in the location of patch	Dong Fang Huo Xue	Not stated	Not stated
Guo, 2008 [36]	Xiong Zhi Tong Xiao	0.66% (1/152)	Itching	Tong Luo Qu Yu	2% (1/50)	Itching
Hao, 1999 [70]	Feng Shi Shang Tong	6.67% (4/60)	Contact dermatitis and exit, itchy skin	NA	NA	NA
Hao, 1999 [64]	Fu Fang Ling Zhi	6.67% (4/60)	Contact dermatitis and exit, itching after 48 hours	NA	NA	NA
Li, 2009 [66]	Yao Tong Ning	2.08% (1/48)	Terminated with locally severe blister	NA	NA	NA
Li, 2009§ [71]	Ba Wei	No data	Local discomfort, burning sensation, itching, or rash	Shang Shi Zhi Tong	No data	Local discomfort, burning sensation, itching, or rash
Li, 2005 [67]	Mei Pu Zheng Gu	No data	Rash, blister, and itching	NA	NA	NA
Lin, 2006 [25]	Shang Ke Xiao Yan	No data	No significant allergic reaction	Diclofenac sodium tablets	No data	Not stated
Liu, 2011 [72]	Xiao Tong	8.89% (4/45)	Rash, burning sensation, and itching	Gu Tong	6.67% (3/45)	Rash
Liu, 2008 [49]	Hei Hu	No data	Redness, oozing, purulent or itching, and rash	Qian Shan Huo Xue	Few people	Local itching
Ren, 1998 [68]	Gu Ci Ting	No data	Skin redness and blister	NA	NA	NA
Su, 2010 [73]	Jie Gu	6.41% (5/78)	Gastrointestinal discomfort, unsatisfied	Glucosamine sulfate	5.71% (4/70)	Gastrointestinal discomfort, unsatisfied
Tao, 2005 [69]	Xiao Zhong Zhi Tong	No data	Skin redness, itching, and blister	NA	NA	NA
Wang, 2002 [85]	Fu Fang Yan Tong Ning	1.00% (2/200)	Rash and itching	Gou Pi	4.00% (4/100)	Rash and itching
Wang, 2012 [4]	Fu Fang Nan Xing and Shang Shi Jie Tong	7.50% (9/120)	Rash, itching, and erythema; contact dermatitis	Placebo	0.00% (0/30)	None
Wang, 2008 [57]	Feng Shi Gu Tong	2.00% (2/100)	Rash	Gou Pi	4.44% (4/90)	Allergic reactions
Xu, 2000 [48]	Fu Fang San Sheng	2.64% (2/76)	Itchy skin after 48 hours	Zhuang Gu Guan Jie pill	0.00% (0/20)	None
Yang, 1999 [30]	Gu Zheng Sheng Zheng	4.00% (2/50)	Rash	Gu Yong Ling liniment	8.00% (2/25)	Mild rash, flushing
Wu, 2005 [41]	Blistering therapy	50.00% (15/30)	Pain and itching rash	He Luo Zhi Tong	6.67% (2/30)	Allergic reactions
Zeng, 2010 [74]	Tong Yu	8.00% (2/25)	Mild stomach discomfort and mild nausea in the beginning	Xiao Tong	Not stated	Not stated
Zhang, 2008 [20]	Zhi Tong Tou Gu	12.24% (6/49)	Skin rash, erythema, and so forth.	Diclofenac ointment	24.00% (6/25)	Skin rash, erythema, and so forth.

Table 7: Continued.

First author (year)	Intervention group			Control group		
	Patches	Incidence	AEs	Patches	Incidence	AEs
Zhang, 2005 [35]	She Xiang Tong Bi Ba Bu	5.22% (6/115)	Rash and itching	Tong Luo Qu Gu	7.96% (9/113)	Itching, flushing, swelling, and so forth.
Pan, 2008 [32]	Gu Tong Ning	5.65% (19/336)	Redness and itching	Gu Tong	8.93% (10/112)	Redness and itching
Zhang, 2011 [86]	Qu Yu Zhi Tong	No data	Few AEs	Sodium hyaluronate	Not stated	Not stated
Zhou, 2003 [87]	Wei Ling Xian	Few patients	Blistering	NA	NA	NA

Values are based on identified data. *No specific data reported for each AEs. $Lower AEs in intervention group. #A special therapy mainly for blistering. NA: not applicable.

