European Journal of Integrative Medicine 79 (2025) 102531

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.sciencedirect.com/journal/european-journal-of-integrative-medicine

Efficacy and safety investigation of LIMAN technology based curcumin formulation on knee osteoarthritis: a randomized double-blind placebo-controlled trial☆

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ARTICLE INFO

Keywords:
Curcuminoids
LIMAN
Maxicuma
Osteoarthritis
Treadmill and Functional improvement

ABSTRACT

Introduction: Knee osteoarthritis is the most common and extensively studied form of osteoarthritis, with varying prevalence reported across studies. Although the presentation of knee osteoarthritis can differ among individuals, it typically manifests as joint pain, stiffness, and restricted mobility, often accompanied by muscle weakness and balance issues. The present clinical study aimed to evaluate the safety and efficacy of Maxicuma®, a highly bioavailable form of curcumin, made from ethanolic extract of turmeric, at two different doses in reducing the symptoms and improving the functional status in individuals with knee osteoarthritis.

Methods: A total of 180 subjects with knee osteoarthritis as per NICE criteria were recruited into the study and severity of either Grade II or Grade III was assessed by radiographic analysis as per Kellgren-Lawrence (KL) scale. Participants received a daily single dose of either placebo, Maxicuma 100 or Maxicuam 250 per day for 90 days. Efficacy was assessed using WOMAC (Western Ontario and McMaster Universities Arthritis Index), VAS (Visual analog scale) and treadmill walk test to understand severity, intensity of pain and physical performance respectively, at day 30, day 45, day 60 and day 90.

Results: The test item was well tolerated with no major adverse events reported. A total of 180 and 174 subjects were considered for intention-to-treat and per-protocol analysis, respectively. Both doses of Maxicuma® demonstrated statistical significance ($p < 0.05$) compared to placebo starting from day 30 across all efficacy measures.

Conclusion: Findings from this clinical study indicate that Maxicuma® 100 mg and 250 mg are effective and well-tolerated supplement options for managing knee osteoarthritis. Both dosages showed potential in improving clinical symptoms and enhancing functional outcomes.

1. Introduction

Osteoarthritis (OA) is the most common degenerative joint disease affecting the aging population worldwide. According to a 2019 estimate by the World Health Organization (WHO) estimates that 240 million individuals globally suffer from symptomatic osteoarthritis, with prevalence rates of 10 % in men and 18 % in women aged 60 and older. The Global Burden of Disease (GBD) study reported an age-standardized

Abbreviations: BMI, Body mass index; CTRI, Clinical trial registry of India; GCP, Good clinical practices; ICH, International council for harmonisation; KL scale, Kellgren-Lawrence scale; LIMAN, Lipid matrix nanotechnology; Nf-kB, Nuclear factor kappa B; OA, Osteoarthritis; TNF, Tumor necrosis factor; VAS, Visual analog scale; WHO, World health organization; WOMAC, Western ontario and McMaster universities arthritis index.

☆ Clinical trial registration CTRI/2023/04/052,147.

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https://doi.org/10.1016/j.eujim.2025.102531
Received 20 November 2024; Received in revised form 23 July 2025; Accepted 25 July 2025
Available online 25 July 2025

point prevalence and annual incidence rate of symptomatic OA as 3754.2 and 181.2 per 100,000 respectively [1] Knee osteoarthritis is the most prevalent and extensively studied form of OA, with a wide range of prevalence reported in various studies. The GBD 2010 study estimated the global prevalence of knee OA at 3.8 %, with a higher rate in females (4.8 %) compared to males (2.8 %) [2] In India, epidemiological studies have shown a significant rise in OA cases-inform 23.46 million in 1990 to 62.35 million in 2019. The age-standardized prevalence rate also increased from 4895 (95 % uncertainty interval (UI):4420–5447) in 1990 to 5313 (95 %UI:4799–5898) in 2019, per 100,000 persons [3] The prevalence of knee OA in India was reported to be 28.7 % of all the OA cases [4]

OA is a condition that affects both the morphology and physiology of the entire joint. It results from a complex interplay of risk factors including age (>45 years), female sex, obesity, anatomical factors, muscle weakness, and joint injury [5] The disease process involves an upregulation of pro-inflammatory markers and proteases, leading to degeneration of the joint. Although the exact pathway of degeneration is unknown, early changes typically affect the articular cartilage, resulting in surface fibrillation, irregularity, and focal erosions. These progress to involve deeper layers and larger areas of the joint surface. After cartilage injury, the damaged collagen matrix promotes the proliferation of chondrocytes that leads to the formation of clusters. As more collagen matrix is damaged, chondrocytes undergo apoptosis [6] Poorly mineralized collagen contributes to subchondral bone thickening, bone cysts in advanced disease, and bony erosions in erosive OA. In its late stages, OA is characterized by synovial inflammation and hypertrophy, affecting soft-tissues such as ligaments and joint capsules [7]

Though symptom severity varies, knee OA commonly presents with joint pain, stiffness, and locomotor restriction with muscle weakness and balance issues as additional symptoms. Pain is typically activity-related and subsides with rest. As OA progresses, individuals tend to rest more to alleviate discomfort, leading to increased functional limitations. Candidates may also experience bony swelling, joint deformity, and instability, indicative of underlying muscular weakness [8]

Turmeric, a rhizomatous herbaceous perennial plant, has been utilized for centuries for its medicinal properties. The active chemical moieties of turmeric are collectively called curcuminoids, which principally include three main compounds viz, curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Curcumin, known (chemically) as 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione and also as diferuloylmethane, is the principal natural polyphenol found in the rhizome of *Curcuma longa* [9] Traditionally curcumin has been used across Asia for its antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties [10,11] Recent studies have focused on understanding its bioactive components and mechanisms of action, particularly its anti-inflammatory and antioxidant roles..

