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Are Curcuminoids Effective in Reducing 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 pain in adults with knee osteoarthritis.

STUDY DESIGN: This is a systematic review which evaluates three randomized controlled trials (RCT's) published in peer reviewed journals between 2016-2018.

DATA SOURCES: The data sources used for this review were found using PubMed and Cochrane Library. Data was chosen based on relevance to the clinical question and if patient-oriented evidence that matters (POEMS) were included.

OUTCOMES MEASURED: All three studies measured curcuminoids and its effects on pain reduction in adults with knee osteoarthritis using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a self-administered questionnaire consisting of 24 items divided into 3 subscales: Pain (5), Stiffness (2), Physical Function (17).

RESULTS: All three studies contained continuous data, therefore, p-values were reported for each of the studies. A p-value of ≤ 0.05 was reported by all three RCTs, thus concluding the data to be statistically significant. Each of the studies found with statistical significance that curcuminoids reduced pain in the adults with knee osteoarthritis reported by the participants of the trials. A study by Haroyan et al. (*BMC complementary and alternative medicine*. 2018;18(1):7. https://www.ncbi.nlm.nih.gov/pubmed/29316908. doi: 10.1186/s12906-017-2062-z.) concluded that curcuminoids in combination with boswellic acid may be more effective than curcuminoids alone when evaluating efficacy of pain reduction in adults with knee osteoarthritis.

CONCLUSIONS: After analysis of the three randomized controlled trials, evidence conducted in this review is conclusive that the use of curcuminoids can effectively reduce pain in adults with knee osteoarthritis.

KEYWORDS: Turmeric, curcumin, curcuma, curcuminoids, osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and is often referred to as degenerative joint disease or "wear and tear" arthritis. OA occurs when the articular cartilage within a joint begins to break down, ultimately leading to underlying bony changes of the joint. Among the joints of the body, the knee is the most commonly involved joint.[1] The etiology and risk factors for knee OA are multifactorial and individuals at risk for developing knee OA include women over the age of 50, those with previous injury or overuse to the joint and those who are considered obese or genetically predisposed.[2,3] Knee joint changes usually worsen over time and can eventually lead to pain, stiffness, swelling and decreased range of motion of the damaged joint. In severe cases, knee osteoarthritis can cause reduced function and the inability to complete daily tasks or work— making it the leading cause of chronic disability in the United States.[3,4]

Osteoarthritis is significant for its high prevalence among the general population, affecting 40 million adults in the United States, with nearly ninety percent of the population having radiographic features of OA in weight-bearing joints by age 40.[4] The economic costs of OA remain high especially regarding treatment. In 2013, osteoarthritis was the second most costly health condition to be treated at U.S. hospitals— accounting for 16.5 billion dollars of the combined costs for all hospitalizations.[3] Osteoarthritis also accounted for approximately 20.78 million ambulatory care visits and 2.95 million inpatient hospitalizations in 2013.[5] As the U.S. population continues to age, the prevalence of diagnosed osteoarthritis is expected to increase. According to the CDC, it is estimated that 78.4 million adults aged 18 years and older will have doctor-diagnosed arthritis by the year 2040.[3] This increase in prevalence will create opportunity for more mid-level providers such as physician assistants and nurse practitioners to manage patients with osteoarthritis and contribute to overall patient satisfaction and outcomes.

It is known that knee osteoarthritis occurs when all structures of the joint have undergone pathologic change and is primarily a result of the degeneration of cartilage and hypertrophy of bone at the articular margins.[4] Pain is the most common symptom experienced in knee OA as a result of these degenerative changes and ranges in severity from mild to immobilizing.[2] Pain experienced with knee OA is exacerbated with weight-bearing activities such as walking, standing or climbing stairs, and is typically relieved upon rest.[2]

