2020

Is Curcuma Effective for the Management of Osteoarthritis Knee Pain?

Katherine Grinberg
Philadelphia College of Osteopathic Medicine

Is *Curcuma* effective for the management of osteoarthritis knee pain?

Katherine Grinberg, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 13, 2019

ABSTRACT

OBJECTIVE: The objective of the selective EBM review is to determine whether or not “Is Curcuma effective for the management of osteoarthritis knee pain?”

STUDY DESIGN: Systematic review of three randomized controlled trials (RCT) published in 2009, 2014, and 2016.

DATA SOURCES: Three RCTs studies were found using PubMed. All articles were published in reviewed journals and selected based on correlation to topic choice, date of publication, and evaluation of POEMs.

OUTCOMES MEASURED: The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a questionnaire that evaluates hip and knee osteoarthritis. The questions are divided into 3 subscales: pain, stiffness, and physical function. This paper is focusing on the pain scale when walking.

RESULTS: Kuptniratsaikul et al. (2014) found a decrease in knee pain on the pain scale with *Curcuma domestica* with a statistically significant p-value of 0.018, showing it is as effective as ibuprofen in pain reduction. Srivastava et al (2016) also shows a reduction in pain when using *Curcuma longa* (CL) with diclofenac comparing to a placebo with Diclofenac group. With a significant p-value of 0.0001, showing CL extract along with Diclofenac produces an overall significant improvement in patients with knee OA. Kuptniratsaikul et al (2009) shows a reduction in pain in both the *Curcuma domestica* group and ibuprofen group, but the differences of the outcomes were not statistically significant with the p-value of 0.2. It cannot be definitively concluded if *Curcuma domestica* is as effective as ibuprofen.

CONCLUSION: Two of the three studies shows statistical significance that *Curcuma* can reduce pain in knee osteoarthritis. While one showed no statistical significance with knee OA pain reduction, it is shown to be safe for the treatment of knee OA. *Curcuma* looks to be promising as a long-term treatment, but further research needs to be done.

KEY WORDS: Curcuma, osteoarthritis

INTRODUCTION

Osteoarthritis, abbreviated as OA, is the most common form of arthritis. OA is primarily a disease of aging and with the increase of obesity the prevalence of OA is on the rise. It is caused by degeneration of cartilage that protects the joints. The degeneration of cartilage starts in a nonuniform manner and located focally, causing pain, swelling, and difficulty moving the joints effected.[1,2] Even though it can affect any joint, the most common joints affected are in the hands, primarily the distal and proximal interphalangeal joints, as well as the knees, hips, and spine.[2] Symptomatically, OA of the knee is the most common joint affected, occurring in about 12% of people 60 years and older and 6% of adults 30 years and older in the United States.[2]

The CDC estimates over 30 million US adults have OA.[1] It is especially common in the geriatric population. There is no recent yearly healthcare visit for OA recorded, but in 2006 through 2007 there were 12.3 million office visits and 85,000 hospital visits associated with OA.[3] Since there are many options for the treatment of OA depending on the severity as well as many treatment options that can be bought over the counter for mild OA, it is difficult to calculate the total healthcare costs for OA, however, a 2013 study found the total hospitalization cost of OA was $16.5 billion.[4]

The etiology of osteoarthritis is still not well understood. However, what is known is that it is categorized as a gradual loss of articular cartilage and that there are many risk factors involved. The most common risk factor is age. A study published in 1995 showed an increase incidence of osteoarthritis with age.[4] Typically, the incidence increased after the age of 50 then leveled off or declined in both sexes after the age of 80.[5] Trauma and overuse of the joint as well as being overweight increases the risk of OA. Genetics has shown to play a role in OA as well.

