Review Article

Curcuma longa for Arthritis pain: Systematic review of randomized controlled trial study

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Abstract

Background: *Curcuma longa* is commonly known as turmeric constituents include the three curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Curcumin has anti-inflammatory and analgetic action. It is a promising medication to alleviate pain among arthritic patients. **Objective**: This systematic review aimed to identify the benefit of *Curcuma longa* in arthritis pain. **Materials and Methods**: Systematic research was conducted by using PubMed and Cochrane with following terms to search: "*Curcuma longa*", "curcumin", and "turmeric". The quality of randomized controlled trial (RCT) study is assessed by using the Jadad score and the selected studies were reviewed by using PRISMA checklist as the guidance. **Results**: There were 98 studies related to *Curcuma longa* and arthritis pain. After screening and checking for the eligibility, remains 7 studies. All studies have a good quality indicated by Jadad score of ≥3. The subjects in most studies were osteoarthritis (OA) patients and compared curcumin with placebo. Subjects in all studies dominated by female. VAS is the most common scale to assess the degree of pain. Curcumin was considered to be safe in patients with arthritis. It also improves the intensity of pain in all studies. **Conclusion**: *Curcuma longa* proved to be effective to reduce pain among arthritic patients. It is also found to be safe without any serious adverse event.

Keywords: Curcuma longa, inflamation, pain, curcumin, turmeric

Introduction

Curcuma longa is commonly known as turmeric. It is cultivated in Asia and some tropical countries (Nayak et al., 2016). *Curcuma longa* constituents include the three curcuminoids: curcumin (diferuloylmethane; the primary constituent and the one responsible for its vibrant yellow color), demethoxycurcumin, and bisdemethoxycurcumin, as well as volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins, and resins (Jurenka, 2009).

Curcumin has antioxidant, anticarinogenic, anti-inflammatory, antimicrobial, and hepatoprotective actions (Akram et al., 2010; Li et al., 2011). Some promising effects have been observed in patients with various pro-inflammatory diseases (Gupta et al., 2013), including metabolic syndrome, arthritis, and anxiety (Hewlings and Kalman, 2017).

Turmeric also has been demonstrated to alleviate the pain of inflammation in diseases such as rheumatoid arthritis and psoriasis (Hamidpour et al., 2015). Some animal studies proved the benefit of turmeric to alleviate pain. Study in wister rats concluded that *Curcuma longa* (rhizome) extracts at 100 and 200 mg/kg by single oral dose treatment had an analgesic effect but no antipyretic effect (Neha et al., 2009). Hydroalcoholic extract of *Curcuma longa* (HAECL) at 200 mg/kg and 400 mg/kg body weight showed significant ($p<0.01$) analgesic activity. The HAECL rhizome shows analgesic activity in albino rats and was comparable with pentazocin (Chowdhury et al., 2017).

Arthritis causes disability due to pain and inflammation in joints (Grover and Samson, 2016). There is no treatment for arthritis fundamental causes. The foremost goal of arthritis treatment is to reduce joint pain (Daily et al., 2016). Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are currently endorsed to treat arthritis, such as osteoarthritis, but emerging evidence has challenged this recommendation and revealed the potential for adverse events (Liu et al., 2018). Following consideration of the potential side effects of NSAIDs and the long duration of treatment, one may prefer the use of less toxic compounds

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with a good safety profile (Henrotin et al., 2014). No significant toxicity was noted either acute or chronic administration of turmeric extracts at standard doses (Grover et al., 2015). Curcumin is a highly pleiotropic molecule with an excellent safety profile. Strong molecular evidence has been published for its potential to target multiple inflammatory diseases (Henrotin et al., 2013). This systematic review aimed to identify the benefit of *Curcuma longa* in arthritis pain.

Materials and methods

The keywords used in the research process include: "*Curcuma longa*", "curcumin", and "turmeric". Keywords "arthritis" and "pain" were also added to specify the search. Systematic research was done using PubMed dan Cochrane database. Figure 1 shows the guideline selection process including the number of excluded journal (Liberati et al., 2009).

Included study has the following criteria: (i) the study was conducted between 2008 to 2018, (ii) wrote in English, (iii) the study was identified the benefit of *Curcuma longa* in arthritis pain. Any type of arthritis is involved in this review. This review do not include another species of curcuma, such as *Curcuma domestica*. The study is excluded if the study was not a randomized controlled trial (RCT) study and the full text was not available.