Once an individual is diagnosed with osteoarthritis, the focus of treatment is to control symptoms by reducing pain and improving joint function. Conservative approaches to pain reduction in individuals suffering from knee OA include exercise, weight loss and supportive measures such as braces.[4] However, more commonly, individuals with knee OA will turn to pharmacological treatments to address their pain. Current knee OA treatments rely on oral analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) such as acetaminophen, ibuprofen, naproxen and celecoxib as well as topical therapies like diclofenac gel.[4,6] In severe cases where oral or topical therapies fail, intra-articular corticosteroid or hyaluronic acid injections are considered.[4] Surgical options such as arthrocentesis debridement and partial or total knee replacements are reserved for individuals who have failed the previously mentioned treatment modalities.[4]

While these conventional treatment options seem to be effective, most current OA treatments are associated with a wide range of adverse effects and drug interactions.[6] Particularly, NSAIDs are one of the most commonly used medications for the treatment of knee OA. However, prolonged use of NSAIDs may be intolerable to some patients due to its side effects on the gastrointestinal system, which include dyspepsia, ulceration, upper gastrointestinal bleeding and perforation of the stomach or duodenum.[2] Additionally, long-term use of NSAIDs

has also shown to cause damage to the kidneys. Therefore, it is proposed that curcuminoids, a family of natural chemical compounds found in the plant *Curcuma longa*, commonly known as Turmeric, may provide an alternative medicinal option for pain relief in patients with knee osteoarthritis with fewer side effects. Through research, curcuminoids have shown to possess anti-inflammatory properties by inhibiting enzymes involved in inflammation such as cyclooxygenase (COX-2), and by inhibiting the production of inflammatory cytokines such as interferon, interleukins and tumor necrosis factor.[2]

OBJECTIVE

The objective of this selective evidence-based medicine (EBM) review is to determine whether or not curcuminoids are effective in reducing pain in adults with knee osteoarthritis.

METHODS

The studies selected for analysis included three randomized, double-blind, clinical controlled trials evaluating both male and female patients over the age of 40 years old diagnosed with primary knee osteoarthritis (see Table 1). Each study included a randomized group that received some form of oral curcuminoid therapy compared to a control group which received a placebo or ibuprofen. Outcomes measured in each study include knee pain, joint stiffness and physical function. The focus of this systematic review will be on knee pain.

Minor variations in each of the studies did exist, including age groups, curcuminoid product and dosage, adjunctive treatment, group size and duration of treatment (see Table 1). The study conducted by Haroyan et al. compared the change in baseline of patients between the ages of 40 to 77 years old receiving CuraMed® 500 mg capsules (333 mg curcuminoids) and patients receiving Curamin® 500 mg capsules (350 mg curcuminoids and 150 mg boswellic acid) and a control group receiving a placebo taken three times daily for 12 weeks.[6] The study

conducted by Srivastava et al. compared the change in baseline of patients between the ages of 40 to 80 years old receiving 500 mg of curcuma longa extract and a control group receiving 500 mg of placebo capsules taken twice daily along with the standard treatment of Diclofenac 50 mg twice daily for 4 months.[1] The study conducted by Ross compared the change in baseline of patients older than 50 years old receiving 1500 mg daily of curcumin extract and a group receiving 1200 mg daily of ibuprofen with the exception of tramadol for severe pain as needed for 4 weeks.[2]

All articles selected for this systematic review were found using the search engine on PubMed and Cochrane Library databases with the use of key words “turmeric”, “curcumin”, “curcuma”, “curcuminoids” and “osteoarthritis”. The studies were further filtered by articles published in the English language and in peer reviewed journals. Articles were then selected based on their relevance to the clinical question and if patient-oriented evidence that matters (POEMs) were the outcomes measured. Inclusion criteria included studies that were RCTs published during or after 2016 due to a systematic review being completed prior to 2016. Exclusion criteria included studies published before 2016, systematic reviews published after selected RCTs and rheumatoid arthritis. All three studies selected contain non-dichotomous data with data reported in p-values, confidence intervals, and mean change from baseline. See Table 1 for characteristics and demographics of the included studies.

