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ORIGINAL ARTICLE

Efficacy of High- and Low-Dose, Highly Bioavailable Curcumin (Curcurouge®) for Treating Knee Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Prospective Study

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Abstract:

Purposes : To evaluate the clinical effects of orally administered CurcuRouge® in patients with knee osteoarthritis (OA) after 12 weeks of treatment.

Methods: In this randomized, double-blind, placebo-controlled, prospective clinical study. 90 patients over the age 40 with knee OA of Kellgren-Lawrence (KL) Grade II or III were enrolled. A placebo or CurcuRouge® containing 60 mg or 180 mg/day of curcumin was administered orally every day for 12 weeks. To monitor adverse events, blood biochemical analyses were performed before and after 12 weeks of each intervention. The patients' knee symptoms were evaluated for 12 weeks using the Japanese Knee Osteoarthritis Measure (JKOM) criteria, a knee pain visual analog scale (VAS), the Japanese Orthopedic Association (JOA) knee scoring system, the need for nonsteroidal anti-inflammatory drugs (NSAIDs) and a timed up-and-go test (TUG).

Results: The declining trend in NSAIDs needs was significantly greater in high-dose CurcuRouge® group than in placebo group. The decrease of highly sensitive CRP was significantly greater in high-dose of CurcuRouge® than placebo group. In patients with KL Grade II, JOA and VAS scores improved significantly more in the high-dose CurcuRouge® group than in the placebo group. We didn't find CurcuRouge® related adverse event during the study period.

Conclusion: CurcuRouge® has succeeded in proofing a potential for treating human knee OA, particularly at an early stage.

Trial Registration: jRCTs 051200058

Keywords: Knee osteoarthritis, treatment, safety, highly bioavailable curcumin, CurcuRouge®

Level of Evidence: Level I, a randomized, double-blind, placebo-controlled prospective study

Introduction

Osteoarthritis (OA) is a common degenerative disease that causes disability and poor quality of life. It affects approximately 240 million people worldwide, with 10% of men and 18% of women affected [1]. Hip or knee OA is a chronic condition mostly treated with analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), but these medications can cause serious gastrointestinal and cardiovascular adverse events, especially with long-term use [2,3]. Thus, disease-modifying agents that not only alleviate joint pain but also slow the progression of the condition are required.

Curcumin is a polyphenol extracted from turmeric, that has long been used safely in foods like curry [4]. Curcumin, a promising therapeutic food material with anti-inflammatory and anti-oxidative properties; has long been used as an anti-inflammatory treatment in traditional Chinese and Ayurvedic medicine [4]. It regulates various biochemical and molecular pathways by modulating several molecular targets, including transcription factors, cytokines, enzymes, and genes, that regulate cell proliferation or apoptosis [5]. It appears to have anti-inflammatory effects comparable to steroidal drugs and NSAIDs such as indomethacin and phenylbutazone [6]. Some studies have linked curcumin's anti-inflammatory properties to the suppression of prostaglandin synthesis by its effect on cyclooxygenase [7], a key enzyme responsible for the conversion of arachidonic acid to prostaglandins. It has also been shown to inhibit proteasome activity and induce apoptosis in human colon cancer cells, both in vitro and in vivo [8]. Furthermore, it inhibits nuclear factor-kappa B (NF-kB) activation [9], which is a key event in the chronic inflammatory process. Based on these findings, curcumin is expected to be effective for a wide range of diseases related to chronic inflammation, including cancer, cardiovascular disease, metabolic syndrome, Alzheimer's disease, OA, and other common diseases and aging conditions [4,5,10,11]. Furthermore, it has been shown to be a potent inhibitor of the chondrocyte production of inflammatory and catabolic mediators [10].

However, curcumin has a very low bioavailability. Theracurmin®, which is a submicron-particle colloidal dispersion of curcumin [12], has better oral bioavailability in humans [13]. In a randomized, double-blind, placebo-controlled, prospective clinical trial in patients with OA to evaluate the efficacy of Theracurmin®, Nakagawa showed that Theracurmin® improved the knee pain visual analog scale (VAS) scores [14]. To further improve bioavailability, Sunagawa developed CurcuRouge®(Therabiopharma, Kanagawa, Japan), a novel amorphous formulation of curcumin. They confirmed that CurcuRouge® was 3.4-fold higher bioavailable than Theacurmin® in a single-dose, double-blind, two-way crossover study in 12 volunteers [15].

The purpose of the current study was to determine the clinical efficacy of orally administered CurcuRouge® in patients with knee OA after 12 weeks of treatment. We hypothesized that consuming CurcuRouge® ingestion for 12 weeks would improve the symptoms and functional abilities of patients with knee OA.

Materials and Methods

To test our hypothesis, we conducted a randomized, double-blind, placebo-controlled, prospective clinical study with three treatment groups: high dose (180 mg/day curcumin) and low dose (60 mg/day curcumin) CurcuRouge® and placebo. At the start of the treatment period, randomization was

performed after baseline tests and using a computer-generated numbers table without stratification. Based on randomization, the allocation was performed by someone who was not involved in the current project. From September 2020 to October 2022, 90 patients over the age of 40 with knee OA confirmed by the radiographic analysis were selected and enrolled in the study. They were divided into three groups of 30 patients each. Before participating, all subjects provided written informed consent. All procedures were reviewed and approved by the Nara Medical University Certified Review Board (nara0017), and this study was performed in accordance with the World Medical Association's Declaration of Helsinki. This study was registered at Japan Registry for Clinical Trials (jRCTs051200058).

