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Curcumin supplementation for relief of pain associated with osteoarthritis

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Abstract:

List of Abbreviations

NSAID	Nonsteroidal Anti-inflammatory drug
OA	Osteoarthritis
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
VAS	Visual analogue scale
LPFI	Lequesne Pain and Function Index
KOA	Knee osteoarthritis
ROS	Reactive oxygen species
ADL	Activity of daily living
BMI	Body mass index

Objective*:* To determine if curcumin supplementation compared to nonsteroidal anti-inflammatory drugs (NSAIDs), placebo, and rescue medications is an effective treatment of arthritic symptoms in males and females between the ages of 50 and 80 with a diagnosis of osteoarthritis.

Design: Systematic Literature Review

Methods: Searches were done in PubMed, Google Scholar, and Scopus utilizing the terms "turmeric", "curcumin", "osteoarthritis", "NSAIDs", "ibuprofen", and "placebo." The following limits were applied: excluded if compared greater than two remedies for treatment of osteoarthritis or if turmeric was used as an "add-on" for treatment. Articles were included if they only dealt with human subjects, were published in 2014 or later, and were full-text.

Results: A randomized control trial by *Kuptniratsaikul, V. et al* concluded that curcumin was as efficacious as ibuprofen in reducing pain and improving function associated with Osteoarthritis (OA) with the benefit that curcumin resulted in less gastrointestinal complaints. *Srivastave, S. et al* concluded that curcumin can be used with diclofenac to provide relief in patients with knee OA. The results demonstrated that patients in the curcumin and diclofenac group had improvement in all three measures of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score when compared to patients in the placebo group. *Panahi Y. et al* study showed a statistical significant improvement in measures of the WOMAC score in the curcumin group while the placebo group showed no change in WOMAC parameters. The curcumin group also had significant reduction in Visual Analogue Scale (VAS) and Lequesne Pain and Function Index (LPFI) scores compared to placebo.

Conclusion: Curcumin may provide relief of osteoarthritic symptoms as demonstrated by subjective measures of pain and objective measures of inflammation. Additionally, curcumin has a strong safety profile, a low potential for toxicity, and few adverse side effects those of which include gastrointestinal symptoms such as diarrhea and flatulence. Further research is needed to investigate the relationship between curcumin and the impact on osteoarthritic symptoms

independent of NSAIDs. Additionally, population based studies are needed to see if the results of a small sample size can be applied to the general population.

Introduction:

Osteoarthritis (OA) is a degenerative joint disease characterized by joint pain, stiffness, and restricted movement and is a leading cause of chronic disability in adults. Also called degenerative joint disease, OA is characterized by sclerosis, osteophytosis, and joint space narrowing. Weight bearing joints are frequently impacted and lead to increased disability and impaired functioning of daily living activities (6). Commonly affected joints include the hands, hips, knees and shoulders. A study conducted in 2005 estimated that over 27 million Americans live with OA representing nearly 10% of the US population (1). Two major risk factors for the development of OA include age and obesity. According to one study, the lifetime risk of developing symptomatic knee arthritis was one in two people will develop symptomatic knee arthritis by the age of 85 and two thirds of obese individuals will also develop OA (1). Despite the prevalence and the impact on daily living, there are limited treatment options for OA.

The development of osteoarthritis is multifactorial, and the pathogenesis is complex. OA is characterized by inflammation at the molecular level rather than the cellular level. The development of OA involves the production of pro-inflammatory mediators and alterations in the synovium and soft tissue of joints. When individuals are affected with OA, the body produces pro-inflammatory mediators, including cytokines that stimulate the production of proteolytic enzymes leading to breakdown of the articular cartilage. The synovium is also affected which contributes to the development of pain and swelling. Over time, with increased breakdown of the cartilage, the pain and inflammation worsens. Due to this effect, patients may experience pain that worsens with activity and improves with rest.

Current treatment modalities for osteoarthritis are centered on symptom management which encompass lifestyle changes such as weight loss, pharmacological treatment, and surgical intervention. Treatment for OA targets relief of symptoms with the use of nonsteroidal anti-inflammatory agents (NSAIDs), opioid analgesics, and intraarticular injections. Although research has investigated the development of disease modifying drugs for the treatment of OA, currently there is no FDA approved pharmacological treatment designed to change the progression of the disease (3).

While NSAIDs remain the agent of choice for pain management in OA, long term use of NSAIDs is associated with several adverse side effects, including gastrointestinal, renal, and cardiovascular symptoms. This has led to an increased interest in herbal supplements for the treatment of OA including curcumin. Curcumin is a yellow substance that comes from the rhizomes of *Cercuma Longa*, otherwise known as turmeric (4). Although curcumin was discovered in 1748, its first documented use in humans was not until 1937 when a paper was published demonstrating the effect of curcumin in treating cholecystitis. Since then, further studies have demonstrated that curcumin is safe, tolerable, and nontoxic in humans (5). Later research has found curcumin to have anti-inflammatory and antioxidant properties, and it is capable of inhibiting some of the pro-inflammatory mediators frequently seen in the development of OA.