Studies have shown there is an increase of OA occurrence in monozygotic twins.[6] Other genetic traits that have shown to increase OA are a defect in producing collagen, a defect in bones fitting together, and a genetic defect called FAAH that increases pain sensitivity causing a higher risk of developing OA.[7] Other risk factors for OA are low bone density, low diet of vitamins C and D, and ethnicity. OA is more prominent in Europeans than Asians and Africans.[2,7]

Even though there is an understanding of the different risk factors for osteoarthritis, it is unknown why OA can vary from person to person and why there is a faster progression in some. Treatments are not considered curative, often resulting in joint replacement if it hinders the patient's activities in daily living.[7] There is still much more that needs to be learned about this common disease.

The methods to treat OA depend on the severity and pain of the joint affected. Usually assisting devices are used along with exercise and weight loss, if applicable. Acetaminophen or NSAIDs are used to control pain. If a patient has moderate to severe OA of the knee and oral NSAIDs are ineffective, intra-articular injections of corticosteriods, hyaluronate, or platelet-rich plasma can be administered to relieve pain temporally. If the knee or hip affected with OA severely restricts the patient from walking and causes them pain at rest, then total joint replacment is used to improve their mobility and pain.[2,8]

Osteoarthritis can cause chronic use of NSAIDs which can lead to multiple health risks. Chronic use of NSAIDs can lead to increased risk of peptic ulcer diease, acute renal failure, decreased glomerular filtration rate, stroke, or a myocardial infarction. Since OA usually targets the older population, the long-term use of NSAIDS can exacerbate heart failure and hypertension.[9] *Curcuma*, also known as turmeric, is a possible treatment method for OA pain.

Curcuma contains anti-inflammatory properties that could possibility replace NSAID use. Curcumin is shown to be well tolerated with few side effects. The most common side effects are usually gastrointestinal, such as constipation, diarrhea, and nausea.[10] This paper evaluates three randomized controlled trials comparing the efficacy of *Curcuma* extract as an oral medication for improving osteoarthritis knee pain.

OBJECTIVE

The objective of the selected evidence-based medicine (EBM) review is to determine whether or not, "Is Curcuma longa effective for the management of osteoarthritis knee pain?"

METHODS

The criteria used for the selection of the studies were based on the population, interventions, comparisons, outcomes measures and types of studies. The population included both female and male adult patients with knee OA. The studies compared *Curcuma* extract to either ibuprofen or a placebo to determine a difference in the pain while walking. The pain was measured by Western Ontario and McMaster Universities Osteoarthritis index (WOMAC). Three randomized controlled trials were selected and evaluated for this paper. Two of which were double blinded studies and one single blind RCT where the physicians were unaware of patients group of treatment. Two of the studies compared *Curcuma* with ibuprofen and one study compared *Curcuma* with a placebo.

In order to find the appropriate studies for this paper while searching through the data sources, certain criteria was placed. Key-words included were "*Curcuma*" and "osteoarthritis". All articles were found in PubMed and are published in peer reviewed journals in English. The articles were selected based on their applicability to the clinical question and included patient-

oriented outcomes (POEMS). The inclusion criteria used were clinical trials, human studies, and studies published in the past 10 years. Studies published greater than 10 years ago and studies on animals were excluded. Statistics are reported using P-values.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Kuptniratsaikul[10] (2009)	Single Blind RCT	107	>50 years	>50 years with primary knee OA, morning stiffness <30 minutes and crepitus on motion. With a pain score rating scale of ≥ 5 of 10.	Any patient with peptic ulcer disease, hepatobiliary tract disease, or known allergy to ibuprofen or curcumin	16	Controlled group took ibuprofen 400mg b.i.d daily, *C. domestica* extract patients 500 mg 4 times daily for 6 weeks
Kuptniratsaikul[11] (2014)	Double blind RCT	367	≥50 years	≥50 years, primary knee OA with a numerical rating scale of knee pain of ≥5 out of 10	Patient with abnormal liver function or renal function, history of peptic ulcer, allergy to curcuma or ibuprofen, unable to walk	36	Ibuprofen group received 1,200 mg/day *and C. domestica* extract group received 1,500mg/day for 4 weeks
Srivastava[12] (2016)	Double blind RCT	160	40-80 years	40-80 years old, have knee OA with stiffness <30 min, crepitus, bony tenderness, bony enlargement and no palpable warmth	Patients less than 40 or greater than 80 years old. Have rheumatoid arthritis, diabetes mellites renal insufficiency, hepatic disease, cardiovascular disease, gout, pregnant women, with any systemic disease	27	500mg placebo with 50 mg/day of Diclofenac, 500 mg *Curcuma longa* extract with 50 mg/day Diclofenac for 4 months