In this study, patients over the age of 40 with primary medial knee OA and KL Grades of II or III with radiographic classification were eligible. However, patients with severe renal dysfunction or on dialysis, severe liver dysfunction or cirrhosis, severe cardiovascular diseases, severe cerebrovascular dysfunction, severe diabetes mellitus, curcumin abuse, or pregnancy were excluded from this study. Furthermore, those who had received more than two types of anticoagulants, previous knee surgeries, knee injection treatment including hyaluronic acid during the study, knee steroid injections two months before the study, or other steroids four weeks before the study were excluded. If patients required NSAIDs during the study, oral celecoxib two pills per day (100 mg per pill) were prescribed. The other combined therapy we allowed was pain relief patches.

A high or low-dose of CurcuRouge® or placebo was administered orally twice a day, for 12 weeks. Patients in the high-dose CurcuRouge® group took two capsules containing 90 mg of curcumin per capsule, while those in the low-dose CurcuRouge® group took two capsules containing 30 mg of curcumin per capsule per day. Similarly, patients in the placebo group took two placebo capsules per day that were similar in shape and color to those of CurcuRouge®. The placebo was primarily made of crystalline cellulose, silicon dioxide, calcium stearate and food colorings. For the compliance check, the patients were asked to report the number of remaining capsules and the prescribed celecoxib pills at their 2, 4, 6, 8, 10 and 12-week visits at our outpatient clinic.

The study's flow chart is depicted in Figure 1. The high- and low-dose CurcuRouge® and placebo groups included 30 patients. The drop-out cases due to adverse events were two in the high-dose group (due to severe lumbago and buttock pain in one case and vertigo and nausea in one case), four in the low-dose group (due to dermatitis in one case, consent withdrawal in one case, severe knee pain in one case and un-wellness in one case), and none in the placebo group. The study's safety committee decided that all of the aforementioned adverse events were unrelated to CurcuRouge®. One case in the high-dose group was excluded due to poor drug intake compliance. Finally, 83 patients (27 in the high-dose CurcuRouge® group, 26 in the low-dose CurcuRouge® group, and 30 in the placebo group) were included for further analysis.

Blood biochemical analyses were performed before the study and after 12 weeks of each intervention, and blood curcumin concentrations were analyzed after 12 weeks using a previously described analytical method [15]. The patients' knee symptoms were assessed at 0, 2, 4, 6, 8, 10 and 12 weeks according to the Japanese Knee

Osteoarthritis Measure (JKOM) criteria [16], the JKOM knee pain VAS, and the knee scoring system of the Japanese Orthopedic Association (JOA) knee scoring system [17]. The JKOM consists of 25 questions divided into four subcategories for patient self-assessment (pain and stiffness, condition in daily life, general activities, and health conditions) and is based on the World Health Organization's International Classification of Functioning, Disability, and Health, validated in the same way as the Western Ontario and McMaster Universities' Arthritis Index. The JOA scale assesses four functions: the ability to walk (30 points), the ability to climb up and down stairs (25 points), the range of motion (ROM; 35 points), and joint swelling (10 points). Each knee joint can achieve a maximum score of 100 points on the JOA scale. The improved JKOM, VAS, and JOA scores (the differences between the scores at each time point and before the study) were calculated. Furthermore, adverse events and the number of celecoxib pills taken during the 12-week period were recorded. We also calculated NSAIDS necessity in 3 groups.

A timed up-and-go test (TUG) and the ROM of their knee joints were measured before the study and after 12 weeks of each intervention. These performance-based measures are recommended as validated outcome measures by the Osteoarthritis Research Society International to assess physical function in adults with knee OA [18,19]. In TUG, participants were asked to stand up, walk around a cone three meters away, and then return to their chairs at their regular pace. The chair had no arms, and a height of 50 cm from the seated position. The time and number of gaits required to complete this task were recorded. The primary endpoints were JKOM, VAS, and JOA knee score, as well as NSAID necessities. The secondary endpoints were TUG, knee ROM, blood biochemistry analyses, and adverse events.

The primary analysis was performed following the full-analysis-set principal. Data were expressed as mean and standard deviation (SD) and compared among groups using a three-factor analysis of variance for parametric variables or the Kruskal-Wallis test for non-parametric variables. A paired student's t-test was used to compare data at 0 and 12 weeks of treatment in each group. Categorical data were compared using the chi-squared test. The level of statistical significance was set to a p value of less than 0.05. All statistical analyses were performed using EZR, a modified version of the R commander designed to include statistical functions frequently used in biostatistics.