Table 1— Demographics of Included Studies							
Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W /D	Interventions
Haroyan[6] (2018)	Double blind RCT	201	40-77	Patients aged 40 to 80 years of both sexes and a BMI 18-29 kg/m^2 with degenerative hypertrophic osteoarthritis of knee bone joints	Inflammatory or secondary arthritis, synovitis, meniscal tears, chronic diseases of kidneys, liver, gastrointestinal, cardiovascular, endocrine, or nervous system, NSAIDs or analgesics within 2 weeks, glucosamine sulphate, intra-articular hyaluronate, systemic or intra-articular glucocorticoids within 3 months, addiction to medicine/narcotics/tobacco, pregnancy or nursing	22	CuraMed® (333 mg curcuminoids) 500 mg capsules taken orally 3x/day Curamin (350 mg curcuminoids + 150 mg boswellic acid) 500 mg capsules orally 3x/day Placebo 500 mg capsules orally 3x/day X 3 months
Srivastava[1] (2016)	Double blind RCT	160	40-80	Patients aged 40-80 years of both sexes with primary knee osteoarthritis	Less than 40 years and more than 80 years old, and those with rheumatoid arthritis, diabetes mellitus, renal insufficiency, hepatic disease, cardiovascular disease, gout, pregnant women and other systemic disease	27	Curcuma longa extract 500 mg taken with diclofenac 50 mg orally 2x/day Placebo 500 mg 2x/day Both taken with diclofenac 50 mg 2x/day X 4 months
Ross[2] (2016)	Double blind RCT	367	>50	Patients with primary knee osteoarthritis with a numerical rating of knee pain of >5/10	No exclusion criteria noted– assume less than 50 years old and those with knee pain rating of <5/10	36	Curcumin extract 250 mg 2 capsules orally 3x/day (exception of tramadol for severe pain) Ibuprofen 1200 mg daily X 1 month

OUTCOMES MEASURED

The outcomes measured in all three RCTs were patient-oriented evidence that matters (POEMs) with these outcomes focusing on knee pain, joint stiffness and physical function in patients with primary knee osteoarthritis. The Haroyan et al. study used Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a self-administered questionnaire asking patients to measure their symptoms of knee pain, joint stiffness and physical function at baseline and at weeks 4 and 12 of treatment.[6] This study also used OA physical performance measures such as 30-second stand test, 40-meter fast-paced walk test, the "timed up and go" test, and the stair climb test.[6] The Srivastava et al. study used WOMAC scores and a visual analog scale (VAS) to evaluate change at baseline, 2 months and 4 months.[1] The Ross study assessed outcomes using a modified Thai version of WOMAC scores and a 6-minute walk distance at weeks 0, 2 and 4.[2] The focus of this systematic review will be on knee pain and WOMAC pain measurement scores due to consistency of this measurement throughout all three RCTs. A higher WOMAC score is indicative of greater pain and poorer function.[1]

RESULTS

This systematic review includes three randomized controlled trials evaluating the efficacy of curcuminoids on knee pain in patients with knee osteoarthritis. All three studies use some form of curcuminoids as experimental therapy while the control group of the studies vary between the use of placebos and ibuprofen. The inclusion and exclusion criteria also vary between each of the studies (see Table 1). All three selected studies did not have dichotomous data; therefore, results were reported as continuous data. Statistics among the selected studies were reported through mean changes from baseline, p-values and confidence intervals (CI).