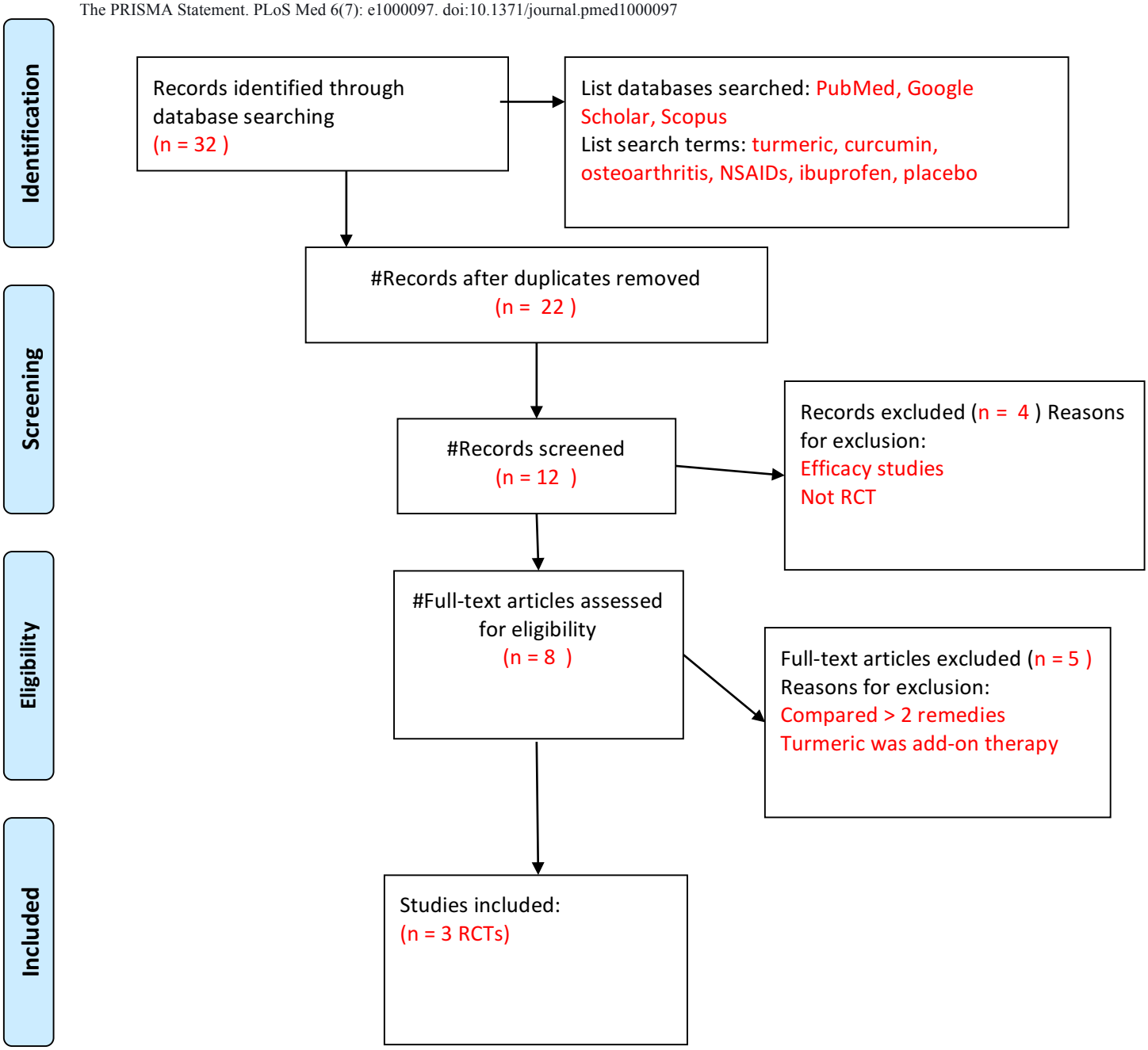
To date there is limited research on the effects of curcumin on symptom relief for osteoarthritis; however, the research may suggest curcumin to have the same effect as NSAIDs with the addition of limited gastrointestinal side effects. Therefore, the present study sought to evaluate the effectiveness of curcumin in relieving symptoms of OA in males and females between the ages of 50 and 80 when compared with placebo and NSAIDs.

Methods

An initial search of PubMed, Google Scholar, and Scopus was performed in September 2017 using the search terms “turmeric”, “curcumin”, “osteoarthritis”, “NSAIDs”, “ibuprofen”, and “placebo” yielding 32 results (See Figure 1). Duplicate articles were removed, and the articles were further searched and only included if they were randomized control trials published in 2013 or later with full text articles available. This narrowed the results to 12 articles. The 12 full-text articles were assessed for eligibility and were excluded if they compared greater than two remedies for treatment of osteoarthritis or if curcumin was used as an “add-on” for treatment, yielding eight articles. Individual articles were reviewed, and three randomized control trials were chosen as they were the only three comparing curcumin to a different treatment options for osteoarthritis.

Figure 1. PRISMA flow diagram summarizing the article search process.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097



Results:

Study #1

Efficacy and safety of Curcuma domestica extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. Kuptniratsaikul, V. et al 2014

Objective:

This randomized control trial's goal was to determine the efficacy and safety of curcumin in pain reduction and functional improvement compared with ibuprofen in patients with osteoarthritis.