The quality of the RCT was measured using the Jadad score by two appraiser. Jadad score has 5 assessment components. One point will be added if the study meets each component, therefore the maximum score is 5 (Berger and Alperson, 2009). The study will be ruled out if it scores less than 3. After passing the assessment by using the Jadad score, two authors reviewed the study using PRISMA checklist as the guidance. PRISMA checklist has 27 items to assess the content of systematic review and meta-analysis (Liberati et al., 2009). Two authors work were resolved by discussion between two review authors. The variables reviewed include: diagnosis of inflammatory pain, intervention, comparison, number of subjects, length of the study, outcome, and results. The results are described by p value.

Results

Figure 1 showed the detail of the selection process. There were 98 studies related to *Curcuma longa* and arthritis pain. After screening and checking for the eligibility, remains 7 studies.

The quality of each study was evaluated by using the Jadad score. Table 1 showed all studies have a good quality indicated by Jadad score of ≥3. The highest score is in a

Table 1. Quality of Study by Using Jadad Score

Author (Year)	Was the study described as randomized?	Was the method used to generate the sequence of randomization described and appropriate?	Was the study described as double blind?	Was the method of double blinding described any appropriate?	Was there a description of withdrawal and dropout?	Total Score
Chandra & Goel (2012)	Yes	Yes	No	No	Yes	3
Pinsornsak & Niempoog (2012)	Yes	No	Yes	Yes	Yes	4
Kizhakkedath (2013)	Yes	Yes	No	No	Yes	3
Nakagawa, et al. (2014)	Yes	No	Yes	No	Yes	3
Panahi, et al. (2014)	Yes	Yes	Yes	No	Yes	4
Srivastava, et al. (2016)	Yes	Yes	Yes	No	Yes	4
Haroyan, et al. (2018)	Yes	Yes	Yes	Yes	Yes	5

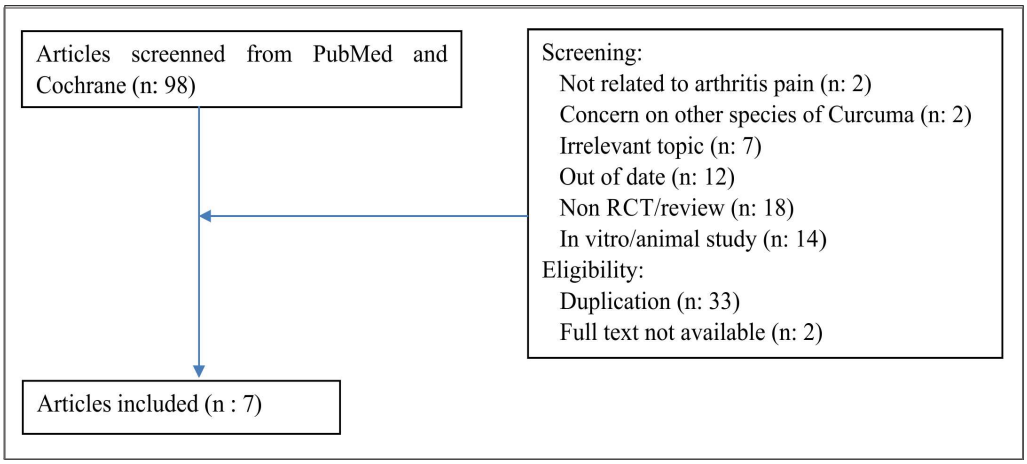

Figure 1. Study Selection Process

study by Haroya et al. (2018). All studies continued to be further review.

Table 2 is a summary of selected study. The subjects in all studies were osteoarthritis (OA) patients and compared curcumin with placebo, except in the study by Chandra and Goel (2012). Subjects in all studies dominated by female. VAS is the most common scale to assess the degree of pain.

Table 3 summarized the conclusion of each study. Curcumin was considered to be safe in patients with arthritis. It also improves the intensity of pain in all studies.

