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Are Curcuminoids Effective in Reducing Knee Pain in Adults with Knee Osteoarthritis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not curcuminoids are effective in reducing knee pain in adults with knee osteoarthritis.

STUDY DESIGN: A review of two English language double-blind placebo-controlled randomized controlled trials and one double-blind randomized control trial (RCT) published within peer-reviewed journals after the year 2013. The studies include adult participants age 40 and over.

DATA SOURCES: Double-blind randomized controlled trials were found using PubMed database. These studies compared treatment with curcuminoids with ibuprofen or a placebo.

OUTCOMES MEASURED: Clinical outcomes of pain, stiffness and function were measured using the traditional Western Ontario & McMaster Universities Arthritis Index (WOMAC) and Visual Analog Scale (VAS); 6-minute walk distance to measure function; use of adjunctive non-steroidal anti-inflammatory drugs (NSAIDs) for pain management. This review will primarily focus on the areas of pain outcome.

RESULTS: One RCT found that curcuminoids provided a significant drop from baseline pain after 4 weeks using the Thai modified WOMAC scale, and showed a better safety profile versus ibuprofen. Two RCTs found that curcuminoids provided a significant decrease in baseline as well as a greater decrease in pain outcomes when compared to that of the placebo control group measured using the traditional WOMAC scale and VAS after 6 and 8 weeks, respectively. It is also worth noting that both of these RCTs also showed significant reduction in patient use of NSAIDs as an adjunctive in pain management when compared to the placebo group.

CONCLUSION: The results of the three randomized controlled trials present evidence that curcuminoids, given short-term, can effectively reduce knee pain in adults with knee osteoarthritis and coincidentally decrease the dependence on NSAIDs as adjunctive pain management. Curcuminoid dosages and dosing schedules, duration of therapy, and safety of treatment need to be more accurately determined through future trials.

KEY WORDS: curcumin, curcuma domestica, knee osteoarthritis, therapy

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and is the leading cause of disability in adults, effecting over 30 million adults in the United States.[5] Osteoarthritis is a progressive disease of the entire joint most commonly affecting adults age 40 and above, but can severely hinder quality of life at any age.[5] Osteoarthritis accounts for more than twenty-five percent of all arthritis related health care visits, contributing to more than 27 billion dollars in health care expenditures annually.[1] According to the Arthritis Foundation, in 2012 over one million total joint arthroplasties were performed at a cost of 18.8 billion dollars.[1] In addition to extensive healthcare costs, earning losses due to osteoarthritis cost an estimated 80 billion dollars per year between 2008 and 2011.[1] There is currently no cure available for osteoarthritis, and treatment methods have continually plateaued over the last decade. This paper evaluates three double-blind randomized controlled trials (RCTs) comparing the efficacy of curcuminoids in reducing knee pain in patients with knee osteoarthritis when used as an oral therapeutic agent.

Osteoarthritis is a progressive disease of one or multiple joints, characterized by the breakdown of cartilage, bony changes in the joints, deterioration of the tendons and ligaments, and various degrees of inflammation of the joint lining.[5] Most commonly, osteoarthritis occurs in the hand joints, spine, and weight bearing joints such as the hips, knees, and great toes.[5] Symptoms of osteoarthritis include joint pain and stiffness, knobby swelling of the joint, cracking or grinding noise with movement, and decreased joint function.[5] Diagnosis of osteoarthritis is primarily a clinical diagnosis based on a complete history and physical, and may include joint imaging using X-ray or higher level technology.[5] Risk factors for osteoarthritis include a positive family history, repetitive use or overuse of joints, and joint deformity.[5] An individual's risk of developing osteoarthritis significantly increases with obesity, traumatic joint

injury, and increasing age.[5] The lifetime risk of knee and hip osteoarthritis are 46% and 25%, respectively.[5]

Traditionally, treatment methods begin with the most conservative options and follow a stepwise progression as needed. Because there is no cure for osteoarthritis, the goal of treatment is to manage pain and improve functionality.[5] Symptoms appear to be best controlled when focusing on the anti-inflammatory processes, including cyclooxygenase (COX) and other enzymes.[5] Most commonly, patients suffering from osteoarthritis will be encouraged to increase physical activity and lose weight.[5] Current standard of care for osteoarthritis patients mainly relies on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics.[3] If symptoms persist, physical therapy, prescription pain medication, and/or periodic joint injections may be pursued.[5] As the disease progresses and becomes increasingly debilitating patients may begin to use supportive devices and the most invasive option, joint surgery or replacement, may be explored at this time.[5]