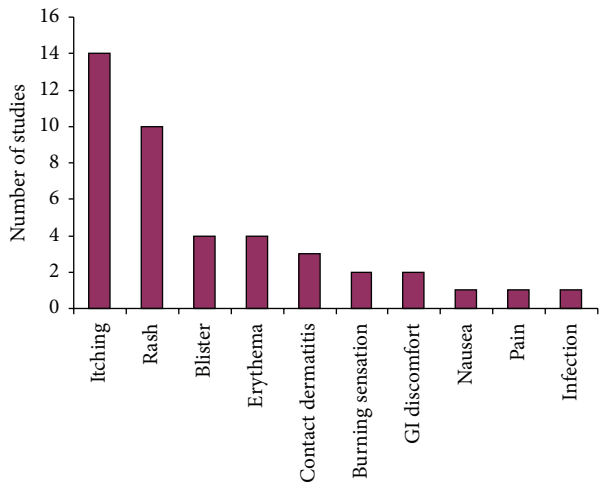

Figure 5: Number of studies recording different AEs for TCHPs in the treatment of OA.

TCHPs for OA. As there is no current data to support a particular group of patches possessing overwhelming efficacy in the treatment of OA, and since there was no meta-analysis available, we therefore comprehensively sourced all the evidence from both clinical studies and China Pharmacopoeia (one).

The review showed that TCHPs, which were mostly of low quality, could obviously improve global effectiveness rate, reduce local pain, and/or raise function comparing with diclofenac ointment or placebo. The result of meta-analysis showed a statistically significant improvement to global effectiveness rate of OA participants [RR = 0.50, 95% CI 0.29 to 0.87; 6 trials; $n = 417$]. Formulae of TCHPs were mainly based on Xiao Huo Luo Dan and Du Huo Ji Sheng Tang. The incidence of AEs was less than diclofenac ointment group. Ten AEs mainly concerning itching and/or rashes of local skin were identified.

The efficacy of Chinese herbal medicine for OA was found to be better than or similar to conventional therapies [8, 75]. Consistent with our study, a previous review which detected the external use of Chinese herbal medicine has also documented a good efficacy and safety for OA. Apart from TCHPs, it has included other intervention methods and the control group was also of diversity (NSAIDs, Cox-2 inhibitors, sodium hyaluronate intra-articular injection, and pain spot blocking), so results were combined and the incidence of AEs was therefore smaller than that of our result (1.87% versus 2.82%) [8].

Although the review demonstrates that TCHPs could ease OA symptoms, it may be affected by low methodological quality of included RCTs and potential publication bias indicated by asymmetry funnel plot. It is known that low methodological studies indicated greater differences between test and control group than those well conducted [76]. Therefore, further trials with more rigorous design and unpublished studies are needed in this area.

This study has documented those herbs with the effect of dispelling cold-damp, promoting blood circulation, and relieving pain, such as Chuan Wu, Cao Wu, Mo Yao, Ru Xiang, and Dang Gui which were the major components of TCHPs. Furthermore, results of analyzing both the herbs' frequencies and their effects were consistent. Formulae of TCHPs were mainly based on Xiao Huo Luo Dan and Du Huo Ji Sheng Tang. Xiao Huo Luo Dan was documented in formulae by the Taiping Pharmaceutical Bureau for Benevolence to relive pain, so that the wind-cold-damp evil might be relieved [77]. Pharmacological studies have confirmed its anti-inflammatory, analgesic, and immunosuppressive role [78], so it has a good therapeutic effect on the early and mid-OA [79]. Du Huo Ji Sheng Tang is derived from "Bei Ji Qian Jin Yao Fang." Topical use is mainly for removing wind-damp evil to warm and dredge meridians and cure *Bi*-arthralgia [4, 80]. Whether via oral administration or topical use, its efficacy in the treatment of knee OA has been confirmed [81–83].