Study Design:

Participants were recruited from eight tertiary hospitals in Thailand from July 2010 to March 2012. Eligibility requirements included being a primary knee osteoarthritis patient according to the American Rheumatism Association criteria and having a numerical score of knee pain of ≥ 5 out of 10 and age ≥ 50 years. Patients were excluded if they had abnormal liver function or renal function, history of peptic ulcer, allergy to curcumin or ibuprofen, or were unable to walk. All inclusion and exclusion criteria is summarized in Table 1. All participants received a knee x-ray to indicate severity of OA according to the Kellgren-Lawrence criteria, a method of classifying the severity of knee osteoarthritis using a 0-4 scale depicted in Table 2 (6).

Table 1. Patient Inclusion and Exclusion Criteria; Kuptniratsaikul, V. et al 2014

Inclusion Criteria
Primary knee osteoarthritis patients according to American Rheumatism Association criteria Numerical score of knee pain at least 5 out of 10 Age at least 50 years old
Exclusion Criteria
Abnormal liver or renal function History of peptic ulcers Allergy to curcumin or ibuprofen Unable to walk

Table 2. Kellgren/Lawrence Osteoarthritis grading

Grade	Classification
Grade 0	no radiographic features of OA are present
Grade 1	doubtful joint space narrowing (JSN) and possible osteophytic lipping
Grade 2	definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
Grade 3	multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4	large osteophytes, marked JSN, severe sclerosis and definite bony deformity

Subjects were randomized by computer to receive either 1,200 mg/day of ibuprofen or 1,500 mg/day of curcumin. Patients took two capsules after meals three times a day for four weeks and were not allowed to take other medications during the study. Outcomes were measured at week 2 and week 4 by the same assessor. Outcomes measured included the Western Ontaria and McMaster Universities Osteoarthritis Index (WOMAC) and a 6-minute walk distance. WOMAC is a widely used standardized questionnaire used to evaluate the condition of patients with osteoarthritis of the knee and hip. WOMAC is broken down into 3 subscales; pain, stiffness, and function, each on a scale from 0-10, the higher the score the worse off (7). Adverse events were also compared between the two groups. Further, compliance of treatment was assessed using pill count at each visit. At the end of the study, patient's global assessment and satisfaction was evaluated.

The final sample size included 331 patients; 160 ibuprofen and 171 curcumin participants. The mean score of WOMAC and the 6-minute walk distance at week 4 were compared between groups using analysis of covariance and the unpaired t-test. The adverse events and satisfaction levels were analyzed using chi-square and the compliance of the drug intake was compared using the t-test for equality.

Study Results:

The primary outcome focused on for this study was the WOMAC scores and the 6-minute walk test. Eligible treatment group distribution is shown in table 3. The baseline characteristics of participants were no different between the two randomized groups.

Table 3. Distribution of patients randomized to the treatment groups; Kuptniratsaikul, V. et al 2014

Patients	Curcumin	Ibuprofen
Initial	185	182
Withdrawal Week 2	3	8
Withdrawal Week 4	11	14
Completed study	171	160

Group comparison of the WOMAC scores showed statistically significant improvement from baseline, however, the between-group comparison showed no difference in WOMAC scores showing that the curcumin group was non-inferior to the ibuprofen group. Concerning the

effectiveness of curcumin, the primary outcomes of WOMAC and the 6-minute walk were compared at week 4. The total WOMAC score for the curcumin was 3.36 while the ibuprofen group total was 3.23. Broken down by section WOMAC pain subscale was a 3.25 for curcumin versus 3.17 for ibuprofen. The WOMAC stiffness subscale was 3.28 for curcumin and 3.16 for ibuprofen, and WOMAC function was 3.41 for curcumin compared to 3.26 ibuprofen. The 6-minute walk in meters was 345.43 for the curcumin group compared to 347.99 for the ibuprofen group. In summary, both the ibuprofen and the curcumin group showed improvement from baseline. The WOMAC total score, pain, and functional ratings were equivocal between the two groups. However, the curcumin group had greater reductions in the WOMAC stiffness scale compared to the ibuprofen group which trended towards statistical significance (P value= 0.060). Additionally, the number of patients that reported abdominal discomfort was significantly higher in the ibuprofen group compared to the curcumin group (P value= 0.046) (see Table 4).

Table 4. Mean and SD for WOMAC and 6-minute walk distance at week 4 in ibuprofen and curcumin groups; Kuptniratsaikul, V. et al 2014

Mean score at week 4	**Ibuprofen (n = 160)**	**Curcumin (n = 171)**	**P-value**
WOMAC score total	3.23 ± 1.97	3.36 ± 2.04	0.010
WOMAC pain subscale	3.17 ± 1.98	3.25 ± 2.11	0.018
WOMAC stiffness subscale	3.16 ± 2.36	3.28 ± 2.38	0.060
WOMAC function subscale	3.26 ± 2.05	3.41 ± 2.09	0.010
6-minute walk (meters)	347.99 ± 86.60	345.43 ± 91.66	0.320

Secondary outcomes showed that overall there was no difference between adverse effects between the groups, 35.7% in ibuprofen and 29.7% in the curcumin group, P = 0.222. Common adverse effects included dyspepsia, abdominal pain/distension, nausea, loose stool, and pitting edema. The rate of abdominal pain/distension was significantly lower in the curcumin group at 10.8% than in the ibuprofen group at 18.1%. Rates of dyspepsia, nausea, and pitting edema were higher in the ibuprofen group compared to the curcumin group. Only the symptom of loose stool was higher in the curcumin group 11.9% compared to 8.8% in the ibuprofen group (see Table 5).

