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ARTICLE

Mitigation of Systemic Oxidative Stress by Curcuminoids in Osteoarthritis: Results of a Randomized Controlled Trial

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ABSTRACT. Oxidative stress is implicated in the pathogenesis of osteoarthritis. Curcuminoids are natural polyphenols with strong antioxidant capacity and may thus be helpful in the treatment of osteoarthritis. The present randomized double-blind placebo-controlled trial investigated the efficacy of curcuminoids in reducing systemic oxidative burden in patients suffering from knee osteoarthritis. Forty patients with mild-to-moderate primary knee osteoarthritis were given curcuminoid capsules (1500 mg/day in 3 divided doses; $n = 19$) or matched placebo capsules ($n = 21$) for a period of 6 weeks. Curcuminoids were co-administered with piperine (15 mg/day) in order to improve the bioavailability. Serum activities of superoxide dismutase (SOD) and concentrations of reduced glutathione (GSH) and malonedialdehyde (MDA) were determined spectrophotometrically at baseline and at the end of the treatment period in both groups. Serum activities of SOD as well as GSH and MDA concentrations were comparable between the study groups at baseline ($p > 0.05$). There was a significant elevation in serum SOD activities (mean change: 2.94 ± 3.73 vs. -0.38 ± 1.33; $p < 0.001$), a borderline significant elevation in GSH concentrations (mean change: 1.39 ± 2.78 vs. -0.02 ± 1.62; $p = 0.064$) and a significant reduction in MDA concentrations (mean change: -5.26 ± 4.46 vs. -2.49 ± 3.81; $p = 0.044$) in the curcuminoids compared with the placebo group. Changes in serum activities of SOD and concentrations of GSH and MDA during the course of trial were significantly correlated. Short-term supplementation with curcuminoids attenuates systemic oxidative stress in patients with osteoarthritis. These

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antioxidant effects may account for the reported therapeutic effects of curcuminoids in relieving osteoarthritis symptoms.

KEYWORDS. Antioxidant, *Curcuma longa* L., Curcumin, Lipid peroxidation, Osteoarthritis, Randomized controlled trial

INTRODUCTION

Osteoarthritis (OA) is the most common musculoskeletal disorder in the elderly population (Suri, Morgenroth, & Hunter, 2012). OA has a chronic, progressive and degenerative nature and causes joint cartilage destruction, significant joint pain and mobility impairment (Neogi, 2013). Whilst degradation of articular cartilage is the hallmark of OA, other pathological changes also occur in the joint space including subchondral bone remodeling, osteophyte formation, synovitis and periarticular muscle spasm (Fernandes, Martel-Pelletier, Pelletier, 2002). During the past decade, understanding of the pathophysiology of OA has gone beyond the simple theory of "mechanical stress." In light of the recent findings, biochemical change that occurs in the chondrocytes and synoviocytes is a key factor in the etiopathogenesis of OA. One of the most important biochemical alterations in OA is oxidative stress, characterized by increased formation of reactive oxygen species (ROS) and the insufficiency of biological defense mechanisms to detoxify these species (Henrotin, Bruckner, & Pujol, 2003). Overproduction of ROS in the joint tissue causes several structural damages to biological membranes and extracellular matrix proteins (Tiku, Shah, & Allison, 2000). In addition, oxidative stress triggers the release of matrix metalloproteinases (MMPs) such as collagenases, gelatinases and stromelysins, which cause cartilage matrix degradation (Loeser, Carlson, Del Carlo, & Cole, 2002; Kapoor, Martel-Pelletier, Lajeunesse, Pelletier, Fahmi, 2011). Elevated levels of pro-oxidant species and altered levels of antioxidants have been reported in plasma and synovial fluid of OA patients by a number of previous studies (Karan et al. 2003; Sarban, Kocyigit, Yazar, & Isikan, 2005; Sutipornpalangkul, Morales, Charoencholvanich, & Harnroongroj, 2009; Angthong et al., 2013). All these findings open new avenues of research to test the effectiveness of antioxidants as adjuvant therapies in patients suffering from OA (Henrotin & Kurz 2007).

