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Curcuminoid Treatment for Knee Osteoarthritis: A Randomized Double-Blind Placebo-Controlled Trial

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Treatment of osteoarthritis (OA) is challenging owing to the inefficacy and long-term adverse events of currently available medications including non-steroidal anti-inflammatory drugs. Curcuminoids are polyphenolic phytochemicals with established anti-inflammatory properties and protective effects on chondrocytes. The aim of this study is to investigate the clinical efficacy of curcuminoids in patients suffering from knee OA. A pilot randomized double-blind placebo-control parallel-group clinical trial was conducted among patients with mild-to-moderate knee OA. Patients were assigned to curcuminoids (1500 mg/day in 3 divided doses; $n = 19$) or matched placebo ($n = 21$) for 6 weeks. Efficacy measures were changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analogue scale (VAS) and Lequesne's pain functional index (LPFI) scores during the study. There was no significant difference in age, gender, body mass index, and VAS, WOMAC and LPFI scores between the study groups at baseline ($p > 0.05$). Treatment with curcuminoids was associated with significantly greater reductions in WOMAC ($p = 0.001$), VAS ($p < 0.001$) and LPFI ($p = 0.013$) scores compared with placebo. With respect to WOMAC subscales, there were significant improvements in the pain and physical function scores ($p < 0.001$) but not stiffness score ($p > 0.05$). There was no considerable adverse effect in both groups. To conclude, curcuminoids represent an effective and safe alternative treatment for OA. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: curcumin; herbal medicine; arthritis; pain.

INTRODUCTION

Osteoarthritis (OA) is the most common disease of joints in adults, and its prevalence is predicted to rise owing to the increasing pattern in risk factors such as sedentary life style and obesity (Neogi, 2013; Suri *et al*., 2012). The most common symptoms of OA are pain, stiffness of the joint, crepitation on motion and limitation of joint motion (Neogi, 2013). Current standard of care for patients with OA mainly relies on the use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). These treatments have partial efficacy in controlling disease symptoms, and their long-term use has been reported to cause several gastrointestinal, renal and cardiovascular side effects (Baraf *et al*., 2007; Towheed *et al*., 2003). These limitations necessitate further research to find more efficacious treatments that can be used safely in patients with OA.

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In recent years, there has been a surge of interest to find herbal remedies for OA owing to the strong ethnobotanical evidence and identified analgesic, anti-inflammatory and muscle relaxant properties for such therapies (Chopra *et al*., 2013; Fehri *et al*., 2011; Lee *et al*., 2013; Yu *et al*., 2013). Turmeric is a widely used spice with numerous applications in the Asian traditional medicine, including treatment of joint pain and inflammation. Curcuminoids are coloring and bioactive constituents of turmeric that, despite their low occurrence of about 2–5%, are responsible for most of the biological and pharmacological properties of turmeric. Curcuminoids are among the most extensively studied natural products with a plethora of known biological actions important for the treatment of different diseases (Belcaro *et al*., 2014; Gupta *et al*., 2013a; Gupta *et al*., 2013b; Kim *et al*., 2012; Mohammadi *et al*., 2013; Na *et al*., 2013; Panahi *et al*., 2014a, b; Sahebkar, 2010; Sahebkar *et al*., 2013; Sahebkar, 2014a, b; Shehzad *et al*., 2013a). Among the biological effects of curcuminoids important for joint health are anti-inflammatory (Buhrmann *et al*., 2011; Buhrmann *et al*., 2010; Csaki *et al*., 2009; Mathy-Hartert *et al*., 2009), anti-catabolic (Buhrmann *et al*., 2011; Buhrmann *et al*., 2010; Csaki *et al*., 2009) and antioxidant effects (Panahi *et al*., 2012a; Sahebkar *et al*., 2013). However, clinical studies investigating the therapeutic efficacy of curcuminoids in patients with OA

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have been scant (Badria *et al*., 2002; Belcaro *et al*., 2010). The aim of this pilot study was to evaluate the efficacy of dietary supplementation with a bioavailability-boosted preparation of curcuminoids in the alleviation of symptoms in patients suffering from knee OA.

