

## Original Papers

# Efficacy and Safety of *Curcuma domestica* Extracts in Patients with Knee Osteoarthritis

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### Abstract

**Objective:** The objective of this study was to determine the efficacy and safety of *Curcuma domestica* extracts in pain reduction and functional improvement in patients with knee osteoarthritis.

**Study design and setting:** The design and setting were a randomized controlled study at a university hospital in Bangkok, Thailand.

**Methods:** One-hundred and seven (107) patients with primary knee osteoarthritis (OA) with pain score of  $\geq 5$  were randomized to receive ibuprofen 800 mg per day or *C. domestica* extracts 2 g per day for 6 weeks. The main outcomes were improvement in pain on level walking, pain on stairs, and functions of knee assessed by time spent during 100-m walk and going up and down a flight of stairs. The adverse events were also recorded.

**Results:** Fifty-two (52) and 55 patients were randomized to *C. domestica* extracts and ibuprofen groups, respectively. Baseline characteristics of the patients in both groups were not different. The mean scores of the aforementioned outcomes at weeks 0, 2, 4, and 6 were significantly improved when compared with the baseline values in both groups. There was no difference in those parameters between the patients receiving ibuprofen and *C. domestica* extracts, except pain on stairs ( $p = 0.016$ ). No significant difference of adverse events between both groups was found (33.3% vs. 44.2%,  $p = 0.36$  in *C. domestica* extracts and ibuprofen groups, respectively).

**Conclusions:** *C. domestica* extracts seem to be similarly efficacious and safe as ibuprofen for the treatment of knee OA.

### Introduction

Osteoarthritis (OA) is the most common degenerative joint disorder and a major public health problem throughout the world.<sup>1</sup> The prevalence of knee OA in Thai elderly ranged from 34.5% to 45.6%.<sup>2</sup> Knee OA causes pain and dysfunction in 20% of elderly persons.<sup>3</sup> It is the fourth most important global cause of disability in women and the eighth most important in men.<sup>4</sup> Physical disability arising from pain and loss of functional capacity reduces the quality of life and increases the risks of morbidity and mortality.<sup>5</sup> Among treatment modalities, nonsteroidal anti-inflammatory

drugs (NSAIDs) are the most common treatment modality to relieve pain for OA, but most of them can cause undesirable effects on the gastrointestinal tract (i.e., ulceration, bleeding, and perforation of stomach and duodenum).<sup>6,7</sup>

The extracts from *Curcuma domestica*, a spice used as a coloring agent (yellow) and a preservative in Thai food, have been used for a century. *In vitro* studies showed that curcumin had an inhibitory effect on substances playing an important role in the inflammatory pathway. The mechanisms by which curcumin prevents inflammation are postulated through inhibition of lipo-oxygenase,<sup>8</sup> cyclo-oxygenase,<sup>9</sup> and phospholipase.<sup>10</sup> Curcumin also inhibited the secretion of

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collagenase, elastase, and hyaluronidase.<sup>11</sup> Moreover, curcumin was found to inhibit the activation of free radical activated transcription factors such as AP-1 and nuclear factor  $\kappa$ B (NF $\kappa$ B)<sup>12</sup> and reduce the proinflammatory cytokines such as tumor necrosis factor alpha, interleukin-1 beta- $\beta$ , and interleukin-8.<sup>13</sup> Furthermore, curcumin exhibited anti-oxidant properties by the inhibition of nitric oxide synthase production.<sup>13,14</sup> Recently, there was evidence of curcumin in inhibiting collagenase and stromelysin expression at micromolar concentrations, which suggested its therapeutic potential for the treatment of arthritis.<sup>15</sup> There were six studies of curcumin in humans including a phase 1 trial with 25 subjects using up to 8,000 mg of curcumin per day for 3 months and five other trials using 1125–2500 mg of curcumin per day.<sup>16</sup> All studies revealed that curcumin was safe and contained anti-inflammatory activity.