The 2018 study by Haroyan et al. is a three-armed randomized, double-blind, controlled trial that evaluates the efficacy of CuraMed versus Curamin versus that of a placebo group through WOMAC scores at baseline and at 4 and 12 weeks.[6] Patients included in this trial were of the ages 40 to 80 years old and selected based on their diagnosis of degenerative hypertrophic knee osteoarthritis— ultimately, 201 patients were enrolled for evaluation with a total of 179 patients completing treatment.[6] All patients were randomly allocated to groups by the principal investigator with a randomization code, which was not revealed until the end of the study.[6] See Table 1 for details of interventions and exclusion criteria of this trial. A compliance rate is not reported within the trial, however, the author noted that compliance was measured individually through special forms given to the participants to record their daily consumption of capsules.[6] These forms were then evaluated periodically throughout the trial by the investigators to ensure compliance. This trial found that the baseline WOMAC pain score of 5.91 ± 2.77 significantly decreased in the CuraMed (curcuminoids) group after twelve weeks of treatment with a 12-week WOMAC pain score of 3.84 ± 2.88.[6] A statistically significant difference was found within the CuraMed group with a p-value less than 0.001 and a confidence interval of 95 percent, however, when comparing CuraMed to the placebo, the calculated p-value was greater than 0.05.[6] The Curamin group (curcuminoids and boswellic acid combination) when compared to the placebo group had a p-value < 0.05.[6] There was no intergroup comparison between CuraMed and Curamin. Ultimately, this study concluded that statistically significant pain relief was observed in all study groups, including the placebo, but that these plant extracts when used in combination prove to be more effective.[6] Refer to Table 2 for WOMAC pain scores at different intervals for each of the respective groups. Regarding safety profile, all the medications were well tolerated.[6] Similar and minor adverse effects were noted in 13 of the 201 patients including 7 in the

CuraMed group, 2 in the Curamin group and 4 in the placebo group with nausea being the only side effect noted in the curcuminoid-containing supplements.[6] Other common side effects included gastrointestinal symptoms and weight gain.[6]

Table 2— CuraMed vs. Curamin vs. Placebo WOMAC Pain Index subscale (Haroyan et al. 2018)[6]

	Baseline	Week 4	Week 12	P-value within group	Intergroup comparison, mean change from baseline to week 12, p-values	
					Placebo vs CuraMed	Placebo vs Curamin
CuraMed (n=66)	5.91 ± 2.77	4.37 ± 2.88	3.84 ± 2.88	P<0.0001	> 0.05	< 0.05
Curamin (n=67)	6.39 ± 3.47	5.02 ± 3.46	4.49 ± 3.86	P<0.0001		
Placebo (n=68)	5.85 ± 3.25	4.92 ± 3.09	5.22 ± 3.58	P<0.003		

The 2016 study by Srivastava et al. is a two-armed randomized, double-blind, controlled trial which compares the efficacy of curcuminoid extract to a placebo group in 160 patients using WOMAC scores at baseline, 2 months and 4 months.[1] VAS scores were also assessed during this trial but will not be included in this review due to the focus of this analysis being on knee pain and WOMAC scores. Patients included in this trial were of ages 40 to 80 years old and diagnosed with primary knee osteoarthritis. Of the 160 patients, 27 patients were lost to follow up during the trial.[1] All subjects were assigned to their respective groups by computerized randomization.[1] See Table 1 for details regarding exclusion criteria and interventions. Overall, this trial found that treatment with curcuminoids extract was associated with a significantly greater reduction in WOMAC pain scores ($p<0.05$) compared to the placebo group.[1] The mean difference baseline WOMAC pain score in the curcuminoid group started at 15.10 ± 0.31 and decreased to a pain score of 9.48 ± 0.17 by the end of the study at month four.[1] Refer to Table 3 for WOMAC pain scores and p-values at different intervals for each of the respective groups.

More adverse effects were noted in the placebo group (n=4) compared to the curcuminoid group (n=2) with nausea, vomiting and dyspepsia being the most common side effects in both groups.[1]

Table 3— Effect of Treatment on WOMAC Pain Scores (Srivastava et al. 2016)[1]			
	Baseline	2-Month	4-Month
Curcuma longa extract (n=78)	15.10 ± 0.31	11.19 ± 0.26	9.48 ± 0.17
Placebo (n=82)	15.29 ± 0.26	12.05 ± 0.21	10.16 ± 0.16
P-values	0.64	0.01	0.06