There has been a surge of interest during the past two decades in finding dietary natural antioxidants for the treatment of human diseases. Curcuminoids are among the strongest and most extensively studied natural products (Masuda et al., 2001; Menon & Sudheer, 2007; Kelkel et al., 2010). These lipophilic compounds have a polyphenolic structure, and constitute approximately 2–5% of the content of famous spice and food-coloring agent turmeric (Chattopadhyay, Biswas, Bandyopadhyay, & Banerjee, 2004). Although the quantity of curcuminoids in turmeric is low, they are responsible for the yellow color and most of the biological and medicinal properties of turmeric (Mohammadi et al., 2013; Panahi et al., 2012a, 2014a, 2014b, 2014c, 2014d; Sahebkar, 2010, 2013a, 2013b, 2014; Shehzad, Lee, & Lee, 2013a, 2013b). Curcuminoids typically comprise three components: curcumin (75%), demethoxycurcumin (10–20%) and bisdemethoxycurcumin (5–10%). The diversity of pharmacological actions of curcuminoids is unique, and a plethora of experimental evidence and several randomized controlled trials have shown

therapeutic efficacy of curcuminoids in controlling different diseases (Gupta, Patchva, & Aggarwal, 2013). A possible mechanism for the versatile actions of curcuminoids in different diseases is the potent antioxidant effects of these compounds. Curcuminoids are chain-breaking antioxidants capable of quenching lipid peroxidation (Masuda et al., 2001). Moreover, curcuminoids can scavenge free radicals such as superoxide, hydroxyl and nitrite, up-regulate several antioxidant enzymes (Meghana, Sanjeev, & Ramesh, 2007) and suppress ROS generation (Chan, Huang, Fenton, & Fong, 1998; Joe & Lokesh, 1994). Although the protective effects of curcuminoids in mitigating systemic oxidative stress has been shown in several human diseases (Durgaprasad, Pai, Vasanthkumar Alvres, Namitha, 2005; Kalpravidh et al., 2010; Panahi et al., 2012b, 2014d; Sahebkar et al., 2013c), data regarding the antioxidant effects of these compounds in patients with OA is lacking. This prompted the authors to evaluate the changes in three important biomarkers of systemic oxidative stress following short-term supplementation with curcuminoids in patients with knee OA.

METHODS AND MATERIALS

Design and Participants

This study was a randomized double-blind placebo-controlled parallel-group trial that was conducted in the Baqiyatallah University Clinic (Tehran, Iran) between 2011 and 2012. Inclusion criteria were: (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, Inoue, Ushiyama, & Fukuda, 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) malabsorption 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.

The primary efficacy measures of this trial were changes in clinical symptoms of OA (Panahi et al., 2014e). Frozen serum samples obtained from the participants were used for this substudy to evaluate changes in serum levels of oxidative stress biomarkers as a secondary efficacy measure of supplementations with curcuminoids.

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 who fulfilled the inclusion criteria were randomly allocated to either curcuminoids (C3 complex®; Sami Labs LTD, Bangalore, India; 1500 mg/day in 3 divided doses ($n = 27$); or placebo ($n = 26$) for 6 weeks. Curcuminoids and placebo capsules were matched in size and shape. Each curcuminoid capsule contained 500 mg curcuminoids plus 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 medication. 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

Efficacy measures in the present study were changes in the serum activities of superoxide dismutase (SOD), and concentrations of reduced glutathione (GSH) and malonedialdehyde (MDA). Serum activities of SOD and concentrations of GSH and MDA were determined spectrophotometrically using routine procedures (Akerboom & Sies, 1981; Chance & Maehly, 1995; Uchiyama & Mihara, 1978).

To evaluate the safety profile of curcuminoids, a pre-designed "adverse drug reactions" checklist was used and patients were asked to report occurrence of any adverse event during the course of study.

Statistical Analysis

Statistical analyses were performed using SPSS software version 16 (SPSS International Inc., Chicago, IL). Comparison of pre-trial versus post-trial values for each of the efficacy measures was made using paired samples *t*-test (for normally distributed data) or Wilcoxon signed-rank test (for non-normally distributed data). Changes in each parameter during the course of trial were compared between the curcuminoids and placebo groups using independent samples *t*-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data). Bivariate correlations were assessed using Pearson correlation coefficients. The level of significance was set at 0.05 and two-tailed p-values were reported.

RESULTS

Fifty-three subjects fulfilled the inclusion criteria and initially entered this trial. Of these 53, 40 subjects (n = 19 and 21 in the curcuminoids and placebo group, respectively) completed the 6-week duration of study and were included in the final analysis. Drop-outs were due to loss to follow-up and not referring to the study center for blood sampling and medical examinations. The number of drop-outs was not different between curcuminoid and placebo groups ($p = 0.493$). The study groups were comparable regarding age, gender and BMI. There was also no significant difference in serum activities of SOD ($p = 0.991$) and concentrations of GSH ($p = 0.758$) and MDA ($p = 0.438$) between curcuminoids and placebo groups at baseline (Table 1). Serum SOD activities were significantly improved in the group