OUTCOMES MEASURED:

Two studies used Western Ontario and McMaster Universities Arthritis Index (WOMAC) to measure the outcome for OA knee pain based on *curcuma* treatment. WOMAC is a questionnaire that evaluates knee osteoarthritis. The questions are divided into 3 subscales: pain, stiffness, and physical function. Each one of these subscales are numerically rated. The higher number signifies more pain, more stiffness, or worst knee function.[11,12] One study used an unspecified numerical scale to rate OA knee pain. [10] This paper focused on the pain scale while walking.

Kuptniratsaikul et Al. 2009 randomly selected patients into two groups. One group was treated by *Curcuma* and the other by ibuprofen. The patients walked 100m on a leveled surface and rated their knee pain numerically. The numerical scale was not specified. The mean scores of the outcomes were collected at weeks 0, 2, 4, and 6.[10] The physicians were unaware of which group of patients they were treating.[10] Kuptniratsaikul et al 2014 used WOMAC modified Thai version comparing *Curcuma* to ibuprofen treatment. Patients walked for 6 minutes and then used a 0-10 scale to quantify their knee pain. The outcomes were recorded at week 2 and 4. Double blinding was achieved in this study.[11] Srivastava et al compared *Curcuma* with a placebo group. The outcomes used were WOMAC rating the knee pain from 0-4, as well as assessing the visual analog scale (VAS) for knee pain. VAS is a questionnaire with a 10-cm horizontal line with word description along with numerical numbers, ranging from 0-10. Zero indicating “no pain” and 10 meaning “unbearable”.[12] Patients were assessed on days 0, 60, and 120. Double blinding was achieved in the study.[12]

RESULTS

Two studies compared the effectiveness of *Curcuma* to ibuprofen for reducing OA knee pain, and one study compared *Curcuma* with diclofenac to a placebo with diclofenac on OA knee pain. All three studies selected patients for the study based off the knee OA guidelines issued by the American College of Rheumatology. These guidelines consist of adults 50 years and older with knee pain and stiffness lasting less than 30 minutes, along with crepitus and osteophytes.[10,11,12]

Kuptniratsaikul et al 2009 was a single blind randomized control study that was conducted in a tertiary hospital in Bangkok, Thailand. A total of 107 patients were selected. The *C. domestica* extract group had 52 randomized patients and 55 were randomized to ibuprofen group. At the end of the trial, 45 patients were left in the *Curcuma* group and 46 in the ibuprofen group. Inconvenience for the follow up return and adverse reactions to either Curcuma or ibuprofen caused patients to not complete the study, resulting in 86.5% compliance for *Curcuma* and 83.6% for ibuprofen. One group received 500mg 4 times a day of *Curcuma domestica* extract while the other received 400mg twice a day of ibuprofen for 6 weeks. They had patients walk 100 meters on a level surface and then they rated their pain on a numerical scale. They calculated the mean score of the rated pain as well as the change score for each group. The confidence interval was obtained from the difference of change score for the past 6 weeks in both groups.

The p-value of 0.2 was calculated showing that there is no statistical significance in OA knee pain for *Curcuma* compared to ibuprofen even though the numerical pain score showed a decrease in pain. The study states their wide range of the confidence interval showed an

inadequate sample size. Another possible factor in a large confidence interval could be a large age range and geographically limited study participants.