METHODS AND MATERIALS

Design and participants. This study was designed as a pilot randomized double-blind placebo-controlled parallel-group trial. Included subjects were those suffering from knee OA who referred to the Baqiyatallah University Clinic (Tehran, Iran) during 2011–2012. Participants were selected among patients with the following inclusion criteria: (i) degenerative primary knee OA with mild-to-moderate severity, (ii) bilateral OA and (iii) age <80 years. Diagnosis of knee OA was based on the clinical and radiological criteria defined by the American College of Rheumatology (ACR) and personal report of pain with mild-to-moderate degree on active movement [minimum of 40 mm on a 100-mm visual analogue scale (VAS)] (Kawasaki *et al*., 1998; Wu *et al*., 2005).

Patients with any of the following conditions were excluded from the trial: (i) allergy to curcuminoids or other herbal medications, (ii) being candidate for surgical joint replacement or any other surgical treatment, (iii) OA secondary to trauma, rheumatoid arthritis, inflammatory disorders and hemophilia, (iv) mal-absorption disorders, (iv) active and generalized inflammatory conditions [erythrocyte sedimentation rate (ESR) > 20], (v) presence of heart, renal and liver failure, (vi) using corticosteroids with doses above 10 mg/day during the preceding 3 months, (vii) history of psychological disorders and (viii) intra-articular injections during the preceding 3 months.

This clinical trial was conducted in compliance with the ethical considerations of the 'Declaration of Helsinki' and subsequent amendments thereof (Nuremburg protocol). The Ethics committee at the Baqiyatallah University of Medical Sciences (Tehran, Iran) approved the study protocol. The study protocol including random placebo prescription was explained to all participants, and written informed consent was obtained from each subject before inclusion in the study.

Medications. Patients meeting the inclusion criteria were randomly allocated to either curcuminoids (C3 complex®; Sami Labs LTD, Bangalore, India; 1500 mg/day; $n = 27$) or placebo ($n = 26$) for 6 weeks. Curcuminoids were administered in 500-mg capsules matched in size and shape with placebo capsules. Each curcuminoid capsule contained 5-mg Bioperine® (Sami Labs LTD, Bangalore, India) to enhance oral bioavailability of curcuminoids. Placebo capsules contained inert starch. Randomization was carried out alternatively with a 1:1 ratio scheme. The subjects were allocated a randomization number in consecutive order and were given the corresponding drug. Patients in both groups were allowed to use analgesic (naproxen) when they had intolerable pain. Regular consumption of study medications was checked during each week of the study period.

Assessments. The primary efficacy measure in the current trial was change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). WOMAC is a standardized and widely used index for the assessment of the severity of OA symptoms (Bellamy *et al*., 1988). The reliability and validity of this index have been approved by several studies (Konstantinidis *et al*., 2013; Nadrian *et al*., 2012). WOMAC subscales consisted of pain (5 items), stiffness (2 items) and physical functioning (17 items). Each item was rated from 0 to 4, totaling scores of 0–20, 0–8 and 0–68 for pain, stiffness and physical functioning subscales, respectively.

Severity of pain was assessed using a VAS which was a 100 mm rating scale ranging from 'no pain at all' (score 0) to 'unbearable pain' (score 100). Patients were instructed to mark a place on the horizontal line of the scale reflecting their knee pain severity.

Lequesne's pain functional index (LPFI) consists of three subscales with a total of ten items. The pain or discomfort scale has 5 items, the 'maximum distance walked' has 1 item, and the functions or activities of daily living (ADL) have 4 items. The pain and ADL scale scores range from 0 (representative of no pain or functional limitation) to 8 (representative of extreme pain or functional limitation). The 'maximum distance walked' subscale score ranges from 0 (representative of unlimited) to 6 (representative of less than 100-m walking distance ability). The score is increased by one point 'if the patient uses one walking stick or crutch or two points if the patient uses two walking sticks or crutches.' Total LPFI ranges from 0 to 24, with higher scores exhibiting a worse health status (Basaran *et al*., 2010; Franchignoni *et al*., 2012; Konstantinidis *et al*., 2013; Nadrian *et al*., 2012).

Occurrence of adverse events during the study was recorded according to a pre-designed adverse drug reactions checklist.

Statistical analysis. All statistical procedures were performed by SPSS software version 16 (SPSS International Inc., Chicago, Ill). Comparison of baseline versus end-trial values for each parameter was performed using paired samples *t*-test. Comparison of the magnitude of changes between the study groups was carried out using independent samples *t*-test. A two-sided *p*-value of <0.05 was considered to be statistically significant.