The objective of the study was to determine the efficacy and safety of *C. domestica* extracts in pain reduction and functional improvement in patients with knee OA.

### Patients and Methods

The study was approved by the Ethics Committee on Human Research of the Faculty of Medicine Siriraj Hospital, Mahidol University and informed consents were obtained from all participating subjects. The study was conducted at Siriraj Hospital, a tertiary care medical center in Bangkok, Thailand, from April 2005 to May 2006. The eligible subject was an adult with primary knee OA according to the criteria proposed by the American Rheumatism Association.<sup>17</sup> The subject must have knee pain and radiographic osteophytes and at least one of the following features: (1) age >50 years, (2) morning stiffness <30 minutes in duration, (3) and crepitus on motion. Patients who had a pain score in the numerical rating scale of  $\geq 5$  of 10 were recruited. Any patients who had peptic ulcer, hepatobiliary tract disease, or known allergy to curcumin or ibuprofen were excluded.

The subjects were asked to discontinue their medications related to the treatment of knee OA (e.g., NSAIDs, glycos-

aminoglycan derivative drugs) 1 week before randomization. The computerized randomization code was kept by a research assistant who was not directly involved in the study. All subjects were randomly allocated to receive either ibuprofen (400 mg twice daily) or *C. domestica* extracts (500 mg four times daily) for 6 weeks. Ibuprofen 800 mg per day was used according to the rheumatologist's recommendation for treatment in Thai elderly patients with OA to correspond with the smaller size of Thai elderly and to minimize the risk of gastrointestinal side-effects. The patients were instructed not to use any other medications or herbs.

*C. domestica* extracts were produced by the Thai Government Pharmaceutical Organization. The preparations were made under the Good Manufacturing Procedures Standard. Dried rhizomes of *C. domestica* were grounded into powder. The turmeric powder was extracted with ethanol and then evaporated at low pressure to obtain ethanolic extracts containing oil and curcuminoids. The oil part was then removed in order to have curcuminoids extracts. Each capsule of *C. domestica* extracts contained 250 mg of curcuminoids.

Only the assistant knew which treatment was being provided to the patient. The physician who assessed the treatment outcomes was unaware of the patient's group of treatment. The patients were assessed every 2 weeks by the same assessor. The main outcomes consisted of pain on level walking and pain on stairs assessed by a numerical rating scale and knee functions assessed by the time spent on a 100-m walk and going up and down a flight of stairs (10 steps). The time was measured by using digital stopwatch. Its resolution was within 0.001 seconds. The study was conducted at the same location for all patients. For safety concern, all patients had blood tests including complete blood count, liver function, and renal function at week 0 and week 6. Adverse events were recorded from new symptoms experienced by the patients as well as a change in laboratory profiles. The medication could be discontinued when the patients rated pain of less than 3, since this pain magnitude is considered mild and the patient is willing to tolerate it. Compliance to medication was assessed by the pill count method. At week

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND BASELINE SCORES OF THE PATIENTS

	<i>C. domestica</i> (n = 52)	<i>Ibuprofen</i> (n = 55)
Mean age $\pm$ SD (years)	61.4 $\pm$ 8.7	60.0 $\pm$ 8.4
Gender: female (%)	41 (78.8%)	45 (81.8%)
Mean BMI $\pm$ SD (kg/m <sup>2</sup> )	26.4 $\pm$ 3.7	26.8 $\pm$ 4.8
Mean duration of symptoms $\pm$ SD (months)	19.1 $\pm$ 19.6	22.3 $\pm$ 26.4
Affected knee		
Right	13 (25.0%)	15 (27.3%)
Left	13 (25.0%)	14 (25.4%)
Bilateral	26 (50.0%)	26 (47.3%)
Using gait aid	4 (7.7%)	1 (1.8%)
Using knee braces	16 (30.8%)	10 (18.2%)
Mean pain scores on level walking	5.3 $\pm$ 2.3	5.0 $\pm$ 1.9
Mean pain scores on stairs	5.7 $\pm$ 2.1	6.2 $\pm$ 2.2
Mean time spent on a 100-m walk $\pm$ SD (sec)	107.9 $\pm$ 24.6	103.6 $\pm$ 22.2
Mean time spent on going up and down a flight of stairs $\pm$ SD (sec)	31.2 $\pm$ 12.6	30.3 $\pm$ 13.8

*C. domestica*, *Curcuma domestica*; SD, standard deviation; BMI, body mass index.

