



## Research Article

# Efficacy and Safety of a Highly Bioavailable Curcumin Formulation in Modulating Outcomes of Mild Knee Osteoarthritis: Multi-Centric, Randomized, Double-Blind, Placebo-Controlled Study

Nilesh Jagtap<sup>1</sup>, Aniket Shah<sup>2</sup>, Sachin Bedmutha<sup>3</sup>, Sathish Kumar Durairaj<sup>4\*</sup>

<sup>1</sup>Royal Hospital, Anupam Arcade, Pune-Satara Road, Katraj, Pune 411046, India

<sup>2</sup>Chopda Medicare and Research Centre Private Ltd., Plot No.3, Patil Colony, Near K.B.H Vidyalaya, Canada Corner, Nashik 422005, India

<sup>3</sup>Sahyadri Asthiring Balrog Dental Nursing Home and Maternity Centre, Plot No. 20, Sr. No. 08, N-2, CIDCO, Aurangabad 431006, India

<sup>4</sup>G7 Synergon Private Limited, 537, 5th Main, 9th Cross, Sahakarnagar Post, Tatanagar, Bangalore 560092, India

\***Corresponding Author:** Sathish Kumar Durairaj, G7 Synergon Private Limited, 537, 5th Main, 9th Cross, Sahakarnagar Post, Tatanagar, Bangalore 560092, India.

**Citation:** Jagtap N, Shah A, Bedmutha S, Durairaj SK (2023) Efficacy and Safety of a Highly Bioavailable Curcumin Formulation in Modulating Outcomes of Mild Knee Osteoarthritis: Multi-Centric, Randomized, Double-Blind, Placebo-Controlled Study. J Orthop Res Ther 8: 1303. DOI: 10.29011/2575-8241.001303

**Received Date:** 17 May 2023; **Accepted Date:** 24 May 2023; **Published Date:** 26 May 2023

### Abstract

**Background:** Osteoarthritis (OA) is a degenerative disease of joints affecting aging population worldwide with significant unmet medical needs. Here we report efficacy and safety of a highly bioavailable curcumin formulation, Curcuwin Ultra+ (CU+) in subjects with mild knee OA. **Methods:** Forty-five subjects each for CU+ 250 mg, CU+ 500 mg, and placebo groups with mild knee OA were randomized in a multi-centric, double-blind, parallel, placebo-controlled study with a treatment period of 84 days. A range of primary and secondary endpoints were assessed at baseline, day 5, 28, 56 and 84. The trial was prospectively registered on Clinical Trials Registry - India (CTRI/2021/10/037187) dated 08/10/2021. **Results:** A significant improvement ( $p < 0.05$ ) was observed in total Western Ontario McMaster Universities Osteoarthritis Index score (WOMAC), VAS pain, walking performance, range of motion (ROM) for knee extension and muscle strength as early as 5 days in CU+ 500 mg group as compared to placebo. Further, both groups of CU+ demonstrated significant reductions ( $p < 0.05$ ) in total WOMAC, WOMAC-pain, WOMAC-stiffness, WOMAC-physical function, VAS pain, and significant increases ( $p < 0.05$ ) in walking performance, knee extension and flexion muscle strength on days 28, 56, and 84 as compared to placebo. Moreover, ROM knee flexion was significantly decreased ( $p < 0.05$ ) on days 28, 56, and 84 in CU+ 500 mg and day 84 in CU+ 250 mg. Serum biomarkers like IL-1 $\beta$ , hsCRP, CTX-II and MMP3 were significantly reduced ( $p < 0.05$ ) on day 84 in CU+ 500 mg group. The use of rescue medication was significantly reduced

( $p < 0.05$ ) in both CU+ groups as compared to placebo. The study products were safe and well-tolerated throughout the study period. **Conclusion:** CU+ showed a significant reduction in joint discomfort, cartilage degradation, inflammation and use of rescue medication for pain with improved joint mobility, flexibility, knee muscle strength, and overall quality of life in subjects with mild knee OA.

**Trial Registration:** <http://ctri.nic.in/> Identifier: CTRI/2021/10/037187

**Keywords:** Cartilage; Curcumin; Curcuwin ultra+; Joint mobility; Muscle strength; Osteoarthritis; VAS pain; WOMAC

## Abbreviations

6MWT: 6 Minutes' Walk Test; ANOVA: Analysis of Variance; AP: Activator Protein; BMI: Body Mass Index; COMP: Cartilage Oligomeric Matrix Protein; CONSORT: Consolidated Standards of Reporting Trials; COX: Cyclooxygenase; CRP: C-Reactive Protein; CTRI: Clinical Trials Registry of India; CTX: Carboxy-Terminal Telopeptides; CU: Curcumin; ELISA: Enzyme-Linked Immunosorbent Assay; HHD: Hand-Held Dynamometer; ICH: International Council for Harmonization; ICMR: Indian Council of Medical Research; LOX: Lipoxygenase; MIA: Monosodium Iodoacetate; MMP: Matrix Metalloproteinases; NF: Nuclear Factor; NSAID: Non-Steroidal Anti-Inflammatory Drugs; OA: Osteoarthritis; PGE: Prostaglandin E; ROM: Range of Motion; TNF: Tumor Necrosis Factor; VA: Visual Analogue; VAS: Visual Analogue Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis.

## Background

Osteoarthritis (OA) is a degenerative disease of joints often associated with underlying inflammation and progressive cartilage degradation. Osteoarthritis begins with cartilage thinning, joint space narrowing, inflammatory reactions [1-8], loss of joint architecture, and deformation of the knee [9]. Osteoarthritis primarily affects the aging population worldwide with higher incidences in females and leading cause of morbidity and healthcare cost across the globe [10-12]. Current OA management includes pharmacological interventions through analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), etc. While these therapies provide temporary relief from pain and improve physical function, they do not address underlying conditions and are frequently associated with several adverse events over long-term use in many individuals [13-18].

Several plant-based multi-functional anti-inflammatory products have been developed in the past which are being used by patients suffering from knee osteoarthritis with limited success [19]. Curcumin, a polyphenolic compound from turmeric (*Curcuma longa*) has been extensively used to treat knee OA [20-24]. Curcumin has been used for centuries in traditional Chinese and Ayurvedic medicine for its anti-inflammatory properties [25].

Meta-analysis of clinical studies has demonstrated the protective role of curcumin in OA with decreased VAS, and WOMAC scores, reduced inflammatory factors such as ILs, TNF- $\alpha$ , MMPs, and increased antioxidant activity as compared to placebo [26]. Curcumin inhibits the synthesis of inflammatory mediators such as interleukin (IL)-1 $\beta$ , tumor necrosis factor (TNF)- $\alpha$ , IL-6, IL-8, prostaglandin E2 (PGE2), cyclooxygenase-2 (COX-2) [27-29], and IL-1 $\beta$ -induced extracellular matrix degradation [30]. The anti-inflammatory function of curcumin is primarily mediated through the inhibition of activator protein 1 (AP-1) [31] and nuclear factor kappa B (NF- $\kappa$ B) activation [31-34]. Further, curcumin suppresses the expression of a number of matrix metalloproteinases (MMPs), which play critical role in the breakdown of cartilage extracellular matrix in OA [7,28,31-33,35-40]. Several human clinical studies have demonstrated efficacy of curcumin leading to reduced pain and improved physical function, and quality of life in OA patients with the efficacy of curcumin shown to be similar to that of ibuprofen [41-42]. Curcumin has been found to be chondro-protective possibly due to their anti-inflammatory, antioxidant and anti-catabolic activity that helps in mitigating OA disease pathogenesis and symptoms [43,44]. Further, curcumin also functions as an antioxidant by scavenging reactive oxygen and nitrogen species that play an important role in the genesis of OA [20].

Despite therapeutic potential, poor bioavailability of curcumin due to low absorption, rapid metabolism, and elimination in the body limits its clinical use [10]. Curcumin is highly hydrophobic and hence insoluble in water [11], unstable in alkaline physiological pH of the small intestine [12,45] resulting in very low plasma curcuminoids levels even after consuming large doses. Numerous formulation approaches have been developed to improve the bioavailability of curcumin, such as the use of piperine that interferes with glucuronidation, development of formulations based on liposomes, nanoparticles, and phospholipid complex [46]. Previously a newly formulated curcumin formulation named as Curcuwin Ultra+ (CU+) was reported with 40% faster intestinal absorption and 144 times higher plasma curcuminoids concentration in human subjects as compared to 95% turmeric extract [47]. Further, CU+ supplementation restored joint architecture and reduced swelling of joint in monosodium iodoacetate (MIA)-induced knee OA in rats with a significant reduction in the levels of inflammatory mediators such as TNF- $\alpha$ ,

IL-1 $\beta$ , IL-6, COMP, and CRP, and expressions of MMP-3, 5-LOX, COX-2 and NF $\kappa$ B in synovial tissue [48]. The current study is designed to demonstrate the improved efficacy of CU+ due to enhanced bioavailability and faster absorption in human subjects suffering from mild knee OA on parameters of joint discomfort, cartilage degradation, inflammation, joint mobility, flexibility, knee muscle strength, quality of life, and use of rescue medication for pain.

