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

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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 0.81 times 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, Argoft 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 “osteoarthrosis”. The search strategy was (curcumin OR curcuminoid OR (curcuma...
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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.

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**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.
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 Osteoarthritis 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. 2:** The quality assessment of the included studies.
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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,
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 Cochrane Q test and $I^2$ test (Higgins et al. 2003). If P <0.05 or $I^2$>50%, indicating that the included studies were heterogeneous, 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
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.

Fig. 6A: Sensitivity analysis of WOMAC; B, Sensitivity analysis of side effect.
The characteristics of the included studies were shown in Table 1.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study type</th>
<th>Country</th>
<th>Disease</th>
<th>Treatment time</th>
<th>Doseage</th>
<th>Treatment</th>
<th>Disease severity</th>
<th>Group</th>
<th>Treatment</th>
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<th>Dosage</th>
<th>Treatment</th>
<th>Disease severity</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belcaro et al., 2010</td>
<td>CCT</td>
<td>Italy</td>
<td>Symptom not OA</td>
<td>3 m</td>
<td>200 mg/day</td>
<td>500 mg four times daily</td>
<td>Control</td>
<td>Treatment</td>
<td>Pain, Stiffness</td>
<td>Control</td>
<td>Treatment</td>
<td>Physical Function</td>
<td>Control</td>
<td></td>
<td></td>
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<tr>
<td>Kuptniratsaikul et al., 2009, 2014</td>
<td>RCT</td>
<td>Thailand</td>
<td>Knee OA</td>
<td>6 w</td>
<td>1,500 mg/day</td>
<td>30 mg/day</td>
<td>Control</td>
<td>Treatment</td>
<td>Knee OA</td>
<td>Control</td>
<td>Treatment</td>
<td>Knee OA</td>
<td>Control</td>
<td></td>
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<tr>
<td>Kuptniratsaikul et al., 2014</td>
<td>RCT, single blind</td>
<td>Iran</td>
<td>Knee OA</td>
<td>6 w</td>
<td>500 mg twice daily</td>
<td>30 mg/day</td>
<td>Control</td>
<td>Treatment</td>
<td>Knee OA</td>
<td>Control</td>
<td>Treatment</td>
<td>Knee OA</td>
<td>Control</td>
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<tr>
<td>Madhu et al., 2013</td>
<td>RCT</td>
<td>India</td>
<td>Knee OA</td>
<td>6 w</td>
<td>400 mg, four times daily</td>
<td>30 mg/day</td>
<td>Control</td>
<td>Treatment</td>
<td>Knee OA</td>
<td>Control</td>
<td>Treatment</td>
<td>Knee OA</td>
<td>Control</td>
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<tr>
<td>Panahi et al., 2014</td>
<td>RCT</td>
<td>Iran</td>
<td>Knee OA</td>
<td>6 w</td>
<td>150 mg/day</td>
<td>30 mg/day</td>
<td>Control</td>
<td>Treatment</td>
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<td>Control</td>
<td>Treatment</td>
<td>Knee OA</td>
<td>Control</td>
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</tbody>
</table>

The results of the quality assessment were summarized in Table 1. 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 Belcaro 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, cyclooxygenase-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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