Cellular oxidative stress acts as both a cause and consequence of inflammation. Inflammatory cells release reactive species at inflammation sites, leading to oxidative stress, highlighting the connection between oxidative stress and inflammation. These reactive oxygen/nitrogen species activate intracellular signaling cascades, enhancing pro-inflammatory gene expression- an important mechanism in the pathogenesis of chronic diseases like OA. Tumor Necrosis Factor-alpha (TNF-α) is a key pro-inflammatory mediator regulated by the nuclear factor-kappa B (NF-κB) signaling pathway [12] TNF-α is the most potent NF- κB activator, which is also stimulated by other inflammatory cytokines. Curcumin has been identified as a potent down regulator of NF- κB and –its down stream gene products. It also has been shown to suppress NF- κB activation triggered by various inflammatory stimuli [13]

Numerous clinical trials have investigated the anti-inflammatory effects of curcumin in the management of OA. A systematic review and meta-analysis of such clinical trials concluded that curcumin, administered at doses around 1000 mg/day for duration of 8 −12 weeks, can reduce the symptoms of various arthritic conditions, particularly pain and inflammation-related symptoms. Its effects were found to be comparable to those of standard non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and diclofenac sodium. These findings suggest that turmeric extracts and curcumin can be recommended for relief of arthritis symptoms, especially in OA, based on robust scientific evidence [14]

Although several phase 1 clinical trials reported that curcumin is safe even at the high doses (up to 12 *g*/day), its clinical efficacy is often limited by poor bioavailability. This limitation is primarily attributed to its poor absorption, rapid metabolism and systemic elimination. Numerous attempts have been made to overcome these challenges and enhance the bioavailability of the curcumin [15]

The present clinical study was designed to evaluate the clinical efficacy of Maxicuma® in reducing the symptoms of knee OA and improving the functional outcomes in affected individuals. Additionally, the study aimed to explore the dose-dependent effects of Maxicuma® by assessing two different strengths: 100 mg and 250 mg.

2. Methods

2.1. Study design and ethical approval

The study was designed as randomized, double blind, placebo controlled, three arm, parallel- group clinical trial involving subjects with knee OA. Participants of both sexes were recruited across four independent clinical sites.. The study protocol was approved by a registered Institutional Ethics Committee (DCGI Reg. No. ECR/141/Indt/KA/2013/RR-19). The participants who gave voluntary informed consent were recruited into the study. The study was registered in clinical trial registry of India (CTRI Number: CTRI/2023/04/052,147) and was conducted in accordance with the International Council for Harmonisation (ICH)- and Good Clinical Practice (GCP) guidelines and the ethical principles stated in the Declaration of Helsinki. The total study duration was approximately 97 days, comprising a 7 days of pre-dose (screening) and 90 days of dosing. Subjects were required to visit the clinical site during the screening period (Day −7 to Day 0), for baseline assessments and randomization on day 1, and for follow-up visits on day 30 ± 2, day 45 ± 2, day 60 ± 2, and the end-of-study visit on day 90 ± 2.

2.2. Sample size calculation

Based on the evidence from the previous placebo-controlled studies conducted to evaluate the effects of curcumin extracts on knee OA, reported a mean difference of reduction of 2.04 on pain VAS scores. The same was considered as allowable difference between the groups. Assuming the standard deviation (SD) of 2 and placebo superiority margin of 1 and a dropout rate of ≈20 %, a sample size of 60 subjects per group/arm was determined to achieve the power of 80 % at a 5 % significance level.

A total of 180 subjects were enrolled in the study and randomized to all the arms in 1:1:1 ratio. (i.e. 60:60:60).

2.3. Study participants

Subjects with a known history of OA and who were consulting the clinical study sites were screened as per the requirements of the study. Screening assessments included the collection of demographic and anthropometric data, medical and surgical history, medication history details. Subjects underwent general physical examination, vitals examination for any clinically significant abnormality. In addition, a questionnaire was used to screen for seasonal or viral flu symptoms. The status and grading of OA were confirmed through radiological examination. And finally blood and urine samples were collected for laboratory investigations that include hematological evaluation, liver and renal function tests, urine analysis and serological tests. Women of childbearing potential were assessed for their reproductive status and

underwent a urine pregnancy test.

Eligible volunteers of either sex aged between 45 and 65 (both inclusive) with unilateral or bilateral knee OA as per NICE criteria [16] and with radiographically confirmed Grade II and Grade III OA according to the Kellgren-Lawrence (KL) scale were included in the study [17–20]

In addition, participants were required to have VAS score between 40 and70 on scale of 0–100 mm indicating mild to moderate pain that was either not adequately or completely controlled with anti-inflammatory drugs or were drug naïve. Subjects willing to refrain from using ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs (NSAIDS) for the duration of trial were considered. However, paracetamol was permitted as a rescue medication, if necessary, as per the discretion of the study physician.

Exclusion criteria included known allergy to NSAIDs (including aspirin), allergic to turmeric and its derivatives, history of inflammatory arthropathy, RA, gout, systemic lupus erythematosus (SLE), bleeding/clotting disorders or any other systemic disorder affecting the joints. Subjects scheduled for a surgery during the trial period, recent injury to the knee with OA, any significant systemic or psychiatric abnormality adjudged by the investigator, alcohol consumption (>2 standard drinks per day) or use of recreational drugs (such as cocaine, methamphetamine, marijuana, etc.) were also excluded. Lactating and pregnant women were not eligible. Participation in any other clinical trials within 30 days prior to the screening visit were excluded and also were those currently taking corticosteroids, indomethacin, glucosamine + chondroitin, or hyaluronic acid or omega-3 fatty acids supplements. Additionally, any condition deemed unsuitable by the investigator was considered as a basis for exclusion from the study.

2.4. Study interventions and randomization

Maxicuma® was made from ethanolic extract of turmeric (*Curcuma longa* L.), standardized to 95 % curcuminoids by high pressure liquid chromatography (HPLC), using green ethanol obtained from sugarcane molasses. The 95 % curcuminoid extract was subjected for patent pending lipid matrix nanotechnology (LIMAN technology), wherein curcuminoid mixture was encapsulated with acceptable excipients to protect from first pass metabolism. Following formulation, the curcuminoid concentration was brought down to 40 % by HPLC comprising approximately 36–42 % of curcumin, 2–4 % demethoxycurcumin and 0–1 % of bisdemethoxycurcumin in the final product, Maxicuma® (B. No: N032300038) [21,22]

The study subjects were equally randomized to either Maxicuma® 250 mg or Maxicuma® 100 mg or placebo as per the predefined randomization schedule. Each test capsule contains Maxicuma® 50 mg or 125 mg and inactive excipients. While each placebo capsule contains inactive excipients without any Maxicuma®. All capsules were identical in appearance, size, and shape to ensure blinding. Participants were instructed to take two capsules once daily after breakfast. Study interventions were dispensed on the day of randomization, day 30 and day 60 of the study to facilitate the documentation of compliance adherence.