Results

The baseline characteristics of the study patients in each of the three groups are summarized in Table 1. The majority of patients were female, accounting for 77.8% in the high-dose of CurcuRouge® group, 88.5% in the low-dose of CurcuRouge® group, and 70.0% in the placebo group. The patient ages were also comparable across the three groups. The KL grading system was used to quantify disease severity in order to effectively randomize disease status upon study entry between groups. For KL Grade II, there were nine cases in the high-dose CurcuRouge® group, eight cases in the low-dose CurcuRouge® group, and 10 cases in the placebo group. For KL Grade III, there were 18 cases in the high-dose group, 18 cases in the low-dose group, and 20 cases in the placebo group. There were no statistical differences in the baseline characteristics, as well as compliance, among the three groups.

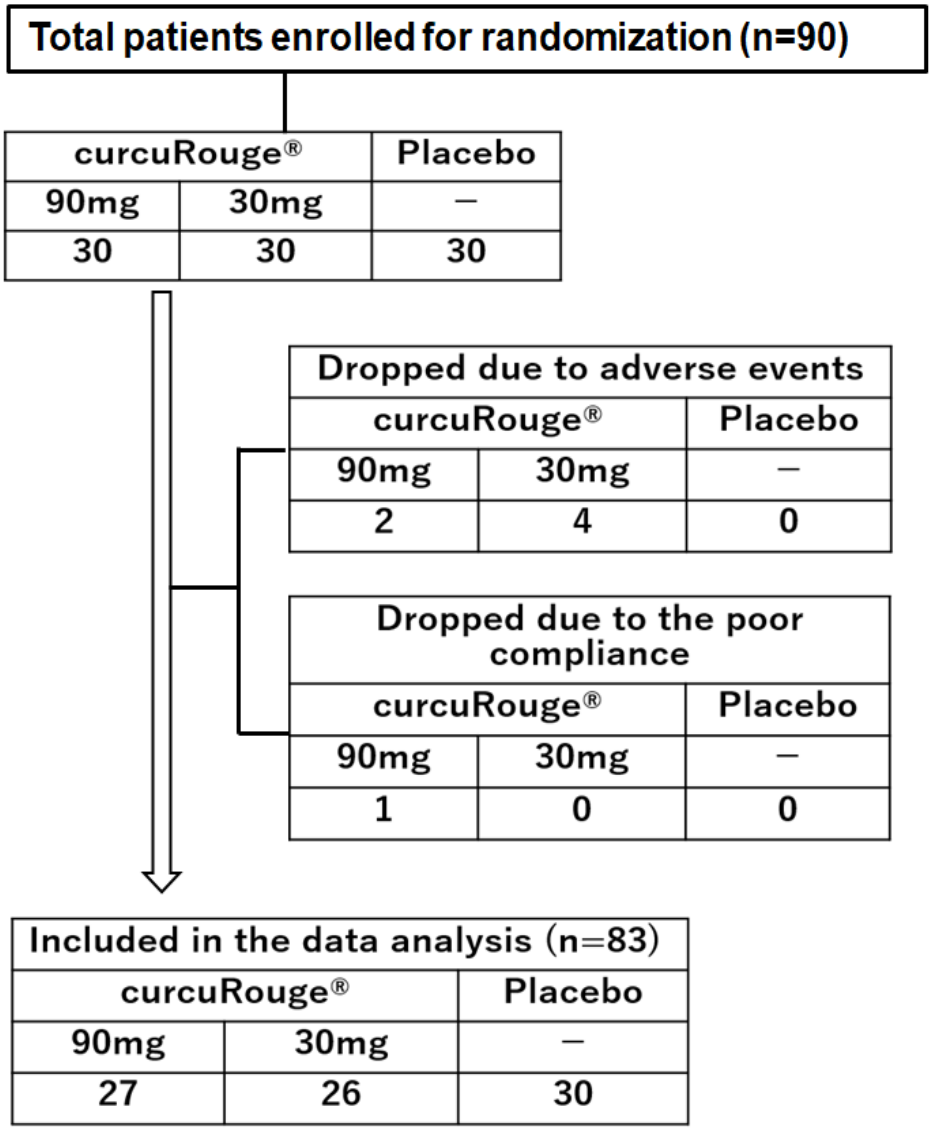

Figure1. Patient flowchart for the study

Table 1. Baseline characteristics of the studied groups.

	curcuRouge® **90 mg**	curcuRouge® **30 mg**	**Placebo**	***P*-value**
Number of patients	**27**	**26**	**30**	
Male/female	**6/21**	**3/23**	**9/21**	**0.251**
Age (mean ± SD)	**71.1 ± 6.5**	**71.4 ± 10.3**	**70.1 ± 9.5**	**0.837**
Kellgren-Lawrence Classification (II/III)	**9/18**	**8/18**	**10/20**	**0.999**
Osteoarthritis lesion (one knee/both)	**19/8**	**18/8**	**19/11**	**0.875**
JOA score (mean ± SD)	**72.3 ± 11.1**	**73.4 ± 9.2**	**73.2 ± 12.1**	**0.933**
JKOM score (mean ± SD)	**30.2 ± 19.0**	**31.3 ± 19.8**	**32.3 ± 16.6**	**0.911**
VAS score (mean ± SD)	**0.46 ± 0.24**	**0.39 ± 0.24**	**0.49 ± 0.23**	**0.283**

JOA, the Japanese Orthopedic Association knee scoring system; JKOM, the Japanese Knee Osteoarthritis Measure; VAS, the knee pain Visual Analogue Scale.