## Methods

### Study Design and Procedures

This was a prospective, randomized, double-blind, parallel, placebo-controlled, clinical interventional study of two doses of CU+ in subjects with mild knee osteoarthritis. The study was initiated after obtaining written approval from respective institutional ethics committees of each site. The study was carried out as per the requirements of the Indian Council of Medical Research (ICMR) ethical guidelines, International Council for Harmonization (ICH) 'Guidance on Good Clinical Practice' (E6R2), and 'Declaration of Helsinki'. The study was registered with the Clinical Trials Registry of India (CTRI/2021/10/037187).

Voluntary informed consent was obtained from every participant before enrolment in the study. Subjects were randomly assigned in a 1:1:1 ratio to receive CU+ 250 mg (total of 50 mg curcuminoids) capsule or CU+ 500 mg (total of 100 mg curcuminoids) capsule or placebo. Curcuwin Ultra+<sup>®</sup>, manufactured by OmniActive Health Technologies Ltd., Mumbai, India contains not less than 20% total curcuminoids and composed of turmeric extract encapsulated in matrix of cellulose polymer, solubilizer, acidifier and antioxidant. The placebo capsules were filled with microcrystalline cellulose in scarlet red colored hard gelatin capsules by OmniActive Health Technologies to look like CU+ capsules and keep the study double-blinded.

The study visits were scheduled as – Screening/baseline visit, Placebo run-in visit, Randomization visit, follow up visits at Day 5, 28, 56 and End of study visit at Day 84. Demographic information such as gender, age, body weight, height, BMI, medical history, concomitant medication history, and physical activities, presence of allergic problems and drug reactions, and oral contraceptives were obtained during the screening visit. After the screening visit, the eligible subjects were provided with placebo capsules for the run-in period and instructed to consume one capsule every morning after breakfast for 7 days. Once the run-in period was completed, the eligible subjects were randomized by study investigators in a double-blinded fashion to receive one of the study products as per the randomization schedule. The randomization schedule was generated using block randomization by a non-study assigned, independent expert ensuring the treatment balance by using SAS<sup>®</sup> Version 9.4. One bottle of study product containing 35 capsules

was dispensed to every subject at Day 0, Day 28 and Day 56 as per the randomization schedule. Subjects were instructed to consume one study capsule every morning after breakfast at the same time every day for 84 days (12 weeks). Subject compliance was calculated by performing study product reconciliation at each follow up visit.

Acetaminophen was prescribed as rescue medication for the subjects who could not withstand pain, and the details of use were recorded.

### Inclusion/Exclusion Criteria

Subjects who met all inclusion and none of the exclusion criteria were enrolled in the study after signing a written informed consent. Inclusion criteria were as follows: male and female subjects aged between 35 and 75 years (both limits inclusive), clinical diagnosis of unilateral or bilateral knee osteoarthritis (OA) for at least greater than 3 months, as presented by pain in the knee at least for last 3 months, knee joint pain rated  $\leq$  44 on a 100-point Pain-VAS scale, knee OA grade II as per Kellgren- Lawrence classification, subjects involved in regular physical activity such as walking, climbing stairs, recording forms, eating, exercise behaviors, etc, subject who could walk for at least 6 minutes at a moderate-to-brisk pace on a treadmill, subjects willing to avoid NSAIDs and other anti-inflammatory medications during the study period and subjects who were 100% compliant with an investigational product during the Run-In Period.

The following criteria were used to exclude subjects in the study: Subjects with moderate to severe knee OA in Grade III or IV as per Kellgren and Lawrence Scale, previous history of knee OA for more than 3 years, previous history of any knee joint replacement surgery or bilateral hip joint replacements, positive urine pregnancy test at screening visit, subjects unwilling to refrain from the use of NSAIDs or herbal/ nutraceutical supplements for joint health or local analgesics during the study duration, habit of smoking or consuming tobacco products, any other chronic disease that could jeopardize the outcomes of the study.

### Efficacy and Safety Parameters

Primary efficacy endpoint included Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index measured for one knee joint at baseline visit, day 5, 28, 56 and 84. Secondary efficacy endpoints included Visual Analogue Scale for pain (VAS - pain), Knee Extension and Flexion Muscle Strength, Range of Motion (ROM) and 6 Minutes' Walk Test (6MWT) measured at baseline visit, day 5, 28, 56 and 84. Further, serum hsCRP and IL-1 $\beta$  were evaluated at baseline visit, day 5, and 84 whereas serum CTX-II, COMP, and MMP-3 were evaluated at baseline visit and day 84. Rescue medication usage was evaluated throughout the study using subject diary.

As part of safety assessments, adverse events were collected throughout the study using subject diary. Physical examination and vital signs measurement was conducted at all study visits. Laboratory assessments, and urine pregnancy tests for females of childbearing age were performed at screening visit and end of study visit.

### Statistical Analysis

A sample size of 135 subjects (45 subjects for CU+ 250 mg, 45 subjects for CU+ 500 mg and 45 subjects for the Placebo group) was based on the assumption that there will be a mean difference in total WOMAC index of 10% between the CU+ formulations and placebo from baseline to end of treatment. With an expected inter-subject standard deviation of 30%, around 37 evaluable subjects per group would be required to estimate the reduction of total WOMAC index score at a 5% level of significance at the end of the study at 80% power. Based on the parallel design and considering possible dropouts, a sample size of 45 subjects was enrolled in each treatment group.

Baseline characteristics were presented separately for the study groups. Continuous variables were summarized using descriptive statistics which included number of observations, mean, median, minimum, maximum, and standard error. Categorical variables were summarized using frequencies and percentages. All statistical analyses were performed using SAS®, version 9.4. Subjects with missing data were excluded only from analyses for which data were not available.

The differences in the analysis variables were tested by using paired t-test and one-way ANOVA (Analysis of Variance) model using PROC ANOVA in SAS®. Kruskal-Wallis test was executed for the ordinal datasets. For the dichotomous variable Z-test was performed using SAS®. The criterion for the significant test by treatment was set at a p-value<0.05.

### Efficacy Endpoints Evaluation

Licensed WOMAC OA Index version VA 3.1 English for India was used as per WOMAC® User Guide XII for maximum of 5 occasions for each subject. WOMAC questionnaire contained 24 items grouped into three sub-categories: pain, stiffness, and physical function (total score range 0-2400). The total WOMAC score was calculated by adding the subscale scores (5 - pain; 2 - stiffness; 17 - physical function). Visual analogue scale for pain was measured using 100 mm pain scale with a calibrated ruler to maintain the uniformity of measurement throughout the visits for all subjects. The VAS scale for pain was calculated for both the right and left legs at each visit for all the subjects. MicroFET2™ Wireless Hand-Held Dynamometer (Hoggan Scientific, Salt Lake City, UT, USA) was used for force evaluation (strength) test during the extension and flexion of both dominant and non-dominant legs for each subject at each visit as per the product's user manual.

Three readings were recorded, and the average was calculated for each leg at each visit.

For the measurement of knee extension and flexion angles, a calibrated goniometer was used. The subjects were allowed to sit in an upright position on a table edge with their backs straight and knee position defined at 90°, and the axis of a goniometer was placed at the intersection of the thigh and shank at the knee joint. The subjects were asked to flex or extend their legs to the fullest ability without changing the position. Three readings were obtained, and the average was calculated for each leg at each visit.

For 6MWT, the participants were asked to walk on treadmill for 6 minutes continuously while making sure that at least one foot was bearing weight at all the times and the distance was measured in meters for each subject at each visit.

For biomarker analysis, serum was separated from blood samples and stored below -20°C until analysis. KRISHGEN BioSystems (Mumbai, MH, India) GENLISA™ ELISA kits were used for IL-1β, MMP-3, CTX-II, and COMP analysis and Calbiotech (El Cajon, CA, United States) ELISA kits and reagents were used for hsCRP. Samples were analysed at baseline and Day 84 while hsCRP and IL-1β was additionally analysed on Day 5.

The subjects were only prescribed acetaminophen as a rescue medication if the symptoms were unbearable for ethical reasons. The subjects were allowed to discontinue the consumption of rescue medication as per their willingness and if they sensed improvement in the symptoms. The rescue medication consumption was evaluated throughout the study.

### Safety Analysis

Safety analyses included haematology, biochemistry, and urinalysis, the incidence of adverse events, physical examination, and vital sign measurements. Physical examinations and vital parameter assessments were performed at all the visits while blood sampling for laboratory tests were performed at baseline and end of the treatment (day 84), allowing evaluation versus baseline. Adverse events details were obtained throughout study duration using subject diary.