RESULTS

Of the 53 patients who met the inclusion criteria and consented to take part in this study, 40 subjects (19 in the curcuminoids and 21 in the placebo group) completed the 6-week study duration. Drop-outs were due to loss to follow-up (Fig. 1). The study groups were matched regarding age ($p = 0.99$), gender ($p = 0.712$) and BMI ($p = 0.48$). Mean WOMAC ($p = 0.74$), LPFI ($p = 0.93$) and VAS ($p = 0.16$) scores were also comparable between the groups at baseline (Table 1). All patients were taking NSAIDs/analgesics at baseline.

Comparison of pre- versus post-trial WOMAC scores revealed a significant reduction in the global ($p < 0.001$)

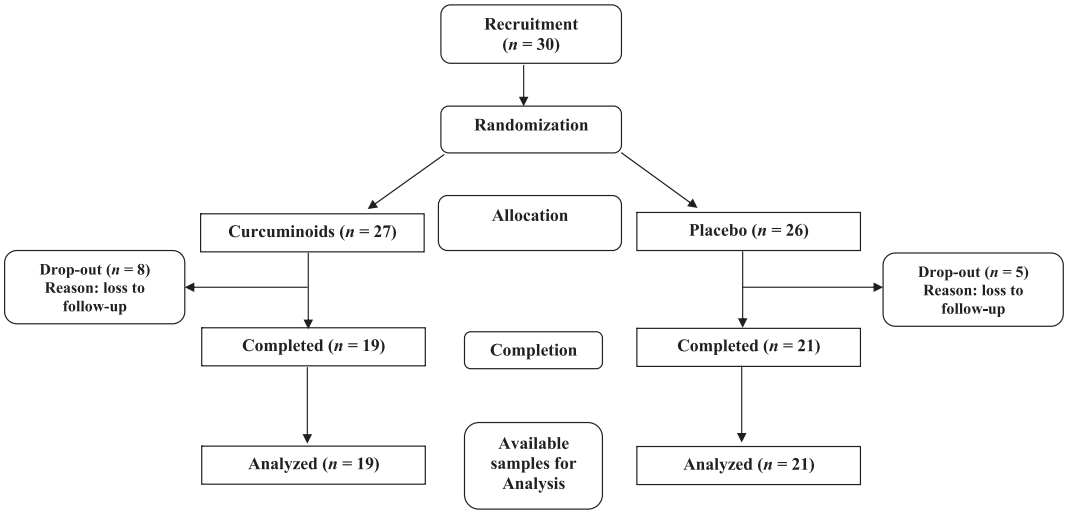

Figure 1. Flowchart of the trial.

Table 1. Baseline clinical and demographic characteristics of the study groups

Item	Curcuminoid group	Placebo group	*p*-value
Age (years)	57.32 ± 8.78	57.57 ± 9.05	0.99
Male (%)	5 (26.3%)	4 (19%)	0.712
BMI	28.75 ± 3.17	29.64 ± 4.46	0.48
VAS	66.32 ± 14.22	59.05 ± 17.29	0.157
WOMAC	42.4 ± 18.3	44.6 ± 17.3	0.74
LPFI	13.8 ± 4.7	13.7 ± 4.3	0.93

BMI: body mass index; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; VAS: visual analogue scale; LPFI: Lequesne's pain functional index.

as well as all subscale ($p < 0.001$ for pain and physical function, and $p = 0.043$ for stiffness) scores in the curcuminoid group by the end of trial. In contrast, there was no change in the global and subscale WOMAC scores in the placebo group ($p > 0.05$) with the exception of a significant decrease in the stiffness subscale score ($p = 0.009$). Between-group comparisons indicated a greater effect of curcuminoids versus placebo in decreasing global ($p = 0.001$), pain ($p < 0.001$) and physical function ($p < 0.001$) WOMAC scores. However, no significant difference in stiffness score was observed between the study groups ($p > 0.05$) (Table 2 and Fig. 2).

With respect to LPFI and VAS scores, significant reductions were observed in the curcuminoids group by the end of trial ($p < 0.001$ for both measures) whilst no significant change occurred in the control group ($p > 0.05$). The magnitude of reduction in both of the abovementioned indices was greater with curcuminoids compared with placebo ($p = 0.013$ and $p < 0.001$ for LPFI and VAS scores, respectively) (Fig. 3).