Figure 2 depicts the blood curcumin concentrations, with mean curcumin concentration in the high-dose and low-dose CurcuRouge® groups, as well as the placebo group, at 12 weeks of treatment being 199.6, 79.1, and 0 ng/mL respectively. The high-dose CurcuRouge® group had significantly higher blood curcumin concentrations than the low-dose group.

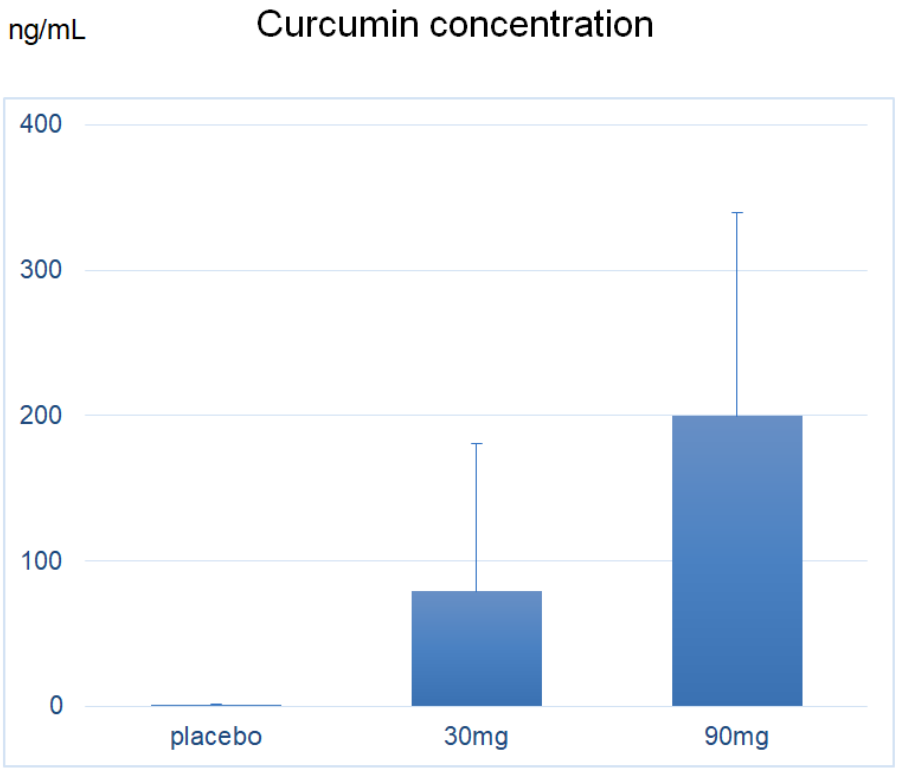

Figure 2. Blood curcumin concentrations 12 weeks after treatment.

In each group, the JOA knee OA scores at 12 weeks were significantly higher than those at 0 weeks. The changes in JOA knee OA scores from 0 to 12 weeks are depicted in Figure 3a. At 8 weeks, the JOA score was significantly higher in the high-dose CurcuRouge® group than in the placebo group, with no significant differences among the three groups at 12 weeks. In addition, JKOM scores at 12 weeks were significantly lower than those at 0 weeks in the high-dose CurcuRouge® and placebo groups, with no significant differences among the three groups. Furthermore, VAS scores at 12 weeks were significantly lower than those at 0 weeks in all groups (Fig. 3b), with no significant differences among the three groups. The NSAID need ratio in the three groups is depicted in Figure 3c. The declining trend in the high-dose CurcuRouge® group was significantly greater than that in the placebo group ($p<0.05$), with respect to the approximate regression line slope.

Points

Figure 3a. Improvement of Japanese Orthopedic Association (JOA) scores in the studied groups over weeks.

