Annals of Internal Medicine ORIGINAL RESEARCH

Effectiveness of *Curcuma longa* Extract for the Treatment of Symptoms and Effusion–Synovitis of Knee Osteoarthritis

A Randomized Trial

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Background: Current pharmacologic therapies for patients with osteoarthritis are suboptimal.

Objective: To determine the efficacy of *Curcuma longa* extract (CL) for reducing knee symptoms and effusion–synovitis in patients with symptomatic knee osteoarthritis and knee effusion–synovitis.

Design: Randomized, double-blind, placebo-controlled trial. (Australian New Zealand Clinical Trials Registry: ACTRN 12618000080224)

Setting: Single-center study with patients from southern Tasmania, Australia.

Participants: 70 participants with symptomatic knee osteoarthritis and ultrasonography-defined effusion–synovitis.

Intervention: 2 capsules of CL (n = 36) or matched placebo (n = 34) per day for 12 weeks.

Measurements: The 2 primary outcomes were changes in knee pain on a visual analogue scale (VAS) and effusion–synovitis volume on magnetic resonance imaging (MRI). The key secondary outcomes were change in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and cartilage composition values. Outcomes were assessed over 12 weeks.

Results: CL improved VAS pain compared with placebo by −9.1 mm (95% CI, −17.8 to −0.4 mm [P = 0.039]) but did not change effusion–synovitis volume (3.2 mL [CI, −0.3 to 6.8 mL]). CL also improved WOMAC knee pain (−47.2 mm [CI, −81.2 to −13.2 mm]; P = 0.006) but not lateral femoral cartilage T2 relaxation time (−0.4 ms [CI, −1.1 to 0.3 ms]). The incidence of adverse events was similar in the CL (n = 14 [39%]) and placebo (n = 18 [53%]) groups (P = 0.16); 2 events in the CL group and 5 in the placebo group may have been treatment related.

Limitation: Modest sample size and short duration.

Conclusion: CL was more effective than placebo for knee pain but did not affect knee effusion–synovitis or cartilage composition. Multicenter trials with larger sample sizes are needed to assess the clinical significance of these findings.

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Knee osteoarthritis is a chronic joint disease characterized by joint pain and functional loss, leading to impaired quality of life and a tremendous socioeconomic burden (1). Despite its large disease burden, no approved disease-modifying drugs currently are available to treat osteoarthritis. The current pharmacologic therapies, such as acetaminophen and nonsteroidal anti-inflammatory drugs, do not slow structural progression and are associated with gastrointestinal, renal, and cardiovascular complications (2). These medications have a low to moderate effect on pain (3, 4), resulting in patient dissatisfaction, which hastens joint replacement (5). Considering the high prevalence of osteoarthritis and the suboptimal pharmacologic management options, an urgent need exists for safer and more effective drugs to treat osteoarthritis symptoms.

Osteoarthritis is thought to be a collection of different disease pathways resulting in the common outcome of joint failure, rather than 1 disease with a common pathway (6). One critical pathway is through inflammatory factors (7). A meta-analysis demonstrated that serum high-sensitivity C-reactive protein levels were elevated in patients with osteoarthritis compared with control participants (8). Proinflammatory cytokines, including interleukin-1β, tumor necrosis factor-α, and interleukin-6, contribute to the progression of cartilage loss of osteoarthritis (9). Likewise, effusion (excess synovial fluid within the joint space) and synovitis (thickening of the synovium) represent localized inflammation within the knee joint and are common in persons with symptomatic and radiographic knee osteoarthritis (>50%) (10). Effusion–synovitis visualized on magnetic resonance imaging (MRI) and ultrasonography is associated with structural and clinical progression of osteoarthritis, including total knee replacement (11–13). Therefore, a subgroup of patients with knee osteoarthritis with local joint swelling may represent an inflammatory phenotype of osteoarthritis that might benefit from anti-inflammatory therapy.

An ideal treatment approach for osteoarthritis would be to use a safe agent with several mechanisms of action. *Curcuma longa* extract (CL) has been used in both Ayurvedic and traditional Chinese medicine to treat arthritis (14). Curcumin, the principal component

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Editorial comment 1

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in CL, is highly pleiotropic, with anti-inflammatory, analgesic, antioxidant, anticancerous, and wound-healing properties (15, 16). A recent systematic review included 7 randomized clinical trials (RCTs) exploring the effect of CL on osteoarthritis (797 participants) and demonstrated that CL substantially reduced knee pain and improved quality of life (17). However, these trials had important limitations. Most of the studies were conducted in Asia and thus have low generalizability to Western populations. They were not methodologically rigorous, because they had a moderate risk of bias, poor reporting of safety data, unlikely treatment effect sizes, and no structural end points, and they included all phenotypes of knee osteoarthritis. Therefore, our pilot study aimed to determine the efficacy of CL on knee symptoms and effusion–synovitis volume in older adults with symptomatic knee osteoarthritis and ultrasonography-defined effusion–synovitis. We hypothesized that CL would decrease knee pain and knee joint effusion–synovitis volume over 12 weeks in patients with an inflammatory phenotype of knee osteoarthritis.

METHODS

Design Overview

This study was a 12-week, single-center, randomized, placebo-controlled clinical trial in patients with symptomatic knee osteoarthritis and effusion–synovitis. Participants were recruited from February to December 2018, and follow-up was completed in March 2019. All participants gave informed consent, and the protocol was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee (reference no. H0016713). Protocol versions and amendments are provided in the **Supplement** (available at Annals.org). This study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618000080224).