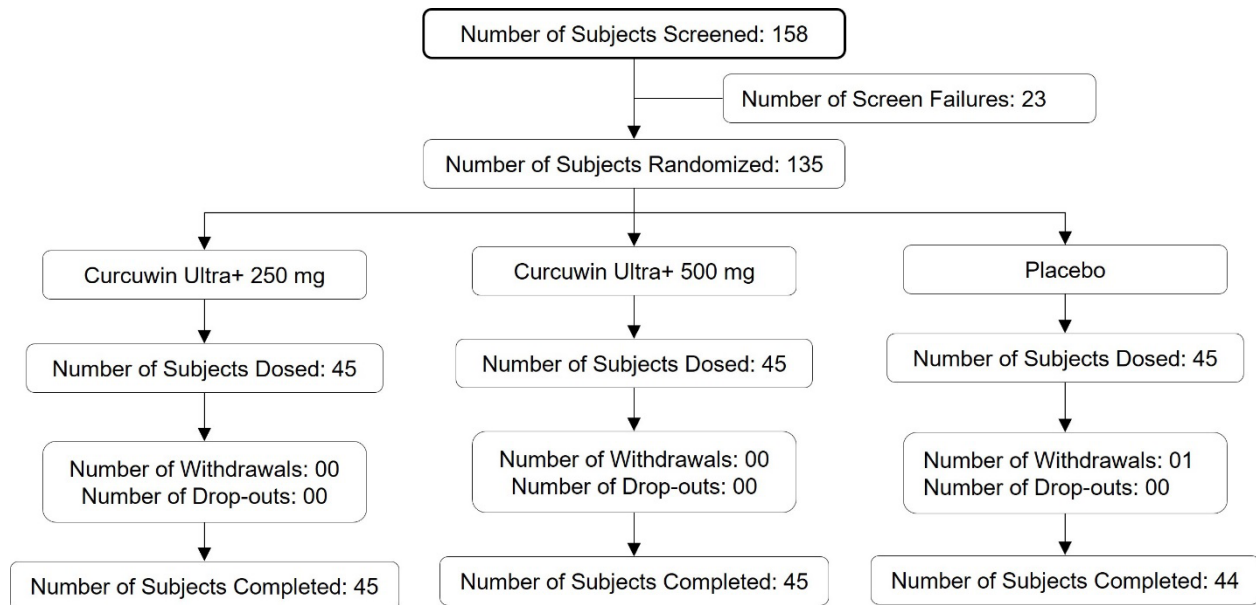
Descriptive statistics included number of subjects, mean, standard deviation, median, minimum, and maximum for continuous safety variables and frequency, and percentage for categorical safety variables such as adverse events were summarized by treatment.

### Results

One hundred fifty-eight subjects were screened, out of which 23 subjects did not fulfil the eligibility criteria and were considered as screen failures (Figure 1). Out of the 135 randomized subjects, 45 subjects were allocated to the CU+ 250 mg, 45 subjects were

allocated to the CU+ 500 mg and 45 subjects to the placebo group. One subject from the placebo group withdrew consent due to personal reason. The demographic characteristics are shown in Supplementary Table S1. The mean age of subjects in CU+ 250 mg group was 51.89±9.27 years, CU+ 500 mg group was 51.38±11.52 years, and placebo group was 53.09±9.30 years. The mean body mass index (BMI) was 25.69±4.23 kg/m<sup>2</sup> for the CU+ 250 mg group, 25.88±4.88 kg/m<sup>2</sup> for the CU+ 500 mg group and 25.79±3.56 kg/m<sup>2</sup> for the placebo group at screening visit.

There was no statistical significance among the three groups for age, and BMI at the baseline.



**Figure 1:** Consolidated Standards of Reporting Trials (CONSORT) diagram for efficacy and safety of Curcuwin Ultra+, in a randomized clinical interventional study on joint health and muscle strength in mild knee osteoarthritis subjects, showing subject disposition including screening, randomization, withdrawals, and completion.

## Efficacy

The efficacy analysis was performed for 134 subjects who completed the study as 1 subject from the placebo group withdrew consent due to personal reason.

## Efficacy Analyses

### Total WOMAC Score

The within-group analysis indicated that subjects in both CU+ 250 mg and 500 mg groups showed a significant decrease in total WOMAC score on Days 5, 28, 56, and 84 ( $p < 0.05$ ), while subjects in placebo group showed a significant decrease only on Day 5 ( $p < 0.05$ ) as compared to baseline.

According to the between-group analysis, subjects in the CU+ 250 mg and 500 mg groups showed significant decrease in their total WOMAC score on Days 5, 28, 56, and 84 compared to placebo ( $p < 0.05$ ), and CU+ 500 mg significantly outperformed CU+ 250 mg on Days 56 and 84 ( $p < 0.05$ ) (Supplementary Table S2a; Supplementary Figure 1; Figure 2a).

### WOMAC Pain Score

When compared to baseline, WOMAC pain scores for subjects in the CU+ 250 mg and 500 mg groups significantly decreased on Days 5, 28, 56, and 84 ( $p < 0.05$ ). In contrast, WOMAC pain scores for subjects in the placebo group did not significantly decrease at any visit.

In comparison to the placebo group, subjects in the CU+ 250 mg and 500 mg groups demonstrated a statistically significant decrease in WOMAC pain score on Days 28, 56, and 84 ( $p < 0.05$ ). In addition, CU+ 500 mg performed significantly better than CU+ 250 mg on Days 56 and 84 ( $p < 0.05$ ) (Supplementary Table S2b; Supplementary Figure 1; Figure 2b).

### WOMAC Stiffness Score

According to the within-group analysis, subjects in the CU+ 250 mg and 500 mg groups demonstrated a significant decrease in WOMAC stiffness score on Days 5, 28, 56, and 84 ( $p < 0.05$ ), while those in the placebo group demonstrated a significant decrease only on Day 5 ( $p < 0.05$ ) as compared to baseline.

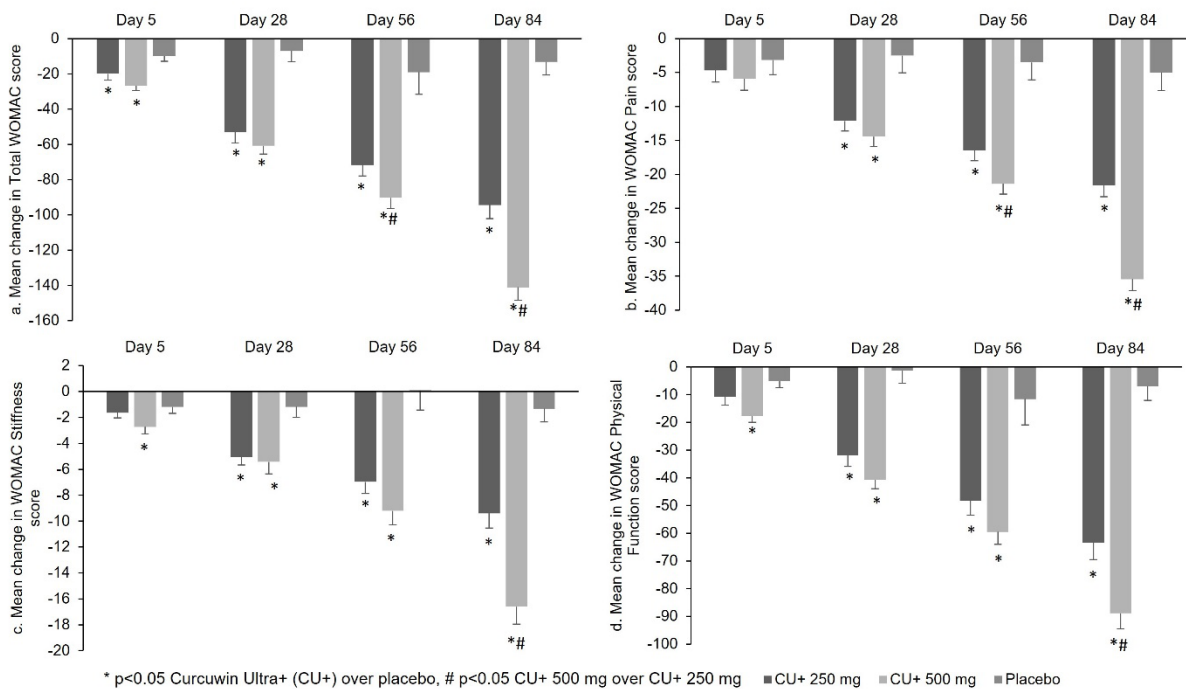
In comparison to the placebo group, the CU+ 500 mg group experienced a significant decrease in WOMAC stiffness score as early as Day 5 ( $p < 0.05$ ). Furthermore, both CU+ 250 mg and 500 mg groups significantly decreased ( $p < 0.05$ ) WOMAC stiffness score on Days 28, 56, and 84. Additionally, CU+ 500 mg demonstrated a significantly greater reduction in WOMAC stiffness score on Day 84 compared to CU+ 250 mg ( $p < 0.05$ ) (Supplementary Table S2c; Supplementary Figure 1; Figure 2c).

