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**Dr. K Rajeshwar Reddy**  
M.S, Professor, R.A. Podar  
Medical College and M.A. Podar  
Hospital, Worli, Mumbai,  
Maharashtra, India

**Dr. Arif A Faruqui**  
M.D, Clinical Pharmacologist,  
Mumbai, Maharashtra, India

## Efficacy and tolerability of fixed dose combination of curcumin and piperine in Indian osteoarthritic patients

**Dr. K Rajeshwar Reddy, Dr. Arif A Faruqui**

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### Abstract

Osteoarthritis is a common degenerative joint disorder affecting millions of people worldwide. Its prevalence is expected to rise due to increase in risk factors such as obesity and sedentary life style. Currently available treatments generally have limited efficacy as they are more focused in controlling disease symptoms. This study was undertaken to evaluate the efficacy and tolerability of fixed dose combination of curcumin and piperine in 44 osteoarthritic patients (16 men, 28 women, mean age: 55.5 years). This was a non-randomized, open labeled, non-comparative, single-centric, and post-marketing surveillance study. Informed consent was obtained and study was conducted at R.A. Podar Hospital Mumbai between June-August 2016. Patients were administered a combination of curcumin 500 mg and piperine 5 mg twice daily for 12 weeks. Patients were also provided with NSAIDs as a rescue medication and asked to note daily NSAID consumption in their diaries. WOMAC scores and NSAID consumption was evaluated at baseline and at each follow up visit (i.e. end of week 4, week 8 and week 12). Assessment of WOMAC score at the end of 12<sup>th</sup> week showed statistical significant change from baseline with reduction in pain, stiffness and physical function ( $P < 0.001$ ). A trend of decrease in need of NSAIDs was also noted with each follow up visits. Interestingly, when compared the NSAIDs consumption between baselines to the end of 12<sup>th</sup> week, significant difference was noted ( $P < 0.012$ ). Three patients reported mild gastrointestinal adverse effects. From this study, it can be concluded that curcumin in combination with piperine is an effective and safe option in the management of osteoarthritis, leading to better disease control, decreased use of NSAIDs and least GI disturbances. Curcumin along with piperine thus represents a new paradigm in the management of OA and therefore should be considered based on its safety and efficacy.

**Keywords:** Curcumin, piperine, osteoarthritis, WOMAC score, NSAID dependence

### 1. Introduction

Osteoarthritis (OA), a type of degenerative joint disease, is a slow destructive process of the joints that affects millions of people worldwide. It is the commonest joint disease in adults, and its prevalence is predicted to rise due to the increasing pattern in risk factors such as obesity and sedentary life style. About 80% of individuals of both genders above 60 years age and nearly 15% of population is affected by this degenerative disease. The exact biochemical cause of osteoarthritis remains unknown and the process usually begins when the joint structures are abnormal or the stress placed on joint surfaces is unusually high. Although additional crucial etiological factors have been described includes pressure (physical or mechanical), hereditary history, injury and hormonal alterations. Pain, stiffness of the joint, crepitation on motion and limitation of joint motion are the commonly reported symptoms of OA. [1-3]

Use of non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics are the current standard of care for patients suffering from OA. However, efficacy of these treatments in controlling the disease symptoms is limited, and their long-term use has been associated with gastrointestinal (GI), cardiovascular and renal adverse effects. In fact, the currently available therapeutic options are only useful for controlling the disease symptoms, mainly pain. Due to these shortcomings, there is an urgent need to find more efficacious and safe treatment alternatives for OA patients. [2]

Traditionally, plants have been used for centuries as a popular method for the treatment of various health disorders.