Setting and Participants

Persons living in southern Tasmania were recruited through local advertising and social media. They were invited to attend the study center (Menzies Institute for Medical Research, Hobart, Australia) for face-to-face screening after an initial telephone evaluation. The patients were evaluated by clinical examination, ultrasonography, knee radiography, and MRI. To be eligible to participate in the study, patients had to be older than 40 years and have knee pain of at least 40 mm on a visual analogue scale (VAS), clinical knee osteoarthritis defined according to the American College of Rheumatology clinical criteria (18), and a moderate amount of ultrasonography-defined effusion–synovitis (≥4 mm effusion depth in the suprapatellar region) (19). Persons were excluded if they were unable to have an MRI scan; had grade 3 joint space narrowing, according to the Osteoarthritis Research Society International (OARSI) atlas (20); were unwilling to stop using CL medications 2 weeks before randomization; had rheumatoid arthritis or gout; sustained a substantial knee injury within the previous 6 months; had arthroscopic or open surgery in the index knee in the previous 12 months or were planning to have such a procedure; received injections of corticosteroids (previous 3 months) or hyaluronic acid (previous 6 months) in the index knee; were pregnant or breastfeeding; were using any investigational drugs or devices within 30 days before randomization; had any serious medical illness or condition that might preclude 12-week follow-up; could not provide informed consent; or were otherwise considered ineligible by study investigators. After clinical and ultrasonographic examination, 1 knee was nominated as the study knee to be evaluated throughout the trial. If both knees were eligible, the most symptomatic knee was chosen as the study knee.

Randomization and Interventions

Participants were allocated in a 1:1 ratio to the 2 groups on the basis of computer-generated random numbers prepared by a statistician with no involvement in the trial. We used block randomization, with a block size of 4, stratified by the enrollment in a pilot substudy (additional contrast-enhanced MRI sequence). Participants were randomly assigned to receive 2 capsules totaling 1000 mg/d of CL (80% wt/wt aqueous-based extract standardized to turmerosaccharides and 20% wt/wt curcuminoids [Turmacin Plus; Natural Remedies], 2 × 500-mg capsules per day) or inert identical placebo. The CL dosage was determined on the basis of the dosage used in previous RCTs of bio-optimized (polysaccharide- and curcuminoid-rich) turmeric extracts (21, 22). Study participants, assessors, MRI readers, and statisticians were blinded to treatment allocation. Allocation concealment and blinding were ensured by using identical capsules for each group (provided by Natural Remedies), having objective measures of knee structural changes assessed by trained observers blinded to group allocation, and having subjective measures recorded by research assistants also blinded to group allocation. The full randomization schedule and codes were maintained by an independent person with no involvement in this trial.

Outcomes and Follow-up

The 2 primary outcomes were change in knee pain, assessed by VAS, and change in knee effusion–synovitis volume, assessed by MRI, over 12 weeks. Secondary outcomes evaluated over 12 weeks were knee pain and function, assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); OARSI-OMERACT (Outcome Measures in Rheumatology Clinical Trials) response to treatment (23); cartilage compositional change, assessed by cartilage T2 relaxation time (in milliseconds); pain medication use; quality of life (Assessment of Quality of Life [AQoL]-4D questionnaire) (24); an OARSI-recommended set of physical performance measures; and adverse events. The AQoL utility scores were obtained by AQoL utility formulas using 4 of the 5 dimensions of the questionnaire assessed at baseline and week 12. Changes in weight-bearing and non–weight-bearing pain (WOMAC) were also prespecified as secondary outcomes, because these pain categories may reflect different pain constructs related to inflammation (25).

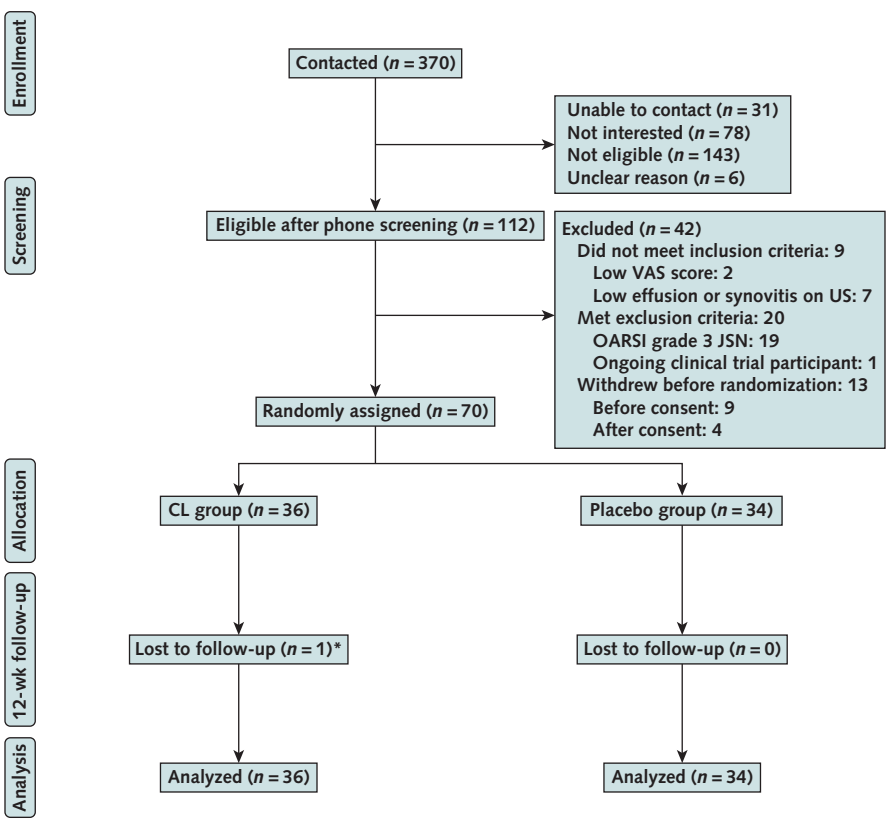
Knee pain was assessed by using a 100-mm VAS over 12 weeks at 3 clinic visits (screening, baseline, and week 12) and 3 additional online questionnaires at weeks 1, 4, and 8 (**Appendix Figure 1**, available at Annals.org). We used the standard question, "On this line, how would you rate your knee pain in the last week?" The WOMAC pain (0 to 500 mm), function (0 to 1700 mm), and stiffness (0 to 200 mm) subscales were also assessed at each time point. Weight-bearing pain (0 to 300 mm, adding subscales of walking, standing, and climbing stairs) and non–weight-bearing pain (0 to 200 mm, adding subscales of sleeping at night and resting) were calculated.

