Efficacy and side effect of curcumin for the treatment of osteoarthritis: A meta-analysis of randomized controlled trials

Jian Wu[#], Ming Lv and Yixin Zhou*
Department of Orthopaedic Surgery, Beijing Jishuitan Hospital, Fourth Clinical College of Peking University, Beijing, China

Abstract: This meta-analysis aimed to confirm the efficacy and safety (side effect) of curcumin for osteoarthritis (OA). Two researchers independently searched the database of Pub Med, EMBASE and Cochrane Library updated to November 2015 to find randomized controlled trials that reported the effect of curcumin on OA. The outcomes of this meta-analysis were Visual analogue scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index scale (WOMAC) and side effect. Furthermore, the quality assessment was performed with Cochrane Collaboration's tool. In addition, standardized mean difference (SMD) and 95% confidence interval (CI) were used for the analysis of continuous data, and the risk ratio (RR) and 95% CI were used to analyze dichotomous data. Sensitivity analysis was performed by using Stata 12.0. A total of 5 studies with 599 patients were included in this study. The results showed that curcumin could significantly improve the WOMAC score (SMD=-0.96; 95% CI:-1.81, -0.10; *P*=0.03) and VAS score of OA patients (SMD=-1.65; 95% CI:-2.11, -1.19). Furthermore, the side effect rate of curcumin treatment was 0.81times higher than that of ibuprofen treatment. Curcumin can treat OA patients effectively, improving WOMAC score and VAS score, and the side effect of curcumin was not higher than that of ibuprofen.

Keywords: Meta-analysis, osteoarthritis, curcumin, treatment efficacy, treatment safety.

INTRODUCTION

Osteoarthritis (OA), also known as degenerative joint disease, degenerative arthritis or osteoarthrosis, is the most common form of arthritis and a major cause of disability and pain in older adults (Control and Prevention 2010, Arden *et al.,* 2014). The breakdown of articular cartilage is a major characteristic of this disease (Kapoor *et al.,* 2011). Furthermore, the most common risk factors for OA are sex, age, prior joint injury, obesity genetic predisposition and mechanical factors (Felson *et al.,* 2000, Blagojevic *et al.,* 2010). In addition, one in every seven adults suffers from OA in their lifetime, and arthritis will affect up to one fourth US adult population by the year 2030 (Hootman and Helmick 2006, Losina *et al.,* 2013). However, no disease-modifying treatment for OA has been found, and thus further studies in finding potential drugs for this disease with minimal side effect are needed (Stannus *et al.,* 2010, Argoff 2011). Curcumin, a polyphenol, possess anti-inflammatory, antioxidant, wound-healing, hypoglycemic and antimicrobial activities (Aggarwal and Sung 2009). Kuptniratsaikul *et al*. indicated that the treatment effect of *curcuma domestica* extracts were non-inferior to ibuprofen for knee OA (Kuptniratsaikul *et al.,* 2014). Furthermore, *curcuma domestica* extracts have similar effects with ibuprofen in safety and efficacy for the treatment of knee OA (Kuptniratsaikul *et al.,* 2009). Curcumin can augment the pro-apoptotic and growth-inhibitory effects of celecoxib in synovial adherent cells of OA (Lev-Ari *et al.* 2006). In addition, curcuminoid-loaded liposomes may have potential effects on slowing the development of OA (Yeh *et al.,* 2015). Theracurmin, a highly bioavailable form of curcumin, may be a possible way to treat knee OA in the future (Nakagawa *et al.,* 2014). Moreover, the vitro researches indicated that curcumin was beneficial for cartilage in OA and curcumin might be a good complement to classical therapy for the treatment of OA patients (Henrotin *et al.,* 2014). Henrotin *et al*. indicated that curcumin was not yet a recommended intervention for the treatment of OA, but it should be considered as an effective way because of its safety and efficacy (Henrotin *et al.,* 2013). Although some former researches have been carried out, the efficacy and safety of curcumin for the treatment of OA are not completely determined. Therefore, it is needed to confirm the efficacy and safety of curcumin for the treatment of OA. In our present study, we searched the database of Pub Med, EMBASE and Cochrane Library updated to November 2015 and used the meta-analysis to find randomized controlled trials that reported the effect of curcumin on OA. We aimed to confirm the efficacy and safety of curcumin for OA in this meta-analysis.