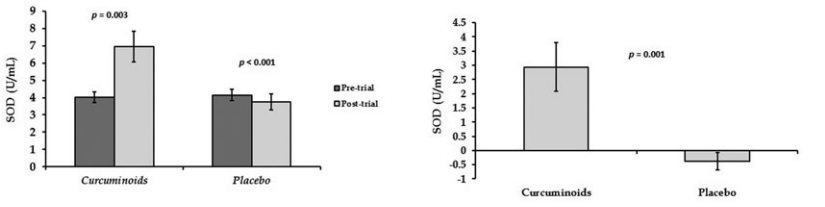

FIGURE 1. Within-group (left) and between-group (right) comparison of serum SOD activities in the study groups. Values are mean ± SEM. SOD: superoxide dismutase.

receiving curcuminoids ($p = 0.003$), whilst the activities were found to be reduced in the placebo group ($p < 0.001$) (Figure 1). Curcuminoid therapy was also associated with a significant elevation of serum GSH concentrations ($p = 0.043$), an effect that was not observed in the placebo group ($p = 0.946$) (Figure 2). Serum MDA levels were decreased by the end of trial in both curcuminoids ($p < 0.001$) and placebo ($p = 0.009$) groups (Figure 3). Comparison of the changes in each parameter during the study revealed a greater efficacy compared with placebo in improving serum activities of SOD ($p = 0.001$) (Figure 1), elevation of serum GSH ($p = 0.064$) (Figure 2) and reducing MDA ($p = 0.044$) (Figure 3) concentrations.

In bivariate analyses, changes in all three evaluated parameters were found to be strongly correlated in the curcuminoids group (SOD and GSH: $r = 0.776, p < 0.001$; SOD and MDA: $r = -0.872, p < 0.001$; GSH and MDA: $r = -0.656, p = 0.002$), placebo group (SOD and GSH: $r = 0.868, p < 0.001$; SOD and MDA: $r = -0.679, p = 0.001$; GSH and MDA: $r = -0.680, p = 0.001$) and total study population (SOD and GSH: $r = 0.791, p < 0.001$; SOD and MDA: $r = -0.790, p < 0.001$; GSH and MDA: $r = -0.688, p < 0.001$) (Figure 4).

DISCUSSION

The present study was the first randomized controlled trial investigating the efficacy of supplementation with curcuminoids in modulating systemic measures of oxidative stress in patients with OA. The results revealed a significant superiority of curcuminoids over placebo in improving antioxidant status (reflected as elevation of serum SOD activities and GSH concentrations) and reducing lipid peroxidation (reflected as reduced serum levels of MDA). These findings are

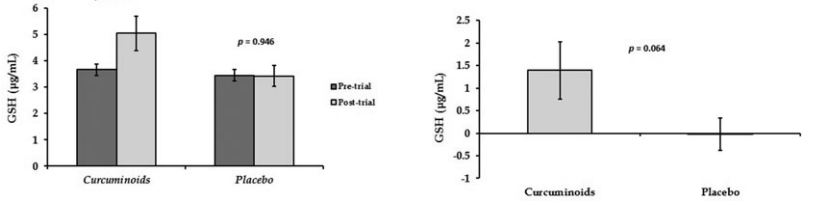

FIGURE 2. Within-group (left) and between-group (right) comparison of serum GSH concentrations in the study groups. Values are mean ± SEM. GSH: reduced glutathione.

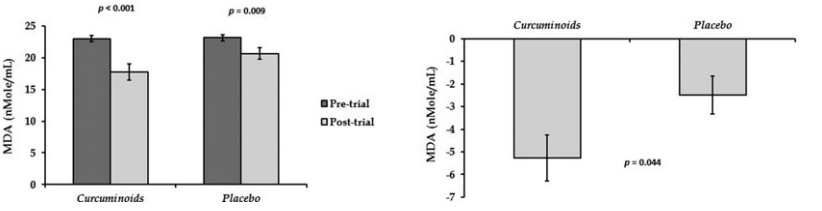

FIGURE 3. Within-group (left) and between-group (right) comparison of serum MDA concentrations in the study groups. Values are mean ± SEM. MDA: malonedialdehyde.