Points

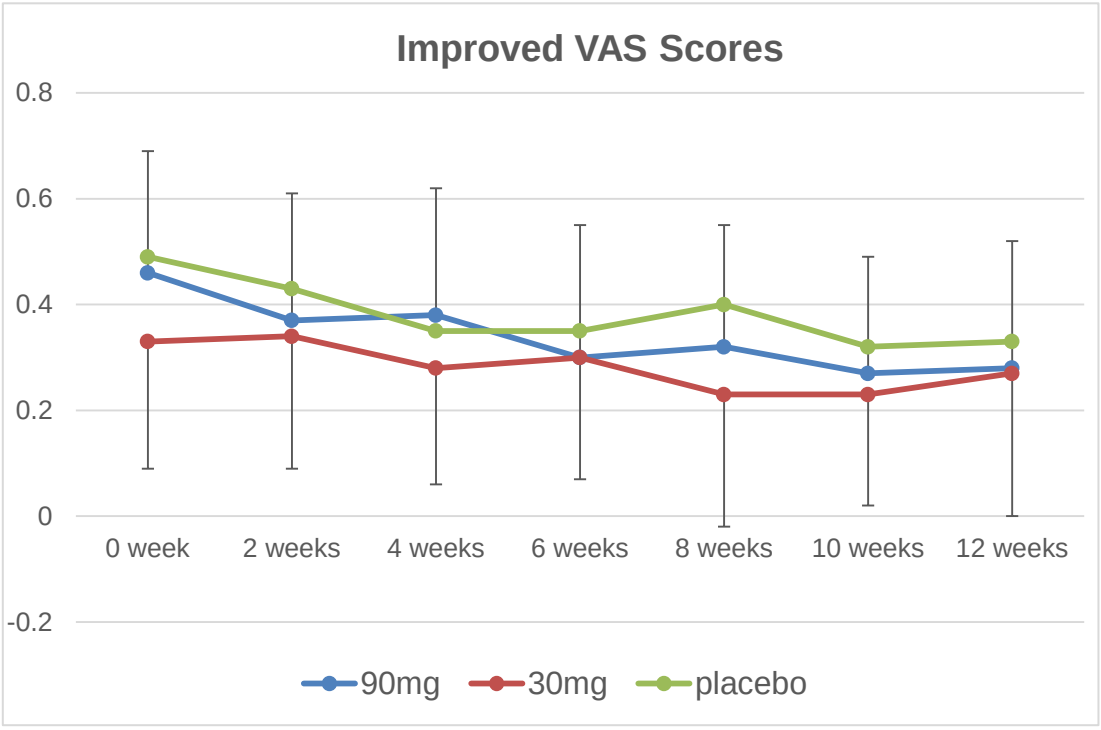

Figure. 3b Improvement of Visual Analogue Scale (VAS) scores in the studied groups over weeks.

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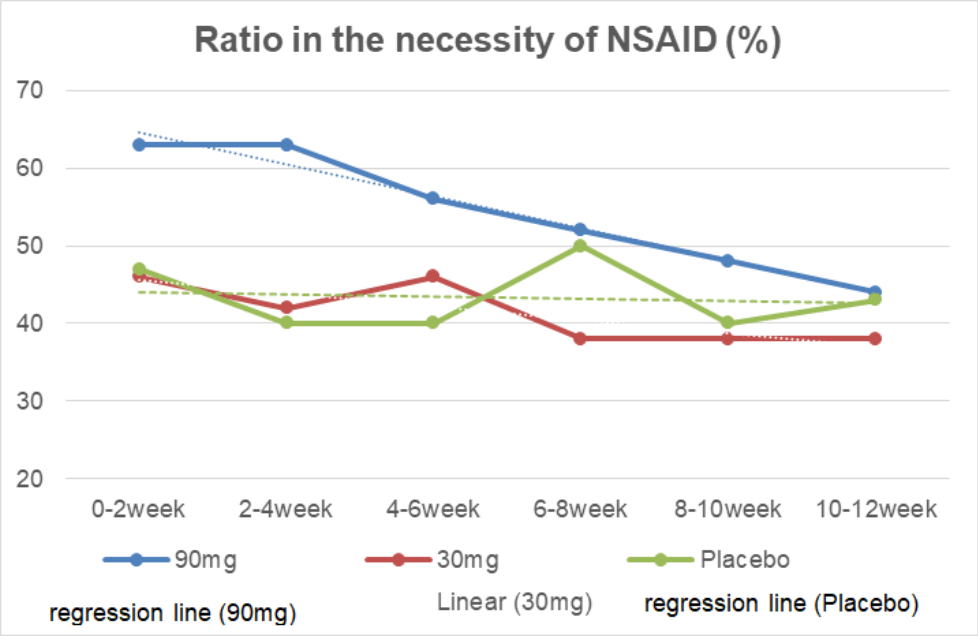

Figure. 3c Nonsteroidal anti-inflammatory drug (NSAID) need ratio changes in the studied groups over weeks.

The number of gaits in TUG in the three groups is depicted in Figure 4. The number of gaits at 12 weeks of treatment was significantly lower than that at 0 weeks in the high-dose CurcuRouge® group, with no significant differences among the three groups. In terms of knee ROM and gait time changes in TUG, there were no significant differences among three groups.

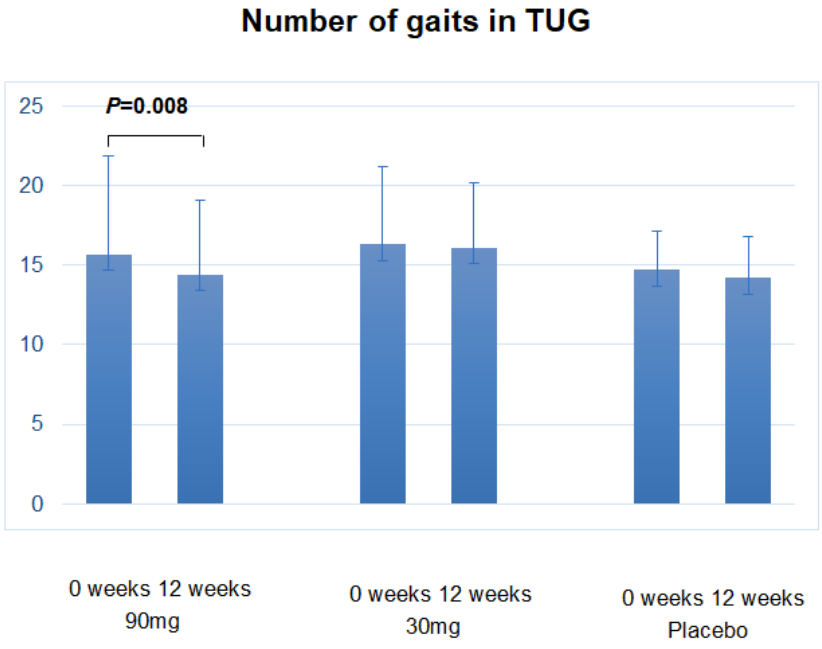

Figure 4. The number of gaits in the timed up-and-go test (TUG) in the studied groups.