MATERIALS AND METHODS

Search strategy

We searched the database of Pub Med, EMBASE and Cochrane Library updated to November 2015 to find randomized controlled trials that reported the effect of curcumin on OA. The key words used in the retrieval were "curcumin", "curcuminoid", "*curcuma domestica* extracts", "turmeric" and "osteoarthritis". The search strategy was (curcumin OR curcuminoid OR (*curcuma*

**Corresponding author:* e-mail: yixinzhouu@163.com

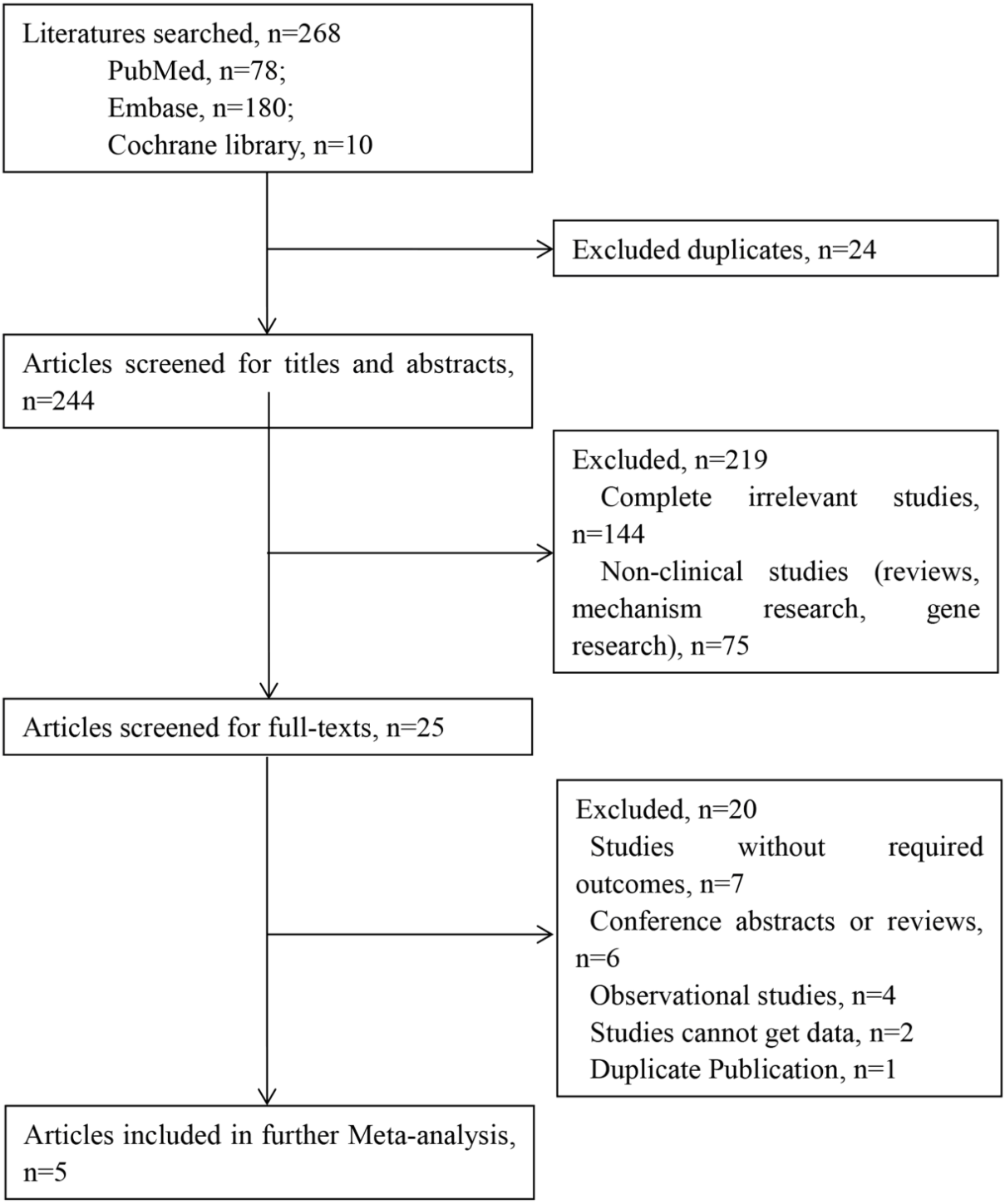

Fig. 1: The flow chart of study selection. It shows the numbers of identified, screened, included, and excluded studies for the systematic review and meta-analysis.

domestica extracts) OR turmeric) AND (osteoarthritis OR OA) AND (random* OR (randomized controlled trail)). In addition to the databases search, literature review was also performed to find additional studies.