TABLE 2. MEAN VALUES OF PAIN ON LEVEL WALKING, PAIN ON STAIRS, TIME SPENT ON 100-m WALK AND GOING UP AND DOWN A FLIGHT OF STAIRS BETWEEN TWO GROUPS AT WEEK 0, WEEK 6, CHANGE SCORE AND DIFFERENCE OF CHANGE SCORES AMONG TWO GROUPS

	C. domestica (n = 52)			Ibuprofen (n = 52)			p-value*
	Week 0 score	Week 6 score	Change score	Week 0 score	Week 6 score	Change score	
Pain on level walking	5.3 ± 2.3	2.7 ± 2.5	2.7 ± 2.6	5.0 ± 1.9	3.1 ± 2.3	2.0 ± 2.3	0.20
Pain on stairs	5.7 ± 2.1	3.1 ± 1.5	2.5 ± 2.2	6.2 ± 2.2	3.8 ± 2.4	2.5 ± 2.6	0.92
Time spent on 100-m walk (sec)	107.9 ± 24.6	96.7 ± 17.0	10.1 ± 16.8	103.6 ± 22.2	97.0 ± 25.7	5.0 ± 16.9	0.16
Time spent on going up and down a flight of stairs (sec)	31.2 ± 12.6	24.8 ± 10.2	6.0 ± 6.9	30.3 ± 13.8	25.9 ± 12.3	3.3 ± 8.3	0.10
						0.67 (-0.35 to 1.68) -0.06 (-1.07 to 0.96) 5.07 (-2.09 to 12.23) 2.75 (-0.50 to 5.99)	

\*Difference = change score of *C. domestica* - change score of ibuprofen.

\*Independent t-test.

6, the patients' satisfaction with treatment was also evaluated by a five-category scale (i.e., high, moderate, little, same, or dissatisfaction).

A sample size of 50 patients per group was calculated as a noninferiority trial, with the assumption that the significant difference in pain score after treatment with ibuprofen and *C. domestica* extracts was  $\pm 1$  point with standard deviation (SD) of 2, 5% type I error, and 20% type II error. Repeated-measures analyses of variance were used to analyze the main outcomes. The differences in mean value of pain and time spent on a 100-m walk and going up and down a flight of stairs at week 6 between ibuprofen and *C. domestica* groups were analyzed by independent *t*-test. The  $\chi^2$  test was used to analyze adverse events and satisfaction level. Student's *t*-test was used to analyze the compliance of drug intake. The per-protocol analysis was chosen for this noninferiority trial.<sup>18</sup>

## Results

Of 190 patients screened, 107 fulfilled selection criteria and were enrolled in the study. Fifty-two (52) and 55 patients were randomized to *C. domestica* extracts and ibuprofen groups, respectively. At the end of the trial, 45 patients (86.5%) in the *C. domestica* extracts and 46 patients (83.6%) in the ibuprofen group completed the study. The reasons for lost-to-follow-up in both groups were inconvenience to return for follow-up visits (6 in the *C. domestica* group and 6 in the ibuprofen group) and having adverse events (1 in the *C. domestica* group and 3 in the ibuprofen group). The baseline characteristics of the patients in each group are shown in Table 1. The majority of subjects were overweight elderly women (average body mass index [BMI] > 25). The duration of symptoms before entering the trial was approximately 20 months. Half of the subjects had bilateral knee OA. Some of