consistent with our recent report in the same group of patients showing significant improvement of clinical symptoms following supplementation with curcuminoids (Panahi et al., 2014e). Current best standard of care of OA patients includes the use of non-steroidal anti-inflammatory drugs (NSAIDS). However, long-term use of NSAIDs, as practiced for the treatment of chronic disease like OA, is associated with multiple side effects in the gastrointestinal, renal, hepatic and cardiovascular systems. Therefore, natural therapies with documented safety and efficacy in relieving the symptoms of OA would be ideal either as alternatives or adjuncts to NSAIDs. The efficacy of curcuminoids in the management of patients with OA and rheumatoid arthritis has been shown by a number of previous trials. Belcaro et al. 2010b investigated the efficacy of supplementation with curcuminoids-phosphatidylcholine complex (Meriva®) in patients with OA. Consumption of Meriva® (equivalent to 200 mg curcuminoids) was associated with a significant reduction in the global WOMAC score, a standard measure of disease severity, as well as measures of pain and stiffness, and physical, social and emotional functions after 2 months of supplementation, with a further improvement at month 3 (Belcaro et al., 2010a). The same results were obtained in a similar study with an extended supplementation period of 8 months (Belcaro et al., 2010b). There have been also other reports indicating comparable efficacy of curcuminoids (1200 mg/day) with phenylbutazone (300 mg/day) in relieving symptoms of OA, rheumatoid arthritis and post-surgical pain (Deodhar, Sethi, & Srimal, 1980).

ROS and MMPs are two important contributors to the extracellular matrix degradation in OA (Henrotin et al., 2003). There is evidence indicating an association between chondrocyte lipid peroxidation and matrix protein oxidation and

TABLE 1. Baseline Characteristics of the Study Groups

Variable	Curcuminoids ($n = 19$)	Placebo ($n = 21$)	p-value
Male (%)	26.3	19.0	0.712
Age (years)	57.32 ± 8.78	57.57 ± 9.05	0.990
BMI (kg/m^2)	28.75 ± 3.17	29.64 ± 4.46	0.480
SOD (U/mL)	4.03 ± 1.36	4.17 ± 1.39	0.991
GSH (μg/mL)	3.66 ± 0.93	3.42 ± 0.99	0.758
MDA (nmole/mL)	23.04 ± 2.30	23.03 ± 2.32	0.438

Values are expressed as median (SD) or number (%). BMI: body mass index; SOD: superoxide dismutase; GSH: reduced glutathione; MDA: malonedialdehyde.

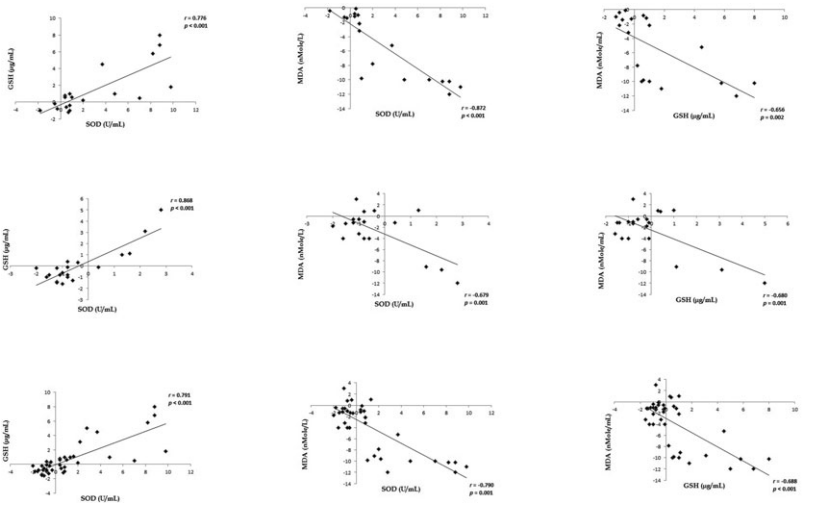

FIGURE 4. Bivariate correlations between changes in serum activities of SOD and concentrations of GSH and MDA during the course of trial. SOD: superoxide dismutase; GSH: reduced glutathione; MDA: malonedialdehyde.

degradation, and the protective effect of vitamin E on these events (Tiku et al., 2000). Oxidative damage has also been identified in OA cartilage specimens, evidenced by an overproduction of ROS and nitric oxide (Loeser et al., 2002). Several epidemiological surveys, including the Framingham Cohort Study, have shown that dietary intake of antioxidants such as vitamin E, vitamin C and β-carotene is inversely associated with the progression – but not incidence—of radiologically defined OA (McAlindon et al., 1996). In this context, supplementation with vitamin E or vitamin C has been shown by a number of trials to alleviate OA symptoms (Bhattacharya, Saxena, & Gupta, 2012; Medhi et al., 2010; Peregoy & Wilder, 2011), yet these findings have not been fully consistent (Brand, Snaddon, Bailey, & Cicuttini, 2001; Scherak, Kolarz, Schodl, & Blankenhorn, 1990; Wluka, Stuckey, Brand, & Cicuttini, 2002). Given the role of oxidative stress in the pathogenesis and progression of OA on the one hand, and potent antioxidant properties of curcuminoids on the other hand, it is plausible that reported positive effects of curcuminoids in OA patients are due to the suppression of systemic oxidative stress.