Rather than continue to depend on NSAIDs and prescription pain medications, patients are turning to more natural sources and alternative medicines to manage their osteoarthritis pain. Recently, the supplement known as Turmeric, a curcuminoid, has been called into question as an anti-inflammatory agent.[2,3,6] Curcuminoids are a classification of medication that use a pigment isolated from the plant Curcuma longa, more commonly known as turmeric.[4] Curcuminoids possess anti-inflammatory properties as a result of the inhibition of enzymes involved in inflammation, such as COX;[4] they also disrupt cell signal transduction by various mechanisms, including inhibition of protein kinase C.[4] Due to the pharmacotherapeutics and safety profile of curcuminoids, this class of medication has been shown to be effective in reducing knee pain in adults with knee osteoarthritis.[2,3,6]

OBJECTIVE

The objective in this systematic review is to determine whether or not curcuminoids are effective in reducing knee pain in adults with knee osteoarthritis (OA).

METHODS

All three studies selected for this systematic review included randomized controlled trials evaluating primary knee osteoarthritis patients over the age of 40 with no contraindications to curcuminoid therapy (see Table 1). Each study included a randomized group that received oral curcuminoid therapy compared to a control group, which received an oral placebo and/or a non-steroidal anti-inflammatory drug (NSAID). Outcomes measured in each study include knee pain, stiffness, and function. This systemic review will focus on knee pain.

Slight variations in each of the studies did exist, including age groups, curcuminoid product and dosage, duration of therapy, and scales used to measure outcomes (see Table 1). The study conducted by Kuptniratsaikul et al. compared the change in baseline between patients older than 50 years old receiving ibuprofen (control group) and patients receiving curcuma domestica for 4 weeks using a modified WOMAC scale (1200mg and 1500mg per day, respectively).[2] The study conducted by Nakagawa et al. compared the change in baseline between patients older than 40 years old receiving 1080 mg of Theracumin, a curcuminoid, per day and a control group receiving a placebo at two, four, six and eight weeks using the Visual Analog Scale (VAS).[3] The study completed by Panahi et al. focused on an older age group, older than 80 years old, comparing a placebo group with a group that received 1500mg of curcuminoid product per day for 6 weeks using both the traditional WOMAC scale and VAS.[6] Additional inter-study differences are mentioned in Table 1 and elsewhere in this review.

Articles for this review were found using the search engine on the PubMed database, using the key words "curcumin, knee osteoarthritis, therapy" and "curcuma domestica." The search was further filtered by only including papers published in peer-reviewed journals in the English language within the past 10 years. From this search, articles were selected based on their relevance to the objective, and if the studies included outcomes that focus on patient-oriented evidence that matters (POEMs). The specified search criteria excluded studies not published within the past 10 years, studies that did not include pain and functionality outcome measurements, and patients under the age of 40 years old. All three selected studies contain non-dichotomous data, and statistics evaluated in each study include p-values, confidence intervals (CI), and change in mean from baseline.

Table 1 – Demographics of Selected Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W /D	Interventions
Kuptniratsaikul[2]	Double-blind RCT	367	> 50	Primary knee OA per the ARA criteria with numerical rating of knee pain greater than or equal to 5/10, age greater than or equal to 50 years old	Abnormal liver or renal function, history of PUD, allergy to curcumin or ibuprofen, unable to walk	36	Ibuprofen 1200mg qd x 4 weeks VS Curcuma domestica extracts 1500mg QD x 4 weeks
Nakagawa[3]	Double-blind placebo-controlled RCT	50	> 40	Primary medial knee OA, age > 40, kellgren-lawrence grades II or III	History of knee surgery, injection treatment during study, knee steroid injection treatment within 2 months of study, steroids within 4 weeks of study	9	Theracurmin 180mg QD x 8 weeks VS Placebo QD x 8 weeks
Panahi[6]	Double-blind placebo-controlled RCT	53	> 80	Degenerative primary knee OA with mild to moderate severity, bilateral OA, age > 80, diagnosis based on criteria defined by ACR	Curcuminoid allergy, joint replacement, malabsorption disorders, heart failure, liver failure, renal failure, corticosteroid use, joint injections w/i 3 mo, hx of psych d/o	13	Curcuminoid 1500mg QD x 6 weeks VS Placebo QD x 6 weeks

OUTCOMES MEASURED

All outcomes measured were those of patient-oriented evidence that matters (POEMs). The outcomes measured in the selected studies were knee pain, stiffness, and function. One study used the 6-minute walk distance and a modified Thai version of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a health status questionnaire asking patients to measure symptoms on a scale of 0-10, with higher scores representing increased pain, at baseline and 4 weeks.[2] One study measured outcomes on the Visual Analog Scale (VAS), a continuum used to measure intensity or frequency of symptoms, at baseline, two, four, six, and eight weeks.[3] One selected study measured outcomes using both the traditional WOMAC, on a scale of 0-4, and VAS at baseline and six weeks.[6]