Study selection

Titles, abstracts and full text were screened by two researchers independently. Disparities were resolved by discussion with the third researcher.

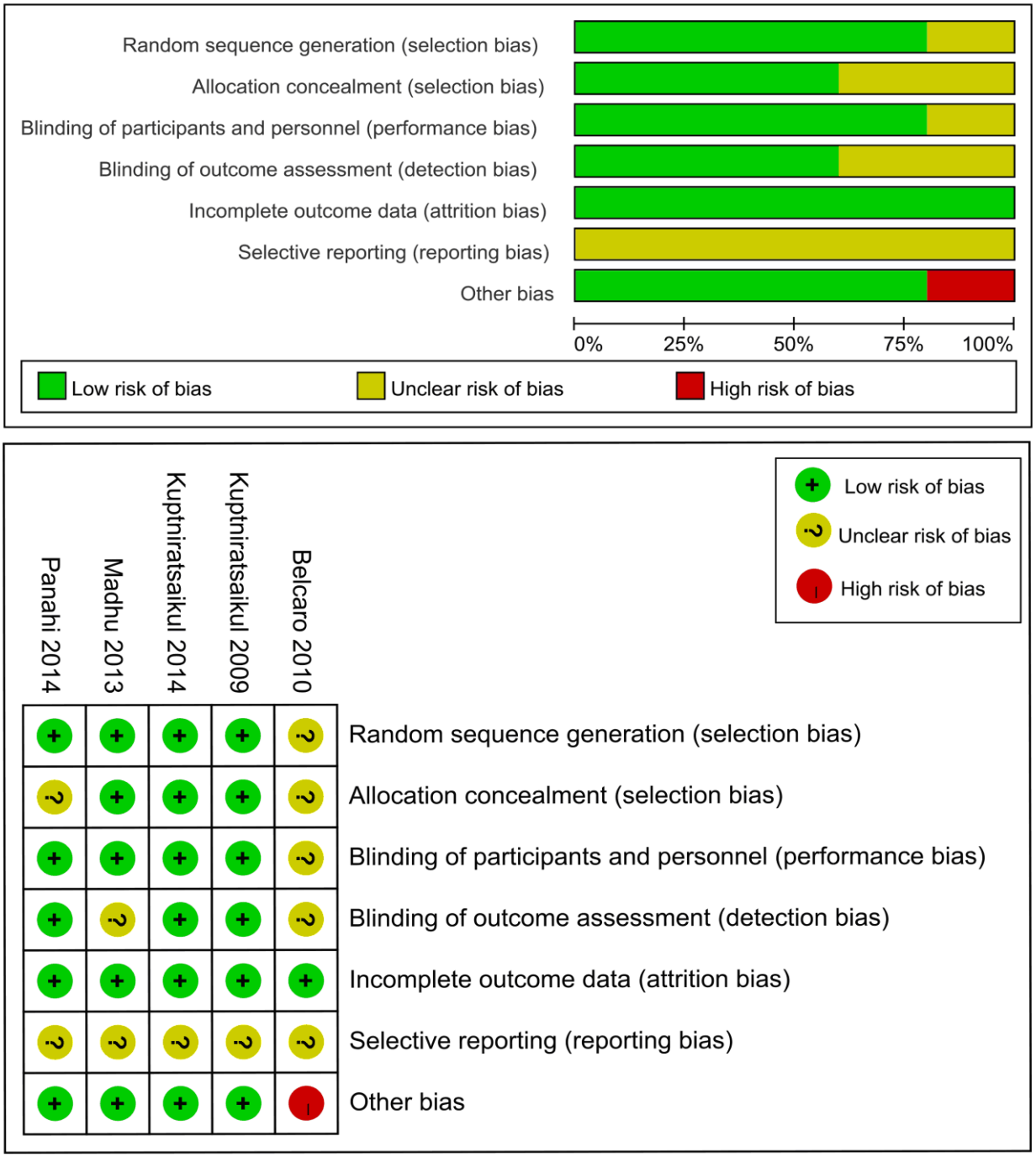

Fig. 2: The quality assessment of the included studies.

Studies were included in this meta-analysis if they met the following criteria: (1) the studies were clinical randomized controlled trials that reported treatment of OA with curcumin or *curcuma domestica* extracts; (2) participants were patients diagnosed with OA; (3) the treatment group was treated with curcumin or *curcuma domestica* extracts or its products (whole, power, extract and standardized mixture); (4) the control group was placebo or ibuprofen; (5) At least one of the following outcomes was reported: visual analogue scale (VAS), Western Ontario and McMaster Universities Osteo arthritis Index scale (WOMAC) and side effect.