Discussion

Measurement

The primary end point in the study by Chandra and Goel (2012) is DAS 28. DAS 28 is a composite index based on assessment of 28 joints. ACR is the secondary end point. ACR criteria measure improvement in tenderness or swollen joint counts and improvement in three of five parameters: patient global assessment, physician assessment, pain scale disability, functional questionnaire, acute phase reactant. Pain scale disability in ACR measured

Table 2. Summary of Selected Studies

Authors (Year)	Diagnosis	Intervention	Control	Subjects Characteristics	Length of Treatment	Outcome Measure
Chandra and Goel (2012)	RA	Group 1: curcumin 500 mg b.i.d Group 2: diclofenac sodium 50 mg + curcumin 500 mg b.i.d	Group 3: Diclofenac sodium 50 mg b.i.d	N: 45 subjects 38 female, 7 male Group 1: 47.8±8.6 y Group 2: 47±16.2 y Group 3: 48.87±10.7 y	8 weeks	DAS 28, ACR
Pinsornsak and Niempoog (2012)	OA	Group 1: curcuminoid 250 mg 2 caps b.i.d + diclofenac 25 mg t.i.d	Group 2: placebo 2 caps b.i.d + diclofenac 25 mg t.i.d	N: 75 subjects 62 female, 13 male Mean age (?)	3 months	VAS, KOOS
Kizhakkedath (2013)	OA	Group 1: CB formulation 500 mg (Curcuma longa extract 350 mg + Boswellia serrata extract 150 mg) b.i.d	Group 2: Celecoxib 100 mg b.i.d	N: 30 subjects 16 female, 12 male Group 1: 49.70±8.2 y Group 2: 47.20±9.7 y	12 weeks	Symptom scoring, clinical examination
Nakagawa et al. (2014)	OA	Group 1: theracurmin 180 mg b.i.d	Group 2: placebo b.i.d	N: 41 subjects 32 female, 9 male Group 1: 71.9±5.3 y Group 2: 66.1±7.2 y	8 weeks	JKOM, knee scoring system of the JOA
Panahi et al. (2014)	OA	Group 1: curcuminoid 1500 mg/day	Group 2: placebo	N: 40 subjects 31 female, 9 male Group 1: 57.32±8.7 y Group 2: 57.57±9.0 y	6 weeks	WOMAC, VAS, LPFI
Srivastava et al. (2016)	OA	Group 1: Curcuma longa extract 500 mg	Group 2: placebo + diclofenac 50 mg/day	N: 160 subjects 103 female, 57 male Group 1: 50.23±8.0 y Group 2: 50.27±8.6 y	12 weeks	VAS, WOMAC
Haroyan et al. (2018)	OA	Group 1: Curamed 500 mg t.i.d Group 2: Curamin 500 mg t.i.d	Group 3: placebo t.i.d	N: 201 subjects 187 female, 14 male Group 1: 54.65±8.8 y Group 2: 57.91±9 y Group 3: 56.04±8.5 y	12 weeks	WOMAC, PPM test, ESR, CRP

RA: Rheumatoid Arthritis, OA: Osteoarthritis, DAS28: Disease Activity Score 28, ESR: Erythrocyte Sedimentation Rate, VAS: Visual Analog Scale, ACR: American College of Rheumatology, CRP: C Reactive Protein, KOOS: Knee injury and Osteoarthritis Outcome Score, CB: *Curcuma longa* and *Boswellia serrata*, JKOM: Japanese Knee Osteoarthritis, JOA: Japanese Orthopedic Association, WOMAC: Wetern Ontario and McMaster Universities Osteoarthritis, LPFI: Lequesne's pain functional index, PPM: Physical Performance Measures

Table 3. Conclusion of the Studies

Author (Year)	Results
Chandra and Goel (2012)	The curcumin group showed the highest percentage of improvement in overall DAS and ACR scores. Curcumin treatment was found to be safe and did not relate with any adverse events.
Pinsornsak and Niempoog (2012)	There was no difference in VAS. The curcumin with diclofenac group had tendency to be better in pain and function in daily living, but there were no statistic different in all group.
Kizhakkedath (2013)	CB formulation 500 mg, administered twice daily demonstrated a greater improvement in the treatment of OA than celecoxib 100 mg twice daily in the scores for pain, walking distance and joint line tenderness.
Nakagawa et al. (2014)	Theracurmin lowered the celecoxib dependence significantly more than placebo. No major side effects were observed with Theracurmin treatment.
Panahi et al. (2014)	Treatment with curcuminoids was associated with significantly greater reductions in WOMAC, VAS, and LPFI scores compared with placebo. Curcuminoids represent an effective and safe alternative treatment for OA
Srivastava et al. (2016)	Curcuma longa suppresses inflamation and brings clinical improvement including decrease level of VAS/WOMAC score.
Haroyan et al. (2018)	Combining *Curcuma longa* and *Boswellia serrata* extracts in Curamin increases the efficacy of OA treatment. The treatments were well tolerated.

by using VAS for pain. The ACR20 category is defined as a reduction in tender and swollen joint counts by 20%, ACR50 by 50% and ACR70 by 70%, from baseline.