The OARSI-OMERACT responder criteria were used to generate a responder categorical variable (0 = nonresponder, 1 = responder) based on improvement in WOMAC pain and function and the patient's global assessment. Patients' global assessment was evaluated by using a 100-mm VAS (26).

At baseline and week 12, MRI of the study knee was performed in the sagittal plane on a 1.5-T whole-body MRI unit (SIGNA [GE Healthcare]) using T2-weighted fat saturation 3-dimensional (3D) fast spin echo (Cube [GE Healthcare]) and T2 mapping sequences. The parameters for the MRI sequence are shown in **Appendix Table 1** (available at Annals.org). Effusion–synovitis was defined as the presence of intra-articular fluid-equivalent signal on the T2-weighted images. The volume of effusion–synovitis (10) was measured by using semiautomated segmentation, and the final 3D volume rendering was generated by using free open-source imaging software (3D Slicer, version 4.10 [www.slicer.org]) (27). The MRI scans were measured by a trained assessor (Z.W.) under the direct supervision of a radiologist (R.J.) and MRI processing engineer (J.F.). Intra- and interobserver repeatability for this measurement is excellent, with intraclass correlation coefficients of 0.99 and 0.84, respectively (28). Cartilage composition was assessed as the average lateral femoral cartilage T2 relaxation time (in milliseconds) by using the READY View module in Advantage Workstation (GE Healthcare).

Core physical function measures, including the 30-second chair stand test, 40-m (10 m × 4) fast-paced walk test, and stair climb test, were performed as recommended by the OARSI guidelines for clinical trials at baseline and week 12, using the same equipment at the same location (29). The total number of chair stands in 30 seconds, time to complete a 40-m walk with 3 turns, and time to ascend and descend 9 stairs (20-cm step height and handrail) were recorded.

Figure 1. Flow chart of the study participants.



CL = *Curcuma longa* extract; JSN = joint space narrowing; OARSI = Osteoarthritis Research Society International; US = ultrasound; VAS = visual analogue scale.
* Withdrew at week 8 because of an adverse event.

Table 1. Patient Demographics and Baseline Characteristics, by Treatment Received

Characteristic	CL (*n* = 36)	Placebo (*n* = 34)
Mean age (SD), *y*	61.3 (8.5)	62.4 (8.8)
Female, *n* (%)	18 (50)	21 (62)
Mean BMI (SD), kg/m^2	29.9 (6.3)	30.6 (7.2)
Mean knee VAS score (0–100) (SD), *mm*	55.6 (16.1)	54.4 (17.8)
Mean effusion–synovitis volume (SD), *mL*	22.6 (15.1)	25.9 (21.0)
Mean cartilage T2 relaxation time (SD), *ms*	44.3 (1.8)	44.7 (2.5)
Radiographic joint space narrowing, *n (%)**	24 (67)	25 (76)
Mean total WOMAC score (0–2400) (SD), *mm*†	975.1 (449.3)	1103.9 (374.2)
Pain (0–500)	194.9 (92.8)	218.7 (80.4)
Function (0–1700)	690.4 (331.0)	788.9 (273.1)
Stiffness (0–200)	89.7 (45.6)	96.4 (38.9)
Pain medication, *n (%)*‡	10 (28)	11 (32)
Paracetamol/acetaminophen	7 (19)	9 (26)
NSAIDs§	4 (11)	4 (12)
Opioids‖	1 (3)	1 (3)
Supplements, *n (%)*	19 (53)	19 (59)
Glucosamine and/or chondroitin	9 (25)	4 (12)
Vitamins	13 (36)	14 (41)
Fish oil	6 (17)	7 (21)
Coenzyme Q10	2 (6)	1 (3)

BMI = body mass index; CL = *Curcuma longa* extract; NSAID = nonsteroidal anti-inflammatory drug; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
* Radiographic joint space narrowing was determined according to the Osteoarthritis Research Society International atlas, with grade 2 and grade 1 assigned as presence of radiographic joint space narrowing.
† Higher scores on the WOMAC and VAS for pain indicate a more severe symptom.
‡ *Pain medication* means use of any of the following: acetaminophen, NSAIDs, cyclooxygenase-2 inhibitors, or opioids.
§ Use of meloxicam, diclofenac, ibuprofen, and celecoxib was noted among participants.
‖ Opioids, such as codeine and tramadol.

All participants were asked to continue therapy with the medications they were receiving at their screening visit for the duration of the trial. They also were asked to keep their medication use as stable as possible; any medication changes were documented with the reason, drug name, and dose and were classified as commenced or increased, discontinued or decreased, or stable use or nonuse. A rescue medication, paracetamol, was provided if the participant requested it. Medication use was recorded at baseline and weeks 1, 4, 8, and 12 of each treatment period. Participants' adherence to medications was assessed by counting the number of capsules left in the bottles when they returned for the final visit.

Adverse events were defined as any untoward event occurring during the trial, regardless of its relation to treatment. Serious adverse events were defined as unplanned hospital admissions, new cancer diagnoses, or death during the study. Adverse events were recorded throughout the study, and chief investigators were notified of any serious events within 24 hours.