Studies were excluded if one of the following existed: reviews, letters, notes of meeting and prospectus; repeatedly published studies; studies without requisite outcomes.

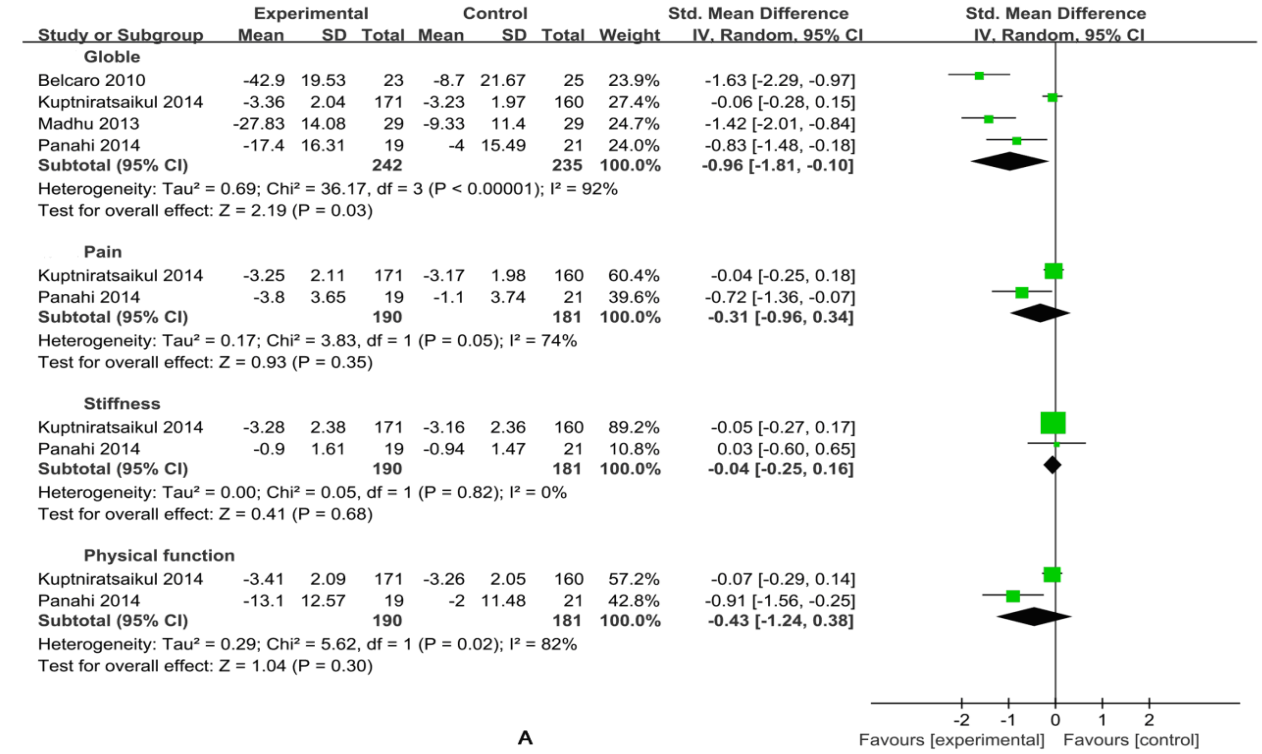

Fig. 3A: The meta-analysis for Western Ontario and McMaster Universities Osteoarthritis Index scale (WOMAC) score of curcumin; **B:** The meta-analysis for WOMAC score of curcumin group *vs* control group.

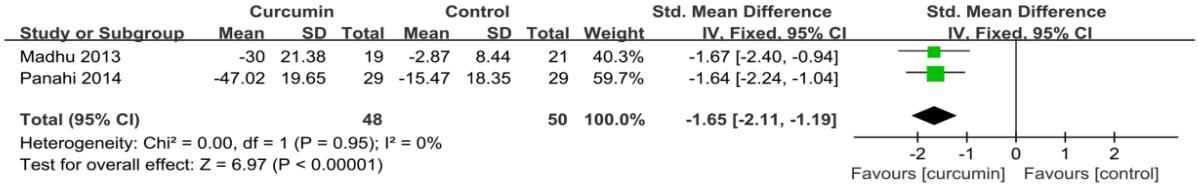

Fig. 4: The meta-analysis of visual analogue scale (VAS) score.