**Correspondence**  
**Dr. Arif A Faruqui**  
M. D, Clinical Pharmacologist,  
Mumbai, Maharashtra, India

Turmeric, also known as *Curcuma longa* is one of the most studied plants. The active ingredient of *Curcuma longa* plant is curcumin. Curcumin is a highly pleiotropic molecule with an excellent safety profile. Strong molecular evidence has been published to support its potency for targeting various inflammatory diseases such as osteoarthritis, rheumatoid arthritis and inflammatory bowel diseases. The beneficial effects of curcumin includes anti-inflammatory, antioxidant, anticancer, antimicrobial, hepatoprotective and anti-hyperlipidemia. The anti-inflammatory effect of curcumin seems to be comparable with NSAIDs such as indomethacin and phenylbutazone. Anti-inflammatory properties of curcumin are related to the inhibition of prostaglandin (PGE<sub>2</sub>) synthesis and its effect on cyclooxygenase (COX), an important enzyme responsible for the conversion of arachidonic acid to prostaglandins. Another interesting action of curcumin is inhibition of nuclear factor κB (NF-κB) activation, which is another important event in the chronic inflammatory process of joint. Given these findings, curcumin is expected to be effective for a range of disorders related to chronic inflammation, including osteoarthritis and rheumatoid arthritis.<sup>[3-4]</sup>

Furthermore, it has been reported that curcumin is a potent inhibitor of the production of inflammatory and catabolic mediators by chondrocytes. As inflammation is the characteristic feature of OA and related osteoarticular conditions of synovial joints, beneficial biological actions of curcumin in joint tissues may thus facilitate the development of clinically safe, orally administered therapeutic agents for treating these joint diseases.

In spite of potential therapeutic benefits of curcumin, the bioavailability of curcumin is low due to a relatively less intestinal absorption, and faster hepatic metabolism, followed by elimination through the gall bladder. Due to this limitation only small amount of curcumin is absorbed after oral administration which is an obstacle to realizing beneficial health effects of curcumin. To overcome this bioavailability problem, researchers are currently investigating various techniques of increasing its oral absorption. Few such techniques involve a surface-controlled water-dispersible formulation of curcumin and curcumin complexes with phosphatidylcholine.<sup>[3, 5]</sup> Apart from these methods, piperine, an alkaloid from black pepper (*Piper nigrum*) has also been studied to enhance the bioavailability of curcumin. In humans 20 mg piperine given concomitantly with 2 g curcumin increased serum curcumin bioavailability 20-fold, which was attributed to piperine's inhibition of hepatic glucuronidation and intestinal metabolism.<sup>[6, 7]</sup> Apart from its bioavailability enhancement property, piperine also inhibits the production of two important proinflammatory mediators' e.g. interleukins (IL-6) and prostaglandins (PGE<sub>2</sub>). Inhibition of PGE<sub>2</sub> production is important due to its central role in triggering pain. Furthermore, matrix metalloproteinases (MMP13 collagenases) play dominant roles in arthritic disorders because they are the rate-limiting components of the collagen degradation process. Piperine significantly decreases the production of MMP-3, MMP-13 and cyclooxygenase (COX-2) in human OA chondrocytes.<sup>[8, 9]</sup>

The aim of the present study is to evaluate the efficacy and tolerability of fixed dose combination of curcumin and piperine in the management of arthritic patients.

## 2. Materials and Methods

This was a non-randomized, open labeled, non-comparative, single-centric, and post marketing surveillance (PMS) study. Fifty outpatient cases with known osteoarthritis visiting R.A.

Podar Medical College and M. A. Podar hospital, Worli, Mumbai, were enrolled in this study. These patients were not getting satisfactory pain relief from standard NSAIDs treatment.

### 2.1 Inclusion Criteria

Patients with osteoarthritis in one or both knees were diagnosed by the physician. Subjects had mild-to-moderate pain not adequately or completely controlled with anti-inflammatory drugs.