Statistical Analysis

We estimated the sample size on the basis of the minimum clinically important difference (MCID) for VAS knee pain; an MCID for effusion–synovitis has not yet been defined. For change in VAS pain from baseline to 12 weeks, we used in-house data from the 4Jointz trial (30) (SD of VAS pain change, 24). We powered the study to detect an MCID of 18 mm between CL and placebo on the 100-mm VAS pain scale. To detect this difference, 35 participants recruited to each group would provide 80% power with 5% probability of type I error ($\alpha = 0.05$), allowing for 10% loss to follow-up over 12 weeks.

The detectable difference in effusion–synovitis volume with this sample size was calculated on the basis of data from our RCT of vitamin D for knee osteoarthritis (31), which found a 1.18-mL (SD, 7.70) difference between groups in participants with effusion–synovitis at baseline. For 80% power, the detectable difference was 5.2 mL.

Pain, function scores, quality-of-life–derived utility values, effusion–synovitis volume, and cartilage relaxation times were compared by using a repeated-measures mixed-effects linear regression model with terms of treatment, time, and corresponding baseline values as covariates (in addition to age, sex, and body mass index). The correlation within the repeated measures was addressed by using individual participant identification as a random effect. The effect of treatment at baseline and weeks 1, 4, 8, and 12 was evaluated by adding an intervention-by-time interaction to the models (**Appendix**, available at Annals.org). The linear mixed-effects model incorporates all patients and assumes that data are missing at random (only 1 withdrawal and minimal missing data [from <5 patients] from online visits and for MRI data). Both the absolute difference and risk ratio of responders and the number of participants reporting at least 1 adverse event between groups were obtained by binomial regression.

The protocol did not prespecify WOMAC stiffness; it was analyzed post hoc. We also examined potential interactions between treatment effects (treatment over time) and baseline volume of effusion–synovitis (below or above the median effusion–synovitis volume [20.45 mL]).

All data analyses were performed on the basis of the original allocation group. Analyses were performed by using Stata, version 15 (StataCorp). A 2-sided *P* value of 0.050 was deemed statistically significant.

Role of the Funding Source

This investigator-initiated clinical trial was financially supported by the University of Tasmania Institutional Funds and a natural products company (Natural Remedies; Bengaluru, India). The funders had no role in the study design, conduct, and analysis; manuscript preparation; or the decision to submit the manuscript for publication.

RESULTS

Of 370 persons contacted for telephone screening, 112 were evaluated in the clinic (**Figure 1**). Seventy participants were randomly assigned to receive CL (*n* = 36)

or placebo (n = 34). One participant in the CL group withdrew from the study after week 8 because of an adverse event (a feeling of uncomfortable fullness at the top of the stomach, considered "possibly related to medication"). Sixty-four participants (91%) completed questionnaires, and 66 (94%) had MRI scans at week 12. Sixty-one participants (87%) consumed more than 80% of the capsules. Baseline characteristics of the members of the CL and placebo groups were generally well matched (Table 1). Differences in WOMAC scores at baseline were not clinically significant and were close to the smallest detectable difference (32, 33). Moreover, we adjusted for the corresponding baseline scores to account for any baseline differences.

Primary Outcomes

Over 12 weeks, VAS knee pain improved more in the CL (−23.8 mm [95% CI, −29.8 to −17.7 mm]) than the placebo group (−14.6 mm [CI, −20.8 to −8.5 mm]), with a between-group difference of −9.1 mm (CI, −17.8 to −0.4 mm [P = 0.039]) (Table 2 and Figure 2, *A*), equivalent to a standardized mean difference (SMD) of 0.50 (CI, −0.97 to −0.18).

The changes in MRI-assessed effusion–synovitis volume in the CL (1.1 mL [CI, −1.3 to 3.2 mL]) and placebo (−2.1 mL [CI, −4.6 to 0.4 mL]) groups were small, and there was no difference between the groups (3.2 mL [CI, −0.3 to 6.8 mL]; P = 0.075) over 12 weeks (Table 2).

Secondary Outcomes

Curcuma longa extract improved WOMAC pain (P = 0.006) and function (P = 0.047) over 12 weeks compared with placebo (Table 2 and Figure 2, *B* and *C*). The SMD for WOMAC pain reduction was 0.66 (CI, −1.14 to −0.18). Likewise, CL reduced both weight-bearing pain (P = 0.018) and non–weight-bearing pain (P = 0.005) over 12 weeks (Table 2). The percentage of OARSI-OMERACT responders in the CL group (22 of 35 [62.9%]) was 24.6 percentage points (CI, 1.7 to 47.5 percentage points [P = 0.035]) higher than the percentage in the placebo group (13 of 34 [38.2%]) over 12 weeks.

Table 2. Change in Study End Points Over 12-Week Follow-up Between the CL and Placebo Groups*†