Data extraction and quality assessment

Data extraction and quality assessment were also performed by two reviewers independently. Discrepancies were resolved by discussion with a third reviewer. The following data were collected for each study: first author name, year of publication, study type, country/area,

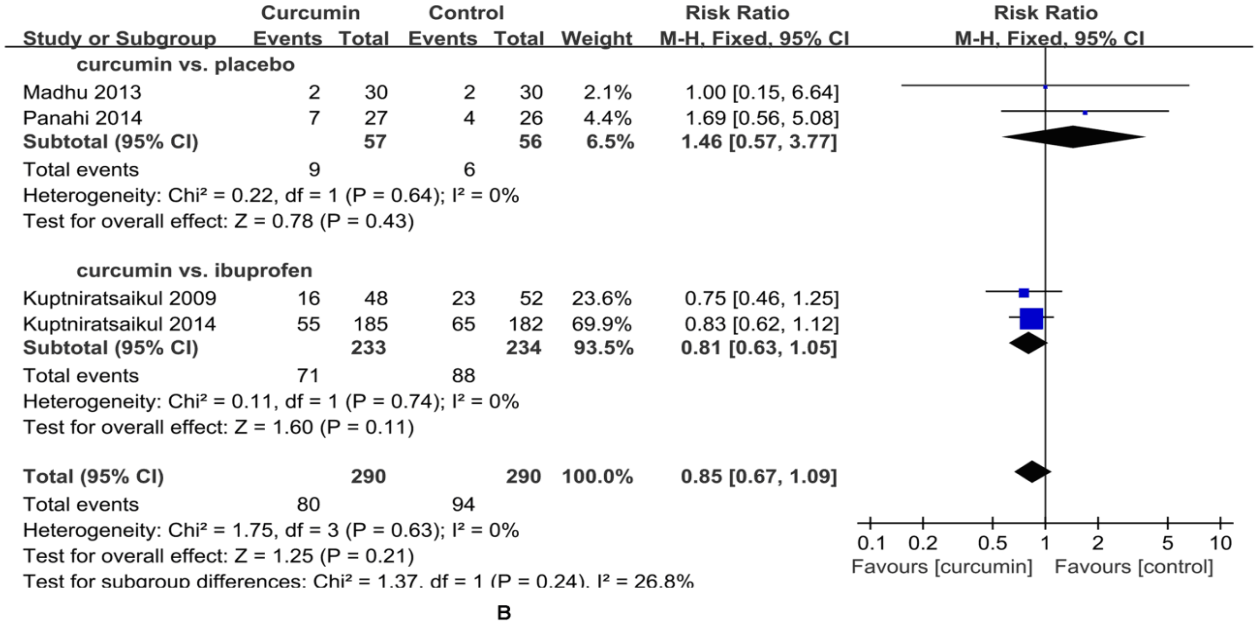

Fig. 5A: The meta-analysis for the side effect of curcumin; **B,** The meta-analysis for the side effect of curcumin group *vs* control group.

characteristics of included cases (number of cases and age), specific treatment strategy of treatment group and control group, time of therapy and treatment outcome.

The quality assessment of all the included studies was performed with Cochrane Collaboration's tool for assessing risk of bias (Higgins and Green 2008).

STATISTICAL ANALYSIS

The outcomes of this meta-analysis were VAS, WOMAC and side effect. The WOMAC scores were composed of 3 subscales: pain, stiffness and physical function. Furthermore, the higher WOMAC scores represented more pain, more stiffness and worse knee functions.

Standardized mean difference (SMD) and 95% confidence interval (CI) were used for the analysis of continuous data (VAS and WOMAC), and the risk ratio (RR) and 95% CI were used to analyze dichotomous data (side effect rate).The heterogeneity was analyzed with Cochran Q test and I^2 test (Higgins *et al.* 2003). If P <0.05 or I^2>50%, indicating that the included studies were heterogeneity, the random effects model was chosen. If not, the fixed effect model was selected. At the same time, the analysis of subgroups grouped by different drugs (ibuprofen, placebo) was performed. All statistical analyses were performed by using Stata 12.0 (StataCorp 2011) and Review Manger 5.3 (Collaboration 2014) software.

Sensitivity analysis

Sensitivity analysis was performed by using Stata 12.0. One study was trimmed at a time to compare the difference of pooled effects before and after the trim. If the pooled results reversed after the trim, then it suggested that the results were unstable.