Patients were allowed to use naproxen as needed during the course of trial. Patients were asked to report their use of naproxen during the course of trial (Fig. 3). The proportion of subjects whose use of naproxen was reduced by the end of trial was significantly greater in the curcuminoids (84%) versus placebo group (19%) ($p < 0.001$) (Fig. 4). Based on the patients' reports, the average use of naproxen during the study was 250–500 mg in the group receiving curcuminoids and 500–750 mg in the group receiving placebo.

No serious adverse event was reported in this trial, and none of the drop-outs was due to the adverse event of curcuminoid therapy. Adverse events were mild

Table 2. WOMAC items before and after treatment

WOMAC items	Group	Before treatment	After treatment	*p*-value within group	*p*-value between groups
Pain index	Curcuminoids	9.9 ± 4.1	6.1 ± 2.9	**<0.001**[a]	**< 0.001**
	Placebo	10.5 ± 4	9.4 ± 3.4	**0.025**	
p-value[b]	–	0.66	**0.002**	–	
Stiffness	Curcuminoids	1.05 ± 1.8	0.15 ± 0.5	**0.043**	0.912
	Placebo	1.7 ± 1.7	0.76 ± 0.9	**0.009**	
p-value	–	0.25	**0.020**	–	
Physical function	Curcuminoids	31.8 ± 14	18.7 ± 10.3	**<0.001**	**< 0.001**
	Placebo	32.4 ± 12.8	30.4 ± 9.4	0.227	
p-value	–	0.89	**0.001**	–	
Global Score	Curcuminoids	42.4 ± 18.3	25.0 ± 13	**<0.001**	**0.001**
	Placebo	44.6 ± 17.3	40.6 ± 12.6	0.072	
p-value	–	0.74	**<0.001**	–	

[a]Represents statistical significance;
[b]Denotes comparison of baseline versus end-trial values.
Significant *p*-values are shown in bold.

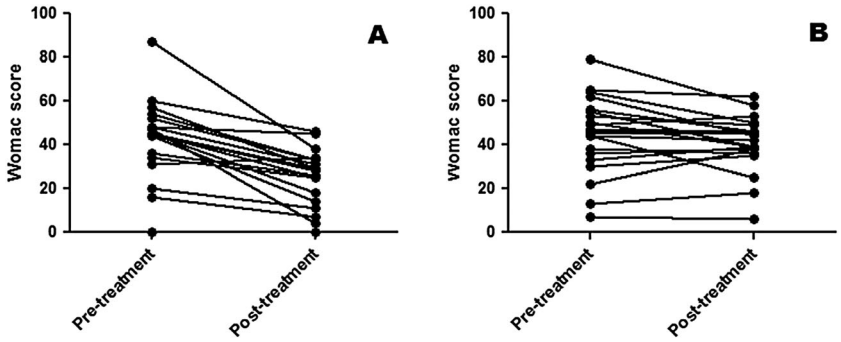

Figure 2. Intra-individual changes of WOMAC score in the curcuminoids (left) and placebo (right) groups.