Randomization numbers and it's associated test items were assigned sequentially according to the randomization schedule prepared using SAS version 9.4. The unblind pharmacist blinded the samples by removing the product label and adhered a blinded label according to the randomization code. This randomization code was exclusively made available to the unblind pharmacist, ensuring that both the investigators and participants remained unaware of test item allocations. Although investigator had the privilege to unblind individual subject assignments in the event of a clinical emergency (via telephonic/written request), no such unblinding happened during the study.

2.5. Study assessments

2.5.1. Intensity of pain assessed through pain visual analog scale (pain VAS 0–100 mm)- [23]

The pain visual analog scale (pain VAS 0–100 mm) was used to assess the primary endpoint of the study. It is a subjective scale to assess the intensity of the pain. The study subjects were asked to rate the intensity of the pain on a horizontal scale of 0–100. The pain intensity was truncated with '0-no pain, 100- worst pain ' with decrease in scores indicating reduction of pain intensity and vice versa.

2.5.2. Western Ontario and McMaster universities arthritis index (WOMAC) [24]

The WOMAC Index is a widely used, self-administered questionnaire designed to assess the severity of hip and knee OA.It consists of 24 items divided into 3 subscales as below:

- Ø Pain (5 items): Pain experienced during walking, using stairs, in bed, sitting or lying, and standing upright.
- Ø Stiffness (2 items): Stiffness after sleep in the morning and later in the day.
- Ø Physical Function (17 items): Difficulty experienced while using stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on / off toilet, heavy domestic duties, light domestic duties.

Both VAS and WOMAC assessments were performed on all the scheduled study visits. The baseline and the end of the study evaluations were used as the primary outcome measures.

2.5.3. Treadmill walk test

As an objective measure of physical performance, a treadmill walk test was included. The test evaluated the maximum distance a participant could walk without experiencing pain, on a treadmill set at a speed of 3 km/h and an incline of 10 % [25,26] The participants were familiarized with the procedure during the screening visit. They were instructed to walk "as far as possible" without jogging or running. The test was terminated when the participant reported the onset of pain, and the distance walked was recorded. This test served as a surrogate measure of functional capacity in individuals with knee OA.

2.6. Safety assessment

Along with study specific tests, regular haematology, biochemistry, urinalysis and serology were performed during screening. Vitals and adverse events were recorded during all the interim visits. As a part of post study safety assessment, haematology, liver function tests and renal function tests were conducted and adverse events were recorded throughout the study duration.

2.7. Statistical analysis

An individual subject specific dosing compliance of ≥ 80 % was considered acceptable for inclusion in the efficacy evaluation and statistical analysis. ANOVA (analysis of variance) for independent means was used to evaluate the variance among all the study arms and followed by a post-hoc Tukey's HSD (honest significant difference) to evaluate the significant difference among paired comparisons of study arms. Additionally, the student's *t*-test for independent measures was used as applicable, to evaluate the differences between active study arms. A *p*-value of less than 0.05 was considered statistically significant.

Subjects who have completed the dosing without any major protocol deviations and with a dosing compliance of at least ≥ 80 %, were considered for per-protocol (PP) population and whereas all the randomized subjects i.e., 180 were considered for intention-to-treat (ITT)

analysis by considering LOCF (last observation carried forward) for missing values.

3. Results

3.1. Study population

Out of the 180 eligible subjects who were randomized, 5 subjects dropped out before study completion and were considered lost to follow-up. One subject was excluded from the statistical evaluation as the subjects' age did not meet the inclusion criteria. Therefore, 174 subjects were considered per-protocol (PP) population and whereas 180 subjects were considered ITT analysis. The schematic representation of subject disposition and the study design has been provided in the flowchart as Fig 1.

The mean age of the per-protocol subjects was found to be 52.52 ± 5.69 years and comprised 75 male subjects and 99 female subjects. In PP population, 105 subjects were found to have Grade III OA and 69 subjects found to have Grade II OA. Whereas in ITT population, 71 and 109 subjects were found to have Grade II OA and Grade III OA, respectively as per the KL grade. The demographic characteristics of the study subjects across the groups were not statistically significant for anyaspect including age ($p = 0.68$), body weight ($p = 0.18$), height ($p = 0.14$), BMI ($p = 0.86$). This suggests that all the study groups were comparable with respect to demographic characteristics at baseline level as mentioned in Table 1. The data pertained to PP population was mentioned under Appendix (Fig A.1-Fig A.7 and Table A.1) and data of ITT is below.

Table 1
Baseline characteristics of ITT subjects.

Parameter	Placebo	Maxicuma 100	Maxicuma 250	p value for comparison of groups
Number of subjects	60	60	60	NA
Male	24	22	31	
Female	36	38	29	
Age in years (Mean±SD)	53.1 ± 6.1	52.2 ± 5.0	52.5 ± 6.0	0.68
Height in cms (Mean±SD)	162.39 ± 5.34	164.09 ± 6.11	163.30 ± 4.97	0.14
Body weight in Kgs (Mean ±SD)	70.42 ± 5.61	72.11 ± 6.61	70.96 ± 6.24	0.18
Grade II	21	27	23	NA
Grade III	39	33	37	
VAS (Mean±SD)	58.8 ± 6.5	58.3 ± 6.6	58.3 ± 7.0	0.87
Total WOMAC (Mean±SD)	33.2 ± 8.8	32.4 ± 8.8	33.1 ± 8.4	0.94
Total distance travelled (Mean±SD)	117.15 ± 40.25	118.84 ± 40.42	113.95 ± 34.82	0.70

*p- values derived from ANOVA; NA: Not applicable.

3.2. Outcome measures

3.2.1. Visual analog scale

The mean VAS scores at baseline were found to be 58.8 ± 6.5 for placebo, 58.3 ± 6.6 for Maxicuma 100 and 58.3 ± 7.0 for Maxicuma 250. The difference among the groups was not statistically significant ($p = 0.87$). The mean VAS scores of the study groups at the end of the study were found to be 46.2 ± 7.6 for placebo, 18.2 ± 9.5 for Maxicuma 100 and 12.7 ± 5.7 for Maxicuma 250. The data is presented in Fig 2 (represented as mean±SD; ***$p \leq 0.0001$ vs Placebo; ##$p \leq 0.01$; ###$p \leq 0.001$ vs 100 mg). The relative change in VAS scores from baseline to the end of the study was statistically significant with both the active groups of the study, Maxicuma 250 vs placebo ($p < 0.0001$) and Maxicuma 100 vs placebo ($p < 0.0001$). This indicates that both active groups were