RESULTS

Study selection

A total of 268 (Pub Med:78; EMBASE:180; Cochrane Library:10) studies were identified after the initial search in databases. Firstly, 24 duplicates were excluded. We then excluded 144 complete irrelevant studies and 75 non-clinical studies (reviews, mechanism research and gene

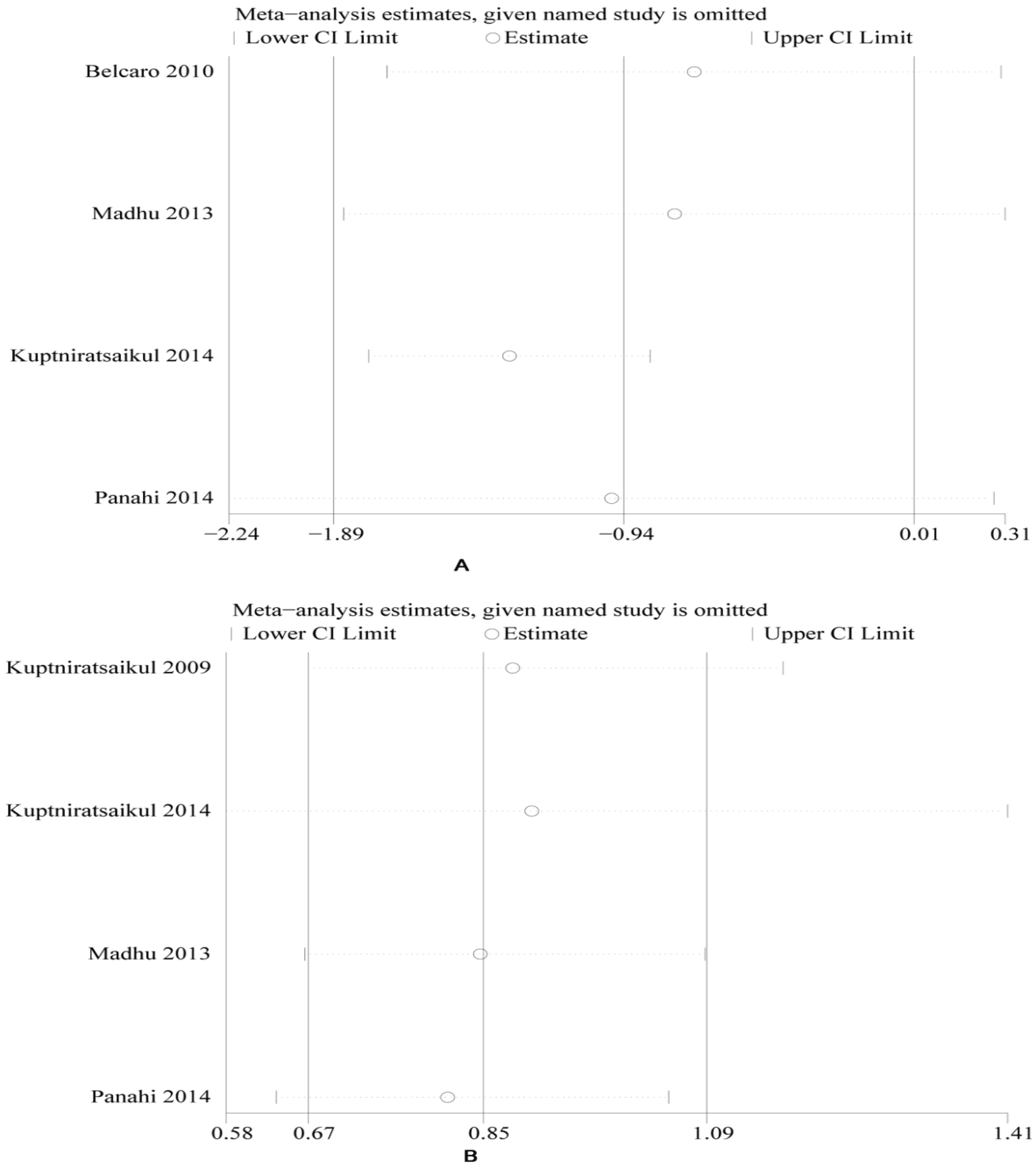

Fig. 6A: Sensitivity analysis of WOMAC; B, Sensitivity analysis of side effect.

research) after screening based on titles and abstracts. Subsequently, 20 studies (7 studies without required outcomes, 6 conference abstracts or reviews, 4 observational studies, 2 studies cannot get data and 1 duplicate publication) were excluded by reviewing full-text. Finally, 5 studies (Kuptniratsaikul *et al.* 2009, Belcaro *et al.* 2010, Madhu *et al.* 2013, Kuptniratsaikul *et al.* 2014, Panahi *et al.* 2014) were included in this meta-analysis. The flow chart of study selection was shown in fig. 1.