They were required to perform the treadmill walking test and to understand all questions from the WOMAC questionnaire (Western Ontario and McMaster Universities Osteoarthritic Index function subscale).<sup>[10]</sup>

### 2.2 Exclusion Criteria

Exclusion criteria were cardiovascular disease requiring drug treatment, diabetes, severe metabolic disorders, surgery or arthroscopy within three months prior to inclusion, any oncological condition, or severe bone or joint deformation or condition making the patient unable to walk. Pregnancy, breast feeding, and planned conception were also exclusion criteria.

### 2.3 Evaluation of Signs/Symptoms of Osteoarthritis

Informed consent was obtained from these patients & the post marketing surveillance was carried out in accordance with the clinical principles laid down in declaration of Helsinki. Subsequent approval from ethics committee was also sought. At the time of study entry, base-line characteristics (including patient demographics, age, gender, body mass index) were recorded. Consumption of analgesics/NSAIDs by patients at baseline (total NSAIDs consumed in last 4 weeks before initiation of the study) was also noted by taking thorough patient history. Fixed dose combination (FDC) of curcumin (95%) 500 mg and piperine (95%) 5 mg was administered to these 50 osteoarthritic patients twice daily for 12 weeks. Furthermore, patients were also prescribed with NSAIDs (Aceclofenac and paracetamol combinations) but advised to take these NSAIDs only during intense pain. Patients were asked to undertake the WOMAC score evaluation in presence of investigator at baseline and at each follow up visit i.e. at the end of 4<sup>th</sup> week, 8<sup>th</sup> week and 12<sup>th</sup> week of the treatment. The WOMAC questionnaire was applied to describe and rate the symptoms of OA. Patients were also instructed to record the intake of NSAIDs each day with date, time and number of pills consumed. The primary efficacy variable of the study was change in WOMAC score from baseline to 12<sup>th</sup> week. The secondary end points included the monitoring the reduction in need of NSAIDs at each follow up visit and any adverse events observed throughout the study. At the end of the study, investigators have also recorded the global efficacy and tolerability of this curcumin and piperine combination.

### 2.4 Statistical Analysis

The statistical analysis was carried out by using Graph Pad Prism-7 software. Comparison of WOMAC score from baseline to each follow up visit was performed using paired samples t-test. Values of  $P < 0.05$  were considered statistically significant.

## 3. Results

Of the 50 patients who met the inclusion criteria, 44 patients completed this 12 week study with all three follow up visits. Drop out of 06 patients was due to loss to follow up. Baseline demographic parameters of 44 patients were described in table no. 1. All patients were taking NSAIDs/analgesics at baseline.

**Table 1:** Baseline characteristics

Sr. No.	Parameter	N (Mean ± SD)
1	Total number of patients completed study	44
2	Age (years)	55.59 ± 08.60
3	Gender (Male/Female)	16/28
4	BMI (body mass index)	28.75 ± 3.17