### WOMAC Physical Function Score

The within-group analysis indicated that subjects in CU+ 250 mg and 500 mg groups showed a significant decrease in WOMAC

physical function score on Days 5, 28, 56, and 84 ( $p < 0.05$ ), while subjects in placebo group showed a significant decrease only on Day 5 ( $p < 0.05$ ) as compared to baseline.

In comparison to the placebo group, the CU+ 250 mg and 500 mg groups showed significant decreases in WOMAC physical function score on Days 28, 56, and 84 ( $p < 0.05$ ). Additionally, this significant difference was seen as early as Day 5 ( $p < 0.05$ ) in the CU+ 500 mg group. Further, CU+ 500 mg demonstrated a significantly greater reduction in WOMAC physical function score on Day 84 compared to CU+ 250 mg ( $p < 0.05$ ) (Supplementary Table S2d; Supplementary Figure 1; Figure 2d).



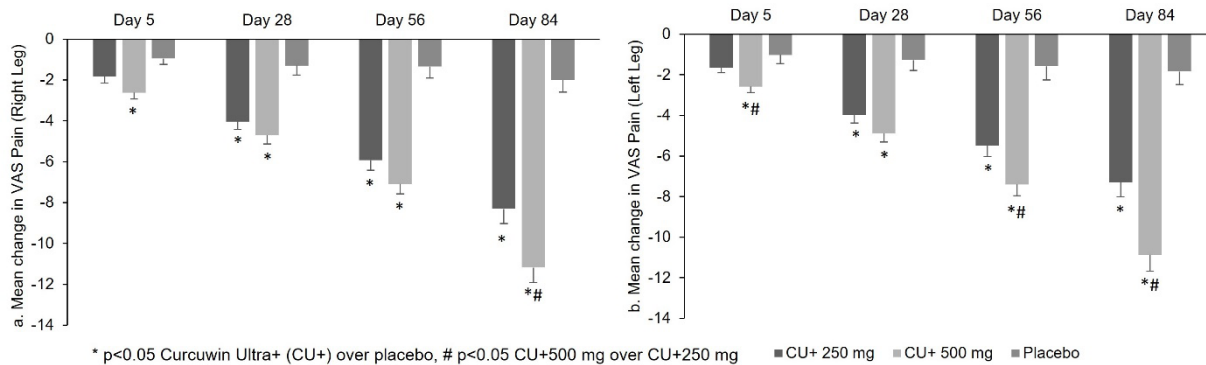
**Figure 2:** Summary of efficacy endpoint results (WOMAC) –Mean change in Total WOMAC score (a), WOMAC pain score (b), WOMAC Stiffness score (c), and WOMAC physical function score (d). \* P-value $<0.05$  CU+ significant over placebo, # P-value $<0.05$  CU+ 500 mg significant over CU+ 250 mg.

### Visual Analogue Scale for Pain

When compared to baseline, pain scores for subjects in all the study groups (CU+ 250 mg, CU+ 500 mg and placebo) significantly decreased on Days 5, 28, 56, and 84 ( $p < 0.05$ ).

In comparison to placebo, CU+ 500 mg group showed a significant decrease in pain score as early as Day 5 ( $p < 0.05$ ), whilst

the CU+ 250 mg and 500 mg groups showed significant reductions in pain score on Days 28, 56, and 84 ( $p < 0.05$ ). Additionally, CU+ 500 mg demonstrated significantly better reduction in pain than CU+ 250 mg on Day 84 ( $p < 0.05$ ) for the right leg and Days 5, 56, and 84 ( $p < 0.05$ ) for the left leg (Supplementary Table S2e and S2f; Figure 3a and 3b).



**Figure 3:** Summary of efficacy endpoint results (VAS Pain) –Mean change in VAS pain – right leg (a), Mean change in VAS pain – left leg (b). \* P-value<0.05 CU+ significant over placebo, # P-value<0.05 CU+ 500 mg significant over CU+ 250 mg.

### Muscle Strength Assessed by Hand-Held Dynamometer (HHD) Knee Extension (Dominant Leg)

The within-group analysis revealed that subjects in the CU+ 250 mg and 500 mg groups demonstrated significant increase in knee extension muscle strength for the dominant leg on Days 5, 28, 56, and 84 ( $p<0.05$ ), while subjects in the placebo group demonstrated significant increases on Days 5 and 56 ( $p<0.05$ ) compared to baseline.

Compared to placebo, the CU+ 500 mg group demonstrated a significant increase in knee extension muscle strength for the dominant leg on Day 5 ( $p<0.05$ ). In addition, both 250 mg and 500 mg CU+ groups showed a significant increase in knee extension muscle strength on Days 28, 56, and 84 ( $p<0.05$ ). Further, CU+ 500 mg outperformed CU+ 250 mg by a statistically significant margin on Days 5, 28, 56, and 84 ( $p<0.05$ ) (Supplementary Table S2g; Figure 4a).

### Knee Extension (Non-Dominant Leg)

The within-group analysis revealed that subjects in all the study groups (CU+ 250 mg, Cu+ 500 mg and placebo) demonstrated significant increase in knee extension muscle strength for the non-dominant leg on Days 5, 28, 56, and 84 ( $p<0.05$ ) compared to baseline.

Both CU+ 250 mg and 500 mg groups showed significant increase in knee extension muscle strength for the non-dominant leg on Days 28, 56, and 84 ( $p<0.05$ ) as compared to the placebo group where CU+ 500 mg significantly outperformed CU+ 250 mg on Days 56 and 84 ( $p<0.05$ ) (Supplementary Table S2h; Figure 4b).

### Knee Flexion (Dominant Leg and Non-Dominant Leg)

The within-group analysis indicated that subjects in all

the study groups (CU+ 250 mg, Cu+ 500 mg and placebo) demonstrated significant increase in knee flexion muscle strength for the dominant and non-dominant legs on Days 5, 28, 56, and 84 ( $p<0.05$ ) compared to baseline.

Both CU+ 250 mg and 500 mg groups showed significant increase in knee flexion muscle strength for the dominant and non-dominant legs on Days 28, 56 and 84 ( $p<0.05$ ) as compared to placebo with CU+ 500 mg being significantly better than CU+ 250 mg on Day 84 ( $p<0.05$ ) (Supplementary Table S2i and S2j; Figure 4c and 4d).

### Range of Motion (ROM) measured by Goniometer

#### Knee Extension (Dominant Leg)

When compared to baseline, CU+ 250 mg did not show any significant decrease in knee extension ROM for the dominant leg at any visit whereas CU+ 500 mg showed significant decrease on Day 5 ( $p<0.05$ ). In contrast, placebo group showed a significant increase in knee extension from baseline on Day 5 ( $p<0.05$ ).

The CU+ 500 mg group, but not the CU+ 250 mg group, showed a significant reduction in knee extension ROM for the dominant leg on Days 5 and 28 ( $p<0.05$ ) compared to the placebo group. Further, neither CU+ groups differed significantly from the placebo on Days 56 or 84. (Supplementary Table S2k; Figure 4e).

#### Knee Extension (Non-Dominant Leg)

No significant differences in knee extension ROM for the non-dominant leg were seen in CU+ 250 mg, CU+ 500 mg and placebo groups from baseline or between CU+ groups compared to placebo during the study period (Supplementary Table S2l; Figure 4f).

#### Knee Flexion (Dominant Leg)

According to the within-group analysis, CU+ 250 mg

showed significant increase in knee flexion ROM for the dominant leg on Days 56 and 84 ( $p < 0.05$ ), CU+ 500 mg on Days 5, 28, 56 and 84 ( $p < 0.05$ ) and placebo group on Day 28 ( $p < 0.05$ ) compared to baseline.

The CU+ 500 mg group showed significant increase in knee flexion ROM for the dominant leg on Days 56 and 84 ( $p < 0.05$ ) as compared to placebo whereas CU+ 250 mg group did not show any significant difference throughout the study period. Moreover, CU+ 500 mg group performed significantly better than CU+ 250 mg group on Days 5, 28, and 84 ( $p < 0.05$ ) (Supplementary Table S2m; Figure 4g).

### Knee Flexion (Non-Dominant Leg)

According to the within-group analysis, CU+ 250 mg showed significant increase in knee flexion ROM for the non-dominant leg on Days 56 and 84 ( $p < 0.05$ ), CU+ 500 mg on Days 28, 56 and 84 ( $p < 0.05$ ) and placebo group on Day 28 ( $p < 0.05$ ) compared to baseline.