Characteristics of the studies and quality assessment

A total of 5 studies with 599 patients (male:116; female:483) were included in this study. All the included patients were OA patients, and 4 of these patients were knee OA patients. The treatment group of included studies was treated with curcumin or *curcuma domestica* extracts or its products, and the control group was treated with placebo or ibuprofen.

The characteristics of the included studies were shown in table 1.

Table 1: Characteristics of the included studies

Author, year	Study type	Country	Disease	Group	Treatment	Treatment time	Dosage	No. of patients (M/F)	Age, y
Belcaro, 2010	CCT	Italy	Symptomatic OA	Treatment	complex of curcumin with soy phosphatidylcholine	3 m	200 mg/day	23 (12/11)	44.4±7.2
				Control	defined by patient's GP and by specialists			25 (13/12)	45.3±8.6
Kuptniratsaikul, 2009	RCT	Thailand	Primary knee OA	Treatment	C. domestica extracts	6 w	500 mg, four times daily	52 (11/41)	61.4±8.7
				Control	ibuprofen		400 mg twice daily	55 (10/45)	60.0±8.4
Kuptniratsaikul, 2014	RCT, multicenter	Thailand	Knee OA	Treatment	C. domestica extracts	4 w	1,500 mg/day	171 (14/157)	60.3±6.8
				Control	ibuprofen		1,200 mg/day	160 (21/139)	60.9±6.9
Madhu, 2013	RCT, single blind	India	Knee OA	Treatment	Curcuma longa Linn. extracts	6 w	500 mg/capsule, 2 times	30 (13/17)	56.63±10.58
				Control	Placebo		400 mg/capsule, 2 times	30 (13/17)	56.77±9.98
Panahi, 2014	RCT, double-blind	Iran	Knee OA	Treatment	Curcuminoids	6 w	1500 mg/day	27 (5/22)	57.32±8.78
				Control	Placebo			26 (4/22)	57.57±9.05

The results of the quality assessment were summarized in fig. 2. One (Belcaro *et al.* 2010) of the 5 included studies was controlled clinical trial and the other 4 studies were randomized controlled trials. The study of Beclaro *et al.* (Belcaro *et al.* 2010) had higher selection bias. Kuptniratsaikul *et al.* (2009 and 2014) performed generation of random sequences, allocation concealment and blinding method strictly, and the risk of bias was relatively small. Overall, the quality of the 5 included studies was relatively high.

Meta-analysis of treatment efficacy

Total 4 studies (Belcaro *et al.*, 2010; Madhu *et al.*, 2013, Kuptniratsaikul *et al.*, 2014; Panahi *et al.*, 2014) reported the change of the overall WOMAC score before and after treatment. Prominent heterogeneity was found between studies with $P<0.01$ and $I^2=92\%$, so the random effects model was applied. The results showed that curcumin could significantly improve the WOMAC score of OA patients (SMD=-0.96; 95% CI:-1.81, -0.10; $P=0.03$) (fig. 3A).

The results of curcumin *vs*. placebo subgroup analysis and curcumin *vs.* ibuprofen subgroup analysis were SMD=-1.30 (95% CI:-1.66, -0.94) and SMD=-0.06 (95% CI:-0.28, 0.15) respectively. It suggested that the treatment efficacy of curcumin was better than that of placebo, and there were significantly statistical differences in the comparison of curcumin and placebo ($P<0.01$). However, there were no significantly statistical differences in the comparison of curcumin and ibuprofen ($P=0.56$) (fig. 3B).

Total 2 studies (Kuptniratsaikul *et al.* 2014, Panahi *et al.* 2014) reported the change of 3 subscales (pain, stiffness and physical function) of WOMAC. The results showed that there were no statistical differences in the comparison of treatment group and control group ($P>0.05$) (fig. 3A).

Total 2 studies (Madhu *et al.* 2013, Panahi *et al.* 2014) reported VAS score indicating severity of the pain for OA. No evidence could prove the prominent heterogeneity among studies ($P=0.95$ and $I^2=0\%$), so the fixed effect model was used. The pooled result was SMD=-1.65 (95% CI:-2.11, -1.19). It suggested that compared with placebo, curcumin could improve the pain of OA patients, and there were significantly statistical differences in the comparison of curcumin and placebo ($P<0.01$) (fig. 4).