End Point	CL Group		Placebo Group		Mean Between-Group Difference in Change (95% CI)	RR (95% CI)	*P* Value‡
	Participants, *n*	Mean Change (95% CI)	Participants, *n*	Mean Change (95% CI)			
Primary							
VAS knee pain score (0–100), *mm*	35	−23.8 (−29.8 to −17.7)	34	−14.6 (−20.8 to −8.5)	−9.1 (−17.8 to −0.4)	–	0.039
Effusion–synovitis volume, *mL*	34	1.1 (−1.3 to 3.2)	32	−2.1 (−4.6 to 0.4)	3.2 (−0.3 to 6.8)	–	0.075
Secondary							
WOMAC score, *mm*							
Pain (0–500)	35	−84.2 (−107.7 to −60.8)	34	−37.0 (−61.1 to −12.9)	−47.2 (−81.2 to −13.2)	–	0.006
Function (0–1700)	35	−292.0 (−368.0 to −216.0)	34	−179.7 (−257.8 to −101.7)	−112.3 (−222.8 to −1.7)	–	0.047
Stiffness (0–200)§	35	−41.1 (−52.7 to −29.4)	34	−20.9 (−32.9 to −9.0)	−20.2 (−36.9 to −3.4)	–	0.019
Weight-bearing pain (0–300)	35	−54.7 (−69.4 to −40.0)	34	−28.8 (−43.9 to −13.6)	−25.9 (−47.3 to −4.5)	–	0.018
Non–weight-bearing pain (0–200)	35	−29.6 (−39.9 to −19.2)	34	−8.3 (−18.9 to 2.4)	−21.3 (−36.3 to −6.4)	–	0.005
OARSI-OMERACT responders, *n (%)*‖	35	22 (62.9)	34	13 (38.2)	24.6 (1.7 to 47.5)	1.6 (1.0 to 2.7)	0.035
Cartilage T2 relaxation time, *ms*	34	−0.2 (−0.7 to 0.3)	32	0.2 (−0.3 to 0.7)	−0.4 (−1.1 to 0.3)	–	0.30
AQoL utility score (0–1)¶	36	0.04 (0.00 to 0.08)	32	0.04 (0.00 to 0.08)	0.00 (−0.06 to 0.06)	–	1.00
Physical function							
30-s chair stand, *repetitions*	36	1.65 (0.91 to 2.38)	32	1.36 (0.59 to 2.13)	0.28 (−0.79 to 1.36)	–	0.60
40-m fast-paced walk, *s*	36	−1.36 (−2.11 to −0.62)	32	−1.31 (−2.09 to −0.54)	−0.05 (−1.14 to 1.04)	–	0.93
Stair climbing, *s*	36	−1.02 (−2.34 to 0.29)	32	−1.86 (−3.24 to −0.48)	0.84 (−1.09 to 2.77)	–	0.40
Pain medication change, *n (%)***							
Commenced or increased	36	4 (11.1)	34	9 (26.5)	–	–	–
Discontinued or decreased	36	4 (11.1)	34	0	–	–	–

AQoL = Assessment of Quality of Life; CL = *Curcuma longa* extract; OARSI-OMERACT = Osteoarthritis Research Society International–Outcome Measures in Rheumatology Clinical Trials; RR = risk ratio; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

* Higher score on WOMAC and VAS for pain indicates a more severe symptom.

† For continuous variables, results are generated from mixed-effects models adjusted for age, sex, body mass index, and corresponding baseline values.

‡ *P* values are for between-group difference in change of outcomes or otherwise specified.

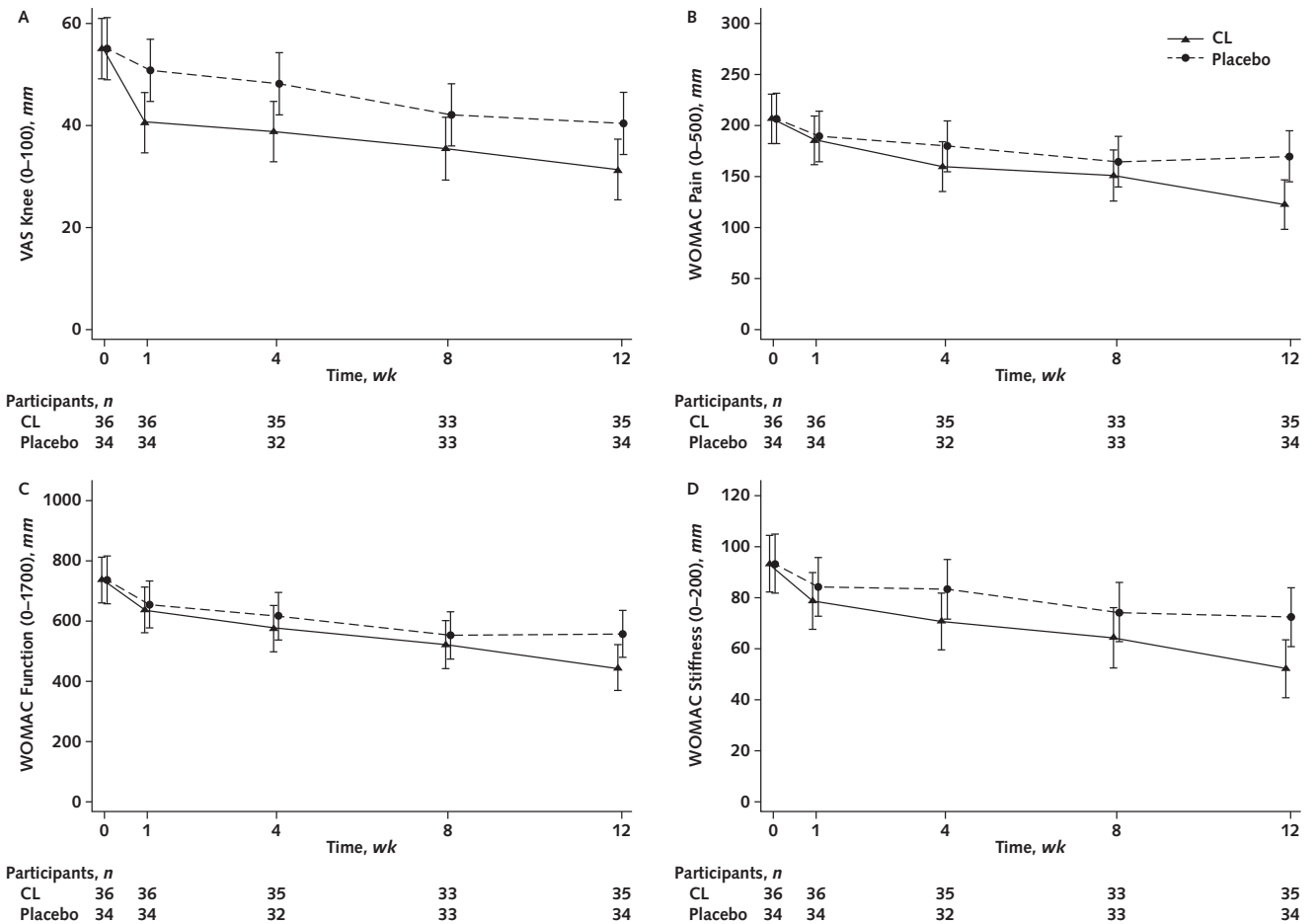
§ WOMAC stiffness was not prespecified in the protocol and was analyzed post hoc.