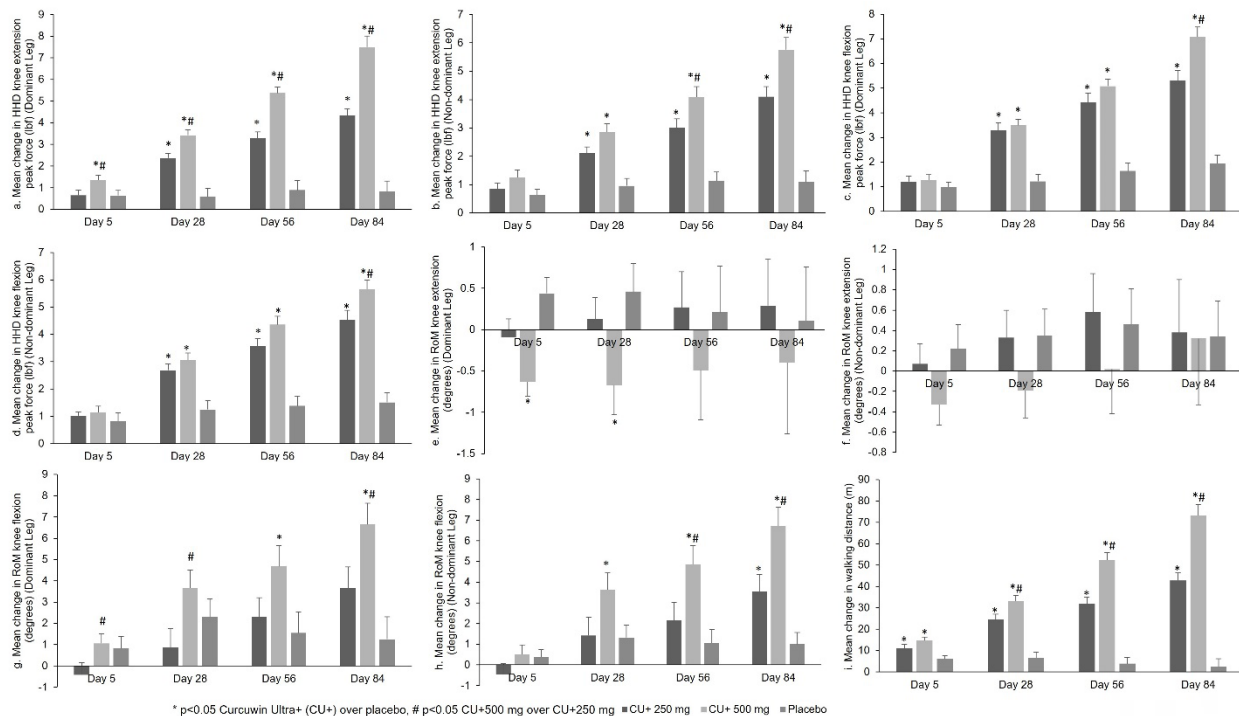
On day 84, both the CU+ 250 mg and 500 mg groups

demonstrated a significant increase ( $p < 0.05$ ) in knee flexion ROM for the non-dominant leg, however only the CU+500 mg group significantly increased the knee flexion ROM on Days 28 and 56 ( $p < 0.05$ ) compared to the placebo group. Furthermore, CU+ 500 mg demonstrated a substantially greater increase in knee flexion ROM than CU+ 250 mg on Days 56 and 84 ( $p < 0.05$ ) (Supplementary Table S2n; Figure 4h).

### Distance covered over a time of 6 minutes' walk on the treadmill

When compared to baseline, CU+ 250 mg and 500 mg groups showed significant increase in walking distance on Days 5, 28, 56 and 84 ( $p < 0.05$ ). Further, placebo group showed a significant increase in walking distance from baseline on Days 5 and 28 ( $p < 0.05$ ).

Both CU+ 250 mg and 500 mg groups showed significant increase in walking distance on Days 5, 28, 56, and 84 ( $p < 0.05$ ) as compared to placebo with CU+ 500 mg group performing significantly better than CU+ 250 mg group on Days 28, 56, and 84 ( $p < 0.05$ ) (Supplementary Table S2o; Figure 4i).



**Figure 4:** Summary of efficacy endpoint results (Handheld Dynamometry-HHD, Range of Motion-RoM, and 6-minute walk test-6MWT)–Mean change in HHD knee extension peak force (lbf) – dominant leg (a), HHD knee extension peak force (lbf) – non dominant leg (b), HHD knee flexion peak force (lbf) – dominant leg (c), HHD knee flexion peak force (lbf) – non dominant leg (d), RoM knee extension (degrees) – dominant leg (e), RoM knee extension (degrees) – non dominant leg (f), RoM knee flexion (degrees) – dominant leg (g), RoM knee flexion (degrees) – non dominant leg (h), and walking distance (meter) (i). \* P-value<0.05 CU+ significant over placebo, # P-value<0.05 CU+ 500 mg significant over CU+ 250 mg.



### Serum high-sensitivity C-reactive protein (hsCRP)

Within-group analysis revealed that subjects in the CU+ 250 mg and 500 mg groups showed significant decrease in hsCRP levels on Days 5 and 84 ( $p < 0.05$ ) compared to baseline, while subjects in the placebo group did not show any significant differences versus baseline.

Compared to placebo, the CU+ 500 mg group had a significant reduction in hsCRP levels on Day 84 ( $p < 0.05$ ) and a non-significant reduction on Day 5 ( $p = 0.0552$ ). The CU+ 250 mg group did not demonstrate any significant reduction in hsCRP levels compared to the placebo group. There was no statistically significant difference between the CU+ groups (Supplementary Table S2p; Figure 5a).

### Serum Interleukin-1 $\beta$ (IL-1 $\beta$ )

Within-group analysis indicated that subjects in the CU+ 500 mg group showed significant decrease in IL-1 $\beta$  levels on Days 5 and 84 ( $p < 0.05$ ) compared to baseline, while subjects in the CU+ 250 mg and placebo groups did not show any significant differences versus baseline.

Compared to placebo, the CU+ 500 mg group showed a significant reduction in IL-1 $\beta$  levels on Day 84 ( $p < 0.05$ ) and a non-significant reduction on Day 5 ( $p = 0.0654$ ). The CU+ 250 mg group did not demonstrate any significant reduction in IL-1 $\beta$  levels compared to the placebo group. No significant difference was seen between the CU+ groups (Supplementary Table S2q; Figure 5b).

### Serum Carboxy-Terminal Teloepitides of Type II Collagen (CTX-II)

Within-group analysis revealed that subjects in the CU+ 250 mg and 500 mg groups showed significant decrease in CTX-II levels on Day 84 ( $p < 0.05$ ) compared to baseline, while subjects in the placebo group did not show any significant difference versus baseline.

Both the doses of CU+ showed significant decrease in CTX-II on Day 84 ( $p < 0.05$ ) as compared to placebo. No significant difference was seen between the CU+ groups (Supplementary Table S2r; Figure 5c).

### Serum Cartilage Oligomeric Matrix Protein (COMP)

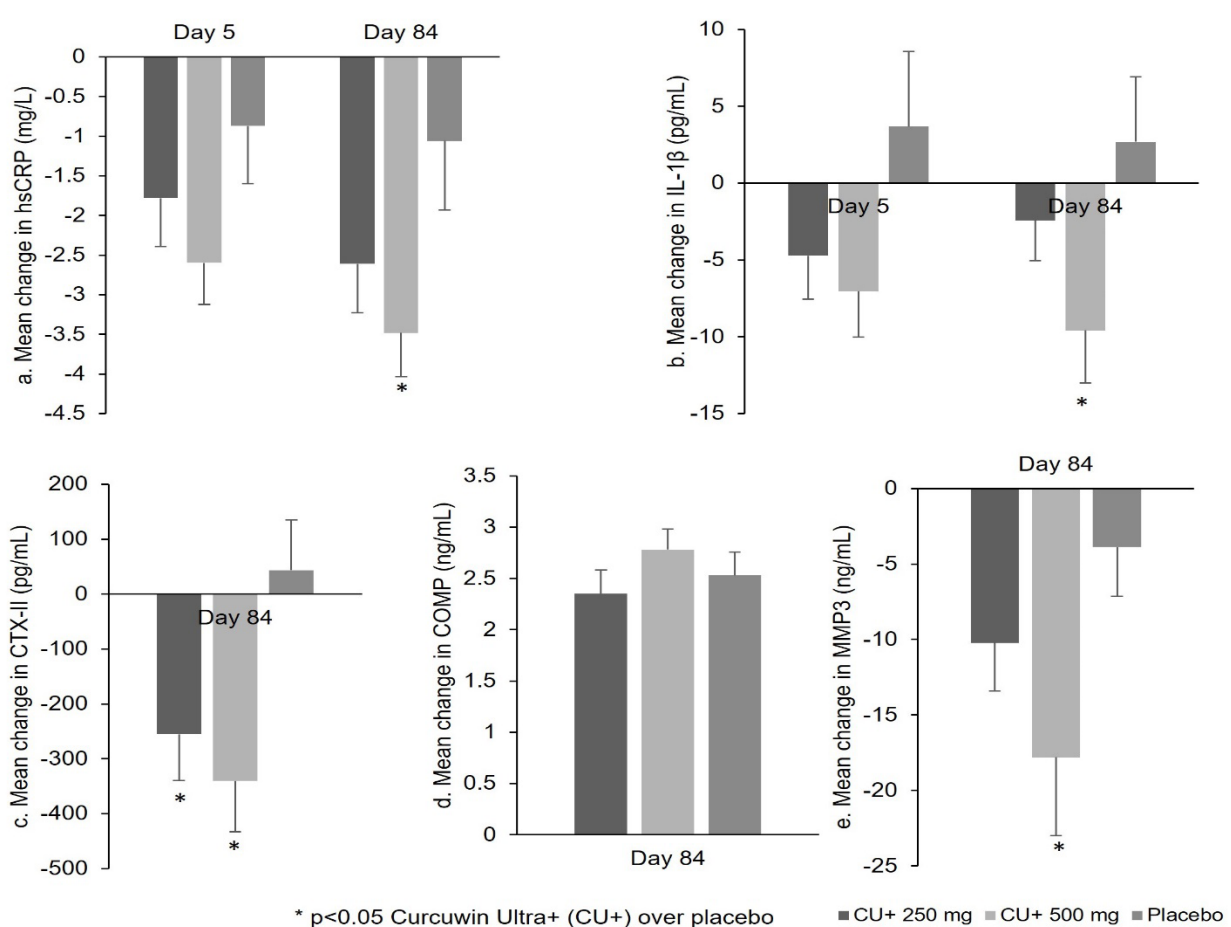
When compared to baseline, all the study groups showed significant increase in COMP levels on Day 84 ( $p < 0.05$ ).