In patients with KL Grade II, JOA score significantly improved from 0 to 12 weeks in the high-dose CurcuRouge® group (19.2±14.7 points) more than in the placebo group (4.5±8.9 points) (Fig. 5a), while VAS score was significantly reduced (high-dose -0.36±0.18, placebo -0.01±0.22) (Fig. 5b). In terms of JKOM scores, ROM of knee joints, and TUG gait time, there were no significant differences among three groups. The number of gaits at 12 weeks of treatment was significantly lower than that at 0 weeks in the high-dose CurcuRouge® group, with no significant differences in the other two groups (Fig. 5c).

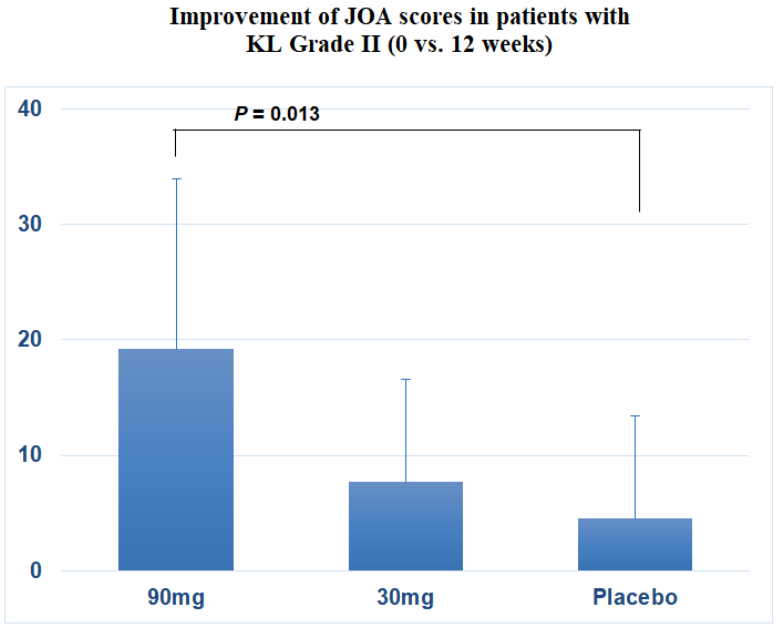

Figure 5a. Improvement of Japanese Orthopedic Association (JOA) scores in patients with Kellgren-Lawrence (KL) Grade II in the studied groups.

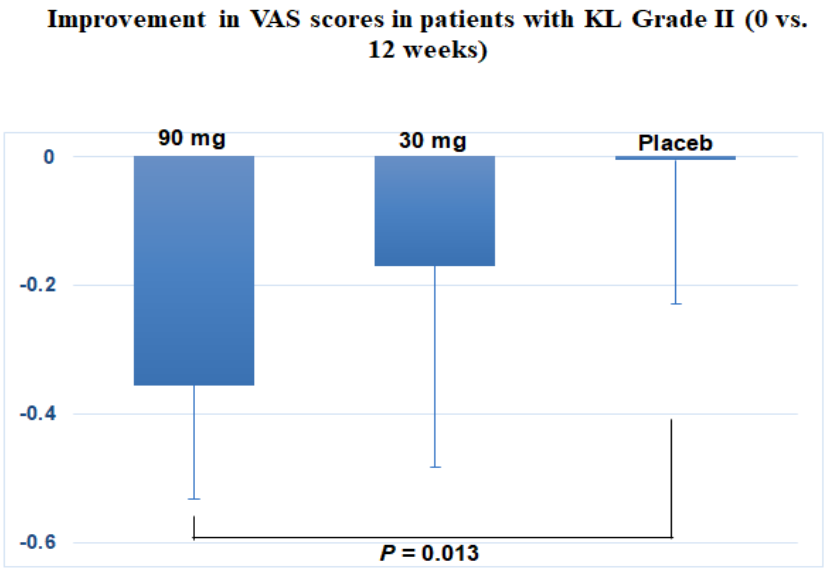

Figure 5b. Improvement of Visual Analogue Scale (VAS) scores in patients with Kellgren-Lawrence (KL) Grade II in the studied groups.