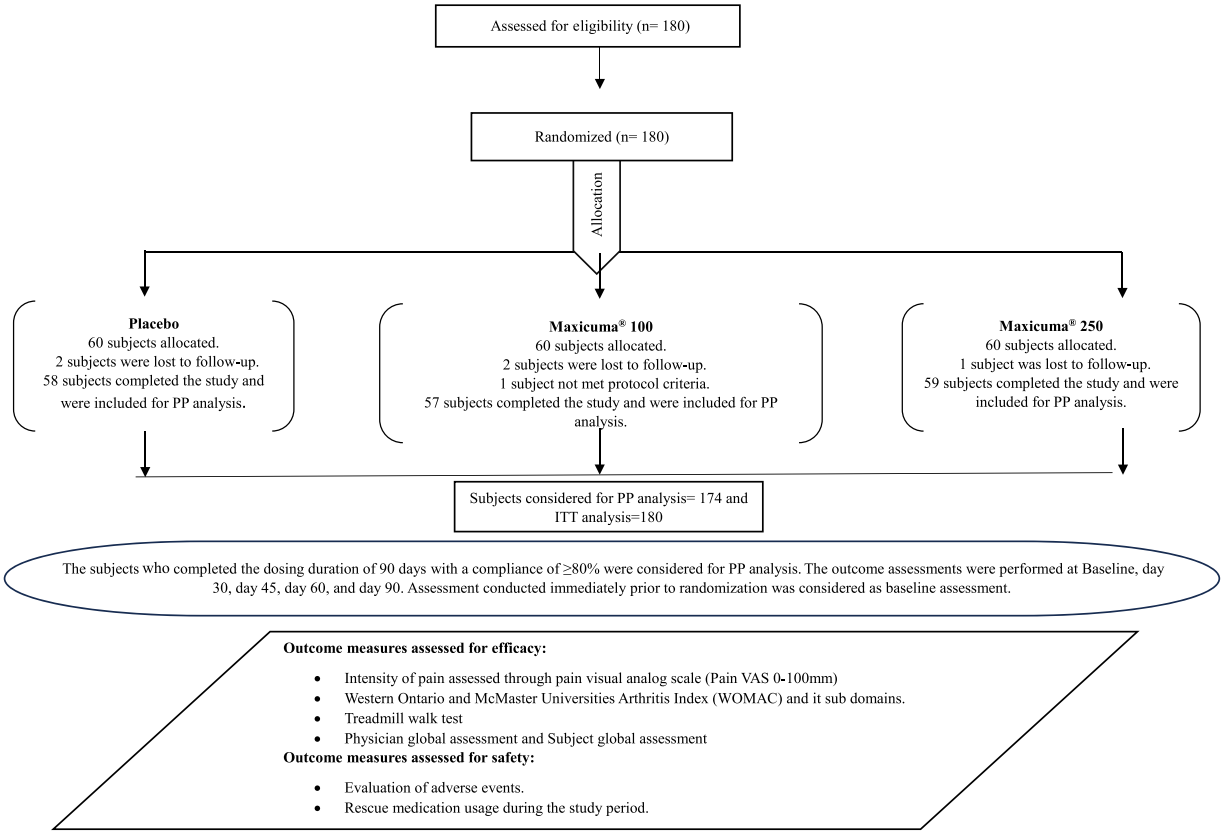

Fig. 1. Flowchart for subject disposition and study design.

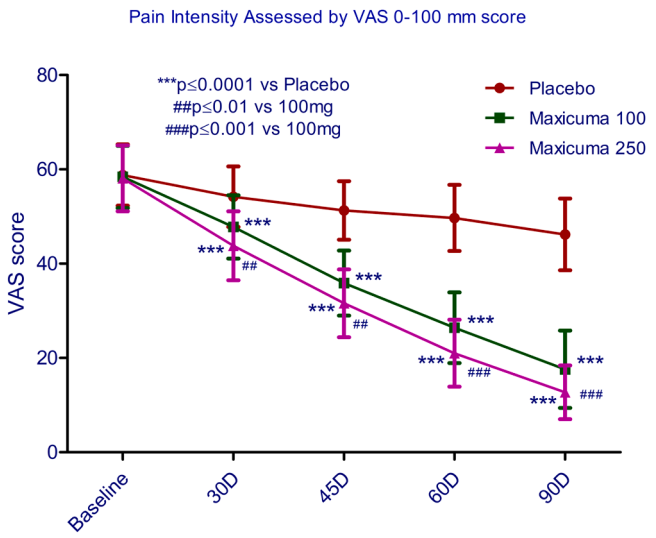

Fig. 2. Changes in pain intensity assessed by visual analogue scale (VAS) on 0–100 mm Score.

superior to placebo in reducing VAS scores.

The VAS score reduction effect with both the doses of Maxicuma was statistically significant ($p \leq 0.0001$) and evident from Day 30. A gradual, dose-dependent reduction in VAS scores was observed throughout the study. Among the active groups, Maxicuma 250 resulted in the lower VAS score than Maxicuma 100 by the end of the study. This implies that Maxicuma 250 mg is effective among the used study doses in reducing the VAS scores.

3.2.2. *Western Ontario and McMaster universities arthritis index*

3.2.2.1. Western Ontario and McMaster universities arthritis Index- overall scores. The mean WOMAC overall scores at baseline were found to be 33.2 ± 8.8 for placebo, 32.4 ± 8.8 for Maxicuma 100 and 33.1 ± 8.4 for Maxicuma 250 and the difference between the groups was not statistically significant ($p = 0.94$). The mean WOMAC overall scores of the study groups at the end of the study were found to be 26.9 ± 6.2 for placebo, 10.0 ± 5.9 for Maxicuma 100 and 6.9 ± 3.4 for Maxicuma 250. The data was presented in Fig 3 (represented as mean±SD; $^{**}p \leq 0.001$; $^{***}p \leq 0.0001$ vs Placebo; $\#p \leq 0.05$ vs 100 mg; $\#\#p \leq 0.01$ vs 100 mg). The relative change in WOMAC overall scores from baseline to the end of the study was statistically significant with both the active groups of the study, Maxicuma 250 mg vs placebo ($p \leq 0.0001$) and Maxicuma 100 mg vs placebo ($p \leq 0.0001$). This infers that both the active groups are superior to placebo in terms of reducing WOMAC overall scores. The WOMAC overall score reduction effect of both the active groups when compared to placebo was statistically significant ($p \leq 0.001$) and prominent from the day 30 of the dosing.