RESULTS

This selective systematic review contains three studies of randomized controlled trials evaluating the efficacy of curcuminoids in knee osteoarthritis pain. All three studies follow a per-protocol analysis. Two of the selected studies compare curcuminoid oral therapy to a placebo group, while one study compares the effectiveness of curcuminoids to that of ibuprofen (see Table 1). All three selected studies contain non-dichotomous data, and statistics evaluated in each study include p-values, confidence intervals (CI), and change in mean from baseline. Variations in each study are discussed elsewhere, including differing interventions and length of time.

The 2014 study by Kuptniratsaikul et al. evaluated the efficacy and safety of curcuminoid extracts versus that of ibuprofen, a currently accepted treatment for osteoarthritis, by measuring WOMAC scores in 367 patients at baseline and four weeks.[2] See Table 1 for the interventions carried out in this study. The compliance rate of both treatment groups in this study was greater

than 90%.[2] The trial found that the baseline WOMAC pain score of 5.3 +/- 1.8 was nearly cut in half after four weeks of treatment with curcuminoid extracts, with a four week WOMAC pain score of 3.25 +/- 2.11.[2] The estimate of the treatment effect is accurate, demonstrated by a confidence interval (CI) of 95% and a p-value of 0.018.[2] Ultimately, this study concluded that curcuminoid extracts are equally effective to ibuprofen in pain reduction for patients suffering with knee osteoarthritis.[2] Table 2 shows the WOMAC pain scores at different intervals for each of the respective groups. Not shown in the table includes the total WOMAC score, stiffness and function subscales of the WOMAC score, and the 6-minute walk distance, since this selective review is focusing only on knee pain. In addition, the study also found that curcuminoid extracts have a better safety profile, as more patients were lost in the ibuprofen group due to gastrointestinal adverse effects (n=7) than compared to the curcuminoid treatment group (n=1).[2]

Table 2 – Curcuminoids vs Ibuprofen (Kuptniratsaikul et al. 2014)[2]

	Baseline WOMAC pain	4-week WOMAC pain	Confidence Interval (CI)	P-Value
Ibuprofen (n=160)	5.2 +/- 1/7	3.17 +/- 1.98	95%	0.018
C. Domestica (n=171)	5.3 +/- 1.8	3.25 +/- 2.11		

The 2014 study by Panahi et al. compared curcuminoid treatment in 40 knee osteoarthritis patients compared to a placebo group using traditional WOMAC and VAS scores at baseline and six weeks.[6] There was no significant difference in age, gender, body mass index, and VAS and WOMAC scores between the study groups at baseline ($P>0.05$).[6] The treatment group received 1500mg of curcuminoid per day, while the alternative group received a placebo daily for 6 weeks. Treatment with curcuminoids was associated with significantly greater reductions in WOMAC scores ($p=0.001$) and VAS scores ($p <0.001$) compared with the placebo group scores.[6] When comparing specific WOMAC subscales, there were significant

improvements in pain and physical function scores, however, there was no significant change in stiffness score.[6]

Pain scores can be seen below in Table 3. In addition to the pain score improvements, this study found that the proportion of subjects whose use of naproxen (NSAID) was reduced by the end of the trial was significantly higher in the curcuminoid group (84%) versus the placebo group (19%).[6] No considerable adverse effects were noted in this study.

Table 3 – Curcuminoids vs Placebo (Panahi et al. 2014)[6]

	Group	Before Treatment	After Treatment	P-value
WOMAC overall	Curcuminoids	42.4 +/- 18.3	25.0 +/- 13.0	<0.001
	Placebo	44.6 +/- 17.3	40.6 +/- 12.6	0.072
WOMAC pain	Curcuminoids	9.9 +/- 4.1	6.1 +/- 2.9	<0.001
	Placebo	10.5 +/- 4.0	9.4 +/- 3.4	0.025
VAS score	Curcuminoids	66	36	<0.001
	Placebo	30	58	>0.05

The 2014 study by Nakagawa et al. also compares the short-term effects of curcuminoid therapy as compared to a placebo group at baseline, two, four, six, and eight weeks.[3] Patients randomly assigned to the treatment group received 180mg of Theracurmin, a research developed surface-controlled dispersible curcumin product, per day for eight weeks.[3] Knee pain VAS scores were significantly lower in the Theracurmin group than in the placebo group, with the exception of the six patients with initial VAS scores of equal to or below 0.15.[3] The average baseline VAS score in the placebo group was 0.42, and after eight weeks dropped to 0.21.[3] The mean VAS in the Theracurmin group at baseline and eight weeks were 0.52 and 0.20, respectively, with a p-value of 0.023.[3] Additionally, this study found that Theracurmin lowered the celecoxib (NSAID) dependence significantly when compared to the placebo group.[3] No considerable adverse effects were mentioned in this study. Data from this study can be found below in Table 4.