‖ Responders were evaluated by using the OARSI-OMERACT responder criteria. The number and proportion of responders in each group are shown at 12 weeks; absolute difference and RR were calculated by treatment group minus placebo group using binomial regression.

¶ AQoL utility scores were obtained by AQoL utility formulas using 4 of the 5 dimensions of the AQoL questionnaire.

** *Pain medication* means use of any of the following: acetaminophen, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, opioids, or other analgesics. *P* value for pain medication change was generated by comparing numbers of participants with commenced or increased use, those with discontinued or decreased use, and stable users or nonusers, by using the χ^2 test.

Figure 2. Mean VAS and WOMAC subscale scores (and 95% CIs) in the CL and placebo groups during the study.



Data are estimates from linear mixed-effects models. CL = *Curcuma longa* extract; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. **A.** VAS knee pain (0 to 100 mm). **B.** WOMAC pain (0 to 500 mm). **C.** WOMAC function (0 to 1700 mm). **D.** WOMAC stiffness (0 to 200 mm, post hoc).

No differences were seen in the T2 relaxation time of lateral femoral cartilage, AQoL-derived utility, or physical function assessed by performance measures between the 2 groups over 12 weeks (**Table 2**). Nine participants in the placebo group began or increased pain medication treatment compared with 4 in the CL group. Four participants in the CL group and none in the placebo group discontinued or decreased their use of pain medication (**Table 2**; **Appendix Table 2**, available at Annals.org).

Post Hoc Analyses

Curcuma longa extract improved WOMAC stiffness over 12 weeks compared with placebo (−20.2 mm [CI, −36.9 to −3.4 mm]) (**Table 2** and **Figure 2**, *D*). Participants were categorized as having baseline effusion–synovitis greater than or equal to the median value of 20.45 mL or less than this value. Participants with smaller baseline effusion-synovitis volume receiving CL had reductions in VAS score (−18.5 mm [CI, −30.9 to −6.1 mm]) and WOMAC knee pain (−96.4 mm [CI, −142.3 to −50.5 mm]), function (−252.5 mm [CI, −401.9 to −103.2 mm]), and stiffness (−37.9 mm [CI, −61.9 to −14.0 mm]) compared with the placebo group, whereas those with higher baseline effusion–synovitis volume had no changes in any of these outcomes ($P < 0.050$ for all interactions) (**Appendix Figure 2**, available at Annals.org).

Adverse Events

Fourteen participants (39%) in the CL group and 18 (53%) in the placebo group reported at least 1 adverse event over 12 weeks. The risk for reporting at least 1 adverse event in the CL group was 17 percentage points (CI, −40.1 to 6.1 percentage points [$P = 0.149$]) lower than in the placebo group, although this difference is not statistically significant. Two adverse events in the CL group and 5 in the placebo group were thought to be possibly treatment related. Severe adverse events were reported in 2 participants (6%) in the placebo group, none of which was considered treatment related (**Table 3**).

DISCUSSION

This study examined the effect of CL on an inflammatory phenotype of patients with knee osteoarthritis and used MRI to quantitatively assess CL's effects on

knee structural outcomes. Compared with placebo, CL modestly but statistically significantly reduced knee pain over 12 weeks, as assessed by both VAS and WOMAC, with no increase in adverse events; however, it did not change effusion–synovitis volume or cartilage composition as assessed by MRI.

Our findings are consistent with those of previous clinical trials on the efficacy of CL for knee pain. A 6-week, 4-group, placebo-controlled, single-blind RCT on the efficacy of a turmerosaccharide extract of *Curcuma longa* reported a significant improvement in clinical symptoms and a reduction in the use of rescue medication compared with placebo (22). A 3-group RCT with 2 different doses of bio-optimized CL showed a rapid and significant decrease in pain of knee osteoarthritis, and positive trends in measurements of patients' global assessment of disease activity over 12 weeks (34). We did not find any difference in the number of reported adverse events between groups, indicating that CL was safe and modestly effective in treating osteoarthritis in this short-term study.

We observed an effect of 9.1 mm between the treatment groups, which is a modest effect size for pain reduction, but of a magnitude smaller than the MCID (18 mm) for which the study was powered. Therefore, the modest pain reduction in this study may be of uncertain clinical importance. However, the first recommended drug therapy in most knee osteoarthritis treatment guidelines until 2019 was paracetamol, which reportedly showed only a 3.7-mm difference on a 100-mm scale and had a less favorable safety profile (35). The CL group had more OARSI-OMERACT responders and fewer participants who received new medications for pain relief. The SMDs for VAS and WOMAC pain in our trial were 0.50 and 0.66, respectively. Previous systematic reviews reported an unlikely pain-relieving effect (SMD >2) for CL compared with placebo (17). Using a rigorous study design, we observed a smaller but more plausible treatment effect compared with previous trials (17). The most commonly used drug categories, including acetaminophen, cyclooxygenase-2 inhibitors, and nonsteroidal anti-inflammatory drugs, have SMDs ranging from 0.18 to 0.44 (3, 4). The pattern of increased pain medication use in the placebo group and decreased use in the CL group may have reduced the between-group difference in change in pain in our study. Overall, these results suggest that the modest effect on knee pain in our study may be clinically relevant and that CL may be a treatment option for managing knee osteoarthritis symptoms.