Table 5. Adverse events occurring during study compared between two groups; Kuptniratsaikul, V. et al 2014

Adverse events	Ibuprofen (n = 182)	Curcumin (n = 185)	P-value
Percentage of patients with adverse event	35.7%	29.7%	0.222
Abdominal pain/distension	18.1%	10.8%	**0.046***
Dyspepsia	15.9%	11.4%	0.201
Nausea	8.2%	4.9%	0.191
Loose stool	8.8%	11.9%	0.330
Melena	1.1%	0%	0.245
Pitting edema	7.1%	3.8%	0.156

In addition, there was no statistical difference in drug compliance between the groups, 93.8% compliance in the ibuprofen group and 92.6% in the curcumin group; p-value 2.202. The patient's global assessment and satisfaction at week 4 also showed no difference between groups, however, 96% and 97% of subjects in the ibuprofen and curcumin groups respectively, were satisfied with the treatment. Further 63.8% and 64.3% respectively rated themselves as improved (Table 6).

Table 6. Percentage of patient's global assessment and satisfaction at week 4; Kuptniratsaikul, V. et al 2014

Variables	Ibuprofen (n=160)	Curcumin (n=171)	P-value
Global assessment			0.665
Improved	63.8%	64.3%	
Indifferent	32.5%	33.9%	
Deteriorated	3.7%	1.8%	
Satisfaction index			0.707
Satisfied	95.6%	97.1%	
Indifferent	4.4%	2.3%	
Unsatisfied	0.0%	0.6%	

Based on all of the results stated above, Kuptniratsaikul concluded that curcumin is as effective as ibuprofen for the treatment of knee osteoarthritis. The side effect profile was similar but with fewer gastrointestinal adverse effects in the curcumin group.

Study Critique:

A strength of this article was the fact that it is a double-blind randomized controlled trial. Further, strict inclusion and exclusion criteria were used to avoid confounding variables. Examples of this include defining osteoarthritis according to the American Rheumatism

Association criteria and not including patients with co-morbid conditions such as renal and liver disease. Both medications were manufactured by the Department of Pharmacy, Siriraj Hospital, Bangkok, Thailand, in the form of a capsule, to make them identical in appearance. The treatment codes were further kept by a pharmacist who was not involved in the study process. An additional strength of this study was the large sample size, with a total of 331 participants completing the study. Most other articles comparing curcumin had sample sizes much smaller, typically with twenty to fifty patients total.

One drawback to this study was the use of multiple subjective results. These included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), adverse events reported, as well as global assessment and overall satisfaction. The only objective data measured in this study was the 6-minute walk test. Another limitation to the study was the short duration at only 4 weeks. The short duration of the study may have skewed the results, thus resulting in no statistical significance overall.

Another consideration when evaluating this article is when it comes to comparing the patient population in Thailand to the population in the United States. Although the study was completed in Thailand, the results can still be applied to a United States population. This is because osteoarthritis is a degenerative joint disease which can affect anyone regardless of where they live. There are different degrees of severity of OA, however, this is true regardless of what country a person lives in. Further, the strict inclusion and exclusion criteria of this study, which were according to the American Rheumatism Association, makes the study easily replicable in any country.

Study #2

Curcuma longa extract reduces inflammatory and oxidative stress biomarkers in osteoarthritis of knee: a four-month, double-blind, randomized, placebo-controlled trial. Srivastava, S et al. 2016.

Objective:

This double-blind randomized placebo-controlled clinical trials primary goal was to observe the effect of curcumin on clinical improvement in patients with knee osteoarthritis (KOA) as assessed by the Visual Analog Scale (VAS) and the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC).

Study Design:

The study was conducted at King George's Medical University in Lucknow, India. Criteria for establishing a patient suffering from KOA were according to the guidelines proposed by The American College of Rheumatology. Further, participants were included if they were between the ages of 40-80. Radiographic osteoarthritis of the knee was classified according to the Kellgren-Lawrence grading scale (see Table 2). Participants were excluded if they were less than 40 years old or more than 80, if they suffered from rheumatoid arthritis, diabetes mellitus,

renal insufficiency, hepatic disease, cardiovascular disease, gout, were pregnant, or with any other systemic disease. Inclusion and exclusion criteria is summarized in Table 7.

Table 7. Patient Inclusion and Exclusion Criteria; *Srivastave, S. et al 2016.*

Inclusion Criteria
Primary knee osteoarthritis patients according to American Rheumatism Association criteria Age 40-80
Exclusion Criteria
Rheumatoid arthritis Diabetes mellitus Renal insufficiency Hepatic disease Cardiovascular disease Gout Pregnancy Other systemic diseases

Participants were assigned by computerized randomization to receive either 500 mg of curcumin and 50 mg/day of diclofenac or 500 mg placebo capsules along with 50 mg/day diclofenac. The final sample size was 133 patients including 66 in the curcumin group and 67 in the placebo group. Outcomes were measured on days 0, 60, and 120. Measurements included the VAS, WOMAC, and biochemical markers including: Reactive Oxygen Species (ROS), serum IL-1Beta, and serum MDA. The VAS is a subjective measurement, with use of a horizontal line which contains word descriptions at each end, ranging from 0-10 representing pain level. Zero indicates no pain and 10 indicates unbearable pain. The patient marks one of the following options: no pain, mild pain, moderate pain, or severe pain. ROS and MDA are biomarkers of oxidative stress and serum IL-1Beta is a marker of inflammation.