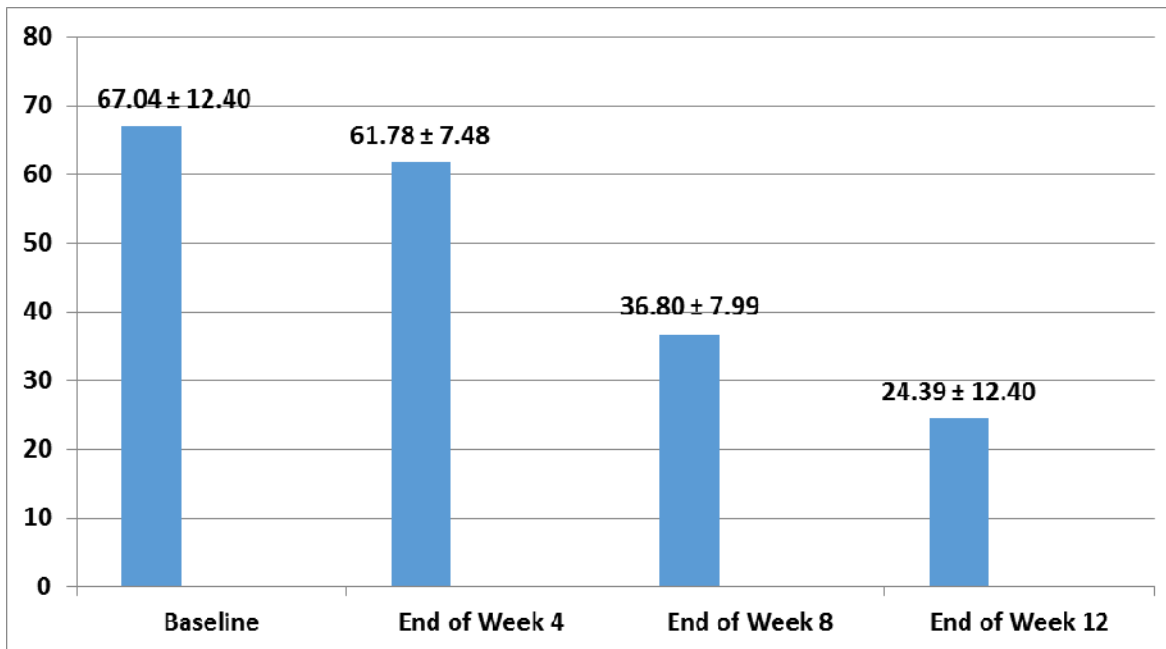
Baseline and follow up visit values of WOMAC score were described in table 2. Comparison of WOMAC scores from baseline to end of 12<sup>th</sup> week showed statistical significant reduction in pain, stiffness and physical function along with global WOMAC score ( $P < 0.001$ ) as seen in figure 1.

**Table 2:** Change in WOMAC Score

Sr. No	Parameter	Baseline	4 <sup>th</sup> Week	8 <sup>th</sup> Week	12 <sup>th</sup> Week
01	WOMAC Score	67.04 ± 12.40	61.78 ± 7.48	36.80 ± 7.99	24.39 ± 12.40

In addition, the change in WOMAC score (as seen in figure 1) from baseline to end of 4<sup>th</sup> week was also found to be statistically significant with P value of 0.019. Statistical

significant difference was further noted with WOMAC score change between ends of 4<sup>th</sup> week to 8<sup>th</sup> week and between 8<sup>th</sup> weeks to 12<sup>th</sup> week ( $P < 0.001$ ).



**Fig 1:** WOMAC Score (Mean ± SD) at Baseline and respective follow up visits

Three subgroups of WOMAC score are pain, stiffness and physical function. After each subgroup analysis (as described in Table-3), it was observed that, reduction in pain sub-score from baseline to end of 4<sup>th</sup>, 8<sup>th</sup> and 12<sup>th</sup> week was found to be

statistically significant ( $P < 0.001$ ). The same was also true for pain sub-score reduction from baseline to 12<sup>th</sup> week as well ( $P < 0.001$ ).

**Table 3:** Results of subgroup analysis

Subgroup analysis	Baseline (Mean ± SD)	Week 4 (Mean ± SD)	Week 8 (Mean ± SD)	Week 12 (Mean ± SD)
Pain	14.7 ± 2.74	12.7 ± 1.25****	7.45 ± 2.23****	4.73 ± 2.73****
Stiffness	4.34 ± 1.84	4.89 ± 1.33 <sup>ns</sup>	3.39 ± 1.08****	2.14 ± 1.25****
Physical function	49.41 ± 7.20	43 ± 5.41****	25.8 ± 6.11****	17.55 ± 9.32****

\*\*\*\*  $P < 0.001$ , ns: non-significant.