We hypothesized that CL would reduce local swelling in the knee joint (effusion–synovitis on MRI). However, the change in effusion–synovitis volume and cartilage composition in the CL and placebo groups was similar, indicating that CL had no effect on the structural measures of osteoarthritis. In post hoc analyses, participants with a lower effusion–synovitis volume at baseline had reductions in pain whereas pain did not change for those with a higher effusion–synovitis volume, which is an important hypothesis-generating finding. A possible explanation is that participants with a higher effusion–synovitis volume may have more severe disease. However, these findings are contrary to our original hypothesis that CL may work best in persons with more local inflammation.

A strength of this study is its exploration of the effect of CL on structural measures of cartilage and synovium. However, the study has several limitations. First, its relatively short duration of 12 weeks may not have been sufficient to detect a change in the cartilage- and synovium-specific outcomes, and because the treatment effect on pain had not plateaued at 12 weeks, CL's effects may be greater with long-term therapy. Second, although statistically significant, the effect on pain was only moderate (9.1 mm) and was smaller than the MCID; thus, the clinical importance of the reduction is uncertain. Finally, the generalizability of these findings may be limited, because we recruited patients with an inflammatory phenotype of knee osteoarthritis and the effect in those with noninflammatory osteoarthritis needs validation.

In conclusion, CL improved knee pain versus placebo in patients with knee osteoarthritis with local inflammation over 12 weeks, with no increase in adverse events. The effect on pain was only moderate; however, it was achieved without any effect on knee structural measures assessed by MRI. Multicenter trials with larger sample sizes are needed to assess the clinical significance of these findings.

Table 3. Adverse Events

Event	Participants, *n* (%)	
	CL Group (*n* = 36)	**Placebo Group (*n* = 34)**
Death	0	0
Occurrence of ≥1 AE	14 (39)	18 (53)
Occurrence of ≥1 SAE	0	2 (6)
Discontinuation of treatment due to an AE	1 (3)	0
SAEs		
Spike in insulin level	0	1 (3)
Bowel obstruction	0	1 (3)
AEs		
Allergy/immunology	1 (3)	1 (3)
Anorectal	2 (6)	1 (3)
Gastrointestinal	2 (6)	4 (12)
Hypertension	0	1 (3)
Infection	3 (8)	3 (9)
Elective surgery (not related to osteoarthritis)	1 (3)	5 (15)
Musculoskeletal	2 (6)	4 (12)
Joint pain	1 (3)	4 (12)
Neurologic	2 (6)	1 (3)
Respiratory	1 (3)	0
Other*	3 (8)	3 (9)

AE = adverse event; CL = *Curcuma longa* extract; SAE = severe adverse event.
* Includes common cold, tightness in chest (possibly related to stress levels), fatigue, burn due to an ironing accident, hematoma formed during a blood test, and vertigo.

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Data Sharing Statement: The following data may be made available at the discretion of the principal investigator beginning 12 March 2020 and ending 12 March 2022: deidentified participant data (contact Benny Antony; e-mail, Benny.EathakkattuAntony@utas.edu.au). The following supporting documents will be made available beginning 12 March 2020 and ending 12 March 2022: statistical/analytic code and informed consent form (contact Benny Antony; e-mail, Benny.EathakkattuAntony@utas.edu.au). These data will be made available for researchers whose proposed use of the data has been approved for legitimate research purposes.

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Obtaining of funding: B. Antony.
Collection and assembly of data: Z. Wang, B. Antony.

Appendix: Statistical Methods (Details of Primary Analyses)

Analyses were performed by using Stata, version 15, and a 2-sided *P* value of 0.050 was deemed statistically significant.

Repeated-Measures Mixed-Effects Model

Stata functions used: *-mixed* function in Stata (version 15) was used to model repeated-measures mixed-effects linear regression. The *-margins* command was used to calculate the estimated value of the outcome measure at each time point. The *-lincom* function was used to calculate the within- and between-group differences over time.

The outcomes for which we used repeated-measures mixed-effects models were VAS knee pain, effusion–synovitis volume, WOMAC subscales (pain, function, stiffness, weight-bearing pain, and non–weight-bearing pain), quality-of-life–derived utility values, cartilage relaxation time, and physical function scores. First, the main effects are treatment group, time, and interaction of treatment group with time. The presence of time interaction allows us to estimate the treatment effect at different times (each follow-up encounter). The baseline value was also included as an outcome variable. Second, the model was also adjusted for baseline values for each continuous outcome, age, sex, and body mass index. Furthermore, the interaction terms for each confounder with time were added. We think the effect of baseline variables (that is, baseline outcome measure, age, sex, and body mass index) on the change in outcome measures is not static and varies over time, which is often termed "time-varying effects." Third, participant identification was included as a random effect, allowing random intercepts. This addresses the correlation within repeated measures. Fourth, the mixed-effects model was fitted by using the default setting of the *-mixed* function (independent covariance and the restricted maximum likelihood method).

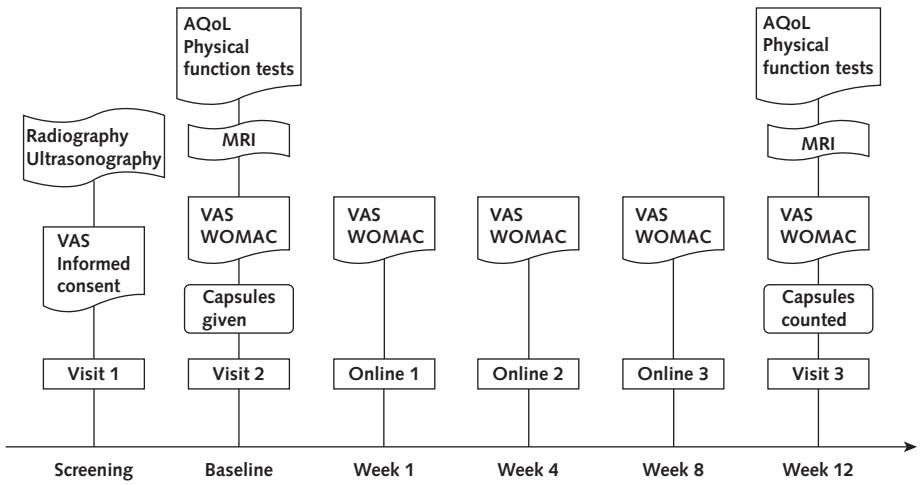
Binomial Regression

For the binomial regression, the *-glm* function was used to estimate the risk ratio or risk difference by specifying the options *family()* and *link()*. Treatment group was included as the univariate predictor of OMERACT response and the number of participants reporting at least 1 adverse event.