Results were analyzed using the chi-square test to compare categorical variables, the unpaired t-test to compare discrete variables, and a paired t-test to compare mean change in discrete variables from day 0 to 60, day 60 to 120, and day 0 to 120.

Study Results:

Outcomes focused on for this study included the VAS, WOMAC, and biochemical markers ROS, MDA, and IL-1Beta. Eligible participant breakdown throughout the study is summarized in table 8.

Table 8. Study participants; *Srivastave, S. et al 2016.*

Participants	Curcumin	Placebo
Initial	78	82
Lost to follow-up after 60 days	7	8
Lost to follow-up after 120 days	5	7
Completed Study	66	67

Group comparison of the visual analog scale (VAS) showed statistical significance (P-value <0.05) on Day 60 and Day 120 with scores being lower amongst the curcumin group. The VAS score for curcumin at day 60 was 4.96 while the placebo group was 6.00. At day 120 the VAS for the curcumin group was 4.03 and the placebo 5.11. Further, statistical significance was seen amongst the WOMAC subcategories of pain and patient function between the two groups for follow-up day 60 and day 120. In regards to pain, at day 60, the curcumin group was at 11.19 and the placebo group 12.05. At day 120, curcumin group was at 9.48 and the placebo group at 10.16. For patient function, at day 60 curcumin was 41.28 and placebo was 45.11, whereas, at day 120, curcumin was 32.14 and placebo at 33.88 (see table 9).

Table 9. Effect of treatment on VAS and WOMAC scores between groups; *Srivastave, S. et al 2016.*

Parameters	Curcumin	Placebo	P value
VAS Score			
Day 0	7.94 ± 0.13	7.66±0.14	0.15
Day 60	**4.96±0.07**	**6.00±0.11**	**0.0001***
Day 120	**4.03±0.08**	**5.11±0.14**	**0.0001***
WOMAC Score			
Pain			
Day 0	15.10±0.31	15.29±0.26	0.64
Day 60	**11.19±0.26**	**12.05±0.21**	**0.01***
Day 120	**9.48±0.17**	**10.16±0.16**	**0.06***
Stiffness			
Day 0	5.55±0.21	5.31±0.12	0.53
Day 60	4.51±0.21	4.70±0.23	0.54
Day 120	4.08±0.17	4.16±0.18	0.73
Patient Function			
Day 0	54.03±0.68	50.99±0.68	0.008
Day 60	**41.28±0.51**	**45.11±0.37**	**0.0001***
Day 120	**32.14±0.40**	**33.88±0.50**	**0.008***

Biochemical outcomes, which is objective data, also showed statistical significance amongst groups for ROS at days 0. 60, and 120 respectively, and for MDA at day 60 and 120. The ROS for the curcumin group at day 0 was 3798 MFI compared to 2584 MFI for the placebo group. For day 60, curcumin was 2553 MFI and the placebo 2144 MFI, and for day 120 the curcumin was 1200 MFI and the placebo group 2197 MFI. For MDA at day 60 the curcumin group was 3.85 nmol/ml and the placebo 5.00 nmol/ml. At day 120, the curcumin group MDA was 3.96 nmol/ml and the placebo group 4.91 nmol/ml (see Table 10).

Table 10. Effect of treatment on biochemical parameters between the study groups; *Srivastave, S. et al 2016.*

Parameters	**Curcumin**	**Placebo**	**P value**
IL-1b (pg/ml)			
Day 0	126.4 ±19.94	131.5 ±19.79	0.85
Day 60	65.61 ±21.59	74.83 ±22.31	0.76
Day 120	21.11 ±1.176	35.82 ±7.53	0.55
ROS (MFI)			
Day 0	**3798 ±1507.77**	**2584 ±671.74**	**0.001***
Day 60	**2553 ±775.67**	**2144 ±1275.97**	**0.001***
Day 120	**1200 ±864.08**	**2197 ±1378.90**	**0.0001***
MDA (nmol/ml)			
Day 0	5.02 ±0.16	5.15 ±0.14	0.57
Day 60	**3.85 ±0.12**	**5.00 ±0.11**	**0.0001***
Day 120	**3.69 ±0.12**	**4.91 ±0.11**	**0.0001***

Overall clinical assessment amongst participants showed statistically significant improvement in presence of joint crepitation, joint stiffness, and joint effusion between the two groups. There was an overall reduction of 60% of participants with presence of joint crepitation for the curcumin group and 20% reduction for the placebo group. A 64% overall reduction was seen in the curcumin group in regards to presence of joint stiffness and a 31.8% reduction for the placebo group. Lastly, an overall reduction of 75.8% was seen in the curcumin group for joint effusion presence and 37% for the placebo group (see Table 11).