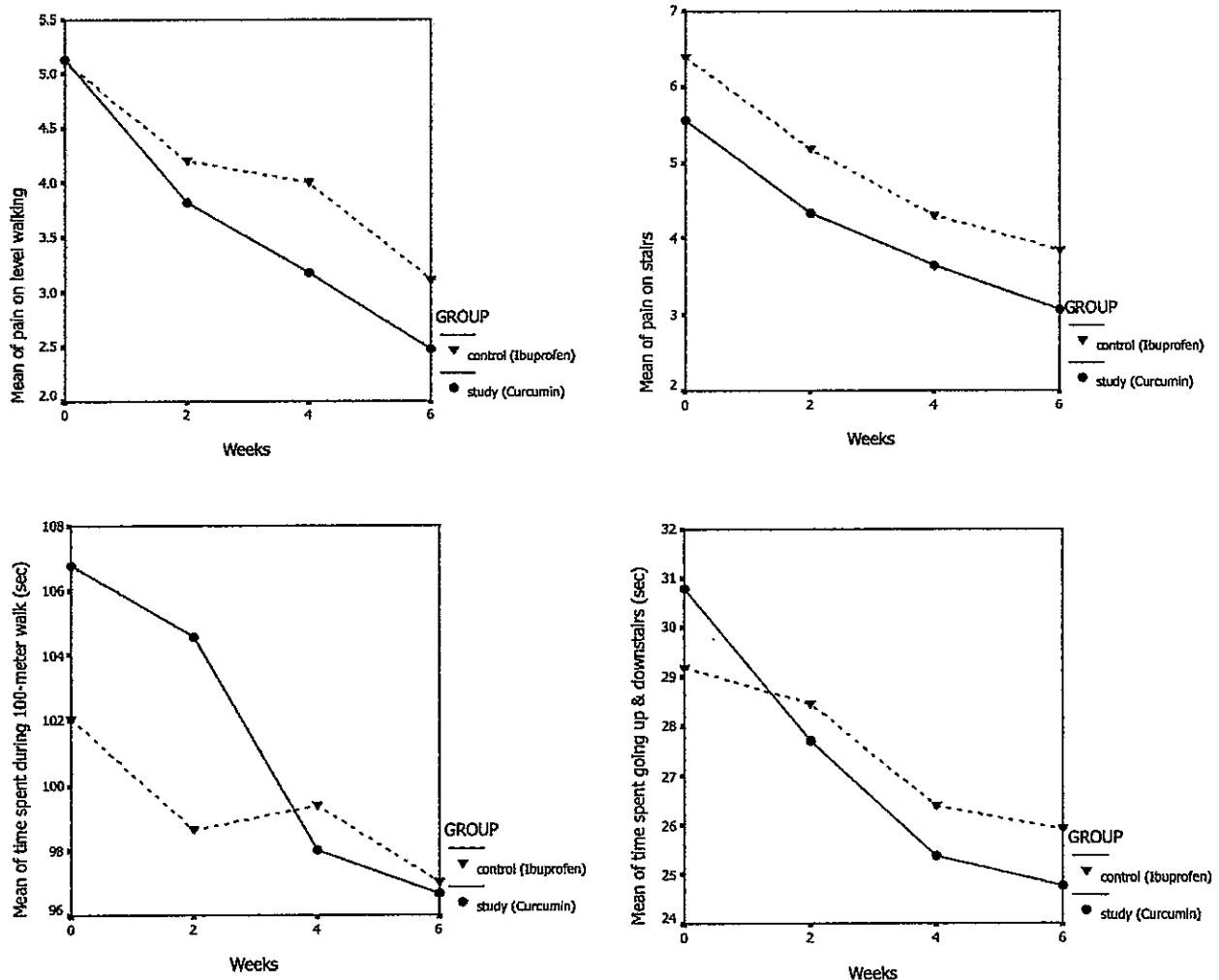


FIG. 1. Mean pain scores on level walking, pain on stairs, time spent on a 100-m walk, and going up and down a flight of stairs at week 0, 2, 4, and 6 (per protocol analysis).