KOOS is a knee-specific instrument used in RCT by Pinsornsak and Niempoog (2012). It developed to assess the patients' opinion about their knees and associated problems. KOOS has 42 items with 5 seperate score subscales: pain, other symptoms, activity of daily living (ADL), function in sport and recreation and knee-related quality of life (QOL).

Symptom scoring in research by Kizhakkedath (2013) was evaluating the subjects for joint pain (measured as 'no', 'mild', 'moderate' or 'severe') and walking distance (recorded as, >1000, 500-1000, 100-500 or <100 m). Clinical examination of the joints was performed for the following parameters: joint tenderness (no, improved, same, or worsened), crepitus (no, mild, moderate, or severe), swelling (measured in centimeters using a measuring tape, bilaterally), range of movements (measured in degrees using a goniometer, bilaterally), thigh measurements (measured using measuring tape around the thigh at a distance 5 cm from the upper border of the patella and recorded in centimeters), warmth (yes or no), and gait (normal or abnormal).

Study in Japan by Nakagawa et al. (2014) was using JKOM criteria and JOA scale. JKOM is a criteria with 4 subcategories pain and stiffness, condition in daily life, general activities, and health conditions. VAS for knee pain has already included in JKOM criteria. The JOA scale evaluates four items: ability to walk (30 points), ability to climb up and down stairs (25 points), range of motion (35 points), and joint swelling (10 points).

There were 3 outcomes measured in the study by Panahi et al. (2014). WOMAC is an index for the assessment of the severity of OA symptoms. The subscale of WOMAC including pain (5 items), stiffness (2 items) and physical functioning (17 items). Each item was rated from 0 to 4, thus the total score of pain is 0–20, stiffness is 0–8, and physical functioning is 0–68. LPFI is an index consists of three subscales with a total of ten items. The pain or discomfort scale, the 'maximum distance walked', and the functions or activities of daily living (ADL). The pain and ADL scale scores range from 0 (representative of no pain or functional limitation) to 8 (representative of extreme pain or functional limitation). The 'maximum distance walked' subscale score ranges from 0 (representative of unlimited) to 6 (representative of less than 100 m walking distance ability). Total LPFI ranges from 0 to 24, with higher score exhibiting worse health status (Panahi et al., 2014).

WOMAC in research by Kizhakkedath (2013) and Haroyan et al. (2018) is same as WOMAC in research by Panahi et al. (2014), but with one additional items in study by Haroyan, et al. (2018): patients' global assessment of disease severity considering the 48 hours prior to the assessment (11 questions). OA physical performance measures (PPM) using the OARSI recommended set of physical function performance-based tests including the 30-s chair stand test (30s–CST), 40 m (4x10 m) fast-paced walk test (40 m FPWT), the “timed up and go” test (TUG), the stair climb test (SCT). (Haroyan et al., 2018).

Chandra and Goel (2012), Pinsornsak and Niempoog (2012), Panahi et al. (2014), Nakagawa et al. (2014), Srivastavan et al. (2016) use VAS in their study to assess the pain. Kizhakkedath (2013) and Haroyan et al. (2018) did not use VAS for pain measurement.

***Curcuma longa* for pain treatment**

Mean VAS scores among RA patients in the curcumin group showed the highest reduction in VAS score (59.9%) from baseline (68.57±17.14) to end of treatment (27.5±9.35). Percentage changes in VAS score were statistically significant ($p < 0.05$). In ACR responses, the highest reduction of total painful joints from baseline (18.64) to end of treatment (3.14) was also in the curcumin group ($p < 0.05$) (Chandra and Goel, 2012).

Among Thailand patients, the efficacy of diclofenac alone and curcumin with diclofenac in VAS had significant improvement in pain in both group when compared with the first visit. Pain scale reduction tended to be better in group curcumin with diclofenac at the end of the present study, but there was no statistic significant (p: 0.923). More improvement in symptom was seen in curcumin with diclofenac group, but there was no statistically significant (p: 0.412). The pain improvement was also tended to be better in curcumin with diclofenac group at the first, second and third month after medication, but there was also no statistically significant (p: 0.814).