Table 11. Clinical assessment parameters between the two groups; *Srivastave, S. et al 2016.*

Parameters	**Curcumin**	**Placebo group**	**P value**
Reduction of joint crepitation	60%	20%	**0.001***
Reduction of joint stiffness	64%	31.8%	**0.027***
Reduction of joint effusion	75.8%	37%	**0.003***

In conclusion this study showed that adjuvant therapy curcumin along with diclofenac produces overall significant improvement in patients with knee osteoarthritis. Thus, it is proposed that patients with KOA should be given curcumin as soon as the diagnosis is made to help improve outcomes.

Study Critique:

One strength of this article is that it was performed as a double blind randomized control trial which helps eliminate some potential confounding variables. Additionally, its use of objective data including measurements of reactive oxygen species (ROS), IL-1Beta, and MDA, which are biomarkers of inflammation and oxidative stress provide a more accurate account of efficacy. Objective data provides concrete evidence of improvements of knee osteoarthritis among the curcumin treatment group. Another strength of the study is the use of multiple follow-up days, measuring all data at day 60 and then again at day 120. This allows for continuous monitoring to see if improvements are shown throughout the four months and not just at the end of the study.

One of the drawbacks of this study was the small sample size. In the end, only 133 participants completed the study, 66 in the curcumin group and 67 in the placebo group. This is not a very large number, and significance could have changed if the sample size was larger. Another drawback of the study was the fact that both groups used diclofenac, an NSAID used to treat knee osteoarthritis. Because of the combination of treatment, in the end, it remains unknown how much the curcumin really benefited the treatment group versus if the diclofenac was what benefited the group.

Another consideration is if this study can be applied to the United States as it was performed in India. However, osteoarthritis is a degenerative joint disease that can affect any person regardless of where they live in the country. Further, the inclusion and exclusion criteria for this study were set according to the American College of Rheumatology, and due to this standard criteria, the study can easily be replicated and repeated in any country.

Study #3

Curcuminoid Treatment for Knee Osteoarthritis: A Randomized Double-Blind Placebo-Controlled Trial. Panahi, Y et. al, 2014.

Objective:

This double-blinded randomized placebo-controlled study sought to determine the clinical efficacy of curcumin in reducing clinical symptoms of knee osteoarthritis as assessed by the McMaster Universities Osteoarthritis Index (WOMAC) score, Lequesne's pain functional

index (LPFI), and visual analogue score (VAS). The aim of this pilot study was to determine the efficacy of curcumin in alleviating OA symptoms when co-administered with the brand name Bioperine, also known as the generic agent, piperine, an extract that enhances the absorption of curcumin.

Study Design:

The study included patients with a diagnosis of knee OA who were referred to the Baqiyatallah University Clinic in Tehran, Iran during 2011 and 2012. Participants were permitted to participate if they had primary knee OA with mild to moderate severity, as determined by radiological and clinical criteria. The radiological criteria is defined by the American College of Rheumatology, and the clinical criteria was determined by patients scoring on the VAS score. Participants had to score at least 40 mm on a 100 mm VAS score rating when assessed for the degree of pain on active movement. The study had several exclusion criteria which are listed in table 12.

Table 12. Patient Inclusion and Exclusion Criteria; *Panahi Y. et al 2014.*

Inclusion Criteria
Primary knee osteoarthritis with mild to moderate severity as defined by the American College of Rheumatology and the Visual Analogue Scale score of at least 40 mm on a 100 mm scale Bilateral OA Age less than 80 years old
Exclusion Criteria
Allergy to curcuminoids or other herbal medications Candidates for surgical joint replacement or any other surgical treatment OA secondary to trauma Rheumatoid arthritis Hemophilia Malabsorption disorders Active or generalized inflammatory disorders (erythrocyte sedimentation rate (ESR) greater than 20) Heart, renal or liver disease Corticosteroid use over 10 mg/day in the preceding 3 months History of psychological disorders Intra-articular injections administered within the preceding 3 months

Participants were randomly assigned using a 1:1 ratio scheme in consecutive order to receive either curcumin 1500 mg/day or placebo for 6 weeks. Patients in the curcumin group were instructed to take three 500 mg tablets each day. The curcumin capsules each contained 5 mg Bioperine to enhance the absorption of the curcumin; the placebo tablets contained starch. During each week of the trial, regular consumption of the tablets was monitored. Both the

curcumin group and the placebo group were allowed to take naproxen when they experienced intolerable discomfort. The final sample size that completed the trial included 19 participants in the curcumin group and 21 in the placebo group.

Outcome measurements were assessed using the WOMAC, VAS and the LPFI. The WOMAC index was used to determine the severity of OA symptoms and included 5 items relating to pain, 2 items relating to stiffness, and 17 items to assess physical functioning. Each item is then rated on a scale of 0 to 4, with a total score of 0-20 for pain, 0-8 for stiffness, and 0-68 for physical functioning.

This study determined the severity of pain by using the VAS scores collected from participants. The VAS score ranges from a score of zero, indicating no pain at all, to a score of 100 which signifies unbearable pain. The VAS scores are collected by having the patient mark on a horizontal line the number that correlates to his or her level of knee pain severity.