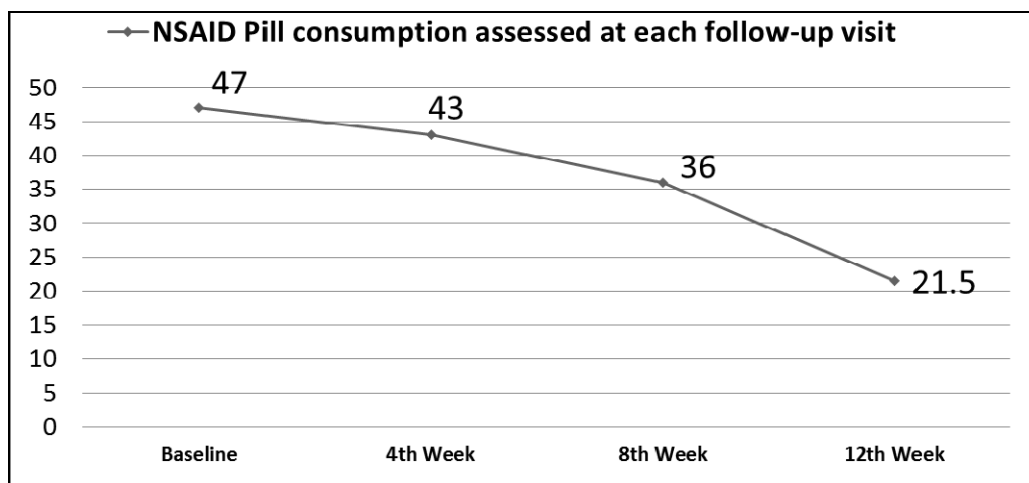
In stiffness sub-score, change from baseline to week 4 was not statistically significant, however, change in stiffness sub-score from end of week 4<sup>th</sup> to end of week 8<sup>th</sup>, week 12<sup>th</sup> was found to be statistically significant with  $P < 0.001$ .

In physical function sub-score, reduction from baseline to end of 4<sup>th</sup>, 8<sup>th</sup> and 12<sup>th</sup> week was also noted as statistically significant ( $P < 0.001$ ).

After analyzing the patient’s diary record for NSAIDs consumption, it was observed that, at baseline visit all patients reported daily consumption NSAIDs. A trend of decrease in

need of NSAIDs was noted by patients with each follow up visits. However, statistically significant change in need of NSAIDs was not reported from baseline to 4<sup>th</sup> week, 4<sup>th</sup> week to 8<sup>th</sup> week and 8<sup>th</sup> week to 12<sup>th</sup> week.

Interestingly, when compared the NSAIDs consumption at baseline to NSAIDs consumption at the end of 12<sup>th</sup> week, statistically significant difference was noted ( $P < 0.012$ ). The decrease in NSAIDs consumption at the end of 12<sup>th</sup> week was found to be 54.25% when compared to NSAIDs consumption at baseline as described in figure 2.



**Fig 2:** Mean consumption of NSAIDs at Baseline and respective follow up visits

The patients were interviewed during each visit as well at the end of the study for the detection of any adverse events. In all, 03 patients' reported GI adverse effects and investigator noted the severity of these adverse effects as mild. Furthermore, the intensity of these adverse effects was found to be reducing in nature with each completed week of the study.

None of the patient was withdrawn from this 12 week study due to adverse effects. Investigator assessed the reason for these GI adverse effects and it was likely reported due co-administration of NSAIDs during the study.

As per investigators assessment about global efficacy and tolerability of curcumin and piperine combination, 100% of patients tolerated the treatment very well and got benefitted. Moreover in 38.6% of patients, investigator reported the global efficacy and tolerability as excellent and in 56.8% of patients the global efficacy and tolerability was reported as good.

#### 4. 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 in arthritic disorders. The results of the present trial clearly favour the efficacy of curcumin in alleviating the symptoms of OA, as reflected by marked improvement in assessed efficacy measures namely WOMAC scores. Chandran *et al.* [11] investigated the efficacy of proprietary bioavailability-enhanced curcumin 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. Curcumin monotherapy was reported to be superior to both diclofenac monotherapy and curcumin/diclofenac combination in reducing overall Disease Activity Score (DAS) and ACR score<sup>8</sup>. In contrast to NSAIDs, curcumin has no gastrointestinal side effects and can even protect the gastric mucosa<sup>12</sup>. Therefore, curcumin is thought to be beneficial in the management of chronic inflammation-related joint disease, including osteoarthritis [13].