Table 2: change scale and Confidence interval of Pain on level walking between week 0 to 6[10]

	Change score of *C. Domestica*	Change score of ibuprofen	*Difference of change score (95% CI)	P-Value
Pain on level walking	2.7 ± 2.6	2.0±2.3	0.67 (-0.35 to 1.68)	0.20

*Difference= change in score of C. *domestica* – Change in score of ibuprofen

Kuptniratsaikul et al 2014 conducted their double blind RCT in tertiary Thailand hospitals.185 patients were randomly assigned to *C. domestica* and 182 to ibuprofen. At the end of the trial there were 171 patients left for *C. domestica* and 160 for ibuprofen, making the compliance for *C. domestica* 92.4% and 88.9% for ibuprofen. One patient from the *C. domestica* withdrew from the adverse effects and 6 withdrew from ibuprofen. The rest were unable to be contacted, inconvenienced, or left for other reasons which were not specified. The *C. domestica* group was given 1,500 mg/day for 4 weeks and ibuprofen group were given a dosage of 1,200 mg/day for 4 weeks. The participants walked for 6 minutes then used the WOMAC pain scale, rating the pain from 0 to 10. The p-value of 0.018 shows statistical significance since it is less than 0.05.

Table 4. Mean Standard deviation (SD) and Mean Difference of WOMAC Pain at Week 4 Adjusted by Week 0 in Ibuprofen and *Curcuma domestica* Groups[11]

Mean score at week 4 adjusted by week 0 ±SD	Ibuprofen (n=160)	C. *domestica* (n=171)	Mean difference (95% CI)	P-value
WOMAC pain scale	3.17±1.98	3.25±2.11	-0.09 (-0.43 to 0.29)	0.018

Srivastava et al conducted a 4-month double blinded RCT at the out-patient department of orthopedics at King George's Medical University, India. Inclusion and exclusion criteria can be reviewed on table 1. Initially, 78 patients were randomly placed in *Curcuma longa* group and 82 in the placebo group. At the end of the 4 months, 66 patients from the *Curcuma longa* group and 67 patients from the placebo group were analyzed, making 84.6% for *Curcuma* and 81.7% for placebo completion. The reason for the low completion is that the patients failed to follow up. Both groups received 500mg capsules twice daily. One group received *Curcuma longa* and the other a placebo. Both groups also received 50mg of diclofenac daily. Patients were evaluated at day 0, 60 and 120. OA knee pain was evaluated using VAS rating the pain 0 to 10 and WOMAC pain scale of 0 to 4. The results were presented as mean with standard error. An unpaired t-test was used to compare the variables among VAS and WOMAC scores. A paired t-test was used to compare the mean change between days 0 to 120 from the VAS and WOMAC pain scores. A p-value <0.05 is considered significant. The p-value of both scores showed a statistically significant reduction in pain compared to the placebo group.

Table 6. Mean Change Comparison From Day 0 to 120 in VAS and WOMAC Pain Score[12]

	Curcuma Longa (n=78) Mean difference	*Curcuma Longa* (n=78) p-value	Placebo (n=82) Mean difference	Placebo (n=82) p-value
VAS score day 0 to day 120	3.91 ± 0.14	0.0001	2.54 ± 0.21	0.0001
WOMAC pain score day 0 to 120	5.61 ± 0.34	0.0001	5.13 ± 0.33	0.0001

DISCUSSION

Curcuma extracts can be found in many grocery stores or over the counter at a pharmacy. However, many insurances are reluctant to cover it since herbal therapy falls under alternative medicine. It is important to note that Medicare only covers chiropractors when it comes to complementary and alternative medicine[13]. Herbal coverage is not covered under Medicare.

Curcumin is not currently widely used in pharmacology for its low systemic bioavailability when used orally. Historically, tumeric has been used medically for centuries throughout the world. It is widely used in India for wound healing properties and in China for abdominal pain. Even though this herb has been around for centuries, there are not many clinical trials on it.[14] Clinical trials conducted on curcumin show its possible effectiveness are for allergic rhinitis, depression, hyperlipidemia, and nonalcoholic fatty liver diease. It is a known anti-inflammatory. Research shows it decreases inflammatory markers such as cytokines, collagenase, elastase, and hyaluronidase.[14,15] Curcumin is shown to be well tolerated with few side effects. As noted in all 3 studies, the adverse effects are mild. Curcumin should be avoided prior to surgery since it can slow blood clotting. It can also interact with anticoagulation and antiplatelet medications since it increases bleeding.[14] It can also interact with CYP2D6 and CYP3A substrates. Patients with gall stones, bile duct, passage obstruction or turmeric hypersensitivity should not take curcumin.[15]