The 2016 study by Ross is a randomized, double-blind, controlled trial which assessed the efficacy of curcuminoid extract in pain reduction compared with ibuprofen in 367 patients over the age of 50 years old diagnosed with primary knee osteoarthritis using WOMAC scores and 6-minute walk test.[2] For the purpose of this review, only WOMAC pain scoring will be discussed for relevancy to topic. All patients were randomly allocated to receive either 1500 mg of curcuminoids or 1200 mg of ibuprofen daily for 4 weeks.[2] Of the 367 patients, 36 were lost to follow up during the trial.[2] See Table 1 for exclusion criteria and interventions. This study concluded that the mean of all WOMAC scores at baseline, week 2, and week 4 showed a significant improvement in pain in both the curcuminoid and ibuprofen group from baseline ($p<0.05$).[2] A confidence interval of 95 percent and WOMAC pain score with a p-value of 0.018 was noted in the curcuminoid group.[2] The number of patients experiencing adverse effects was similar among both groups, however, gastrointestinal side effects were much higher in the ibuprofen group compared to the curcuminoid group ($p=0.046$).[2] Compliance with treatment was not measured for this trial.

DISCUSSION

All three studies evaluated in this systematic review suggest that short-term use of curcuminoids may be beneficial in the reduction of pain in patients suffering from knee osteoarthritis, however, certain limitations in the studies should be taken into consideration. All three studies used similar populations by utilizing adults diagnosed with primary knee

osteoarthritis over the ages of 40 years old of both sexes. Sample size is also an important factor in determining the validity of a study. All three trials seemed to have larger population sizes including a total of 167, 201 and 367 patients, however, the duration of the trials varied between all three with final treatments occurring at 1 month, 3 months and 4 months. This variation in time between the studies may be considered a limitation.

The Haroyan et al. study calculated that a sample size of 180 participants was enough to be statistically significant study, therefore, a total of 201 patients were enrolled to compensate for non-compliance.[6] Ultimately, 22 patients (10.5%) were lost to follow up due to various reasons, with a total of 179 patients completing the treatment.[6] Even though sample size does not limit this study, the means of intervention may be considered a constraint on the study. Due to the hydrophobic nature of curcuminoids, turmeric volatile oil and other sesquiterpenes were added to curcuminoids to make an extract known as BCM-95 to increase bioavailability in CuraMed and Curamin.[6] These additives may have a direct effect on the outcome evaluated in the study.

Likewise, two of the studies used adjunctive treatment throughout the trials which may have skewed the outcomes. The Srivastava et al. study allowed patients to use diclofenac 50 mg twice daily, a standard treatment for osteoarthritis, along with the experimental therapy of curcuminoids.[1] The Ross study allowed patients to use Tramadol as needed for severe pain with curcuminoid therapy without mentioning the frequency and dosage of Tramadol taken by the participants.[2]

Curcuminoids, sold commonly under the turmeric, are widely available at nearly any grocery, drug or vitamin store in the United States. While several forms of curcuminoid products exist, no form of curcuminoids has been approved by the Food and Drug Administration (FDA)

for the treatment of a specific medical condition. According to the National Institutes of Health (NIH), curcuminoids are generally considered safe when taken in oral or topical form but high-doses or long-term use may cause gastrointestinal symptoms.[7] The three RCTs used for this analysis all stated that a small number of participants experienced some form of gastrointestinal symptoms which supports this statement by the NIH. While no absolute contraindications or black box warnings exist for curcuminoids, it is suggested those allergic to curcuminoids and those with gallstones, bile duct obstruction, or diabetes caution use due to the possibility for curcuminoids decreasing blood sugar.[8] Even though curcuminoids are not approved by the FDA, it is of interest to note whether curcuminoid-containing products would be covered by insurance as a form of pharmacological therapy upon approval.

CONCLUSION

Based on these three studies, curcuminoids are an effective and relatively safe alternative to conventional treatment to reduce knee pain in adults with osteoarthritis. All three studies showed a decrease in pain from baseline which proves its efficacy in therapy. One study concluded that curcuminoids when used in combination with another herbal supplement, boswellic acid, shows more effectiveness than when used alone. This is an interesting finding and further evaluation through future studies is recommended. Other future studies could investigate curcuminoids and its use in the prevention of osteoarthritis rather than treatment. These future studies should include larger sample sizes and longer duration of treatments.

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