No significant differences were seen between CU+ groups and placebo on Day 84 (Supplementary Table S2s; Figure 5d).

### Serum Matrix Metalloproteinase-3 (MMP-3)

When compared to baseline, both the CU+ 250 mg and 500 mg groups showed significant reduction in MMP-3 levels on Day 84 ( $p < 0.05$ ), while no significant difference was observed in the placebo group.

When compared to placebo on Day 84, serum MMP-3 levels were significantly reduced in the CU+ 500 mg group ( $p < 0.05$ ), but not in the CU+ 250 mg group. No significant differences were seen between the CU+ groups (Supplementary Table S2t; Figure 5e).

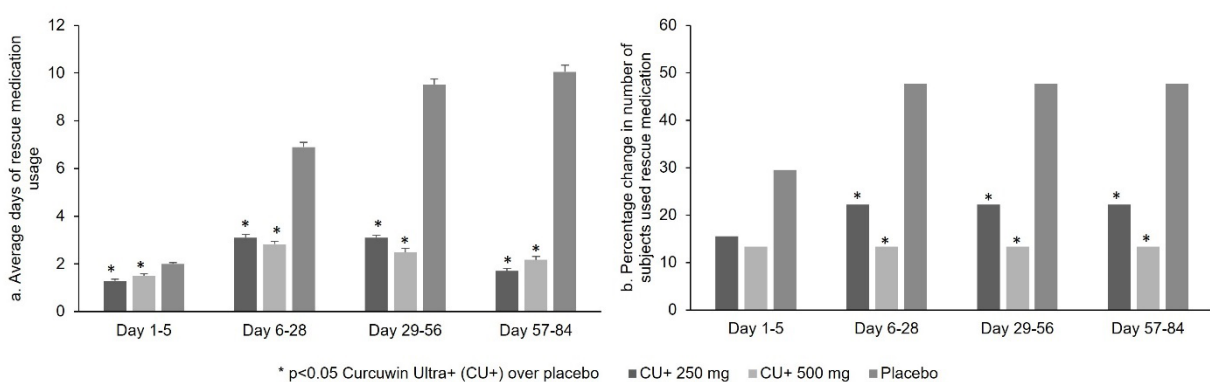


**Figure 5:** Summary of efficacy endpoint results (biomarkers) –Mean change in hsCRP (mg/L) (a), IL-1 $\beta$  (pg/mL) (b), CTX-II (pg/mL) (c), COMP (ng/mL) (d), and MMP3 (ng/mL) (e). \* P-value $<0.05$  CU+ significant over placebo, # P-value $<0.05$  CU+ 500 mg significant over CU+ 250 mg.

### Rescue medication usage and frequency

Between Days 6-28, Days 29-56, and Days 57-84, a significantly lower percentage of subjects using CU+ 250 mg and 500 mg utilised rescue medication than those taking placebo ( $p < 0.05$ ) (Supplementary Table S3a; Figure 6a).

Additionally, compared to the placebo group, subjects in the CU+ 250 mg and 500 mg groups took rescue medication for a significantly smaller number of days on Days 1-5, 6-28, 29-56, and 57-84. (Supplementary Table S3b; Figure 6b).



**Figure 6:** Average days of rescue medication usage (a) and Percentage change in number of subjects used rescue medication (b). \* P-value $<0.05$ . CU+ significant over placebo.

### Safety

The safety analysis set consisted of all subjects who were randomized for the trial and consumed at least one dose of study product. As far as safety is concerned, the composition of CU+ was found to be safe and well-tolerated. A total of 3 subjects reported adverse events, out of which 02 subjects were in the CU+ 500 mg group and 01 subject was in the placebo group. One adverse event (loss of appetite) was possibly related to the CU+ 500 mg group and the remaining 2 adverse events (mouth ulceration and headache) were unrelated to study products.

No severe adverse events were observed, and when occurred were of mild intensity and resolved completely. There were no notable changes in laboratory parameters, vital signs, physical examination, and systemic examination.

### Discussion

Osteoarthritis is a highly debilitating chronic condition of joints associated with inflammation and cartilage damage [2-5].

Current treatment approaches of OA use primarily analgesics and NSAIDs that provide only temporary relief. Curcumin is one of the most popular herbal supplements with widely established biological properties including anti-inflammatory and antioxidant activity and traditionally used for management of OA [20-24]. To overcome the challenges of poor oral bioavailability of curcumin, we developed an improved curcumin formulation that demonstrated 40% faster intestinal absorption and achieved 144 times higher plasma curcuminoids levels in human subjects as compared to 95% turmeric extract. Here we demonstrate that our improved formulation is associated with enhanced efficacy against mild knee OA at both 250 and 500 mg dose with 500 mg performing better than 250 mg dose as measured through widely used OA efficacy parameters.

Widely established WOMAC parameters [49] were used as primary endpoint of efficacy followed by VAS score for determination of relief from pain during CU+ supplementation in subjects with mild OA. We observed that CU+ doses at 250 and 500 mg showed significant ( $p < 0.05$ ) decrease in all WOMAC

parameters as well as VAS pain score on day 28, 56 and 84 as compared to placebo. We believe that WOMAC parameters and VAS pain were significantly improved due to the anti-inflammatory effect of CU+ as was demonstrated by reduced levels ( $p < 0.05$ ) of serum inflammatory biomarkers (hsCRP and IL-1 $\beta$ ) on Day 84. The anti-inflammatory effect of curcumin has been demonstrated previously in human studies with decreased serum concentrations of inflammatory mediators such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, CRP, MMP-3 in response to curcumin supplementation in subjects with knee OA [48,50,51].

Muscle weakness is common in subjects with knee OA and strongly related to the patient-reported outcomes of pain, activity limitations and falls. Muscle strength is the ability to exert a physical force which decreases with age as well as subjects with OA probably due to reduced physical activity [52]. The assessment of muscle strength is extensively used for patient management in OA [53]. Previous studies demonstrate that curcumin not only boosts endurance and muscle strength but also reduced muscle damage possibly due to its antioxidant and anti-inflammatory activity [54]. In the current study we observed significant improvement of knee muscle strength as measured through knee extension and flexion after supplementation with CU+ which further validates previous results where a formulated curcumin at 1000 mg dose improved muscle performance with reduced muscle soreness after the exercise [53]. The improved muscle performance was probably also responsible for improved walking distance in subjects supplemented with CU+ as demonstrated in 6-Minute Walk Test, a sub-maximal exercise test used to assess aerobic capacity and endurance of subjects [52,55,56]. Joint flexibility is critically affected in OA due to pain and stiffness [57,58] and regularly used to assess treatment outcome [57-59]. The reduced pain and stiffness of joints observed in subjects supplemented with CU+ probably due to reduced inflammation may have also helped to improve range of motion in knee flexion for both legs found in our study.

Surrogate molecular biomarkers such as serum levels of cytokines, MMPs, CRP not only play an important role in physiology of OA but also help in patient diagnosis and clinical management [20,59-63]. We observed that CU+ lowered levels of serum hsCRP and IL-1 $\beta$  and cartilage damage biomarker CTX-II, and MMP-3, a proteolytic enzyme responsible for the breakdown of cartilage.