The Lequesne's pain functional index (LPFI) looks at pain, maximum distance walked, and activities of daily living (ADL). The pain and ADL scores range from 0 to 8 with zero representing no pain or no functional limitations and 8 representing maximum level of impairment. The maximum distance walked ranges from 0 to 6, with zero representing unlimited ability to walk and 6 signifying severe limitations with less than 100 meters of walking distance. Further, the LPFI score is increased by one point if the patient uses one crutch and two points if the patient uses two crutches. The LPFI scores range from 0 to 24, with higher scores representing a decreased health and more severe impairment.

The statistical analysis was carried out by computers, and each parameter was assessed at baseline and at the end of the trial using a paired samples T-test. The differences in magnitude were assessed using independent t-tests. A p-value less than 0.05 was considered statistically significant in this study.

Study Results:

Outcomes in this study focused on WOMAC scores, LPFI, and VAS scores among curcumin and placebo groups. The baseline characteristics between the two groups were matched for age, gender, BMI and mean WOMAC, LPFI, and VAS scores.

Participants in the curcumin group had a statistically significant reduction in mean WOMAC scores with respect to global score, physical function, and stiffness at the end of the trial when compared to individuals in the placebo group. The WOMAC scores for individuals in the placebo group had no change in the score, pain, or physical function. However, participants in the placebo group had a statistically significant decrease in the stiffness subscale. When the two groups were compared, curcumin showed a decrease in WOMAC scores for measures of global assessment, pain, and physical functioning. However, no statistical significance was found between curcumin and placebo for a change in stiffness. Refer to table 14 for comparison among groups.

When comparing LPFI and VAS scores among the two groups a statistically significant reduction in scores was seen in the curcumin group compared to the placebo. Additionally, 84% of subjects in the curcumin group reported a reduction in the use of naproxen compared to individuals in the placebo group (P value <0.001). However, reduction in the use of naproxen was based upon patients own recordings of usage. Patients receiving curcumin reported using 250 to 500 mg of naproxen compared to individuals in the placebo group reporting use of 500 to 750 mg of naproxen.

Table 13 shows the breakdown of individuals among groups. The researchers determined that the loss of follow-up was not due to adverse effects associated with curcumin supplementation, with four patients in the placebo group reporting mild gastrointestinal symptoms and seven in the curcumin group which was not shown to be statistically significant.

Table 13. Study participants; *Panahi, Y. 2014*

Participants	**Curcumin**	**Placebo**
Initial	27	26
Lost to follow-up	8	5
Completed Study	19	21

Table 14. Effect of treatment on WOMAC scores between groups; *Panahi, Y. et al 2014.*

Parameters	**Curcumin**	**Placebo**	**P-value within group**	**P-value between groups**
WOMAC Score				
Pain				
Before treatment	9.9± 4.1	10.5±4	**<0.001***	**<0.001***
After treatment	6.1±2.9	9.4±3.4	**0.025***	**<0.001***
Stiffness				
Before treatment	1.05±1.8	1.7±1.7	**0.043***	0.912
After treatment	0.15±0.5	0.76±0.9	**0.009***	0.912
Patient function				
Before Treatment	31.8±14	32.4± 12.8	**<0.001***	**<0.001***
After treatment	18.7±10.3	30.4±9.4		
Global score				
Before Treatment	42.4±18.3	44.6±17.3	**<0.001***	**0.001***
After Treatment	25.0±13	40.6±12.6		

Study Critique:

One of the strengths of this study was that it is a double-blinded randomized placebo-controlled study. Further, if participants did not complete the study or were noncompliant, they

were not included in the overall results of the study. Another strength is the addition of Bioperine to the curcumin group which allowed for greater absorption of the compound and may have produced more efficacious results. The addition of Bioperine has been shown to increase blood concentrations of curcumin in the intestinal tissue and enhance permeability. In previous studies, curcumin has had limited efficacy due to its poor systemic absorption when taken by itself. Another strength of this study is that it is a randomized control trial which helps control confounding variables that otherwise could skew the results.

The major limitation of this study was the small sample size. The study included a total of 40 patients that completed the trial which may make it difficult to generalize the findings to the larger population as a whole. Despite the small sample size, researchers were still able to demonstrate statistical significance for the effect of curcumin on improving WOMAC, VAS, and LPFI scores. A second limitation of this study was that participants were only supplemented with curcumin for a duration of 6 weeks. Considering that OA is a chronic condition, if patients benefited from use of curcumin, it is likely that he or she would supplement indefinitely. This makes it difficult to determine the long-term efficacy of curcumin from a trial lasting such a short duration. The third limitation of this study was that only patients with mild to moderate OA were allowed to participate. The trial does not address if patients suffering from severe OA are likely to benefit from curcumin supplementation.

Another limitation is that the study did not clearly define what intolerable pain was, and therefore, it was up to each patient to determine if they needed naproxen. The study also relied on self -reported data of naproxen use. It is possible patients forgot to keep track of each time naproxen was used which could have significantly altered the results.

Additionally, this study was performed in Iran and not the United States. However, osteoarthritis is a degenerative joint disease that can be seen in any country. Therefore, this study can still be applied to the United States.

Discussion:

To date, there is limited research on the effects of curcumin on symptom relief for osteoarthritis. All three of the articles reviewed concluded that use of curcumin is as effective as other currently used treatments such as NSAIDs. Additionally, curcumin has the added benefit of fewer gastrointestinal adverse effects. Side effects of curcumin supplementation include gastrointestinal upset such as diarrhea, flatulence, and abdominal bloating. Patients taking warfarin or other blood thinners should proceed with caution as long term use can thin the blood. An overview of the three studies including demographics, treatment, tests used, conclusion, and limitations can be seen in Table 15.