Meta-analysis of treatment safety

Total 4 studies (Kuptniratsaikul *et al.*, 2009, Madhu *et al.*, 2013, Kuptniratsaikul *et al.*, 2014; Panahi *et al.*, 2014) reported the treatment safety of curcumin. The heterogeneity between studies was not significant with $P=0.63$ and $I^2=0\%$, hence the fixed effect model was used. The pooled result was RR=0.85 (95% CI:0.67, 1.09) (fig. 5A). Furthermore, the pooled results of curcumin *vs*. placebo subgroup and curcumin *vs.* ibuprofen subgroup were RR=1.46 (95% CI:0.57, 3.77), $P=0.43$ and RR=0.81 (95% CI:0.63, 1.05), $P=0.11$ respectively. It suggested

that the side effect rate of curcumin treatment was 1.46 times higher than that of placebo treatment and 0.81 times higher than that of ibuprofen treatment, but there were no statistical differences in the comparison of curcumin and placebo as well as curcumin and ibuprofen (P>0.05) (fig. 5B).

Sensitivity analysis

Sensitivity analyses of WOMAC and side effect were performed. The pooled results did not reverse after omitting 1 study at a time, and it indicated that the results of this meta-analysis were stable (fig. 6A,B).

DISCUSSION

In this meta-analysis, we analyzed the treatment efficacy and safety of curcumin on OA. The results showed that curcumin could significantly improve the WOMAC score and VAS score of OA patients, and the side effect of curcumin was not higher than that of ibuprofen.

Recently, Shakibaei *et al*. indicated that curcumin had nutritional potential for the treatment of OA by inhibiting interleukin-1β (IL-1β)/ tumor necrosis factors α (TNF-α) catabolic signaling pathway mediated by NF-κB (Shakibaei *et al.* 2007). Schulze-Tanzil *et al*. also indicated that curcumin depressed key catabolic effects of IL-1β signaling that resulted in the pathogenesis of OA (SCHULZE TANZIL *et al.* 2004). In addition, curcumin could restrain the production of inflammatory and catabolic mediators via chondrocytes, and then curcumin could be used to treat OA (Mathy-Hartert *et al.* 2009). Some studies show that curcumin plays anti-inflammatory activity by inhibiting some substances such as phospholipase, leukotrienes, lipoxygenase, cyclooxy genase-2 (COX-2), IL-1, IL-8, and IL-12 (Bengmark 2006, Khanna *et al.* 2007, Saja *et al.* 2007, Oyagbemi *et al.* 2009, Kim *et al.* 2012). Moreover, bio-optimized curcumin can reduce cartilage matrix degradation, which is supported by the findings that curcumin inhibits matrix metallopeptidase (MMP-9) production by chondrocytes (Shakibaei *et al.* 2007, Henrotin *et al.* 2014). Furthermore, one study shows that curcumin domestica extracts are safer than ibuprofen in terms of abdominal pain or distension, and similar to ibuprofen in terms of treatment of OA (Kuptniratsaikul *et al.* 2014). The other one study suggests that the safety of curcumin domestica extracts for the therapy of OA is similar to ibuprofen (Kuptniratsaikul *et al.* 2009). In our present study, curcumin could significantly improve the WOMAC score and VAS score of OA patients and the side effect of curcumin was not higher than that of ibuprofen. Therefore, curcumin can treat OA patients effectively.

There were 2 evidently advantages to this meta-analysis. First, studies related with treatment efficacy and safety of curcumin on OA were included in this meta-analysis, and the overall quality of these studies was relatively high. Second, both the efficacy and safety of curcumin were assessed, which enhanced the comprehensiveness of this study.

Despite above strengths, our present meta-analysis also had some limitations. First, significant heterogeneity was found in this study, and some factors such as different treatment time, WOMAC score and VAS score that affected by subjective factors, and the discrepancy of the severity of OA patients in different studies might be the source of heterogeneity. Second, lesser studies and cases were included in this analysis, and the publication bias was not performed. Therefore, more randomized controlled trials with large sample size were needed to verify the results of this meta-analysis.

CONCLUSION

Curcumin can treat OA patients effectively, improving WOMAC score and VAS score, and the side effect of curcumin was not higher than that of ibuprofen. Because of some limitations of this meta-analysis, some large samples and rigorous researches are needed to support our results.

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