There are some limitations that were found in the studies. Kuptniratsaikul et al 2009 had an inadequate sample size, subtherapeutic dosage of 800mg/daily of ibuprofen given, and it was not a double blinded study.[10] Additionally, WOMAC and VAS scores are subjective.[12] All three studies patients were sampled in either India or Thailand, which limits the generalizability. Pain

and pain rating scores are also subjective, some patients had unilateral knee pain while others were bilateral which can alter the pain score. The third study used rescue medication as an edition to both the groups which could alter the pain score as well. The studies did not look into what would happen if curcumin and ibuprofen were taken together.

CONCLUSION

Studies have shown *Curcuma* to be effective for knee OA pain with little adverse effects and with fewer GI effects than ibuprofen.[10, 15] Further research needs to be done since there were some conflicting evidences with one of the studies and there are no studies conducted in the United States population. Each study also used different amounts and types of *Curcuma* extracts. The three studies show *Curcuma* is promising as a long-term treatment for knee osteoarthritis pain, but further research is necessary.

REFERENCES

1. CDC. Arthritis cost statistics. CDC. https://www.cdc.gov/arthritis/data_statistics/cost.htm. Published January 30, 2019. Accessed September 3, 2019.
2. Felson DT, Neogi T. Osteoarthritis. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 20e New York, NY: McGraw-Hill; 2018.
3. Murphy L, Helmick CG. The impact of osteoarthritis in the united states: a population-health perspective. *AJN*. 2012;112:S13-S19. doi:10.1097/01.NAJ.0000412646.80054.21
4. American Academy of Orthopaedic Surgeons.United States Bone and Joint Decade. The burden of musculoskeletal diseases in the United States. Rosemont, IL:American Academy of Orthopaedic Surgeons;2008.
5. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis Rheum*. 1995;38(8):1134-1141. doi:10.1002/art.1780380817
6. Haq I, Murphy E, Dacre J. Osteoarthritis. *Postgraduate Medical Journal*. 2003;79(933):377-383. doi:10.1136/pmj.79.933.377
7. Osteoarthritis causes. Arthritis Foundtion. http://www.arthritis.org/about-arthritis/types/osteoarthritis/causes.php. Accessed September 23, 2019.
8. Papadakis MA, McPhee SJ, Rabow MW. eds. Current Medical Diagnosis & Treatment 2019 New York, NY: McGraw-Hill; 2018.
9. Marcum ZA, Hanlon JT. Recognizing the risks of chronic nonsteroidal anti-inflammatory drug use in older adults. *Ann Longterm* Care. 2010;18(9):24-27.)
10. Kuptniratsaikul V, Thanakhumtorn S, Chinswangwatanakul P, Wattanamongkonsil L, Thamlikitkul V. Efficacy and safety of Curcuma domestica extracts in patients with knee osteoarthritis. *J Altern Complement Med*. 2009;15(8):891-897. doi:10.1089/acm.2008.0186
11. Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, et al. Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. *Clin Interv Aging*. 2014;9:451-458. doi:10.2147/CIA.S58535
12. Srivastava S, Saksena AK, Khattri S, Kumar S, Dagur RS. Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial. *Inflammopharmacology*. 2016;24(6):377-388. doi:10.1007/s10787-016-0289-9
13. Herman PM, Coulter ID. Advancing complementary and alternative medicine professions: practitioners face many policy hurdles to finding their place in mainstream medicine. https://www.rand.org/pubs/research_briefs/RB9894.html. Published 2016. Accessed March 3, 2020.
14. Turmeric. Lexicomp. https://online.lexi.com/lco/action/login. Accessed November 20, 2019.

15. Turmeric. Therapeutic Research Center -Natural medicines. https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=662#peopleUseThisFor. Accessed November 20, 2019.