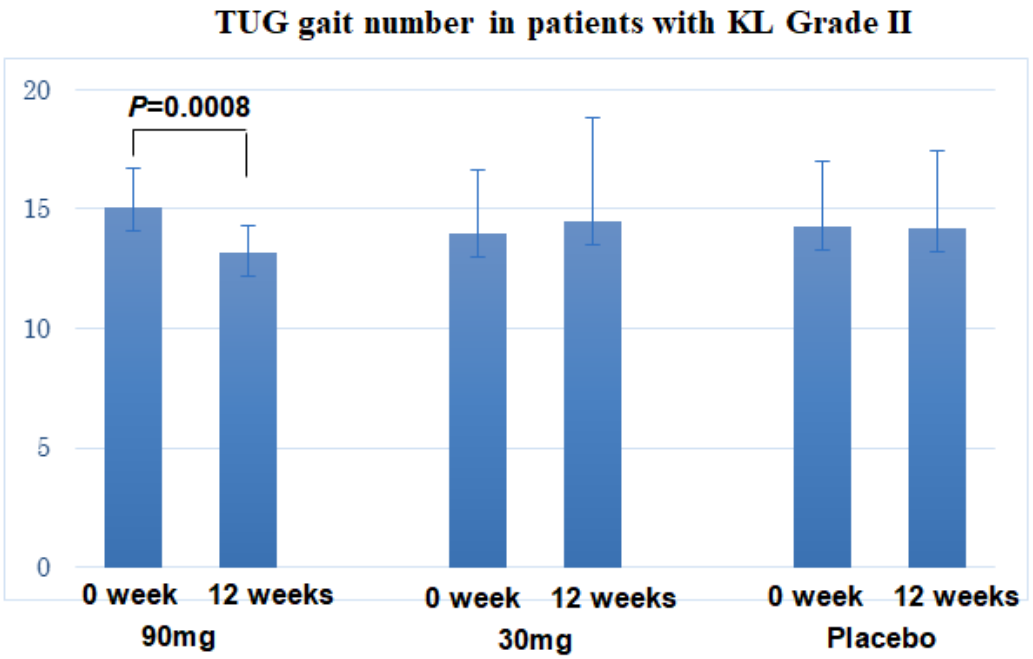

Figure 5c. Timed up-and-go test (TUG) gait number in patients with Kellgren-Lawrence (KL) Grade II in the studied groups.

In patients with KL grade III, there were no significant differences in JOA, JKOM, or VAS scores, as well as ROM of knee joints, and TUG gait time and number, among the three groups.

At 12 weeks of treatment, all laboratory results were comparable to baseline values in each groups, except in some patients in each group for slight increases in triglyceride (four cases in the high-dose group, three in the low-dose group, and three in the placebo group), blood urea nitrogen (two cases in the high-dose group, seven in the low-dose group, and four in the placebo group), uric acid (three cases in the low-dose group and one in the placebo group), and slight decreases in hematocrit (three cases in the high-dose group, two in the low-dose group, and three in the placebo group), and albumin (five cases in the high-dose group, two in the low-dose group, and four in the placebo group) levels. These were all minor changes. On comparing the laboratory results at 12 weeks of treatment to those at 0 weeks, only highly sensitive C-reactive protein (hs-CRP) levels significantly differed, with a greater reduction in the high-dose group than in the placebo group (P=0.0432) (Fig. 6). Table 2 summarizes the adverse events that occurred in all groups during this study. According to the study's safety committee, all of the aforementioned adverse events were unrelated to CurcuRouge® or the placebo.

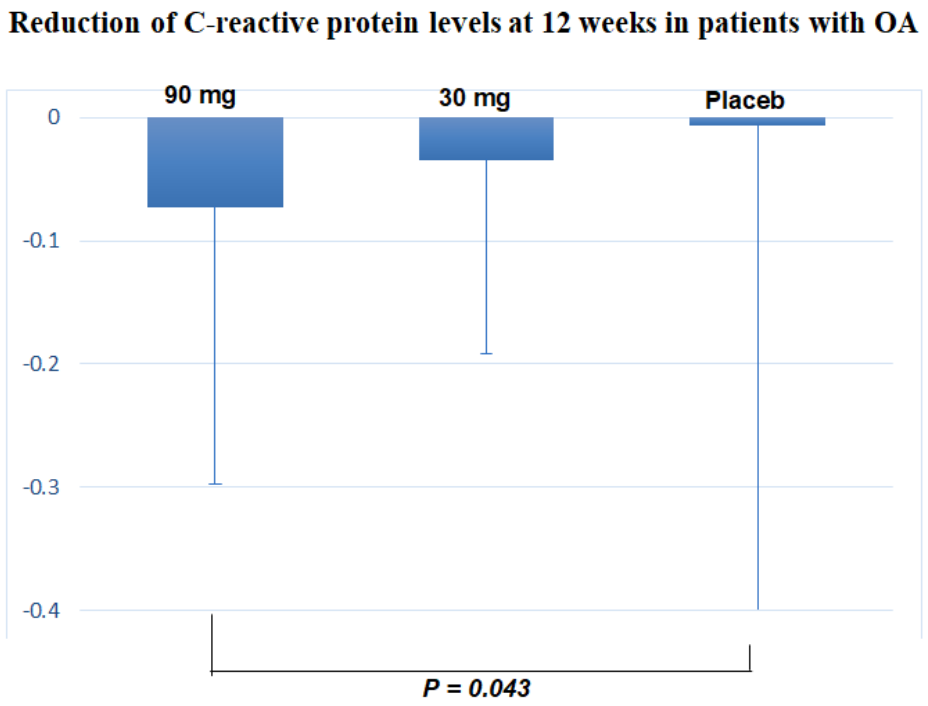

Figure 6. Reduction of highly sensitive C-reactive protein levels at three months in the studied groups.