TABLE 3. ADVERSE EVENTS BETWEEN TWO GROUPS

	<i>C. domestica</i> (n = 48)	<i>Ibuprofen</i> (n = 52)	p-value*
Total no. of patients with an AE	16 (33.3%)	23 (44.2%)	0.36
Adverse events			
Dyspepsia	10 (20.8%)	14 (26.9%)	
Dizziness	5 (10.4%)	2 (3.8%)	
Nausea/vomiting	3 (6.3%)	3 (5.8%)	
Loose stool	2 (4.2%)	1 (1.9%)	
Constipation	0	2 (3.8%)	
Dry mouth	0	2 (3.8%)	
Rash	0	1 (1.9%)	
Fatigue	0	1 (1.9%)	
GI bleeding	0	1 (1.9%)	
Feeling of drug obstructed in the throat	1 (2.1%)	0	

Some patients experienced more than one event. AE, adverse event; GI, gastrointestinal.

\* $\chi^2$  test.

them used gait aids and knee braces. The mean pain scores on level walking were 5.3 and 5.0, and mean pain scores on stairs were 5.7 and 6.2 in the *C. domestica* extracts and the ibuprofen groups, respectively. Time spent on the 100-m walk was approximately 100 seconds and on going up and down a flight of stairs was approximately 30 seconds. Only 2 patients in the *C. domestica* group discontinued medication when the pain score was less than 3.

The mean value of pain on level walking, pain on stairs, time spent on 100-m walk, and going up and down a flight of stairs between two groups at week 0, week 6, and change score and difference of change scores between the two groups are shown in Table 2. The differences of all outcomes were not statistically different. However, the *C. domestica* group seemed to have less time spent on the 100-m walk and going up and down a flight of stairs. Figure 1 demonstrates the mean scores of pain on level walking, pain on stairs, time spent on a 100-m walk, and going up and down a flight of stairs at week 0, 2, 4, and 6 between the two groups. Those aforementioned outcomes in each group were significantly improved when compared with the baseline values. However, there were no differences in those parameters between the patients receiving ibuprofen and *C. domestica* extracts except for pain on stairs ( $p = 0.016$ ). The pain score, time spent on level walking, and stairs showed decreasing trends in both groups.

The adverse events of the *C. domestica* and ibuprofen groups are shown in Table 3. No difference was found (33.3% versus 44.2%,  $p = 0.36$ ). The common adverse events were dyspepsia, dizziness, nausea and vomiting, and loose stool. The blood tests between week 0 and week 6 in both groups did not reveal significant changes. For medication intake, the patients in the ibuprofen group had better compliance than those in *C. domestica* extracts group (90.1% versus 82.8%,  $p = 0.001$ ).

The patients' satisfaction with treatment was not different ( $p = 0.35$ ) in both groups as shown in Table 4. Most subjects rated themselves as having moderate to high satisfaction (91.1% and 80.4% in the *C. domestica* extracts and the ibuprofen groups, respectively).

## Discussion

Curcumin exhibits various pharmacologic activities including anti-inflammatory, anti-oxidant, anticarcinogenic, antiviral, and anti-infectious properties.<sup>19</sup> The anti-inflammatory activity of curcumin extracts was demonstrated by inhibition of many different molecules that play a major role in inflammation.<sup>16</sup> Patients with knee OA suffer with pain from an inflammatory process of the knee joint. Regarding the lack of studies comparing the efficacy of curcumin and NSAIDs in patients with knee OA, this study has pertinently

TABLE 4. PATIENTS' SATISFACTION AT WEEK 6

Satisfaction level	<i>C. domestica</i> (n = 45)	<i>Ibuprofen</i> (n = 46)	p-value*
High	20 (44.4%)	15 (32.6%)	0.15
Moderate	21 (46.7%)	22 (47.8%)	
Little	1 (2.2%)	5 (10.9%)	
Same	3 (6.7%)	3 (6.5%)	
Dissatisfaction	0 (0)	1 (2.2%)	

\* $\chi^2$  for trend.

shown the efficacy of curcumin to relieve pain and to improve knee functions.