Throughout the study we observed that CU+ supplementation is associated with significant ( $p < 0.05$ ) reduction in the use of rescue medication by subjects at both doses of CU+ as compared to placebo. Further CU+ at both doses was well tolerated and safe throughout the study period with no serious adverse events reported.

Overall, we have observed significantly improved efficacy measures in knee OA subjects supplemented with CU+ which is in line with previous clinical trials where improvement in pain, stiffness, and muscle function was observed after 12 weeks of supplementation with curcumin [26,64,65]. The improved benefits observed in our study with lower doses might be due to the superior bioavailability and faster absorption of curcuminoids in CU+ formulation as compared to regular curcumin extracts [47,66].

Current study is limited by recruitment of study subjects suffering from only mild knee OA and supplementation for 84 days. Further studies are required to understand the scope of supplementation of CU+ in subjects suffering from moderate to severe form of OA and supplementation period beyond 84 days.

## Conclusions

The results of this study demonstrate that CU+ supplementation not only reduces discomfort, but also improves joint mobility, flexibility, and knee muscle strength, resulting in an overall improvement in the quality of life for participants with mild OA. Our results indicate that CU+ reduced serum inflammatory markers, markers of cartilage degradation that are associated with pathophysiology of OA during the study period. Throughout the study CU+ was safe, well-tolerated and reduced the requirement of rescue medication in subjects suffering from mild OA.

## Acknowledgments

We thank the participants of the study.

## Authors' contributions

SKD, NJ, AS & SB contributed to the study design. Study conduct, subject recruitment and data collection were performed at respective study centres by NJ, AS & SB. Study was monitored by SKD in a blinded fashion. Statistical analysis and study report were prepared by SKD. The first draft of the manuscript was written by SKD, NJ, AS & SB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## Funding

The study was supported by OmniActive Health Technologies Limited (Mumbai, India).

## Availability of Data

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article and its supplementary information files.

## Declarations

### Ethics approval and consent to participate

Institutional ethics approval was obtained from 1) Institutional Ethics Committee Sai Sneh Hospital & Diagnostic Centre, Pune, India 2) Magna-Care Ethics Committee, Nashik, India 3) Ethics Committee Ajanta Superspeciality Hospital (EC-ASH), Aurangabad, India. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with the International Conference on Harmonization (ICH), Good Clinical Practice (GCP) Guidelines, as well as in strict compliance with the “The New Drugs and Clinical Trial Rules- 2019”, the Ministry of Health and the Government of India at all stages of the trial for adherence to protocol and compliance with ethical and regulatory guidelines. Voluntary consent was obtained in written from all the study participants before commencing any study related activities. The EC was duly apprised of the progress and updates of the trial at regular intervals as per prescribed guidelines

### Consent for Publication

Not applicable

### Competing Interests

The authors declare that they have no competing interests.

## References

- Loeser RF, Goldring SR, Scanzello CR, Goldring MB (2012) Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum* 64:1697-1707.
- Goldring SR, Goldring MB (2016) Changes in the osteochondral unit during osteoarthritis: structure, function and cartilage–bone crosstalk. *Nat Rev Rheumatol* 12:632-644.
- Pritzker KP, Gay S, Jimenez SA, Ostergaard K, Pelletier JP, et al., (2006) Osteoarthritis cartilage histopathology: grading and staging. *Osteoarthritis Cartilage* 14:13-29.
- Gallagher JA, Ranganath LR, Boyde A (2015) Lessons from rare diseases of cartilage and bone. *Curr Opin Pharmacol* 22:107-114.
- Sophia Fox AJ, Bedi A, Rodeo SA (2009) The basic science of articular cartilage: structure, composition, and function. *Sports Health* 1:461-468.
- Cedraschi C, Delézy S, Marty M, Berenbaum F, Bouhassira D, et al., (2013) “Let’s talk about OA pain”: a qualitative analysis of the perceptions of people suffering from OA. Towards the development of a specific pain OA-related questionnaire, the Osteoarthritis Symptom Inventory Scale (OASIS). *PLoS One* 8:e79988.
- Myers SL, Brandt KD, Ehlich JW, Braunstein EM, Shelbourne KD, et al., (1990) Synovial inflammation in patients with early osteoarthritis of the knee. *J Rheumatol* 17:1662-1669.
- Wenham CY, Conaghan PG (2010) The role of synovitis in osteoarthritis. *Ther Adv Musculoskelet Dis* 2:349-359.
- Favero M, Ramonda R, Goldring MB, Goldring SR, Punzi L (2015) Early knee osteoarthritis. *RMD Open* 1:e000062.
- Allen KD, Thoma LM, Golightly YM (2022) Epidemiology of osteoarthritis. *Osteoarthritis Cartilage* 30:184-195.
- Ravalli S, Roggio F, Lauretta G, Di Rosa M, D’Amico AG, et al., (2022) Exploiting real-world data to monitor physical activity in patients with osteoarthritis: the opportunity of digital epidemiology. *Heliyon* 8:e08991.
- Peshkova M, Lychagin A, Lipina M, Di Matteo B, Anzillotti G, et al., (2022) Gender-related aspects in osteoarthritis development and progression: a review. *Int J Mol Sci* 23:2767.
- Choubey J, Patel A, Verma MK (2013) Phytotherapy in the treatment of arthritis: a review. *Int J Pharm Sci Res* 4:2853.
- Long L, Soeken K, Ernst E (2001) Herbal medicines for the treatment of osteoarthritis: a systematic review. *Rheumatology* 40:779-793.
- Lindler BN, Long KE, Taylor NA, Lei W (2020) Use of herbal medications for treatment of osteoarthritis and rheumatoid arthritis. *Medicines* 7:67.
- Crofford LJ (2013) Use of NSAIDs in treating patients with arthritis. *Arthritis Res Ther* 15:1-10.
- Reginster JY, Dudler J, Blicharski T, Pavelka K (2017) Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONDroitin versus CElecoxib versus Placebo Trial (CONCEPT). *Ann Rheum Dis* 76:1537-1543.
- Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, et al., (2000) Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *JAMA* 284:1247-1255.
- Cameron M, Gagnier JJ, Little CV, Parsons TJ, Blümler A, et al., (2009) Evidence of effectiveness of herbal medicinal products in the treatment of arthritis. *Phytother Res* 23:1497-1515.
- Henrotin Y, Priem F, Mobasheri A (2013) Curcumin: a new paradigm and therapeutic opportunity for the treatment of osteoarthritis: curcumin for osteoarthritis management. *Springerplus* 2:56.
- Zhang Z, Leong DJ, Xu L, He Z, Wang A, et al., (2016) Curcumin slows osteoarthritis progression and relieves osteoarthritis-associated pain symptoms in a post-traumatic osteoarthritis mouse model. *Arthritis Res Ther* 18:128.
- Sun Y, Liu W, Zhang H, Li H, Liu J, et al., (2017) Curcumin prevents osteoarthritis by inhibiting the activation of inflammasome NLRP3. *J Interferon Cytokine Res* 37(10):449-455.
- Chin KY (2016) The spice for joint inflammation: anti-inflammatory role of curcumin in treating osteoarthritis. *Drug Des Devel Ther* 10:3029.
- Shokri-Mashhadi N, Bagherniya M, Askari G, Sathyapalan T, Sahebkar A (2021) A systematic review of the clinical use of curcumin for the treatment of osteoarthritis. *Stud Biomark New Targets Aging Res Iran* 265-282.
- Wahlström B, Blennow G (1978) A study on the fate of curcumin in the rat. *Acta Pharmacol Toxicol (Copenh)* 43:86-92.
- Zeng L, Yu G, Hao W, Yang K, Chen H (2021) The efficacy and safety of Curcuma longa extract and curcumin supplements on osteoarthritis: a systematic review and meta-analysis. *Biosci Rep* 41: BSR20210817.