Risk ratio by *-glm* with *family(binomial)* and *link(log)*

Risk difference by *-glm* with *family(binomial)* and *link(identity)*

Appendix Figure 1. Study schedule of the trial.



Medication history was collected at all time points. AQoL = Assessment of Quality of Life; MRI = magnetic resonance imaging; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Appendix Table 1. MRI Sequences and Parameters

Machine and Coils	T2-Weighted Sagittal 3D	T2 Mapping
1.5-T whole-body MR unit (GE Optima 450w), using a dedicated transmit/receive 8-channel knee coil if patient size permits; if body habitus is too large, we use a 16-channel large GEM flex coil (GE Healthcare)	T2-weighted fat-saturated 3D fast spin echo sequence; repetition time, 2300 ms; echo time, 80 ms; field of view, 18 cm; 256 × 256 matrix with interpolation Recon Voxel 0.35 × 0.35 × 1 mm; 2 excitations; slice thickness, 1 mm	T2 mapping; repetition time, 1100 ms; echo time, 6.6 ms; field of view, 16 cm; 320 × 224 matrix Reconstructed Voxel 0.5 × 0.714 × 3 mm; 1 excitation; slice thickness, 3 mm

3D = 3-dimensional; MRI = magnetic resonance imaging.

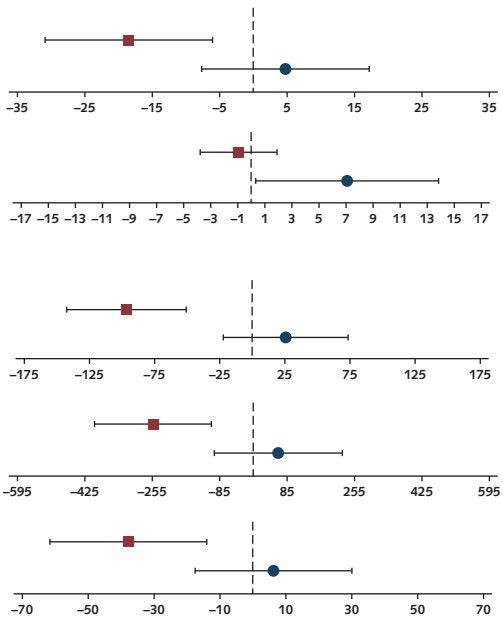
Appendix Table 2. Number of Participants With Concomitant Medication Changes Over 12 Weeks, by Treatment Group

Medication	CL Group (*n* = 36)			Placebo Group (*n* = 34)		
	Stable*	Commenced or Increased	Discontinued or Decreased	Stable*	Commenced or Increased	Discontinued or Decreased
Pain medication, *n* (%)†	28 (78)	4 (11)	4 (11)	25 (74)	9 (26)	0
Paracetamol/acetaminophen	33 (92)	2 (6)	1 (3)	29 (85)	5 (15)	0
NSAIDs‡	30 (83)	3 (8)	3 (8)	29 (85)	5 (15)	0
Other analgesics§	36 (100)	0	0	33 (97)	1 (3)	0
Supplements, *n* (%)‖	31 (86)	1 (3)	4 (11)	33 (97)	0	1 (3)
Glucosamine and/or chondroitin	33 (92)	0	3 (8)	34 (100)	0	0
Other supplements¶	33 (92)	1 (3)	2 (6)	33 (97)	0	1 (3)

CL = *Curcuma longa* extract; NSAID = nonsteroidal anti-inflammatory drug.
* Stable users and nonusers.
† *Pain medication* means use of any of the following: acetaminophen, NSAIDs, cyclooxygenase-2 inhibitors, opioids, or other analgesics.
‡ Ibuprofen, meloxicam, diclofenac, and celecoxib were noted.
§ Opioids and lidocaine were noted.
‖ Supplements that contain glucosamine and/or chondroitin and other supplements.
¶ Other supplements include vitamins, fish oil, methylsulfonylmethane, and coenzyme Q10.

Appendix Figure 2. Change in clinical outcomes (VAS and WOMAC) over 12 weeks, stratified by baseline median effusion-synovitis volume (median value, 20.45 mL) for the CL and placebo groups.

Outcome	Mean Difference (95% CI)	Subgroup	Favors CL	Favors Placebo	*P* Value for Interaction
Primary					
VAS (0–100), *mm*	–18.5 (–30.9 to –6.1)	Smaller volume			0.009
	4.7 (–7.6 to 17.1)	Larger volume			
Effusion-synovitis volume, *mL*	–1.0 (–3.8 to 1.8)	Smaller volume			0.031
	7.1 (0.3 to 13.8)	Larger volume			
Secondary					
WOMAC pain (0–500), *mm*	–96.4 (–142.3 to –50.5)	Smaller volume			<0.001
	26.4 (–21.6 to 74.4)	Larger volume			
WOMAC function (0–1700), *mm*	–252.5 (–401.9 to –103.2)	Smaller volume			0.005
	66.0 (–97.8 to 229.8)	Larger volume			
WOMAC stiffness (0–200), *mm*	–37.9 (–61.9 to –14.0)	Smaller volume			0.010
	6.2 (–17.5 to 30.0)	Larger volume			



All interactions were statistically significant ($P < 0.050$). CL = *Curcuma longa* extract; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.