Table 2. Adverse events in the studied groups occuring during the study period.

	curcuRouge® 90 mg	curcuRouge® 30 mg	Placebo
Gastrointestinal disorders	1 case	2 cases	1 case
Vertigo	2 cases	1 case	0 cases
Diarrhea	2 cases	0 cases	1 case
Lower limb edema	2 cases	1 case	1 case
Itching	1 case	1 case	1 case
Radial nerve palsy	0 cases	0 cases	1 case

Discussion

In this study, we revealed that blood curcumin concentrations were significantly higher in the high-dose CurcuRouge® than in the low-dose CurcuRouge® group. In each group, JOA knee OA scores 12 weeks after treatment were significantly higher and VAS scores were significantly lower than at 0 weeks. The declining trend of NSAID needs in the high-dose group was significantly greater than that in the placebo group ($P<0.05$), with respect to the approximate regression line-slope. Only in the high-dose group, TUG gait number at 12 weeks decreased significantly compared with 0 weeks. In patients with KL Grade II, JOA and VAS scores significantly improved from 0 to 12 weeks in the high-dose group more than in the placebo group. The reduction of hs-CRP levels was significantly greater in the high-dose group than in the placebo group ($P=0.0432$). Several adverse events occurred in all groups during this study, but the study's safety committee determined that all of them were unrelated to CurcuRouge® or the placebo. These results indicate that CurcuRouge® can be an effective and safe treatment for patients with OA, especially those with KL Grade II.

Curcumin has anti-inflammatory as well as anti-oxidative activities and is expected as a treatment of osteoarticular diseases. A high dose of standardized curcumin extract (500 mg twice daily) was reported to associate with the improvements on the TUG, six-minute walk test, and JOA total score in OA patients [20]. But the doubts have been raised about the ability of oral curcumin to reach pharmacologically active concentrations in synovial fluid or joint tissues [21] because its oral bioavailability is only 1% [22]. In the present study, we were able to prove that super-absorbable curcumin formulation, CurcuRouge®, improved symptoms including pain in patients with KL Grade II.

According to the basic research or animal models for the relationship between curcumin and OA, Zeng reported that curcumin could reduce synovial cell viability, inhibit cell proliferation, increase cell apoptosis, and eventually alleviate OA-related inflammation by inhibiting matrix metalloproteinase (MMP)-3 expression [23]. Nicoliche demonstrated that curcumin treatment has a protective effect on cartilage by increasing IHH, Col2, and SOX-5 expressions and the number of chondrocytes, without affecting cartilage thickness or MMP-8 and MMP-13 expressions [24]. In addition, curcuminoid delivery via hyaluronic acids/chitosan nanoparticles suppressed chondrocyte apoptosis by inactivating the nuclear factor-kappa B (NF-Kb) pathway [25]. Curcumin might have the potential to inhibit OA development via suppressing NF-kB/hypoxia-inducible factor 2α pathway activation [26]. Moreover, in the OA rats model, Nakahata demonstrated that curcumin monoglucuronide sodium salt (TBP1901) injections significantly reduced synovial inflammation at weeks 1 and 2 as well as tumor necrosis factor-α expression in the articular cartilage at week 6. TBP1901 injections also suppressed articular cartilage damage, subchondral bone plate thickening, subchondral bone plate perforation, and osteophyte formation at week 10 [27]. TBP1901 intra-articular injections suppressed synovial inflammation in the acute phase of posttraumatic OA in destabilized medial meniscus rats. In the chronic phase, TBP1901 suppressed articular cartilage damage and regulated subchondral bone plate changes [27]. Therefore, curcumin is thought to have anti-inflammatory and chondroprotective effects in the OA model.

In clinical study using CurcuRouge® in elderly volunteers, Kishimoto demonstrated that CurcuRouge® administration significantly reduces the neutrophil-to-lymphocyte ratio, an indicator of prognosis in cardiovascular disease, cancer, infectious diseases, and aging [28]. Curcumin's safety has been reported in several studies. In this regard, Bannuru found no differences between patients receiving curcuminoids and those receiving placebo in the incidence of treatment withdrawal due to adverse events [29]. According to Hsiao's meta-analysis, low-dose (daily dose <1,000mg) and high-dose (daily dose ≧1,000mg) curcuminoids had less adverse event rate than NSAIDs in knee OA [30].

The limitations of our study were the small number of patients (n=90) and the short treatment duration (12 weeks) for knee OA. This was a pilot study to determine the effect of CurcuRouge® on knee OA, but we were able to observe significant improvements in JOA and VAS scores, NSAID (celecoxib) needs, and TUG. Future studies may on a larger number of patients with knee OA over a longer duration are required to validate our findings.

In conclusion, CurcuRouge® has succeeded in proofing a potential for treating human knee OA, particularly at an early stage.

Acknowledgments

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Conflict of Interests

Financial Support and Potential Conflicts of Interest of our article is in the following: This research was financially supported by Therabiopharma Corporation (Kanagawa, Japan). The authors declare that there is no conflict of interest except the above.

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