At the baseline, 85.71% of the subjects were in the moderate/severe pain category in the CB group and 78.57% in the celecoxib group. At the end of the study, only 21.43% of subjects in the CB group were in the moderate/severe pain category whereas 50% of celecoxib group remained in the moderate/severe pain category. There was a significant improvement in pain scores within CB group and celecoxib group in a period of 12 weeks, but there was no significant difference between the groups ($p > 0.05$) (Kizhakkedath, 2013).

The improved VAS scores were significantly higher in the theracurmin group than in the placebo group at 8 weeks, but the improved VAS scores were not significantly different between the two groups (p: 0.10) except in the patients with initial VAS scores of 0.15 or less. Mean VAS score at 0 and 8 weeks in all 41 cases was 0.52 and 0.20, respectively, in the theracurmin group, and 0.42 and 0.21, respectively, in the placebo group. Except the patients with initial VAS score of 0.15 or less, the mean VAS score at 0 and 8 weeks was 0.60 and 0.20, respectively, in the Theracurmin group, and 0.47 and 0.23, respectively, in the placebo group. In each of the two groups there were three patients with initial VAS score of 0.15 or less (Nakagawa et al., 2014).

Analysis on VAS score in 40 subjects showed significant reduction in the curcuminoids group by the end of trial ($p < 0.001$). Patients in this study were allowed to use naproxen as needed during the course of trial. The proportion of subjects whose use of naproxen was reduced by the end of trial was significantly greater in the curcuminoids (84%) versus the placebo group (19%) ($p < 0.001$). The average use of naproxen during the study was 250–500 mg in the group receiving curcuminoids and 500–750 mg in the group receiving placebo (Panahi et al., 2014).

Analysis by Srivastavan et al. (2016) in the level of VAS was significantly reduced in the *Curcuma longa* group than the placebo group at day 60 (4.96±0.07 vs 6.00±0.11) and 120 (4.03±0.08 vs 5.11±0.34) ($p < 0.05$). The last study by Haroyan et al. (2018) assessed pain by 3 type of measurement: WOMAC pain index subscale, pain on standing from a chair, and pain on climbing stairs via the SCT. This study showed a statistically significant pain relief effect was observed in all study groups even in the placebo group. Comparing the pain index among groups between the baseline and the 12th weeks, the pain index significantly decreased in both treatment groups. The improvement was significant in the curamin group (effect size [ES] -0.519; $p < 0.001$) and in the curamed group (ES -0.734; $p < 0.001$).

Curamin and curamed have a significant effect to the maximum number of chair stand repetitions possible in a 30-s period and the time required to ascend/descend a flight of stairs significantly from week 4 to week 12 of treatment. The ES in the Curamin and CuraMed groups in the maximum number of chair stand repetitions possible in a 30-s period were 3.8 and 4.8 fold higher than in the placebo group. Significant differences between the Curamin vs placebo groups are $p < 0.05$ and between the CuraMed vs placebo groups are $p < 0.01$. The ES in the Curamin and CuraMed groups in the time required to ascend/descend a flight of stairs was 6.0 and 4.3 fold higher than in the placebo group.

Safety

In a study by Chandra and Goel (2012) reported adverse event more frequently in diclofenac sodium than in curcumin and curcumin + diclofenac sodium groups. Adverse events reported in the curcumin group were mild fever and a throat infection. Pinsornsak and Niempoog (2012) stated a low complication rate and high safety margin for using combination therapy in clinical practice in their study, but did not describe further about the complication. There were no serious adverse events were observed in either group in the study by Nakagawa, et al. (2014) and Kizhakkedath (2013).

No serious adverse event was reported in a trial by Panahi et al. (2014). Adverse events were mild gastrointestinal symptoms that were reported from7 cases of the curcuminoids group and 4 cases of the placebo group. The frequency of these adverse events was not significantly different between the two groups ($p > 0.05$).

Curamin and curamed were all well tolerated. There were 13 adverse events were observed: 4 in the placebo group, 2 in the curamin group and 7 in the curamed group. Serious adverse events were not observed. Nausea was observed only in patients taking curcumin-containing supplementations. Analysis of adverse events observed in both the treatment and placebo groups revealed that the types and frequency of adverse events were similar in all groups and were presumably not related to the treatment (Haroyan et al., 2018).

Conclusion

Curcuma longa proved to be effective to reduced pain among arthritis patients compared to placebo or NSAIDs, especially diclofenac and celecoxib. It is also found to be safe without any serious adverse event. *Curcuma longa* is a better choise for arthritic patients who need a long-term analgetic.

Conflicts of interest

Nothing to declare.

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