The active groups of the study did not differ much in their WOMAC overall score reduction effect up to day 30 ($p = 0.34$). However, from day 45 onwards, Maxicuma 250 showed significantly better outcomes than Maxicuma 100.

3.2.2.2. Western Ontario and McMaster universities arthritis index - pain domain scores. The mean WOMAC pain domain scores at the baseline was found to be 6.7 ± 2.2 for placebo, 6.6 ± 2.2 for Maxicuma 100 and 6.7 ± 2.1 for Maxicuma 250 and the difference was not statistically significant ($p = 0.99$) between the groups. The mean WOMAC pain domain Scores of the study groups at the end of the study were found to be 6.0 ± 1.5 for placebo, 2.6 ± 1.2 for Maxicuma 100 and 2.0 ± 0.7 for Maxicuma 250. The data is presented in Fig 4 (represented as mean±SD; $^{***}p \leq 0.0001$, $^{**}p \leq 0.001$ vs placebo; $\#p \leq 0.05$ vs 100 mg; $\#\#p \leq 0.01$ vs 100 mg). The relative decrease in WOMAC pain domain scores from baseline to the end of the study was statistically significant with both the active groups of the study, Maxicuma 250 mg vs placebo ($p < 0.0001$) and Maxicuma 100 mg vs placebo ($p < 0.0001$). This infers that both the active groups are superior to placebo in terms of reducing WOMAC pain domain scores. The WOMAC-pain domain score reduction effect of both the active groups when compared to placebo was statistically significant ($p < 0.0001$) and prominent from the day 30 of the study. The active groups of the study did not differ statistically much in their WOMAC pain domain score reduction effect up to day 30. However, statistically significant differences were observed between the active groups in the favour of Maxicuma 250 from day 45.

3.2.2.3. Western Ontario and McMaster universities arthritis index - stiffness domain scores. The mean WOMAC stiffness domain scores across the arms at the baseline was found to be 2.7 ± 0.8 for placebo, 2.6 ± 0.80 for Maxicuma 100 and 2.7 ± 0.8 for Maxicuma 250 and the difference was not statistically significant ($p = 0.84$). The mean WOMAC stiffness domain Scores of the study arms at the end of the study were found to be 1.5 ± 0.5 for placebo, 0.5 ± 0.6 for Maxicuma 100 and 0.1 ± 0.3 for Maxicuma 250 capsules. The data has been presented in Fig 5 (Data was represented as mean±SD; $^{**}p \leq 0.001$; $^{***}p \leq 0.0001$ vs placebo; $\#\#\# p \leq 0.001$ vs 100 mg). The relative decrease in WOMAC Stiffness domain scores from baseline to the end of the study was statistically significant with both the active arms of the study, Maxicuma

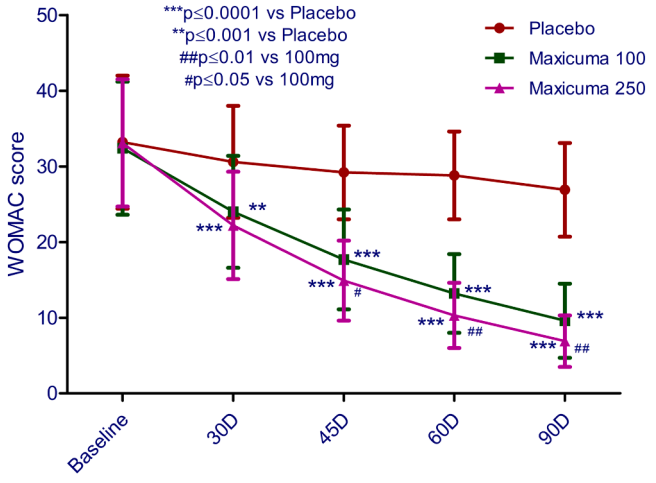

Fig. 3. Summary of changes in Western Ontario and McMaster Universities Arthritis Index (WOMAC) Total Scores.

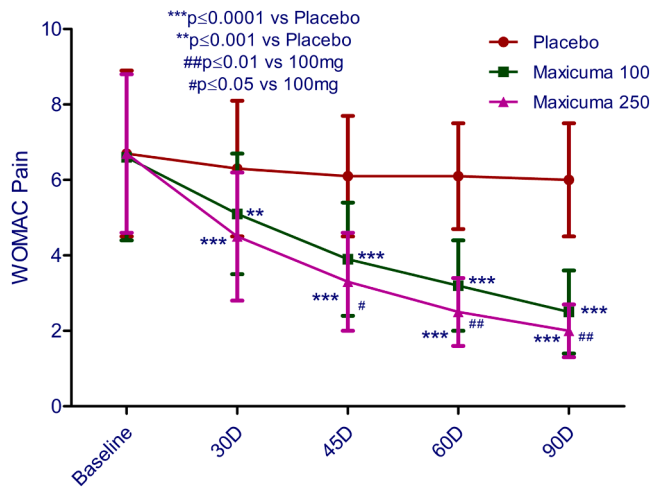

Fig. 4. Summary of changes in WOMAC pain domain scores.

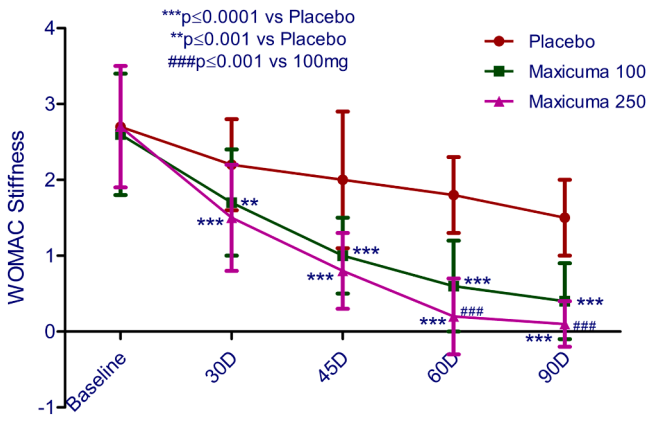

Fig. 5. Summary of changes in WOMAC stiffness domain scores.

250 mg vs placebo ($p < 0.0001$) and Maxicuma 100 mg vs placebo ($p < 0.0001$). This infers that both the active arms are superior to placebo in terms of reducing WOMAC Stiffness domain scores. The WOMAC-stiffness domain score reduction effect of both the active arms when compared to placebo was statistically significant ($p < 0.001$) and prominent from the day 30 of the study. The active groups of the study did not differ much in their WOMAC stiffness domain score reduction effect up to dosing day 45 ($p = 0.13$). However, statistically significant differences were observed between the active groups in the favour of Maxicuma 250 from day 60.