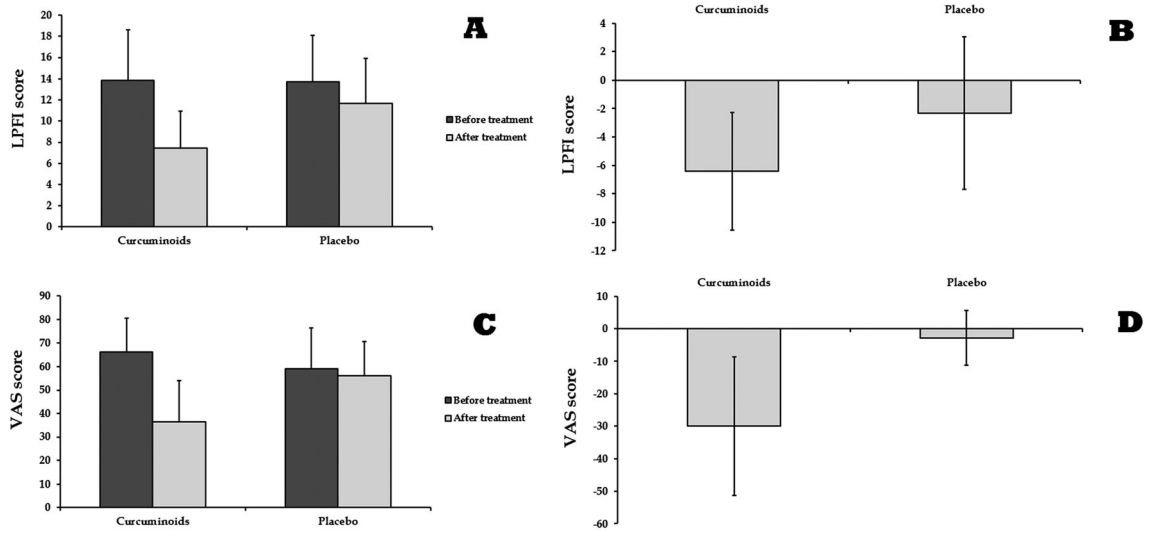

Figure 3. Within- (left) and between-group changes in the LPFI and VAS scores during the course of study. A: within-group changes in LPFI score; B: between-group changes in LPFI score; C: within-group changes in LPFI score; D: between-group changes in VAS score.

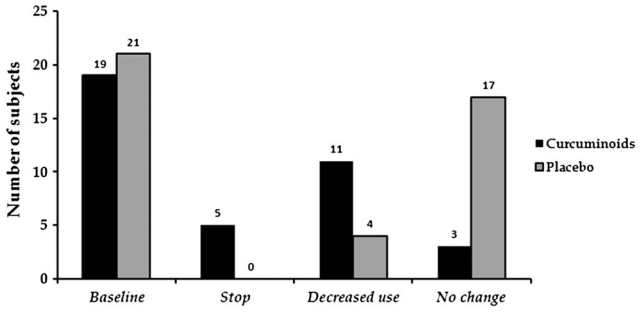

Figure 4. Frequency of the use of NSAIDs/painkillers at baseline and at the end of study. Overall, the proportion of subjects reporting no or decreased use of NSAIDs (naproxen) at the end of study was significantly greater in the curcuminoids versus placebo group ($p < 0.001$).

gastrointestinal symptoms that were reported from 7 cases of the curcuminoids group and 4 cases of the placebo group. The frequency of these adverse events was not significantly different between the two groups ($p > 0.05$).

DISCUSSION

In spite of a great body of preclinical evidence on the effectiveness of curcuminoids for the treatment of various diseases, clinical studies have been few. The results of the present randomized controlled trial clearly favour the efficacy of curcuminoids in alleviating the symptoms of OA, as reflected by marked improvement in all assessed efficacy measures namely WOMAC, LPFI and VAS. In an early cross-over trial, Kulkarni *et al.* (1991) reported a mitigation of pain and disability in OA patients treated with a herbomineral cocktail containing turmeric for 3 months. In another trial, consumption of a multiplant Ayuverdic drug containing turmeric was reported to reduce pain severity and improve WOMAC score in patients suffering from knee OA (36). Consistently, findings of the trial by Badria *et al.* (2002) indicated significant reductions in the degree of knee effusion, pain on passive and active movement, tenderness and prolongation of pain-free walking following 3 months of treatment with curcumin-Boswelia combination. Chandran et al. investigated the efficacy of proprietary bioavailability-enhanced curcuminoid preparation (BCM-95®; 500 mg/day) alone or in combination with diclofenac sodium (50 mg/day) for a period of 8 weeks in patients with active rheumatoid arthritis. Curcuminoid monotherapy was reported to be superior to both diclofenac monotherapy and curcuminoid/diclofenac combination in reducing overall Disease Activity Score (DAS) and ACR score (Chandran and Goel, 2012). Finally, Belcaro *et al.* (2010) tested the efficacy of a proprietary lecithinized formulation of curcuminoids (Meriva®; 200 mg curcuminoids/day) in patients with knee OA. The authors found marked improvements in global WOMAC score and walking distance on treadmill, accompanied by a significant reduction of plasma C-reactive protein concentrations.