**Citation:** Jagtap N, Shah A, Bedmutha S, Durairaj SK (2023) Efficacy and Safety of a Highly Bioavailable Curcumin Formulation in Modulating Outcomes of Mild Knee Osteoarthritis: Multi-Centric, Randomized, Double-Blind, Placebo-Controlled Study. *J Orthop Res Ther* 8: 1303. DOI: 10.29011/2575-8241.001303

27. Abe Y, Hashimoto S, Horie T (1999) Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. *Pharmacol Res* 39:41-47.
28. Mathy-Hartert M, Jacquemond-Collet I, Priem F, Sanchez C, Lambert C, et al., (2009) Curcumin inhibits pro-inflammatory mediators and metalloproteinase-3 production by chondrocytes. *Inflamm Res* 58:899-908.
29. Surh YJ, Chun KS, Cha HH, Han SS, Keum YS, et al., (2001) Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: down-regulation of COX-2 and iNOS through suppression of NF- $\kappa$ B activation. *Mutat Res* 480:243-268.
30. Clutterbuck AL, Mobasheri A, Shakibaei M, Allaway D, Harris P (2009) Interleukin-1 $\beta$ -Induced Extracellular Matrix Degradation and Glycosaminoglycan Release Is Inhibited by Curcumin in an Explant Model of Cartilage Inflammation. *Ann N Y Acad Sci* 1171:428-435.
31. Liacini A, Sylvester J, Li WQ, Zafarullah M (2002) Inhibition of interleukin-1-stimulated MAP kinases, activating protein-1 (AP-1) and nuclear factor kappa B (NF- $\kappa$ B) transcription factors down-regulates matrix metalloproteinase gene expression in articular chondrocytes. *Matrix Biol* 21:251-262.
32. Shakibaei M, John T, Schulze-Tanzil G, Lehmann I, Mobasheri A (2007) Suppression of NF- $\kappa$ B activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: implications for the treatment of osteoarthritis. *Biochem Pharmacol* 73:1434-1445.
33. Schulze-Tanzil G, Mobasheri A, Sendzik J, John T, Shakibaei M (2004) Effects of Curcumin (Diferuloylmethane) on Nuclear Factor  $\kappa$ B Signaling in Interleukin-1 $\beta$ -Stimulated Chondrocytes. *Ann N Y Acad Sci* 1030:578-586.
34. Jin Z, Chang B, Wei Y, Yang Y, Zhang H, et al., (2022) Curcumin exerts chondroprotective effects against osteoarthritis by promoting AMPK/PINK1/Parkin-mediated mitophagy. *Biomed Pharmacother* 151:113092.
35. Clutterbuck AL, Allaway D, Harris P, Mobasheri A (2013) Curcumin reduces prostaglandin E2, matrix metalloproteinase-3 and proteoglycan release in the secretome of interleukin 1 $\beta$ -treated articular cartilage. *F1000Res* 2:147.
36. Banik U, Parasuraman S, Adhikary AK, Othman NH (2017) Curcumin: The spicy modulator of breast carcinogenesis. *J Exp Clin Cancer Res* 36:98.
37. Chai Y sen, Chen Y qing, Lin S hui, Xie K, Wang C jiang, et al., (2020) Curcumin regulates the differentiation of naïve CD4+ T cells and activates IL-10 immune modulation against acute lung injury in mice. *Biomed Pharmacother* 125:109946.
38. Yu Y, Shen Q, Lai Y, Park SY, Ou X, et al., (2018) Anti-inflammatory effects of curcumin in microglial cells. *Front Pharmacol* 9:386.
39. Castaño PR, Parween S, Pandey AV (2019) Bioactivity of curcumin on the cytochrome P450 enzymes of the steroidogenic pathway. *Int J Mol Sci* 20:4606.
40. Moutinho MS, Aragao S, Carmo D, Casaca F, Silva S, et al., (2018) Curcumin and rutin down-regulate cyclooxygenase-2 and reduce tumor-associated inflammation in HPV16-transgenic mice. *Anticancer Res* 38:1461-1466.
41. Kuptniratsaikul V, Thanakhumtorn S, Chinswangwatanakul P, Wattanamongkonsil L, Thamlikitkul V (2009) Efficacy and safety of Curcuma domestica extracts in patients with knee osteoarthritis. *J Altern Complement Med* 15:891-897.
42. Kohli K, Ali J, Ansari MJ, Raheman Z (2005) Curcumin: a natural antiinflammatory agent. *Indian J Pharmacol* 37:141-147.
43. Samarghandian S, Azimi-Nezhad M, Farkhondeh T, Samini F (2017) Anti-oxidative effects of curcumin on immobilization-induced oxidative stress in rat brain, liver and kidney. *Biomed Pharmacother* 87:223-229.
44. Padmanaban G, Nagaraj VA (2018) Curcumin From Turmeric as an Adjunct Drug? *Stud Nat Prod Chem* 57:179-202.
45. Tonnesen HH, Karlsen J (1985) Studies on curcumin and curcuminoids. VI. Kinetics of curcumin degradation in aqueous solution. *Z Leb Unters Forsch* 180:402-404.
46. Yallapu MM, Jaggi M, Chauhan SC (2012) Curcumin nanoformulations: a future nanomedicine for cancer. *Drug Discov Today* 17:71-80.
47. Kothapally S, Alukapally S, Nagula N, Maddela R (2022) Superior Bioavailability of a Novel Curcumin Formulation in Healthy Humans Under Fasting Conditions. *Adv Ther* 39:2128-2138.
48. Yabas M, Orhan C, Er B, Tuzcu M, Durmus AS, et al., (2021) A next generation formulation of curcumin ameliorates experimentally induced osteoarthritis in rats via regulation of inflammatory mediators. *Front Immunol* 12:609629.
49. Haroyan A, Mukuchyan V, Mkrtchyan N, Minasyan N, Gasparyan S, et al., (2018) Efficacy and safety of curcumin and its combination with boswellic acid in osteoarthritis: a comparative, randomized, double-blind, placebo-controlled study. *BMC Complement Altern Med* 18:7.
50. Atabaki M, Shariati-Sarabi Z, Tavakkol-Afshari J, Mohammadi M (2020) Significant immunomodulatory properties of curcumin in patients with osteoarthritis; a successful clinical trial in Iran. *Int Immunopharmacol* 85:106607.
51. Kertia N, Asdie AH, Rochmah W, Marsetyawan (2012) Ability of curcuminoid compared to diclofenac sodium in reducing the secretion of cyclooxygenase-2 enzyme by synovial fluid's monocytes of patients with osteoarthritis. *Acta Medica Indones* 44:105-113.
52. de Zwart AH, Dekker J, Lems W, Roorda LD, Van Der Esch M, et al., (2018) Factors associated with upper leg muscle strength in knee osteoarthritis: A scoping review. *J Rehabil Med* 50:140-150.
53. Jäger R, Purpura M, Kerksick CM (2019) Eight weeks of a high dose of curcumin supplementation may attenuate performance decrements following muscle-damaging exercise. *Nutrients* 11:1692.
54. Sahin E, Orhan C, Erten F, Er B, Acharya M, et al., (2021) Next-generation ultrasound curcumin boosts muscle endurance and reduces muscle damage in treadmill-exhausted rats. *Antioxidants* 10:1692.
55. Bennell K, Dobson F, Hinman R (2011) Measures of physical performance assessments: Self-Paced walk test (SPWT), stair climb test (SCT), Six-Minute walk test (6MWT), chair stand test (CST), timed up & go (TUG), sock test, lift and carry test (LCT), and car task. *Arthritis Care Res* 63:S350-370.
56. Shirley PY, Ferreira ML, Duong V, Caroupaoullé J, Arden NK, et al., (2022) Responsiveness of an activity tracker as a measurement tool in a knee osteoarthritis clinical trial (ACTIVE-OA study). *Ann Phys Rehabil Med* 65:101619.

**Citation:** Jagtap N, Shah A, Bedmutha S, Durairaj SK (2023) Efficacy and Safety of a Highly Bioavailable Curcumin Formulation in Modulating Outcomes of Mild Knee Osteoarthritis: Multi-Centric, Randomized, Double-Blind, Placebo-Controlled Study. *J Orthop Res Ther* 8: 1303. DOI: 10.29011/2575-8241.001303

---

57. Kozanoglu E, Basaran S, Guzel R, Guler-Uysal F (2003) Short term efficacy of ibuprofen phonophoresis versus continuous ultrasound therapy in knee osteoarthritis. *Swiss Med Wkly* 133:333-338.
58. Norkin CC, White DJ (2016) Measurement of joint motion: a guide to goniometry. FA Davis.
59. Trăistaru MR, Kamal D, Maria DT, Zorilă MV, Alexandru DO, et al., (2019) Complex evaluation in patients with knee osteoarthritis. *Rom J Morphol Embryol* 60:167-174.
60. Daghestani HN, Kraus VB (2015) Inflammatory biomarkers in osteoarthritis. *Osteoarthritis Cartilage* 23:1890-1896.
61. Felson DT (2006) Osteoarthritis of the knee. *N Engl J Med* 354:841-848.
62. Mobasher A (2012) Osteoarthritis year 2012 in review: biomarkers. *Osteoarthritis Cartilage* 20:1451-1464.
63. Munjal A, Bapat S, Hubbard D, Hunter M, Kolhe R, et al., (2019) Advances in Molecular biomarker for early diagnosis of Osteoarthritis. *Biomol Concepts* 10:111-119.
64. Madhu K, Chanda K, Saji MJ (2013) Safety and efficacy of Curcuma longa extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial. *Inflammopharmacology* 21:129-136.
65. Wang Z, Jones G, Winzenberg T, Cai G, Laslett LL, et al., (2020) Effectiveness of Curcuma longa Extract for the Treatment of Symptoms and Effusion–Synovitis of Knee Osteoarthritis: A Randomized Trial. *Ann Intern Med.* 173:861-869.
1. Rai D, Morde A, Padigar M, Acharya M (2022) Superior Pharmacokinetic Profile of an Innovative, Next Generation Curcumin Formula. *FASEB J* 36.