3.2.2.4. Western Ontario and McMaster universities arthritis Index- physical function domain score. The mean WOMAC physical function domain scores at the baseline were found to be 23.8 ± 6.1 for placebo, 23.2 ± 6.1 for Maxicuma 100 and 23.7 ± 5.7 for Maxicuma 250 and the difference was not statistically significant ($p = 0.92$) between the groups. The mean WOMAC physical function domain scores of the study groups at the end of the study were found to be 19.4 ± 4.7 for placebo, 7.0 ± 4.4 for Maxicuma 100 and 4.9 ± 2.6 for Maxicuma 250 capsules. The data is presented in Fig 6 (Data was represented as mean±SD; *** $p \leq 0.0001$ vs placebo; # $p \leq 0.05$ vs 100 mg). The relative decrease in WOMAC-physical function domain scores from baseline to the end of the study was statistically significant with both the active groups of the study, Maxicuma 250 mg vs placebo ($p < 0.0001$) and Maxicuma 100 mg vs placebo ($p < 0.0001$). This infers that both the active groups are superior to placebo in terms of reducing WOMAC- physical function domain scores. The WOMAC-physical function domain score reduction effect of both the active groups when compared to placebo was statistically

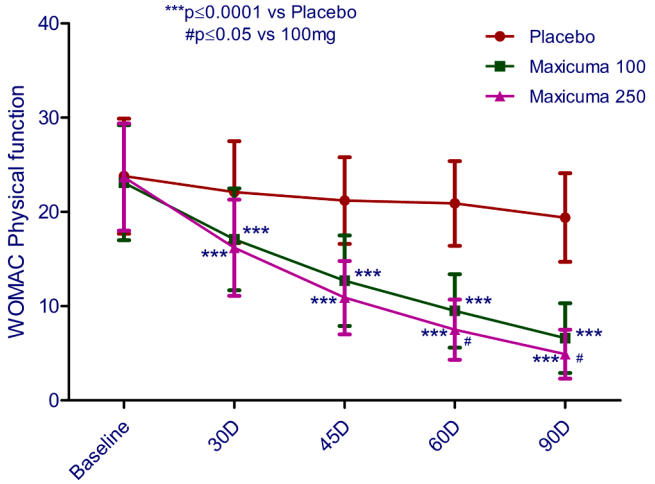

Fig. 6. Summary of changes in WOMAC physical function domain scores.

significant ($p \leq 0.0001$) and prominent from day 30. The active groups of the study did not differ much in their WOMAC physical domain score reduction effect up to dosing day 45 ($p = 0.055$). However, statistically significant difference was observed between the active groups in favour of Maxicuma 250 from dosing day 60.

3.3. Treadmill walk test distance (in meters)

The mean treadmill walk test distances at baseline were found to be 117.15 ± 40.25 m for placebo, 118.84 ± 40.42 m for Maxicuma 100 and 113.95 ± 34.82 m for Maxicuma 250 and the difference was not statistically significant ($p = 0.70$) between the groups. The mean treadmill walk test distances of the study groups at the end of the study were found to be 125.93 ± 65.72 m for placebo, 227.12 ± 64.20 m for Maxicuma 100 and 262.54 ± 57.62 m for Maxicuma 250. The data is presented in Fig 7 (represented as mean±SD; ***$p \leq 0.0001$ vs placebo; # $p \leq 0.05$ vs 100 mg). The relative increase in treadmill walk test distance from baseline to the end of the study was statistically significant with both active groups of the study, Maxicuma 250 mg vs placebo ($p < 0.0001$) and Maxicuma 100 mg vs placebo ($p < 0.0001$). This implies that both the active arms are superior to placebo. The improvement effect of both the active groups when compared to placebo was statistically significant ($p \leq 0.0001$) and evident from the day 30 of the study. The active arms of the study did not differ much in their treadmill walk test distance improvement effect up to dosing day 60. However, statistically significant difference was observed between the active groups in favour of Maxicuma 250 by the end of the study.

3.4. Safety and tolerability

During the study, the rescue medication of paracetamol was used by two placebo subjects and four subjects each in 100 and 250 dose groups. The adverse events observed viz.,.nausea, bloating, headache, gastritis, vomiting and abdominal pain, with test products were similar in duration against placebo (Table 2 and Table A.2) and none of the subjects were observed with any clinically significant changes in the post study assessment although all the groups have compliance percentage of ≥99 %.

3.5. Comparison of efficacy by osteoarthritis grade

In KL Grade II OA, the differences in efficacy between Maxicuma 250 and 100 mg were not statistically significant. In KL Grade III OA, Maxicuma 250 was significantly more effective than 100 mg across all subjective measures (Fig. 8).

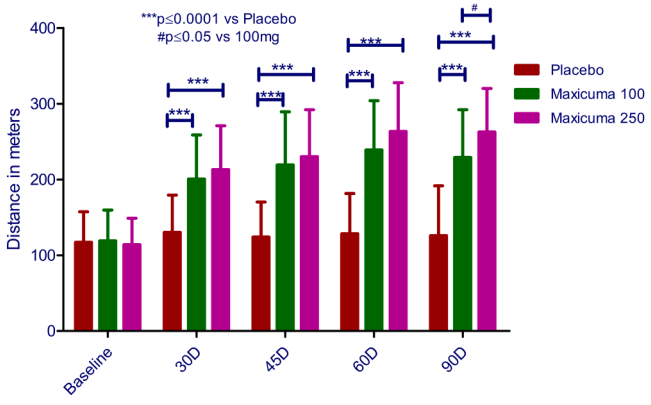

Fig. 7. Summary of changes in distance traversed on Treadmill walk test (in meters).

Table 2
Adverse events reported during the study.

	Placebo	Maxicuma® 100	Maxicuma® 250
Number of subjects reporting adverse events	3	7	5

3.6. Global assessment

The physician's and subject's global assessments (scale 1–5, poor to very good) as shown in Table 3, indicated a clear preference for Maxicuma 250 mg.