Yasuaki Nakagawa *et al.* [3] conducted a randomized double blind placebo controlled study to analyze effects of surface-controlled water-dispersible form of curcumin (Theracurmin) in fifty knee osteoarthritis patients. These researchers concluded that, administration of this form of curcumin leads to significant reduction in knee pain and visual analog scale (VAS) score. Furthermore, administration of curcumin also reduced the need of celecoxib administration during the study [3].

A plausible mechanism for the protective effects of curcumin against OA is the potent anti-inflammatory effects of this phytopharmaceutical. Most of the anti-inflammatory properties of curcumin are due to the inhibition of NF- $\kappa$ B, 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. Curcumin can effectively reduce the release of pro-inflammatory cytokines such as tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, macrophage chemotactic protein-1 and prostaglandin E2 [14]. These anti-inflammatory properties have been verified in cultured chondrocytes. Moreover, inhibition of NF- $\kappa$ B by curcumin 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. Finally, there is evidence indicating that curcumin that increase chondrocyte survival through down-regulation of inflammation-induced apoptosis [4, 15].

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. Reactive oxygen species can disturb cartilage matrix homeostasis and promote MMP expression, chondrocyte apoptosis and production of mediators involved in pain. Curcumin is potent antioxidants and have been shown to modulate oxidative stress through various mechanisms. Curcumin 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 [16-18]. In addition curcumin reduce the formation of free radicals by blocking enzymes such as COX-II, 5-lipoxygenase and inducible nitric oxide synthase, and enhance intracellular antioxidant defense through stimulation of nuclear factor-erythroid-2-related factor 2 (Nrf-2) [1, 18].

All these effects may account for the amelioration of joint health and pain relief following curcumin supplementation. Co-administration of piperine with curcumin can enhance the bioavailability of the latter through several mechanisms including inhibition of curcumin glucuronidation in the intestine and liver, increased blood supply to the intestinal tissue and enhancing membrane dynamics leading to increased permeability of brush border [6-9].

Francesco Di Pierro *et al* [19]. Carried out comparative evaluation of the pain-relieving properties of a lecithinized

formulation of curcumin (Meriva®) with nimesulide, and acetaminophen. Results of their study showed that, lecithinized curcumin showed clear analgesic activity, comparable with that of a standard dose (1 g) of acetaminophen, but lower than that of a therapeutic (100 mg) dose of nimesulide, with greater gastric tolerability than nimesulide [19].

In our study, we have observed an improvement in pain, stiffness and physical function as evidenced in the WOMAC questionnaires. Patients were able to engage more in social activities, reportedly feeling markedly well in various forms of physical functions. Pain and osteoarthritis symptoms are known to limit social interactions, and any improvement in these conditions is likely to have a socio-emotional effect. Another benefit reported in our study was 54.25% decrease in need of analgesics/NSAIDs associated with curcumin use. This was directly related to the marked reduction of NSAID associated gastrointestinal problems.

In summary, findings of the present trial support the findings of previous studies on the efficacy of supplementation with curcumin 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 of the study. However, the number of recruited subjects was sufficient to detect a statistically significant effect size of curcumin with piperine combination on the assessed efficacy measures. Future studies may be needed to validate our findings in a large number of patients with osteoarthritis over a longer duration.

## 5. Conclusion

Curcumin in combination with piperine is effective and safe option in the management of osteoarthritis, leading to better disease control, decreased use of NSAIDs and least GI disturbances. Curcumin along with piperine thus represents a new paradigm in the management of OA and should be considered based on its safety and efficacy.

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