The Kuptniratsaikul, V. et al 2014 study concluded that curcumin is an efficacious and safe alternative to the use of ibuprofen for the treatment of osteoarthritis. Further, in regards to safety concerns, curcumin was been shown to have a better safety profile than ibuprofen in terms of abdominal pain and distension. They found that curcumin can be provided at 2,000 mg/d for 6 weeks or an even higher dose of up to 8,000 mg/d for 3 months without any serious adverse effects.

The Srivastave, S. et al 2016 study concluded that adjuvant therapy of curcumin along with diclofenac produces significant improvement in patients with knee arthritis, and therefore, curcumin should be given as soon as the diagnosis is made. Further, NSAIDs, if required, may

be given for a short period, but curcumin may be prescribed for long durations without fear of gastrointestinal or kidney adverse effects. The Srivastave, S. et al study was the only study included in this review that used biochemical measures including ROS, serum IL-1Beta, and serum MDA. This provided concrete results to support the effectiveness of curcumin.

The Panahi, Y. et al 2014 study found curcumin to be effective in alleviating the symptoms and improving care of patients with osteoarthritis. However, they concluded that these benefits should be exercised with caution due to limitations and further research needed. The Panahi, Y. et al study suggests that due to the positive results in this trial, future larger-scale trials should explore if curcumin can be used as a therapeutic regimen of patients suffering from knee osteoarthritis.

Due to the lack of research on curcumin, all three research articles used in this review used different variables making comparisons difficult. The Kuptniratsaikul, V. et al study compared curcumin to ibuprofen. The Sirvastave, S. et al study compared curcumin and diclofenac versus placebo and diclofenac. The Panahi, Y. et al study compared curcumin with the addition of Bioperine to placebo. A limitation seen in all three studies was that they allowed the use of rescue drugs as needed for severe flare up of osteoarthritic symptoms. Due to this fact, it is difficult to assess whether the curcumin alone had positive effects in relieving OA symptoms versus if it was simply the use of NSAIDs or the combination of the two bringing about the effect. Another limitation of all three trials is the short duration of treatment with curcumin. The longest duration of treatment amongst all three studies reviewed was only three months. This made it challenging to assess benefits of curcumin.

Due to the limitations mentioned above, more research is needed on the use of curcumin alone without the use of rescue medications, and longer trials are needed to assess benefits.

Conclusion

Does curcumin *supplementation when compared to NSAIDs, placebo, and rescue medications provide greater relief of arthritic symptoms in males and females between the ages of 40 and 80 with a prior diagnosis of osteoarthritis?*

Based on the results of these small double-blinded trials, curcumin may be an effective alternative to NSAIDs in controlling pain associated with osteoarthritis symptoms with minimized gastrointestinal side effects. Therefore, curcumin may be a reasonable alternative to patient who cannot tolerate NSAIDs due to the GI and cardiovascular adverse effects. However, due to the lack of research to date, additional studies on the use of curcumin in the treatment of OA are needed before a definitive recommendation can be made to the general population for its usefulness in pain relief in patients with OA. Future studies should include larger population based studies with longer duration of supplementation to better assess the general population as a whole and the effectiveness of curcumin. Further, additional studies would provide more accurate results if the use of rescue medications was limited. However, it may be unrealistic and unethical to ask subjects to limit the use of pain relievers in an effort to obtain clinical data.

Table 15. Overview of Studies

	Kuptniratsaikul, V. et al 2014	Srivastave, S. et al 2016	Panahi, Y. et al 2014
Sample size	331	133	40
Patient age	At least 50 yo	40-80 yo	Less than 80 yo
Gender	Males and Females	Males and females	Males and Females
Location	8 tertiary hospitals in Thailand July 2010-March 2012	King George's Medical University in Lucknow, India	Baqiyatallah University Clinic in Tehran, Iraq 2011-2012
Treatment	Curcumin vs. Ibuprofen	Curcumin and Diclofenac vs. Placebo and Diclofenac	Curcumin vs. Placebo
Study length	4 weeks	3 months	6 weeks
Follow-ups	At 2 weeks, 4 weeks	At day 0, 60, 120	None
Tests administered	WOMAC 6-minute walk distance	VAS WOMAC Biochemical markers: ROS, serum IL-1Beta, serum MDA	VAS WOMAC LPFI
Conclusion	Curcumin is as effective as ibuprofen for the treatment of knee osteoarthritis with fewer gastrointestinal adverse effects in the curcumin group.	Adjuvant therapy of curcumin along with diclofenac produces overall significant improvement in patients of knee OA. NSAIDs, if required, may be given for a short period but curcumin may be prescribed for long durations, without fear of damaging the GI or kidneys.	Curcumin and the addition of Bioperine is an effective and safe alternative treatment for osteoarthritis.
Limitations	-Short duration -Rescue med Toradol used for exacerbations -Results mostly subjective in nature	-Small sample size -Use of adjuvant diclofenac	-Small sample size -Results were all subjective -Rescue med Naproxen used for exacerbations -Only treated mild to moderate OA patients

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