4. Discussion

Osteoarthritis, the most common form of arthritis, affects 12 % of the population and continues to rise due to aging and obesity. Hip and knee

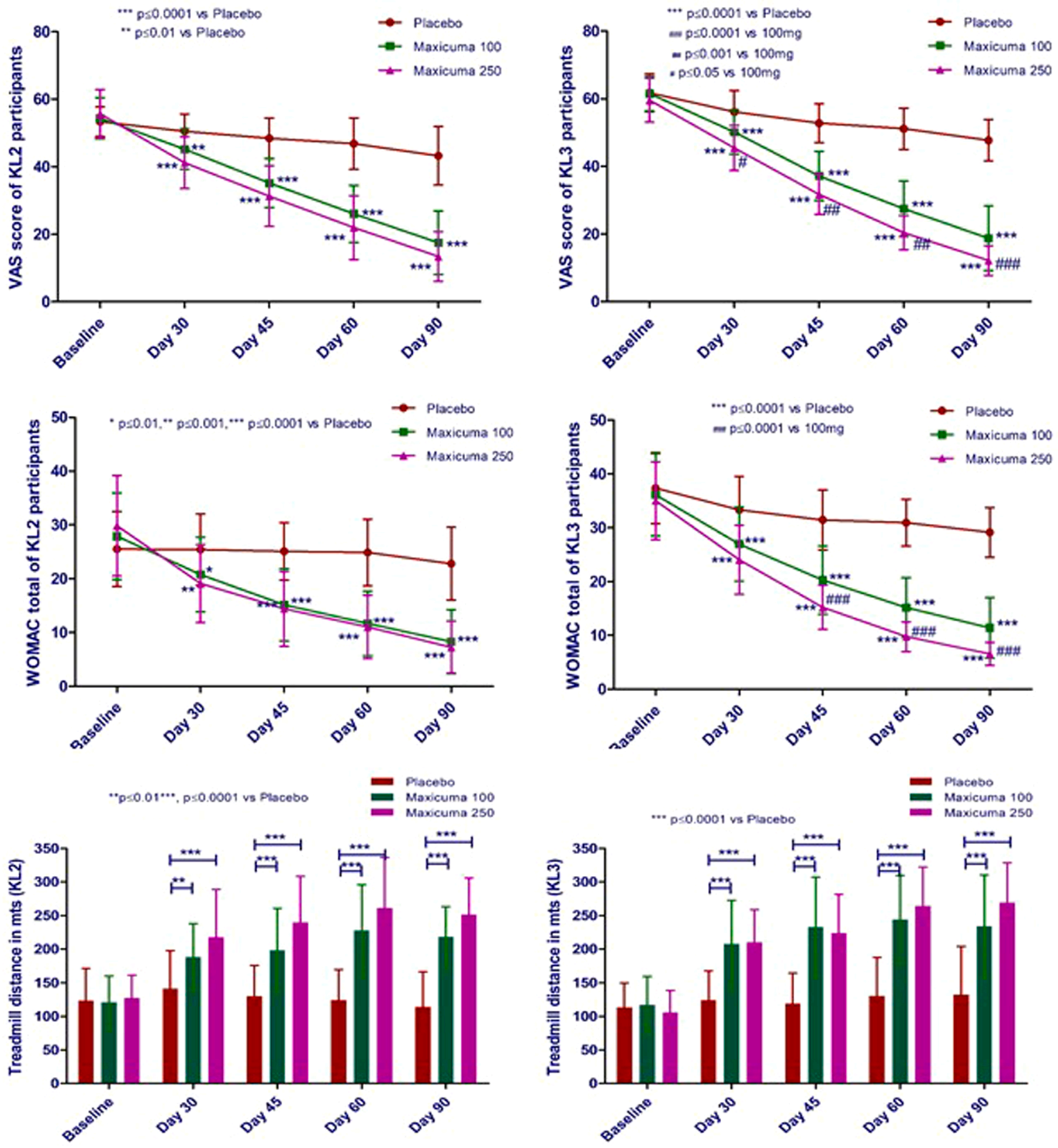

Fig. 8. Comparative assessment of Maxicuma 100 and Maxicuma 250 in KL2 and KL3 grades.

Table 3
Subject's and physician's global assessment.

Global assessment scores of placebo					
Reference scale		Subject's global assessment score (%)		Physician's global assessment score (%)	
	Visit 5 (Day 60)	Visit 6 (Day 90)	Visit 5 (Day 60)	Visit 6 (Day 90)	
Very good	5	0.00	0.00	0.00	1.72
Good	4	3.45	1.72	1.72	0.00
Normal	3	8.62	3.45	15.52	1.72
Average	2	37.93	18.97	29.31	25.86
Poor	1	50.00	75.86	53.45	70.69
Global assessment scores of Maxicuma 100 mg					
Reference scale		Subject's global assessment score (%)		Physician's global assessment score (%)	
Very good	5	5.26	12.28	8.77	38.60
Good	4	52.63	75.44	57.89	52.63
Normal	3	33.33	8.77	26.32	5.26
Average	2	8.77	0.00	7.02	0.00
Poor	1	0.00	3.51	0.00	3.51
Global assessment scores of Maxicuma 250 mg					
Reference scale		Subject's global assessment score (%)		Physician's global assessment score (%)	
Very good	5	37.29	72.88	57.63	86.44
Good	4	47.46	23.73	30.51	11.86
Normal	3	13.56	1.69	10.17	0.00
Average	2	0.00	1.69	0.00	1.69
Poor	1	1.69	0.00	1.69	0.00

OA rank 11th among the leading causes of global disability and causing significant economic burden [27]

Turmeric (*C. longa*) has a long history of safe use as food and also as anti-inflammatory aid. Its yellow-pigmented fraction, mainly curcuminoids, has antioxidant and anti-inflammatory properties, beneficial for osteoarthritis, type 2 diabetes, and dyslipidemia. However, curcumin's systemic bioavailability is limited and prior studies have shown little to no detectable levels in plasma following large doses [28]

A meta-analysis by Daily et al. [14] clearly mentioned that the most studies used a dose of supplements equivalent to 1 g of curcumin for the management of OA symptoms [14]

The clinical observations in several earlier clinical trials were limited by the formulation aspect which would often lead to lower bioavailability of active curcuminoids. Apart from formulation challenges, new generation curcumin products also limited by dosage regimen and efficacy at shorter duration. The current formulation, Maxicuma, addresses the current limitations and was proven to enhance the bioavailability of free plasma curcumin [29–32]

The above research data clearly points the need of the low dose of curcumin supplements which can deliver the "free plasma curcumin" at a significant level in its bioactive form. Since Maxicuma has been proved for significant delivery of free plasma curcumin along with longer $T_{1/2}$, the current study was designed to check clinical efficacy at two low dose levels.