Table 4: Theracurmin vs Placebo (Nakagawa et al. 2014)[3]		
	Theracurmin	Placebo
Baseline VAS score	0.52	0.42
8-week VAS score	0.20	0.21
Baseline Celecoxib use (%)	72	83
8-week Celexicob use (%)	32	61

DISCUSSION

While all three studies showed a significant change in baseline in adult osteoarthritis knee patients, there were certain limitations in each study that need to be taken into consideration. All three selected studies evaluated short-term effectiveness of curcuminoids, measuring final outcomes at four, six, and eight weeks respectively. Both the Panahi et al. and the Nakagawa et al. studies had significantly smaller patient populations, including only 53 and 50 patients.[3,6] These population sizes are large enough to have significance in the given studies, however, larger-scaled studies should be performed in the future to see if these results can be replicated.

The 2014 study conducted by Panahi et al. was completed in patients older than 80 years old, which is typically classified as a different age group rather than "adult."[6] This jump in age classification may be considered as an outlier in this selective review. Although all patients are accounted for, this study had the largest loss of follow-up (24.53%) due to patients dropping out or becoming involved in an alternative therapy that then eliminated the individual from the study, as stated by the exclusion criteria.[6]

In order to best evaluate the effects of curcuminoids, two of the selected studies gave oral medications that had altered pharmacokinetics in order to enhance the absorption of the given curcuminoid. The 2014 Nakagawa study provided patients in the treatment group with Theracurmin, a curcuminoid product that was created by researchers to enhance absorption.[3] In addition, the Panahai et al. study specifies that the curcuminoid oral medication was

administered with Biperine to enhance absorption of the medication, which may have a direct effect on the outcomes evaluated in the study.[6]

The 2014 study completed by Kuptniratsaikul et al. is the only study that mentions adverse effects of the curcuminoid product. This study does not go into detail regarding the specifics of the adverse event, however, there was one patient in the curcuminoid treatment group that dropped out of the trial due to gastrointestinal (GI) adverse effects.[2] The only other mention of adverse effects comes from the 2014 Nakagawa study, where it is stated that curcuminoids can actually be protective of the gastric mucosa, as compared to the damaging adverse effects with non-steroidal anti-inflammatory drugs.[3] The only clearly stated contraindication to curcuminoids is in patients with a curcuminoid allergy.[2,6] Future studies should focus on the side effect profile of curcuminoids in order to paint a more complete picture.

The accessibility of curcuminoids as knee osteoarthritis therapy cannot be ignored when discussing the effectiveness of treatment. Currently, no curcuminoid product is approved or endorsed by the Food and Drug Administration (FDA) for any specific disease treatment. In addition to current studies evaluating curcuminoid effectiveness in treating osteoarthritis, there are studies being conducted surrounding the role of curcuminoids in gastrointestinal and cardiac diseases, some cancers, and other inflammatory conditions.[2,3,6] Access to curcuminoid products parallels the vitamin industry, with availability at almost any drug store, grocery store, and nutrition shop. Curcuminoids are typically available in these location as Turmeric powder, oral pill form, or as oral combination products. If curcuminoids become a FDA approved treatment, the current ease of access may become more difficult as the medication(s) will become regulated. The question remains whether or not insurance will cover curcuminoid products if they become an approved FDA treatment for osteoarthritis.

CONCLUSION

Curcuminoids are an effective and safe therapy to reduce knee pain in adults with knee osteoarthritis, without the aforementioned contraindications. All three studies showed a decrease in pain from baseline with the use of curcuminoids. Coincidentally, curcuminoid therapy in osteoarthritis decreases the dependence on NSAIDs as adjunctive pain management.

Although the popularity of researching curcuminoids has continually grown, additional studies need to be carried out with larger population sizes and with longer follow up periods to see if the treatment effects observed here are carried over on a larger, long-term scale. More studies are needed to evaluate the therapeutic index, potential adverse effects, and/or the maximal tolerable dose of curcuminoids when treating osteoarthritis. Furthermore, future studies should look to evaluate different dosages of curcuminoids and attempt to establish if there is a dose-response pattern.

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