Curcuminoids are among the most potent naturally occurring antioxidants. It has been shown that curcumin has a higher antioxidant activity compared with vitamin E (Reddy & Lokesh, 1992), and inhibits lipid peroxidation stronger than the standard synthetic antioxidant butylated hydroxytoluene (Majeed, Badmaev, Shivakumar, & Rajendran, 2000). Inhibition of lipid peroxidation is a known biological effect of curcuminoids as shown in different *in-vitro* and *in-vivo* models. The present study supported this effect of curcuminoids by showing reduced serum levels of MDA, a well-known biomarker of lipid peroxidation. Curcumin can terminate the free radical-mediated chain reaction of lipid peroxidation by reacting with lipid radicals at the 3′-position, followed by an intermolecular Diels-Alder reaction (Masuda, et al., 2001). Moreover, curcumin is a strong free

radical scavenger capable of neutralizing several reactive oxygen and nitrogen species. These antioxidant properties of curcuminoids are due to the unique structure of these phytochemicals which enables H-atom donation via the central β-diketone or methylenic group, or methoxylated phenols (Barclay et al., 2000; Jovanovic, Steenken, Boone, & Simic, 1999; Priyadarsini et al., 2003; Wright, 2002). Another important mechanism for the antioxidant actions of curcuminoids is modulation of the expression and/or activity of several enzymes involved in the generation or neutralization of free radicals including cyclooxygenase-II, 5-lipooxygenase, inducible nitric oxide synthase, glutathione peroxidase, catalase and SOD (Bengmark, 2006; Lin, 2007; Menon & Sudheer, 2007). In addition to the *in-vivo* stduies, the efficacy of curcuminoids in reducing systemic oxidative burden has been shown by a number of clinical studies. Kalpravidh et al. reported in patients with β-thalassemia an improvement in several serum biomarkers of oxidative stress including SOD, GSH, glutathione peroxidase and erythrocyte GSH following a long-term (12 months) supplementation with curcuminoids (500 mg/day) (Kalpravidh et al., 2010). In patients with tropical pancreatitis, short-term (6 weeks) supplementation with curcuminoids-piperine combination (equivalent to 500 mg curcuminoids daily) resulted in a significant reduction of erythrocyte MDA and elevation of erythrocyte GSH content (Durgaprasad et al., 2005). In patients suffering from dermatologic complications of sulfur mustard, curcuminoids-piperine combination (equivalent to 1000 mg curcuminoids daily) increased serum activities of SOD, glutathione peroxidase and catalase following a 4-week supplementation period (Panahi et al., 2012). In patients with solid tumors receiving standard chemotherapy regimens, 8-week supplementation with a lecithinized curcuminoid preparation (equivalent to 180 mg curcuminoids daily) was associated with significant elevations in serum activities of SOD and catalase, and GSH concentrations whilst the levels of serum MDA were reduced (Panahi et al., 2014a). Finally, the results of a 4-week cross-over trial in obese subjects with dyslipidaemia indicated a significant mitigation of systemic oxidative stress assessed by a measure of pro-oxidant-antioxidant balance (Sahebkar et al., 2013c). The antioxidant effects of curcuminoids observed in the present trial are consistent with the findings of the above-mentioned studies, but in an as yet unexplored population i.e. patients with OA.

The present study is subject to a number of limitations. The main limitation is the pilot nature of this trial and small number of subjects studied. Although, this small population size was enough to show a significant antioxidant effect of curcuminoids, further validation from large-scale trials is still required. As another limitation, this study did not look at all standard biomarkers, particularly plasma and urinary levels of F2-isoprostanes or measures of pro-oxidant antioxidant balance. Analysis of these additional markers would be helpful for a better assessment of antioxidant properties of curcuminoids in osteoarthritis patients. Finally, only a single treatment arm was included in this study. Therefore, the optimum dose of curcuminoids in osteoarthritis patients remains to be clarified. In summary, findings of the present randomized controlled trial indicated a significant improvement in systemic oxidative stress biomarkers following 6 weeks of supplementation with curcuminoids-piperine combination. These findings further validate the clinically relevant antioxidant effects of curcuminoids and provide a plausible mechanism

for the previously reported positive effects of curcuminoids in alleviating OA symptoms.

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Declaration of Interest: The author reports no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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