A plausible mechanism for the protective effects of curcuminoids against OA is the potent anti-inflammatory effects of this phytopharmaceutical (Panahi *et al*., 2012b; Sahebkar, 2013; Shehzad *et al*., 2013b). Most of the anti-inflammatory properties of curcuminoids are due to the inhibition of NF-κB, and effect that leads to the suppression of several key regulators of inflammation such as cyclooxygenase-II, activator protein-1, JNK, MAPK and PI3K/Akt (Shakibaei *et al*., 2007). Curcuminoids can effectively reduce the release of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β (IL-1β), IL-6, macrophage chemotactic protein-1 and prostaglandin E2. These anti-inflammatory properties have been verified in cultured chondrocytes (Chowdhury *et al*., 2008; Csaki *et al*., 2009; Mathy *et al*., 2007; Mathy-Hartert *et al*., 2009). Moreover, inhibition of NF-κB by curcuminoids blocks the catabolic actions of down-stream products, most importantly matrix metalloproteinase (MMP) enzymes. By inhibiting MMPs, curcuminoids promote extracellular matrix accumulation and prevent cartilage degradation (Buhrmann *et al*., 2011; Clutterbuck *et al*., 2009; Csaki *et al*., 2009; Mathy-Hartert *et al*., 2009; Shakibaei *et al*., 2007). Finally, there is evidence indicating that curcuminoids that increase chondrocyte survival through down-regulation of inflammation-induced apoptosis (Csaki *et al*., 2009).

Along with inflammation, oxidative stress plays an important role in the development and progression of OA. Free radicals produced by abnormal chondrocytes can impair intra-articular segments and components of joints such as proteins, lipids and nucleic acids (Sutipornpalangkul *et al*., 2009). Reactive oxygen species can disturb cartilage matrix homeostasis and promote MMP expression, chondrocyte apoptosis and production of mediators involved in pain (Abramson, 2008; Im *et al*., 2008). Curcuminoids are potent antioxidants and have been shown to modulate oxidative stress through various mechanisms. Curcuminoids can scavenge free radicals owing to the presence of phenolic hydroxyl groups, an effect that leads to reduced lipid peroxidation and attenuation of oxidative damage to DNA and proteins. In addition curcuminoids reduce the formation of free radicals by blocking enzymes such as COX-II, 5-lipooxygenase and inducible nitric oxide synthase, and enhance intracellular antioxidant defense through stimulation of nuclear factor-erythroid-2-related factor 2 (Nrf-2) (Ak and Gulcin, 2008; Menon and Sudheer, 2007; Yin *et al*., 2012). All these effects may account for the amelioration of joint health and pain relief following curcuminoid supplementation.

An important novelty issue in the present study was the unique formulation that was used. In this study, curcuminoids were co-administered with Bioperine®, a standardized extract from Piper species [*Piper nigrum* or *P. longum*] containing at least 95% of piperine. Piperine is an alkaloid with known absorption-enhancing effects. Co-administration of piperine with curcuminoids can enhance the bioavailability of the latter through several mechanisms including inhibition of curcuminoid glucuronidation in the intestine and liver, increased blood supply to the intestinal tissue and enhancing membrane dynamics leading to increased permeability of brush border (Kang *et al*., 2009; Khajuria *et al*., 2002; Shoba *et al*., 1998).

In summary, findings of the present randomized double-blind placebo-controlled trial support the findings of previous studies on the efficacy of dietary supplementation with curcuminoids in alleviating the symptoms and improving the care of patients with OA. In spite of the observed benefits, care should be exercised in the generalization of current results. The first and main limitation of the present trial is its limited population size due to the pilot nature of the study. However, the number of recruited subjects was sufficient to detect a statistically significant effect size of curcuminoids on the assessed efficacy measures (WOMAC, LPFI and VAS). The second limitation is the short duration of supplementation and follow-up, hampering a realistic judgment on the long-term efficacy of curcuminoids. Third, only a single dose of curcuminoids was tested in the present study, and it remains to be identified if the observed effects of curcuminoids in OA patients follow a dose–response pattern. Finally, the study population of the present trial was limited to patients with mild to moderate degrees of OA; thus, the relevance of supplementation with curcuminoids in severe cases of OA remains elusive. The efficacy of curcuminoids in relieving the pain associated with OA was clearly shown in the present study. Further research is encouraged to be carried out in order to unveil if curcuminoids can modify OA through analgesic-independent mechanisms, e.g. interaction with oxidative and inflammatory pathways and modulation of circulating as well as synovial fluid concentrations of pro-inflammatory cytokines. Given the established safety of curcuminoids and the availability of several bioavailability-enhanced preparations, the positive results in this trial provide a base for future larger-scale phase III trials to explore if curcuminoids can be used be used in the therapeutic regimen of patients suffering from knee OA.

Acknowledgment

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Conflict of Interest

There is no conflict of interest to declare.

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