In our study, ibuprofen was chosen to be a comparator because scientific evidence from meta-analysis revealed that NSAIDs were superior to acetaminophen for improving knee and hip pain in people with moderate-to-severe levels of pain from OA.<sup>20,21</sup> Additionally, no significant difference in safety was found between acetaminophen and NSAIDs.

There were studies demonstrating the efficacy of curcumin in reducing inflammation in postoperative patients,<sup>22</sup> and rheumatoid arthritis.<sup>23</sup> Recently, an *in vivo* study revealed the efficacy of curcumin in preventing joint inflammation, but it should be started before the onset of inflammation.<sup>24</sup> However, no study reported the efficacy of curcumin in patients with OA.<sup>25</sup>

The effect of weight on drug level or volume distribution should also be considered because the majority of subjects in this study were overweight (mean BMI = 26.4–26.8 kg/m<sup>2</sup>). There was a study demonstrating that peak ibuprofen concentration was significantly decreased and volume of distribution was increased in obese subjects compared to normal body weight subjects.<sup>26</sup> The data indicated that the ibuprofen dose may be increased in obese patients without changing the dose interval in order to achieve necessary plasma concentrations.

Concerning the safety, the prevalence of adverse events was not different between the two groups. Ten (10) patients (20.8%) in the *C. domestica* extracts group experienced dyspepsia. The meaning of dyspepsia varied from bloating, passing gas, to irritation. Many patients in the *C. domestica* extracts group who had bloating symptoms and passing gas notified us that these symptoms were beneficial effects, whereas those in the ibuprofen group reported gastrointestinal irritation symptoms. These dyspeptic symptoms observed in the *C. domestica* extracts group could be due to their digestive properties. No other serious adverse event was found, as well as meaningful changes in blood tests. We were able to provide 2,000 mg/day of *C. domestica* extracts to the patients up to 6 weeks because curcumin was found to be safe even after high dose ingestion up to 8,000 mg/day for 3 months.<sup>27</sup>

At the end of the study, however, we found that compliance of drug intake during 6 weeks in the ibuprofen group was better than that in the *C. domestica* group. This was due to the fact that ibuprofen was given twice a day, whereas *C. domestica* extracts had to be taken four times a day. More subjects evaluated themselves with moderate to high satisfaction in *C. domestica* than in the ibuprofen group. Some patients in the ibuprofen group rated themselves as having little satisfaction and dissatisfaction (10.9% and 2.2%, respectively). None in the *C. domestica* group felt unsatisfied. This may reflect the satisfaction of the patients with *C. domestica* even it had to be taken four times a day.

The results of this study suggested that *C. domestica* extracts might be as effective as ibuprofen in alleviating knee pain and improving knee functions even though there was a trend toward a greater effect in patients receiving *C. domestica* extracts. However, we were unable to claim that efficacy of both treatments was equivalent because the upper limit of the 95% confidence interval (CI) of mean difference of the pain score exceeds the prespecified range of equivalence.

Additionally, the wide range of 95% CI meant that our study had an inadequate sample size. Based on the SD of 2.36, the proper sample size should be 70 patients per group. Therefore, an additional study with adequate sample size and using a higher dose of ibuprofen in the comparison group should be performed to demonstrate the efficacy of *C. domestica* extracts in relieving pain and improving function in patients with knee OA.

## Conclusions

*C. domestica* extracts seem to be efficacious and safe for the treatment of knee OA similarly to ibuprofen. However, more studies with an adequate sample, a higher dose of ibuprofen in the comparison group, and double-blind technique are recommended to demonstrate the efficacy of *C. domestica* extracts in alleviating knee pain and improving knee functions. The safety profiles of *C. domestica* extracts were also demonstrated.

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## Author Disclosure Statement

No competing financial interests exist.

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**Sentence edited as meant?**