The current clinical study demonstrated that the doses of Maxicuma, i.e., 250 mg and 100 mg, were superior to placebo in efficacy across all the endpoints with statistical significance $p < 0.05$. At a shorter duration of up to 60 days both the strengths were equally effective as there were no statistically significant differences between them. However, by day 90 Maxicuma 250 mg was superior in efficacy than 100 mg which indicates that usage of 250 mg dose for longer duration could be beneficial for managing the symptoms of OA given the chronic nature of the disease.

The grade wise analysis revealed that Maxicuma 250 mg brought about a significant clinical and functional improvement in KL Grade III OA, whereas both the strengths were equally effective in case of KL grade II OA. Since the Grade III condition is characterized by more inflammatory condition than Grade II, functional improvement in former condition can be improved by the product that can neutralize higher levels of inflammatory mediators. As the Maxicuma 250 mg delivers more plasma free curcumin than Maxicuma 100 mg, higher dose of maxicuma able to improve the functional outcome in Grade III participants in a statistically significant manner than the lower tested dose, although no statistical significance has been observed in objective assessment.

Although WOMAC, a validated questionnaire for knee OA widely used by many studies, the current study considered all the individual components of the questionnaire at all the measured intervals to understand the efficacy of the tested doses. Although both the tested dose levels have shown significance against placebo at all the subcomponents of WOMAC, 250 mg dose started the superiority over 100 mg from day 30 which indirectly showed that its high potentiality in modifying the pathological characteristics to bring down pain and to improve joint health, which directly corroborates to improved functional outcome and quality of life.

The efficacy findings pertaining to the outcome measures are also justified by the subjects and physicians' global assessment of therapy, where both subjects and the physicians perceived that the dose of 250 mg per day was significantly effective in improving the functional and clinical outcomes of the subjects with knee OA. Although the current study included the utilization of validated scales like VAS and WOMAC that are widely acceptable, to avoid subjective bias, validated treadmill protocol was also implemented as a part of objective assessment as used for other curcuminoid studies [30] Although quality of life (QoL) was not measured through any specific questionnaire in the study, attention to individual components of WOMAC and consideration of global assessment gave the information on the potential impact of the supplementation on QoL, indirectly.

As per Gupte et al. [31], the solid-lipid nano-formulation of curcumin at 800 mg per day dose has shown efficacy comparable to ibuprofen at 400 mg per day through WOMAC and VAS after 60 days [31] The current study demonstrated efficacy from the 30th day, which indirectly indicated action comparable to ibuprofen. Another open-label research study claimed the comparable efficacy of blend of curcumin and turmeric oil at 1.5 g per day with Diclofenac at 100 mg per day against VAS [33] This study also supports the efficacy of Maxicuma indirectly in comparison to Diclofenac. In another study, the mixture of curcuminoid and piperine also has shown efficacy in terms of functional improvement through VAS and WOMAC. Although the achieved significance was $p<0.001$, the tested dose levels were comparatively higher than the current study [34] Since it is the first study to target OA, it aimed to test the efficacy at low doses by using basic validated parameters to justify future objective studies. The efficacy was proven with ideal population size, and the test item has shown efficacy irrespective of the grading of the disease and sex.

As depicted in Table 2, fifteen subjects from the study reported self-limiting, transient adverse events. The duration of all the adverse events experienced by the subjects are not more than 4–5 days. The oral administration of study products was well tolerated and did not produce any significant safety concerns. The adverse events observed viz., nausea, bloating, headache, gastritis, vomiting and abdominal pain, with test products were similar in duration, severity and seriousness to those observed with the placebo as reported elsewhere [33,35–37]

There were no clinically significant laboratory findings in both the active arms for the period between screening and end of the study. Altogether, the safety risk posed by the active study doses were not significantly different than that of placebo. Further to the clinical efficacy, functional improvement and subjective perception, no significant, product limiting adverse events were noticed in the clinical study.

While the current study population was fairly homogenous in terms of disease severity and demographics, the consistency of results supports cautious generalization to similar OA populations. However, broader

applicability to different geographic, ethnic, or high-risk subgroups (e.g., obese patients, those with comorbid diabetes or cardiovascular conditions) should be evaluated in future studies with stratified designs to enhance external validity.

To build upon these findings, subsequent clinical trials should consider longer follow-up durations (e.g., 6–12 months) to better understand the sustainability of therapeutic effects and the long-term safety profile. This would also allow exploration into whether Maxicuma® has any disease-modifying potential—slowing cartilage degradation or delaying progression to more severe OA. Additionally, exploring its role in combination with conventional therapies (NSAIDs, physiotherapy, or intra-articular injections) may yield insights into synergistic effects or dose-sparing benefits.

Clinicians may find this data particularly valuable when tailoring integrative regimen strategies for OA subjects who are either not ideal candidates for long-term NSAID use or are seeking well-tolerated natural alternatives with validated clinical backing. Maxicuma®'s favorable safety and efficacy profile, as demonstrated in this trial, offers a practical addition to the therapeutic arsenal, especially for use in early-to-moderate OA management where maintaining joint function and quality of life is paramount.

5. Conclusion

In conclusion, the data from the current clinical study suggest that Maxicuma® 100 mg or 250 mg could be an effective supplement option for the management of knee OA as they can provide benefits by improving clinical and functional outcomes.

Funding information

Not applicable.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors did not use generative AI for drafting the manuscript.

Acknowledgments

None.

Data availability

All data generated or analyzed during this study are included in this article and also in appendix. Since it is a clinical trial, raw data cannot be made publicly available, as all the subjects were assured raw data would remain confidential and would not be shared due to ethical reasons.

CRediT authorship contribution statement

Girish HR: Supervision, Investigation, Data curation. **Harshith N:** Supervision, Investigation, Data curation. **Nehru Sai Suresh Chalichem:** Writing – original draft, Project administration, Formal analysis, Conceptualization. **Abhijith Phanindra:** Writing – original draft, Project administration, Methodology, Formal analysis, Data curation. **Mohammed S. Khan:** Writing – review & editing, Supervision, Conceptualization. **Jayant Deshpande:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Nehru Sai Suresh Chalichem reports a relationship with India Glycols Limited, Dehradun that includes: employment. Mohammed S. Khan reports a relationship with India Glycols Limited, Dehradun that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eujim.2025.102531.

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