It is commonly believed that the AEs of TCHPs should be less and TCHPs is convenient for topical use, but there are still 10 kinds of self-reported AEs identified by this study. On the one hand, a large part of these studies have no description of AEs, indicating insufficient information about monitoring and reporting of AEs, and, on the other hand, over half of these studies (53.06%; 26 of 49) have demonstrated AEs. Given that OA is a chronic progressive disease, results from current relatively short term studies (mostly 3-4 weeks) seem to have underestimated the incidence of AEs. Nevertheless, for the incidence of AEs, the TCHPs group was less than diclofenac ointment (2.82% versus 8.99%) [25, 28, 58]. AEs

reported were mild to modest, as the majority of allergic reactions were local skin itching and/or rashes.

TCHPs are warm and dry in nature and drastic in potency, so it is appropriate for patients with a strong constitution and should be applied with caution for those with heat syndrome due to damp obstruction, Yin deficiency and/or for pregnant women. As Chuan Wu, Cao Wu, or Ma Qian Zi has potential kidney or liver toxicity, it should be used with caution when administered in high-dose or for long-term use [77]. If blister, itching, and/or rash occurs in the local skin, it should be stopped immediately.

In the included articles, all the prescriptions of TCHPs were based on the medication patterns, and only 18 studies provided information on patients' syndrome differentiation as the basis of effectiveness for using TCHPs [4, 12, 21, 22, 25–27, 29, 32–41]. It is recommended to use TCHPs based on both OA symptoms and TCM syndrome if applicable. Otherwise, the effectiveness might be decreased and the incidence of AEs might be increased theoretically, although there are currently no reports concerning this issue.

This study has had several limitations. Firstly, diagnosis/grade of OA was not clear in most of the trials for insufficient reporting of either ACR or COA criteria and Kellgren-Lawrence scale, so findings would limit the generalization to OA population. It is noteworthy that OA is a chronic longer-term condition; it therefore remains presenting symptoms and signs of disease-stage with the majority of OA participants. Secondly, no data was available to support which Chinese herbs were superior to others. Hence, the top 7 most common herbs and components of formulae were listed so as to provide a broader reference to future study. Thirdly, the funnel plot showed asymmetry, which indicated the possibility of publication bias existed in this review. Although this might also be induced by language bias as we only retrieved literatures in Chinese and English, factors from relatively small sample sizes of these studies could not be excluded. Finally, the included RCTs were low in quality and a meta-analysis could be only applied in the aspect of global effectiveness rate rather than in specific outcome measures such as pain and dysfunction. However these have been synthesized through standard RR or MD. Moreover, the initial evidence for the effectiveness and clue of AEs as well as specific components of formulae may provide beneficial references to practitioners when using TCHPs.

5. Conclusions

In summary, this review suggests that TCHPs have certain evidence for OA in improving global effectiveness rate. Components of formulae were mostly based on Xiao Huo Luo Dan and Du Huo Ji Sheng Tang. The main AEs were itching and/or rashes of local skin, but further studies concerning AEs, effectiveness, and medication patterns are warranted to support their use.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Yuelong Cao conceived study concept and design and edited the paper. Xuezong Wang performed acquisition data and drafted of the paper. Songpu Wei carried out the data collection. Ting Liu and Jian Pang participated in hand search. Ningyang Gao and Tieli Duan provided methodological perspectives. Daofang Ding, Hongsheng Zhan, and Yuxin Zheng participated in the interpretation of data. All authors developed the search strategy, read the paper, and gave final approval of the version to be submitted.

Acknowledgments

The present study was supported by the National Natural Science Foundation of China (no: 81072830, no: 81373665 and no: 81173277), the Innovation Program of Shanghai Municipal Education Commission (no: 11YZ64 and no: 12YZ064), and Shanghai Three Years Initiative of TCM (ZYSNXD-CC-YJXYY).

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